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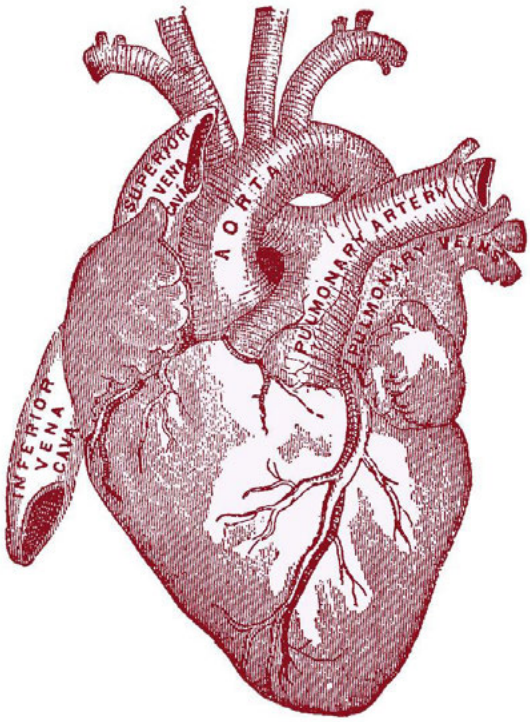
The Red Book

Housestaff Manual for Cardiology



Department of Medicine
Massachusetts General Hospital
Harvard Medical School
July 2019 – June 2020

Editors
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LETTER FROM THE EDITORS

It is our honor to present the 2019-2020 edition of the Housestaff Manual for Cardiology. Former MGH house officer, Andrew Sauer, spearheaded the first edition in 2010, with the intention of offering residents a practical introduction to the major concepts essential to everyday patient care in the Coronary Care Unit (CCU, now the CICU) and the cardiac Step Down Unit (SDU).

For this year's edition, in addition to content updates, we have made several more global changes, the most obvious of which is a change to its name. Formerly the "CCU & SDU Resident Guide," we have chosen to re-title it "The Red Book" to pay homage to several aspects of the MGH culture that date back long before our guide came into existence and represent some of the reasons that MGH is such a special place to train.

In 1994, based on the understanding that exceptional patient care is grounded in a rich foundation of evidence, Albert Shaw and Ravi Thadhani set out to create a reference guide for residents that compiled up-to-date guidelines for clinical management. This resource, entitled "The MGH Department of Medicine Housestaff Manual," has since been updated annually and represents the rigor, autonomy, and pride with which our residents approach their work. We intend for "The Red Book" to encapsulate these same principles within the field of cardiology and to pay tribute to the original DOM housestaff manual, now in its 25th year, and known more affectionately as "The White Book."

This commitment to well-informed practice is grounded in a genuine desire to understand, connect with, and improve the lives of our patients, but a more difficult reality emerges when we feel that our efforts have fallen short. As agents of medical practice, we continuously engage with elusive concepts—illness, intimacy, loss, grief—and wrestle to ascribe meaning to the intangible. In the year 1980, Dr. Ted Stern, an MGH psychiatrist and the psychiatric consultant to the medical intensive care unit (MICU), attempted to confront and respond to these challenges when he purchased a journal, the cover of which was red, and placed it in the MICU. From then, until 2003, the red book served as a collective forum for resident self-reflection. It supplemented his weekly "autognosis" (self-knowledge) rounds. After it was filled, seven more volumes followed. Excerpts from the journals were subsequently complied and incorporated into a book, "On the Edge of Life: Diary of a Medical Intensive Care Unit" edited by Drs. Mikkael Sekeres (a former MGH house officer) and Ted Stern. While Dr. Stern's "Red Book" is no longer in existence, its spirit is still very much alive at MGH, particularly on our cardiology rotations and exemplified by Dr. Hasan Bazari's CICU reflection rounds. With our renaming, we hope that this guide will serve as another reminder to carve out space for introspection and to allow for the projection of kindness and empathy both inward and outward.

Aside from the title, we are excited to announce two new sections, "Infective Endocarditis" and "Vascular Medicine," as well as an updated feature, the Quick Reference Guide. These synopses, which have been added to the end of each chapter, provide a streamlined reference of high-yield content within each section.

In addition to the individuals mentioned above, we would like to thank the many current and former MGH housestaff and faculty who have updated and provided original contributions to this guide. We are deeply appreciative of their dedication, leadership, and commitment, without which "The Red Book" would not be possible.

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The following attending reviewers have provided expert opinion and consultation for each section:

Rajeev Malhotra	Intro, Cardiac Arrest, Tools in the CICU
Sunu Thomas	Heart Failure and MCS
Matthew Nayor	
Nasrien Ibrahim	
Rahul Sakhuja	ACS and Ischemic Heart Disease
Kevin Heist	Arrhythmias and Electrophysiology
Doreen Defaria Yeh	Valvular and Congenital Heart Disease
Evin Yucel	
Jacob Johnson	Infective Endocarditis
Ido Weinberg	Vascular Medicine
Pradeep Natarajan	Primary Prevention and Toxidromes

We would also like to acknowledge Dr. Adam Johnson, for his help with layout and formatting, and the outstanding leadership of our section editors:

Samuel Slavin	Cardiac Arrest and Tools in the CICU
Richard Alexander	Heart Failure and MCS
Lindsay Panah	ACS and Ischemic Heart Disease
Eric Mills	Arrhythmias and Electrophysiology
Yamini Krishnamurthy	Valvular and Congenital Disease & Infective Endocarditis
Alexandra Wick	Vascular Medicine
Brian Mugo	Primary Prevention and Toxidromes

Finally, we would like to provide a special thank-you to Dr. Dave Dudzinski for serving as a global attending reviewer for this year's guide as well as to Dr. Jay Vyas, the DOM Chief Residents, and the DOM Staff for supporting our endeavor.

We hope that this guide will continue to assist with the care of cardiac patients at MGH. As such, it is meant to serve as a reference to be used in conjunction with other resources and never in place of sound clinical judgment. Thank you for continuing to provide the highest level of care and compassion to our patients.

Rachael Venn and Cian McCarthy
The Red Book Editors
2019-2020

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INTRODUCTION TO THE CICU

Below is a brief set of tips for the CICU. Please review OurMGH for the most complete and up-to-date information prior to your rotation.

Admission Note Tips

- Provide the cardiac history in chronological order
- **Treadmill stress test:** remember to include duration of exercise, METS achieved, HR (and % maximum), BP, peak double product ("good test" > 20k), EKG/imaging
- **Echo:** TTE or TEE, EF, valves, wall motion abnormalities, wall and cavity dimensions (IVS, LVID) and atrial dimensions
- **Catheterizations:** Right heart cath values first in the order obtained (RA, RV, PA, PAOP), then LV gram results, then coronary angiography (Left main, LAD, LCx, RCA) finally, interventions and complications
- **CABG:** anatomy is critical; if OSH surgery, you must obtain a copy of the operative report or post-CABG angiogram
- Always document a peripheral vascular exam (femoral, popliteal, DPs, PTs) as this becomes crucial if there is a procedure complication or access on the other side is needed
- Print EKGs and place in chronological order for the team to review during rounds
- Place EKGs in the patient's paper chart for other providers

Admissions from the Cath or EP Lab

- Make sure you ask the following questions during pass-off or prior to patient's arrival:
  - Who is the attending of record? Any specific instructions from him/her?
  - Pass off should contain the following elements:
    - **Procedure**: What was done? Results?
    - **Access**: What was the access? Where and what size? Do you want the sheaths pulled? When? By whom? At what PTT? Duration of bedrest?
    - **Anticoagulation:** What was used in the case? Do you want heparin or bivalirudin restarted?
    - **Antiplatelet**: What was used in the case? What should the patient be on now? Duration of any IIb/IIIa inhibitor (e.g. cangrelor)? The interventional fellow should write these orders.
    - **Complications**?
- Post-cath check:
  - Check groin yourself for expansile mass, tenderness, bruit (suggestive of pseudoaneurysm). Document full bilateral neurovascular exam.
  - Follow CBC for decrease in hematocrit. If drops precipitously post-cath consider retroperitoneal hematoma.
  - For access sheath removal, complications or questions during the day, contact the fellow who performed the procedure; overnight, contact the Cardiac Access/Interventional Unit fellow on Ellison 11 (4-5110)

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PHONE NUMBERS

CICU	
Front desk	4-4910
Fax	4-4950
SDU	
Front desk	4-5010
Fax	4-5050
Workroom (desk)	4-6292
Workroom (wall)	4-5030
Cardiology Division	
Page Operator (attendings, overnight echo, IABP tech)	6-9292
EP fellow	6-9292
Cardiac Access Fellow (Ellison 11)	4-5110
Paul Dudley White (Fellow's) Clinic (Yawkey 5E)	6-2677
Cardiac Studies	
Catheterization Lab	6-7400
Electrophysiology Lab	6-5036
Stress Lab	4-3600
Stress Lab (weekend)	3-8363
Echo (inpatient)	6-8871
Vascular lab (CNIS)	6-2034

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CARDIAC ARREST

See Page 17 for Quick Reference Guide

1. ACLS and Codes

The topic of cardiac arrest is at the beginning of this text because it is one of the most anxiety-provoking experiences of the CICU and SDU. The following includes an editorialized summary and practical approach to American Heart Association guidelines for cardiopulmonary resuscitation (CPR) and Emergency Cardiovascular Care (ECC) most recently updated in 2018.[1] This recent update does include some changes to ACLS, which are reviewed below. Codes are common in the CICU, and the entire protocol should be reviewed in detail prior to (and during) the CICU rotation.

The Code Leader

The most important aspect of an effective resuscitation is proper leadership and execution of ACLS protocol. This begins with rapid identification of roles and clear communication with closed loop communication between the code leader and code participants. In the CICU, the code will typically be run by the most senior resident present, typically CCU senior (day) or Unit Night Teach (night). When the leader is identified, she/he should state loudly, for example, "I am Jane Doe, the CICU senior, and I am leading this code." On rare occasions when a code is called overhead, a critical care fellow and/or intensivist may also be present. They are expected to provide ideas and support, not run the code.

The code leader directs all verbal orders to the code team members. Closed loop communication with a specific person for a specific task should be used to ensure that orders are carried out. Any ideas, questions, or data feedback should be provided directly to the code leader so that all information and direction is filtered through a single team member positioned at the foot of the patient's bed. Since the code leader receives all information and directs all interventions, it is helpful to intermittently announce the algorithm, summarize the patient's case, proposed etiology of arrest, and interventions to that point.

Other Code Roles

In the CICU, codes are generally run by the primary CICU team with the CICU nurses and CICU pharmacist. Overhead "Code Blue" is called only if the primary team needs additional backup (which may be the case overnight). Roles are as follows: (including outside of the units)

Primary nurse: responsible for pushing all ACLS meds, fluids, etc.
Scribe nurse: responsible for writing down the events with associated times
Support nurses: getting meds, code cart, defibrillator, backboard, telemetry review, EKG, blood pressure check, fluids, drugs, IV access, etc.
Pharmacist: Preparing medications requested by the code leader
Residents and nurses: provide effective chest compressions 100-120 times per minute to a depth of 2 inches with full chest wall recoil between compressions; should rotate this role approximately every 2 minutes.
CICU Junior: keeps track of time and ACLS protocol meds, underlying rhythm. Should notify the code leader when it is time to give a medication or shock. May serve as code leader if a SAR is temporarily unavailable. One junior should be assigned to call the attending early on in the code and contact the patient's family to confirm code status.
On-call CICU Junior: primary role is to bring IO kit to code, then assess and obtain access as indicated; may also be responsible for monitoring the pulse. This person should inform team

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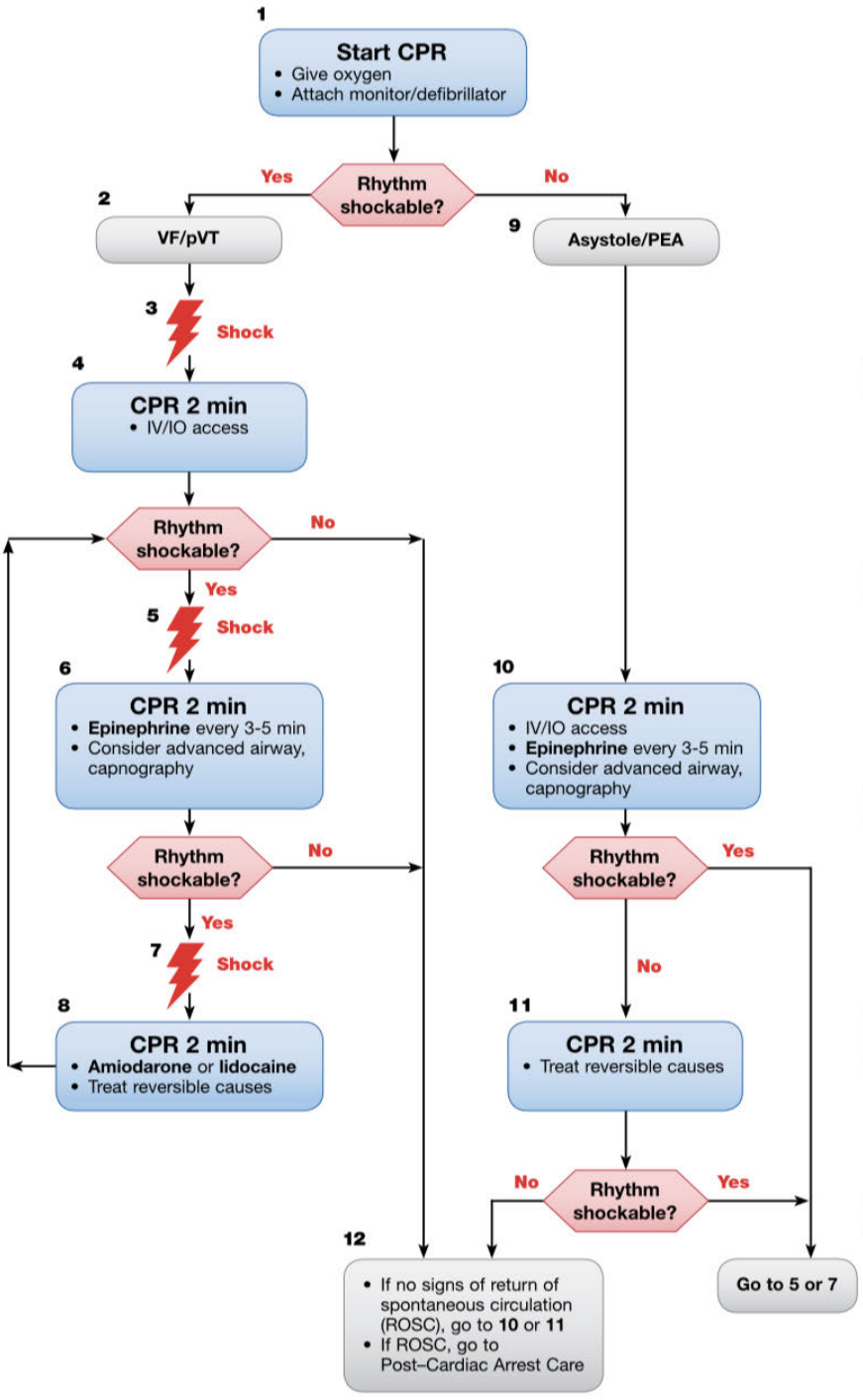
members when chest compressions are ineffective (invasive arterial dBP < 20mmHg or pulse not palpable).
Back-up senior: "big picture" role; provides guidance to the code leader re: etiology of cardiac arrest. Senior should review the chart, telemetry, the nursing flowsheet, and the relevant labs to assist with forming a differential and big picture plan.
Additional roles: including anesthesia, security, respiratory. The nursing supervisor if present and security can help with crowd control.

The Importance of CPR and Defibrillation:
The foundation of ACLS is good BLS care, beginning with prompt high-quality CPR and, for VF/pulseless VT, attempted defibrillation. Patients with witnessed pulseless VT/VF who get prompt CPR and early defibrillation have a higher rate of survival to hospital discharge as compared to patients with PEA arrest, unwitnessed arrest, and/or delay in CPR or defibrillation. By comparison, additional ACLS therapies such as advanced airways and pharmacologic therapies have not been shown to significantly increase the rate of survival to hospital discharge. Therefore, the **first responder should be prepared to immediately start CPR and/or defibrillation** when indicated even BEFORE the code team arrives. In the CICU, this role is often shared between nurses and housestaff.

The first responder(s) should immediately assess the **C-A-Bs** (circulation, airway, and breathing). Once pulseless arrest has been identified, one responder should immediately begin chest compressions while the code is called. The first responder should call for the backboard. The second responder should immediately call for the defibrillator and hook up the pads to the patient to assess the rhythm. If the arrest was witnessed and the patient is found to be in VT/VF a shock should be delivered immediately. All MGH defibrillators are manual biphasic and 120J should be delivered. When in doubt, the defibrillator should be charged to its highest setting. If the arrest is not witnessed, rhythm should be assessed after a full 2 minutes of CPR. A common mistake is holding compressions during defibrillator charging or after a shock is administered – CPR should be restarted promptly after a pulse check, continue while the defibrillator is charging, and resumed IMMEDIATELY after a shock and continued for 2 minutes, at which point the pulse and rhythm should be again assessed, pausing compressions for **≤10 seconds** at each check. On rare occasion patients will have adequate cerebral perfusion with CPR and wake up; although the first instinct is to stop CPR, in most cases the patient will be pulseless again, so CPR should be continued as per protocol, stopping only every 2 minutes for a pulse check. It is difficult to do but better to preserve adequate perfusion.

Adult Cardiac Arrest Algorithm—2018 Update



CPR Quality

- Push hard (at least 2 inches [5 cm]) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Change compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography
  - If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality.
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality.

Shock Energy for Defibrillation

- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

-OR-

Lidocaine IV/IO dose: First dose: 1-1.5 mg/kg. Second dose: 0.5-0.75 mg/kg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Figure 2. Adult Cardiac Arrest Algorithm.

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General Approach to ACLS
There are two goals in a code:

1. Running the ACLS algorithm with effective CPR and rapid defibrillation when appropriate
2. Determining a reversible etiology of the arrest

The back-up senior and other team members should work to identify the etiology of arrest. Support members should then direct data back to the code leader so that she/he can "think out loud" about what she/he would like to initiate as supplementary management to the ACLS protocol. Housestaff who are not directly involved in the code can be helpful by surveying the telemetry for the patient and printing relevant strips to bring into the room to share with the code leader.

Whom to call for help: Call the **Cardiology or Critical Care attending of record ASAP**, as they may have specific suggestions from the options listed below (especially if the patient is on the transplant list or VAD candidate). If the code is suspected to be due to a STEMI, call the **interventionalist on call at 6-8282**, and upload the ECG to MUSE. Patients with ischemic VT/VF can be transported to the cath lab while receiving CPR. If the patient has had a recent surgical or IR procedure, call that team immediately as they will help you identify **post-procedural** complications that may have led to the arrest. If pneumothorax is suspected, a needle decompression may be attempted by housestaff, and general surgery should be called stat for chest tube placement.

If massive PE is suspected, consider tPA and call the **PERT team.** If cardiogenic shock is the cause of the arrest and the patient is a potential ECMO candidate, call the **mechanical support team**. Think about this right away if the patient is waiting for or has received a heart transplant or VAD, or if they are waiting for PCI or CABG. Occasionally patients will be cannulated for ECMO or bypass while getting CPR; more often they will be cannulated at the bedside immediately after ROSC is obtained. **It is vital to think of the ECMO team and call early.**

Useful first-line medications in the ACLS algorithm:
Epinephrine: 1mg IV/IO q3-5 minutes during resuscitation. Improves chance of ROSC in VF/pVT, but no evidence to evaluate survival or neurologic outcomes. Improved ROSC and survival to discharge in PEA/aystole when given early vs. late. Higher doses are not recommended. Amiodarone or Lidocaine: For VF/pVT unresponsive to defibrillation.

Amiodarone: Administer 300mg IV/IO as first dose; 150mg as second dose OR. *Lidocaine:* Administer 1-1.5 mg/kg as first dose; 0.5-0.75 mg/kg as second dose. Theory is reduced recurrence of arrhythmia once a perfusing rhythm is restored. Both drugs associated with higher rates of ROSC and survival to hospital admission for out-of-hospital cardiac arrest (OHCA) due to VF/pVT, but no overall survival benefit.[1] Amiodarone is typically the preferred agent.

Useful medications not in first-line ACLS algorithm:

- Sodium bicarbonate: helpful when low pH is suspected. Will act as short-lived fluid bolus. Is given as 1 ampule a few times during the code.
- Magnesium: 2 grams IV, can repeat, considered helpful in suspected torsades provoked by long QTc, however, no demonstrated benefit in terms of ROSC or survival, not recommended for routine use in all VF/pVT
- Steroids: Patients receiving vasopressin (20 IU/CPR cycle), epinephrine (1 mg/CPR cycle) and methylprednisolone (40 mg) for the first 5 rounds of CPR followed by 300 mg

hydocortisone daily for 7 days if ROSC was achieved had improved survival to hospital discharge, a favorable neurologic status, improved hemodynamics, and less organ dysfunction.[2,3] While methylprednisolone is not readily available on the code cart at MGH, hydrocortisone (200 mg equivalent dose – the entire amount on the code cart) may be used. It is reasonable to administer the bundle of epinephrine, vasopressin, and steroids for in-hospital cardiac arrest; however, this is not standard practice at MGH.

- Vasopressin: the combined use of vasopressin and epinephrine offers no advantage to using standard-dose epinephrine in cardiac arrest. Review of the available evidence shows that efficacy of the 2 drugs is similar. As vasopressin does not offer an advantage over the use of epinephrine alone, the suggestion of the use single dose 40mg IV/IO vasopressin has been removed from the 2018 update to the ACLS algorithm[1]. However, use of vasopressin can be considered when bundled with epinephrine and steroids as above.

Asystole and/or Pulseless Electrical Activity (PEA)
PEA is a broad term that includes pseudo-electromechanical dissociation, pulseless idioventricular rhythms, ventricular escape rhythms and asystole. Research with cardiac echo and PA catheters shows that patients in PEA have appropriate electrical activity and rhythm but the cardiac contractions are too weak to produce a blood pressure that can be detected by palpation or noninvasive monitoring. Survival in PEA is directly related to identifying and treating a reversible cause.

Asystole is associated with an extremely poor prognosis. If a rapidly reversible cause is not identified, the patient will rarely survive. Since both PEA and asystole have many similar etiologies, they are considered analogous in the ACLS protocol. By definition these patients will not respond to defibrillation or anti-arrhythmic medications and the focus of resuscitation should be on adequate CPR with minimal interruptions, early epinephrine administration, and the rapid identification of reversible etiologies (see the H's and T's in Figure 1 above).

Early administration of epinephrine as soon as feasible after the onset of cardiac arrest due to an initial non-shockable rhythm is important.

In the CICU, the echo capabilities are readily available, and with a fellow or attending nearby it is possible to obtain rapid information about heart motion and contraction **however under no circumstances should attempts to obtain echo images delay or impede high quality CPR. Obtaining these images should be limited to the windows during pulse check. Obtaining these images (supine patient who may already have rib fractures) is technically challenging even for experts, and thus we expect residents will NOT attempt bedside ultrasound and instead focus on ACLS and CPR.**

Of note, if massive PE is suspected, request tPA immediately as this can take up to 15 minutes to get from pharmacy. If mixed and not given, the medication can be sent back to the manufacturer and we are not billed.

General principles in approaching treatment of arrhythmia with a pulse:

- If **bradycardia** is unstable (signs of poor perfusion) AND unresponsive to atropine, prepare for EITHER transcutaneous pacing OR inotropic agents (e.g., dopamine, epinephrine). Both are indicated only for patients with a palpable pulse. Additionally, call the cardiology fellow on call for consideration of transvenous pacing (temp wire).

- If **tachycardia** is unstable with signs of hypoperfusion, proceed to immediate synchronized cardioversion; atropine is no longer recommended in this setting.

- If tachycardia is stable, obtain 12-lead ECG to determine narrow or wide complex and implement therapy accordingly; when in doubt assume wide-complex tachycardia is VT. Adenosine can be used safely to diagnose *regular*, wide complex, monomorphic tachycardia when proper precautions are in place (i.e. backboard in place with code cart and defibrillator readily accessible).

- Atropine is no longer recommended routinely in PEA/asystole or pulseless tachycardia.

Vascular Access During ACLS
Central vs. Peripheral Infusions: There is no evidence that central lines improve outcomes as compared to peripheral access. **Moreover, access considerations should never interrupt CPR**. If an ACLS medication is given peripherally it is important to chase the delivery with 20 cc of normal saline and elevate the extremity for 10 to 20 seconds to facilitate delivery.

Intraosseous (IO) cannulation is specifically recommended as the next intervention if peripheral IV access is inadequate. It has been shown in prospective trials to be safe and effective for fluid resuscitation, drug delivery, and blood sampling for laboratory evaluation. However, the maximum infusion rate is lower than that of a Cordis. Central line can be considered if no other access options exist or rapid, large volume infusion is needed (i.e. suspected hemorrhagic or hypovolemic shock). An IO is often a great way to buy time until a clean central line can be placed. Keep in mind that a central line is a relative contraindication for lysis in patients with acute coronary syndrome or stroke.

In the event that no IV access is available, **endotracheal route** is the next preferred. Remember NAVEL - **naloxone, atropine, vasopressin, epinephrine, lidocaine** - can be given via ET tube. The optimal dose for endotracheal administration is unknown, but typically it is recommended to give 2.5 times the recommended IV dose. The dose should be diluted in 5–10 cc of water or saline and injected directly into the endotracheal tube.

Advanced Airway Placement and Ventilation During ACLS
The advanced airway is not specifically required for all patients receiving ACLS. However, in some patients intubation is a therapeutic maneuver which can reverse an underlying cause for PEA arrest (e.g., hypoxia). Regardless, there **should be minimal interruption in CPR** for ventilation via bag mask. Patients should be ventilated after each cycle of chest compressions (30:2 compression-ventilation ratio) with only a brief interruption of CPR until an advanced airway is placed. CPR should be held only briefly for intubation. Ideally, this should take place during a planned pulse check/rhythm check pause, and this pause should be coordinated between the code leader and intubating team (many HCICU staff can intubate, or otherwise RICU). Once intubation is confirmed with bilateral breath sounds and quantitative waveform capnography, CPR should be continuous at 100 compressions per minute without pauses for ventilation. The respiratory therapist should give 8–10 breaths per minute during continuous CPR (one breath every 6–8 seconds).

When to Stop the Code
The decision to stop the code is based on the best judgment of the team facilitated through the code leader. One large study found that among hospitalized patients who achieved ROSC after arrest, 87% had done so by 30 minutes of ACLS. However, there is not enough data to make a

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firm recommendation regarding optimal duration of ACLS attempt.[4] Common sense argues that in a patient with an identified reversible etiology, every attempt should be made to remedy the problem and to continue ACLS until treatment goals cannot be reached and futility is apparent. It is reasonable for the code leader to announce his/her intention to cease resuscitation and invite any member of the team to propose additional strategies that could reverse the etiology and/or complications of the arrest. Survival rates are higher in patients with VF/VT rhythm, though non-VF/VT rhythms are present in > 75% of in-hospitals arrests.[1] Of the small proportion of patients experiencing in-hospital cardiac arrest who achieve ROSC and are admitted to the ICU, 80% die before discharge.[1]

If a patient dies following a code, it is a part of culture at MGH to stop and observe a moment of silence for the patient with all team members present.

After any code, it is recommended to debrief with those who participated in the code. The code leader generally facilitates this. Checking to ensure that team members are okay emotionally is important. If there are particular suggestions and lessons that might apply to structural or process improvement in future codes, please email the CICU medical and nursing directors.

Family Members at Codes

There is no consensus, but the evidence is increasing that family presence at codes reduces their levels of anxiety and depression after the event.[3] It is generally accepted that if a family member wants to stay during the code they are allowed to do so, but a member of the team (housestaff or RN) should stay by their side to explain what is happening and make sure they do not obstruct ACLS protocol.

Post Cardiac Arrest Care

The 2018 AHA guidelines for ACLS recognize the importance of post-cardiac arrest care. Key objectives relevant to the CICU:

- Identification and intervention for ACS (coronary reperfusion, PCI)
    - Obtain post-ROSC ECG ASAP to look for a STEMI as an underlying cause
- Temperature control to optimize neurologic recovery in comatose patients (hypothermia to euthermia between 32 to 36 degrees Celsius)
- Blood pressure goals:
    - Almost all patients with ROSC after an arrest will need to be on a pressor. Hypotension (SBP < 90 mmHg and/or MAP < 65 mmHg) should be corrected, as hypotension post-cardiac arrest is associated with worse mortality and decreased functional recovery. Levophed (norepinephrine) is generally preferred over Neosynephrine (phenylephrine) for patients with a component of cardiogenic shock. Ask for it to be started as soon as ROSC is achieved (and oftentimes still while CPR is ongoing)
- Steroids (hydrocortisone 100mg q8 x 7 days) did not show a benefit for survival or neurologic outcome when started for persistent shock following an ACLS event in one study.[6]

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2. Targeted Temperature Management

Rationale: Devastating neurological injury from global cerebral anoxia is the dominant cause of death in comatose patients with out-of-hospital cardiac arrest whether from VF, VT, PEA, or asystole.[1] Annually, 350,000 to 450,000 out-of-hospital cardiac arrests occur in the US.[2] Among the fraction of patients who regain spontaneous circulation, the neurologic sequelae of hypoxic brain injury are profound. Mild or "therapeutic" hypothermia has been found to improve neurological outcomes after cardiac arrest presumably by reducing the brain's metabolic requirements and dampening a cascade of damage following a global ischemic event.

Early protocol initiation (no later than 6 hours after ROSC) and rapid achievement of goal temperature are imperative; **the earlier the better, and rapid cooling is key.** During hypothermia, patients undergo sedation, paralysis, and close hemodynamic and laboratory monitoring. Using a surface cooling device that circulates chilled water through gel pads, patients at MGH are cooled to 33˚C or maintained at normothermia (36˚C). (See below for selection of goal temperature.) After goal temperature is achieved and maintained ~24 hours, patients are rewarmed to normal temperatures slowly and in a controlled fashion. Sedation and paralysis are lifted during rewarming and the careful assessment of neurological recovery begins after the effects of hypothermia and paralytics have worn off.

Two randomized-controlled trials have demonstrated that cooling improves neurologic outcomes and survival to hospital discharge in comatose patients who regain spontaneous circulation after an out-of-hospital VF or VT arrest.[3,4] No randomized clinical trials have been published to date on cooling for PEA/asystolic arrests or in-hospital arrests. However, at MGH we consider all patients to be potential candidates. Retrospective reviews comparing outcomes in these patients have been mixed, but are subject to confounding.[5,6] One trial compared temperature target of 33°C versus 36°C in 939 patients with out-of-hospital arrest (all rhythms) and found similar survival rates and neurologic outcome in both groups (42% in 33°C group and 39% in the 36°C group).[7]

Based on the available data, the 2015 AHA Guidelines for Emergency Cardiovascular Care have been updated to recommend cooling in all comatose (GCS <8) patients with any in or out of hospital cardiac arrest. This recommendation takes into account the high risk of poor neurologic outcome and low risk of harm with a range of targeted temperatures between 32 and 36 degrees Celsius. The guidelines also now recommended actively preventing fever in comatose patients after 24 hours of cooling.[8]

Candidates for Cooling (32-34°C):

- Any in- or out-of-hospital cardiac arrest (including VT, VF, asystole, or PEA) requiring CPR in which ROSC is achieved.
- GCS < 8 after ROSC

While contraindications in original studies included acute hemorrhage, acute sepsis, pregnancy, and severe inherited bleeding disorders, decisions should be made on a case-by-case basis weighing the benefit against risk. Indeed, good outcomes have been reported in subsequent observational studies. With the exception of some contraindications (listed below),[9] cooling should be *considered* for all other patients meeting the criteria above. The treating team should have conversation with the legally authorized representative or next of kin if patient may have DNR status.

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Relative Exclusion Criteria: (consider targeted temperature management at 36°C rather than no cooling in these cases)

- Pre-existing coma from another cause
- Intractable/unmanageable hemodynamic instability
- Suspected sepsis (hypothermia inhibits immune function)
- Major surgery within 14 days (hypothermia increases risk of infection/bleeding)
- Major active bleeding
- Major head trauma (should get head CT and start cooling; if CT shows major bleed, stop cooling)
- Patient with isolated respiratory arrest
- Previous DNR status should prompt discussion with surrogate decision makers

Important Note Prior to Therapeutic Hypothermia:

- Active bleeding is contraindication to hypothermia, but use of thrombolytics, antiplatelet agents or anticoagulation is not. Patient MUST be carefully monitored for bleeding/coagulopathy.
- Initiation of the hypothermia protocol is NOT a reason to defer cardiac cath.

- Infection can be a major complication of hypothermia. Treatment (aspiration events are common) should be initiated promptly for early sign and symptoms of infection during hypothermia to avoid sepsis. For patients using surface cooling such as the Arctic Sun,
- "Fever workup" should be obtained for water temps < 70°F during active cooling. Low water temperatures indicates that the patient is requiring extra cooling and therefore the equivalent of having a fever.

Elements of the MGH Therapeutic Hypothermia Protocol:
Goal: Cool patient to 33°C (32–34°C) for 24 hours. The cooling protocol should be initiated as soon as possible (<6 hours post-ROSC) and the target temperature achieved as quickly as possible after protocol initiation.

Preparation:

- Consult neurology Stroke/ICU consult pager (pager 20202) to document comatose state prior to initiation of hypothermia and to follow throughout treatment.
- Place arterial line for BP monitoring.

- If needed, obtain central access. Obtain baseline labs and rule out severe coagulopathy (check PT/INR/PTT/D-Dimer). Send Neuron Specific Enolase (NSE) (send-out at MGH) and S-100 (markers of brain injury) at 24 to 72 hours after arrest, as high NSE values may predict poor outcomes, though this should not replace guidelines for prognostication.[10]
- Place continuous temp probe (bladder or Pulmonary Artery temp probe). Note that the bladder probe does not work if there is inadequate urine output and can be slow in reflecting core body temperature changes.
- Obtain any secondary temperature probe (Exergen) compatible with cooling device console.
- Position external cooling device. The Arctic Sun device is standard in the MGH CICU.

- Other techniques include central "cooling catheters" at other centers and ice packs or infusion of cold IVF

- USE THERAPEUTIC HYPOTHERMIA ORDER SET in Epic and refer to MGH Therapeutic Hypothermia Policy is Euclid for question.

Protocol Initiation/Cooling:

- Obtain a baseline train of four (TOF) before initiation of paralytic medication and once the patient is rewarmed to 36.0 °C. TOF is not recommended during the hypothermia period.
- Paralysis: Neuromuscular blockade with cisatracurium (Nimbex) prevents the shivering response which warms the body (inhibiting cooling) and can result in rhabdomyolysis and AKI
- Sedation: Propofol or midazolam. Patient should be deeply sedated before initiation of paralysis.
  - Analgesia: consider fentanyl/dilaudid as considered clinically necessary
  - Begin cooling with external cooling devices.
  - Consider infusion of cold normal saline (30 mL/kg over 30 minutes). Administer via PIV or femoral CVL only, as the safety of IJ or subclavian CVL administration is unknown.

Maintenance:

The **24-hour cooling period begins from initiation of cooling**, NOT the time the target temperature is reached. Once hypothermia is reached remove any ice bags and use cooling blankets/Arctic Sun to maintain temperature.

- *Blood pressure*: Setting and maintaining a MAP goal is very important to maximize cerebral perfusion and may provide additive neuroprotection. The MAP goal is > 70, but treating team must choose a MAP goal that balances cardiac safety with the theoretical advantage of higher cerebral perfusion pressure. Hypothermia can cause either hypertension (due to peripheral vasoconstriction) or hypotension (due to negative inotropy and/or dysrhythmias).
- *Rhythm*: Bradycardia is the most common arrhythmia associated with hypothermia, and does not require treatment unless blood pressures are inadequate. If significant bradycardia dysrhythmias or hemodynamic instability develop, stop active cooling and actively rewarm the patient. Notably, bradycardia can lead to QTC prolongation and precipitate torsades de pointes. If this occurs, a discussion with neurology and the CICU team should be undertaken to determine the next best steps in management once the patient is stabilized.
- *Ventilator*: Monitor ABGs routinely. During hypothermia a patients' true PaCO2 may be lower than that measured. PaCO2 should be corrected for hypothermia by the lab and the corrected value should be maintained between 35-45. Hyperventilation should be avoided as it is associated with constriction of the cerebral vasculature.
- *Temperature*: Always use two temp monitoring devices when using the Arctic Sun. The water temp will help determine the work of the machine in trying to keep the patient at target. Decreasing water suggests the machine doing additional cooling to counter a fever. Water temp < 70F should be interpreted as a fever.
- *Bleeding*: Check coagulation labs, CBC and follow actively. Rewarm very slowly if active uncontrollable hemorrhage occurs.
- *Infection*: Draw blood cultures at 12h and 24h time points since hypothermia will mask fever, and can cause leukopenia. Treat aspiration or other source of infection actively.

- *EEG*: Non-convulsive seizures can occur during hypothermia and EEG monitoring may have prognostic value.
- *Labs*: Hypothermia-induced polyuria or a "cold diuresis" results in urinary wasting of electrolytes that may contribute to hypothermic arrhythmias. Check Chem10 and CBC at least every 12 hours (+ ABG) and address abnormal values. Given the need for frequent blood draws, consider using pedi-tubes to avoid iatrogenic anemia.
- *Hypokalemia*: hypothermia drives potassium into cells, an effect that may be exacerbated by insulin administration. Importantly, this potassium flux may reverse with rewarming, so be cautious with potassium supplementation during the cooling period.
- *Thrombocytopenia*: mild thrombocytopenia is common with cooling and severe thrombocytopenia is possible.

Rewarming:
The rewarming phase may be the most critical phase, as uncontrollable or rebound cerebral edema may cause active cerebral herniation. Peripheral beds which were previously constricted start to dilate and can cause hypotension. Hyperkalemia and hypoglycemia can also occur.

- Rewarming should be slow, controlled, and occur at a rate no faster than 0.5°C (0.3–0.5°C) per hour.
- Actively monitor for seizures and other signs of worsening cerebral edema (e.g less reactive pupillary reflexes, newly fixed/dilated pupils). If there are any signs of worsening cerebral edema, stat page the neurology (Stroke/ICU consult team – pager 20202).
- It will take the patient about 8–12 hours to passively rewarm. Stable normothermia (37°C) with avoidance of hyperthermia is crucial and is the ultimate goal. A period of normothermia is recommended for another 24 to 48 hours once rewarming is achieved.
- If using Arctic Sun, the machine is programmed for controlled rewarming over 8–12 hours. The device should be programmed for desired rewarming rate and then to maintain a target temp of 37°C (98.6°F) for the next 48 hours at least (72 hours total).
- Maintain paralytics and sedation until a temperature of 36°C (96.8°F) is reached, then discontinue the paralysis.
- Sedation is stopped once a train of 4 is achieved (peripheral nerve stimulation and observe muscle contraction to show that paralysis has worn off).

Prognosis:
An estimated 44% of patients with in-hospital achieve ROSC and 17% surviving to discharge.[11] In the outpatient setting, very few patients even survive to hospitalization. Implementing the hypothermia protocol delays the ability to prognosticate, and it is important that neurologic prognostication does not take place too early, as it can result in inappropriate withdrawal of care. There are two outcome scales that are often used to assess outcomes, the Glasgow Outcome Scale and Cerebral Performance Category. They are similar with a scale from 1 to 5. See Horn J, et al: Prognostication after cardiac arrest.[12]

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Table 1. GOS and CPC outcome scales

GOS	Clinical condition	CPC
5	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.	1
4	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.	2
3	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.	3
2	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep and awake cycles. Cerebral unresponsiveness.	4
1	Death or brain death: apnea, areflexia, EEG silence.	5

CPC, Cerebral Performance Category; GOS, Glasgow Outcome Scale.

Signs in Evaluation of Prognosis

Early prediction of poor prognosis based on neurological exam alone, particularly with use of hypothermia treatment, could lead to inappropriate withdrawal of care in up to 20% of patients.[13] The optimal timing of prognostication using neurologic exam is unclear, but should be at least 72 hours after cardiac arrest in patients who have not undergone cooling, and 72 hours after normothermia is achieved (usually 5 to 6 days after arrest) in patients who have undergone cooling.

Many variables (age, cause of arrest, rhythm during arrest, and total time of CPR prior to ROSC, body temperature and initial Glasgow Outcome Scale score) have been reported to differ with respect to neurologic outcomes, but none can predict neurologic outcome after arrest with enough accuracy to withdraw care solely on these factors. EEG, blood biomarkers, somatosensory evoked potentials (SSEPs), and neuroimaging's role in prognostication are evolving with ongoing studies. Neurologic prognostication should ultimately be done on an individual basis with neurology consultants.

Coronary Revascularization

There is conflicting data regarding when to perform coronary angiography after cardiac arrest. Patients with ST elevations should always get immediate angiography. In the absence of ST-elevations, angiography should be considered but can be delayed. In one study, coronary angiography resulted in improved outcomes for patients independent of whether ECG identified ischemia. In this series, significant disease was found in 69% of patients.[14] Moreover, in a European out-of-hospital arrest series, patients with VT or VF had a significant stenosis in more than 70% of patients.[15] However, a 2019 RCT of out-of-hospital without ST-elevation demonstrated that delayed angiography after neurologic recovery was equivalent to immediate angiography with regard to 90-day survival.[16] Because of this, prompt discussion with an interventional cardiologist is reasonable, but in the absence of ST-elevation, angiography may be delayed in favor of more rapid cooling and stabilization. The timing of angiography should be based on the initial ECG, the hemodynamic state of the patient, the temporal arc of cardiac biomarkers and the competing needs for other resuscitation interventions. If needed, patients can have an IABP and be anticoagulated or on antiplatelet agents while cooled.

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QUICK REFERENCE GUIDE: CARDIAC ARREST

ACLS: Code Roles

- The Senior On serves as the code leader on the medical and general cardiology floors. In the CICU, the code will typically be run by the most senior resident present (day: CICU long senior; night: Units Night Teach)
- Junior residents are responsible for calling the attending of record, the patient's family, obtaining access (generally IO), monitoring the pulse, and calling emergency consults early (e.g. shock team)
- Interns are responsible for chest compressions

ACLS: Cardiac Arrest Algorithm

- High quality chest compressions are the foundation of effective resuscitation
- ''Shockable rhythms'' are ventricular tachycardia and ventricular fibrillation. A pulse and rhythm check should be performed every 2 minutes
- Defibrillation, medications, and diagnostics are summarized in the 2018 ACLS flow diagram (page 9)
- One large study found that among hospitalized patients who achieved ROSC after arrest, 87% had done so by 30 minutes of ACLS. However, there is not enough data to make a firm recommendation regarding optimal duration of ACLS attempt. Therefore, the decision regarding when to stop resuscitation efforts is based on the best judgment by the code team and ultimately determined by the code leader (with input from the room)
- If return of spontaneous circulation (ROSC) is obtained, an EKG should be obtained, and blood pressure should be monitored closely. Almost all patients will need a vasopressor such as norepinephrine or epinephrine
- Once the patient is stabilized, triage to an appropriate location will be needed e.g. catheterization lab for PCI (if STEMI) or CICU (post-arrest care)

Targeted Temperature Management

- If ROSC is obtained, all patients with GCS < 8 should be considered for targeted temperature management (TTM) to improve neurologic prognosis
- Neurology should be consulted ASAP to guide this decision (p20202), as cooling should ideally be initiated within 6 hours post-ROSC
- Given the need for close monitoring during the cooling and rewarming phases, cooling can only be performed in an ICU setting. Risks of cooling include hemodynamic instability (bradycardia, hypotension), infection, bleeding, and electrolyte derangements. The greatest risks of re-warming are rebound cerebral edema and hypotension
- Patients may be cooled to hypothermia (32–34°C) or maintained at normothermia (36.0 °C), depending on their clinical status), for a 24-hour period
- The **24-hour cooling period begins from initiation of cooling**, NOT the time the target temperature is reached. Rewarming should be slow, controlled, and occur at a rate no faster than 0.5°C (0.3– 0.5°C) per hour.
- It will take the patient about 8–12 hours to passively rewarm and a period of normothermia is recommended for another 24 to 48 hours once rewarming is achieved.
- The optimal timing of prognostication using neurologic exam is unclear, but should be at least 72 hours after cardiac arrest in patients who have <u>not</u> undergone cooling, and 72 hours after normothermia is achieved (usually 5 to 6 days after arrest) in patients who <u>have</u> undergone cooling

TOOLS IN THE CICU

See Page 40 for Quick Reference Guide

3. Pulmonary Arterial Catheter and Hemodynamic Monitoring

Since its inception in the 1970s by Jeremy Swan and William Ganz, the pulmonary arterial catheter (PAC) has been the gold standard in hemodynamic monitoring, and it is used frequently in our CICU. However, the data to support its use is lacking.

In the ESCAPE trial, 433 patients were randomized in block sizes of 2 or 4 amongst 26 hospital centers for HF with EF < 30%, hospitalization for HF within the past year, symptoms despite use of ACE-inhibitor and diuretics, SBP < 125, and at least one sign or symptom of congestion.[1] In one arm, treatment was guided by clinical assessment alone while in the other arm clinical assessment was aided by the use of a PAC. Although planned enrollment was 500 patients, the trial was stopped early due to concerns of early adverse events (9 patients had catheter related complications, most commonly infection) and an inability for this population to reveal a statistical significance. There was no significant difference in days alive out of hospital in the first 6 months (primary endpoint), although other secondary endpoints were reached. In contrast to our CICU, a minority of patients (180 of 433) in this study required inotropes.[1]

PAC-MAN, another RCT, randomized 1041 patients with potential benefit from PAC to receive a PA line or not. Both medical and surgical patients were used. Ultimately, no significant difference in mortality was found (primary endpoint).[2]

A meta-analysis in JAMA (2005) studied 13 RCTs (5051 patients) and was ultimately a neutral study with no improvement in survival or increase in mortality with use of the PAC.[3] There was no significant difference in number of days hospitalized. A Cochrane systematic review (2013) of 13 RCTs (5686 patients) similarly concluded that the use of a PAC did not alter mortality, ICU or hospital length of stay, or cost for adult patients.[4] Although debates remain over whether to use a PAC and in which populations to use it, it is ultimately thought to be a safe tool when used appropriately, and indeed, no trial has adequately studied the use of the PA catheter in the types of patients that tend to have them in our CICU (e.g. cardiogenic shock, patients requiring continuous titration of inotropic support and mechanical support with simultaneous use of vasodilators and diuretics).

General Indications for CICU Use of PAC:

1. Narrowing differential diagnosis:

- Determining etiology of shock (mixed v. cardiogenic vs. septic vs. hypovolemic vs. obstructive)
- Discrimination between cardiogenic and non-cardiogenic pulmonary edema
- Distinguishing between primary pulmonary arterial hypertension (PAH) vs. pulmonary hypertension (PH) owing to left-atrial hypertension
- Right ventricular vs. left ventricular failure

2. Definitive diagnosis:

- Pulmonary arterial hypertension: mean PA pressure (PAP) > 25 mmHg
- Distinguish restrictive cardiomyopathy, pericardial constriction, & tamponade.
- Intracardiac shunts (infrequent use but has diagnostic function)
- Evaluation of valvular lesions: regurgitation (ie. tall v waves), stenosis (measure pressure gradients)
-

3. Management:

- Cardiogenic shock
- Volume status during aggressive diuresis and heart failure
- Tailored therapy for decompensated heart failure and bridge to heart transplant
- Titration of inotropes
- Complicated myocardial infarction
- Pulmonary hypertension: initiation and titration of pulmonary vasodilators after identifying patients with pulmonary hypertension without significant left heart failure

Absolute Contraindications to PAC Placement

- Infection at the site of insertion
- Right ventricular assist device

Relative Contraindications to <u>Bedside</u> PAC Placement *(instead place in cardiac catheterization lab)*

- LBBB: at risk for developing RBBB and therefore complete heart block
- ICD or PPM placed within the last 6 months (use fluoroscopy to avoid dislodging leads)
- Prosthetic/stenotic/mechanical TV/PV
- Temporary pacing wire in place
- Severe tricuspid regurgitation
- Severe pulmonary HTN: systolic PA pressures > 70 mmHg: increase risk of PA rupture
- Femoral access required: technically challenging to thread without fluoroscopic visualization
- Right atrial enlargement and RV dilation: challenging to get balloon past RV
- Right heart mass (thrombosis or tumor)
- Tricuspid valve/pulmonic valve endocarditis
- Coagulopathy, electrolyte/acid-base disturbances

Complications of the PAC include the following:

- Infection, pneumothorax, bleeding (standard central line placement complications)
- Atrial/ventricular arrhythmias: ventricular tachycardia, RBBB, complete heart block (usually indirectly related to injury of right bundle)
- PA rupture: uncommon but devastating
    - *Presents as:* hemoptysis or shock after placement. *Management*: lie patient on side with catheter, stat CXR, coags, CBC, cardiothoracic surgery consult
- Pulmonary infarction: secondary to prolonged occlusion of a pulmonary artery
- PE
- Catheter knotting: causes removal to be particularly challenging

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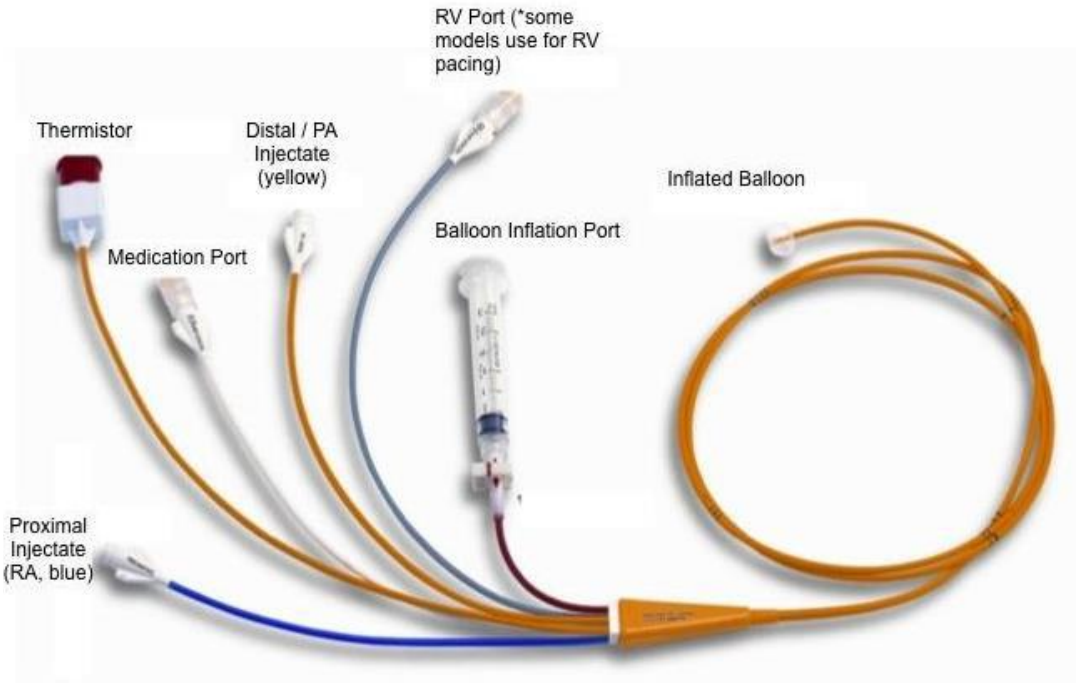
PA Catheter Anatomy - 110cm, 5F or 7F

- *White port* with blue wire terminates 30cm from tip of catheter, usually in right atrium
- *White port* with yellow wire – PA distal port (MVO2 measurement)
- *White port* with red wire – balloon inflation
- *Red port* with yellow wire – contains electrical leads for thermodilution sensor (thermistor), which is located 4cm proximal to the tip
- RV pacing port (seen in figure below, but is not available in some PACs)
- +/– Heparin coated: ask for non-heparin coated if patient known to be HIT +



Insertion

The PAC can be placed in the CICU at the bedside with ECG and waveform monitoring under the supervision of a cardiology or critical care fellow or attending. However, it is often done in the cardiac catheterization lab under fluoroscopy.

Steps:

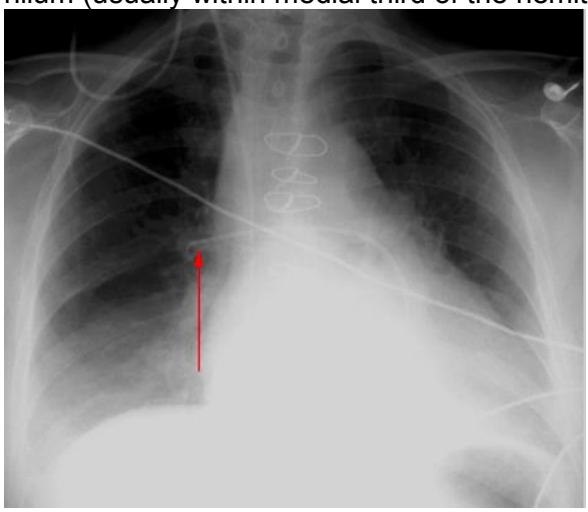
1. Sterile, Seldinger technique as per any CVC insertion
2. Insert sheath first – a.k.a Cordis, or PA introducer
    a. Preferred sites: right IJ > left IJ >left SC
    b. At MGH, Cordis can often be done without fellow supervision
3. Flush all ports, check balloon with 1.5 cc prior to insertion to ensure proper inflation and integrity
4. Ensure that the balloon has no air leaks by inflating while submerged in saline
5. Check pressure transducer by moving catheter prior to insertion
6. Insert PAC through the sterile sheath prior to advancing the catheter through the Cordis
7. Maintain natural curve while inserting
8. **Advance with balloon inflated, and with fellow or attending supervision**
    a. **Usually inflate the balloon in RA at ~ 20cm mark. Look for RA tracing on monitor. From here only inflate with balloon inflated.**
    b. **If necessary, withdraw or retractions only with balloon deflated**

c. *Make sure to print out tracings of RA, RV, and PA pressures as you advance the catheter*.
d. Can also perform oxygen saturations at each chamber to diagnose shunt.

9. If inflation to < 1cc causes wedge: PA line is too distal → **deflate** and withdraw slightly
10. If inflation to 1.5cc (i.e. maximum) cannot cause wedge: PA line is too proximal → advance carefully
11. Must always be "zero'd" before taking measurements – i.e. system adjusted to ensure pressure from ambient air is not falsely elevating or decreasing measurement
    a. *How to "Zero"*
        i. Move HOB to 30-45 degrees
        ii. Adjust transducer on IV stand to 4th ICS in mid axillary line ("phlebostatic axis")
            1. Use the level
            2. One end to transducer, other to patient – mark the placement on chest wall with hand against thorax, fingers pointing into axilla, 3rd digit will be in MAL
        iii. Flush line before use

Confirming placement: use CXR

- Tip of catheter should:
    - Curve into right or left PA, without loops or knots
    - It usually just crosses midline, without extending more than 2cm beyond the hilum (usually within medial third of the hemithoracic distance)

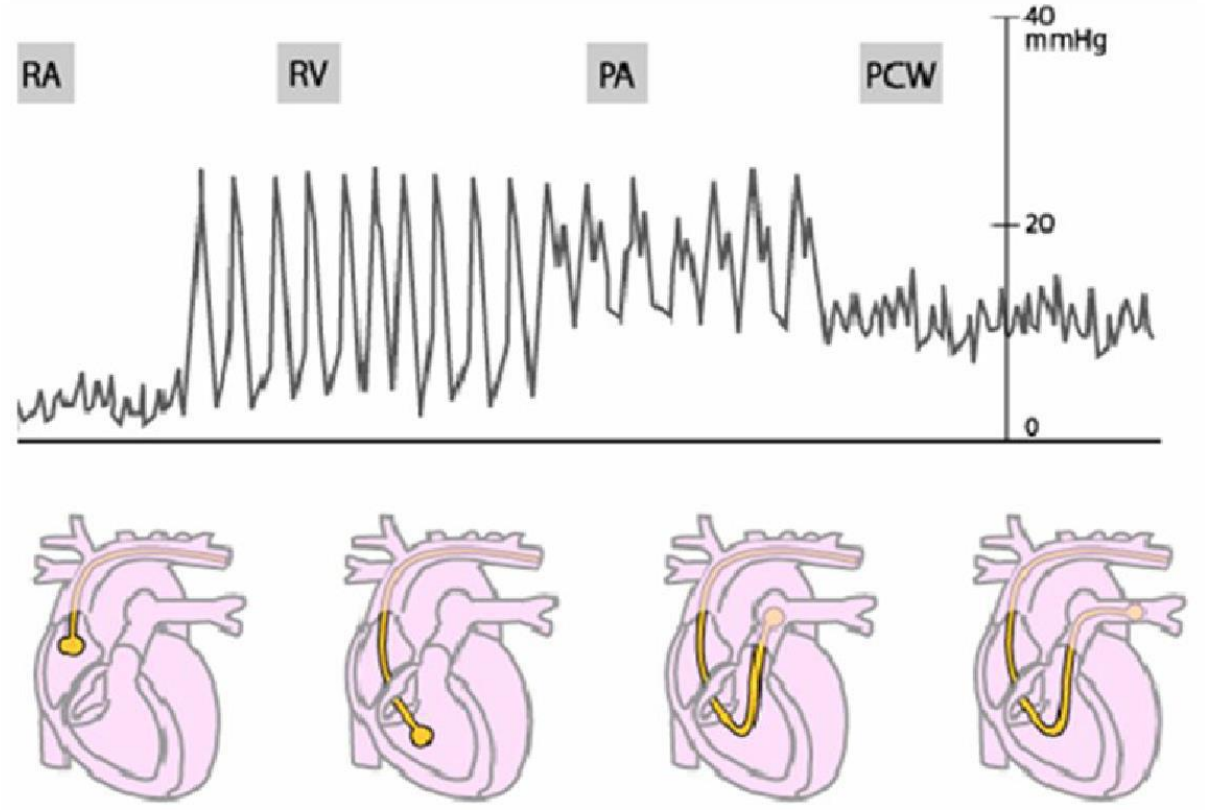


After placing the PA catheter, record:

- Depth of the PA catheter after placement (noted by measurement in *cm* at introducer)
- Volume of air needed to wedge
- Relationship between PA diastolic (PAD) pressure and wedge pressure (indicate whether the two values correlate).
- Measure data at the correct respiratory phase: at the "peak" in a spontaneously breathing patient

There is no data defining optimal or maximal duration of an inserted PA line. At MGH the standard is roughly 7 days. It is fruitful to ask every day when running the plan whether the measurements from the PA line will change management. If not, consider having a team discussion about whether to remove it to avoid line complications (eg CLABSI, PA rupture).

Normal PA line tracing during insertion



15–20cm 25–30cm 35–40cm 45cm

Note these distances are approximate, and depend on body habitus and cardiac chamber dilatation.

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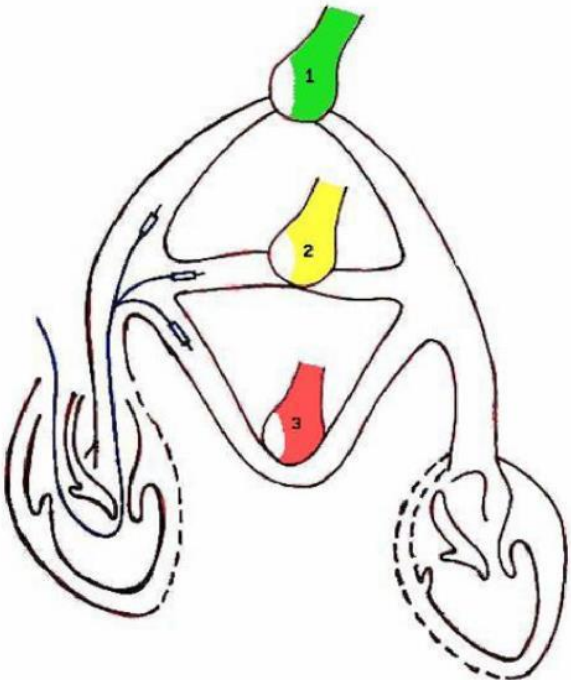
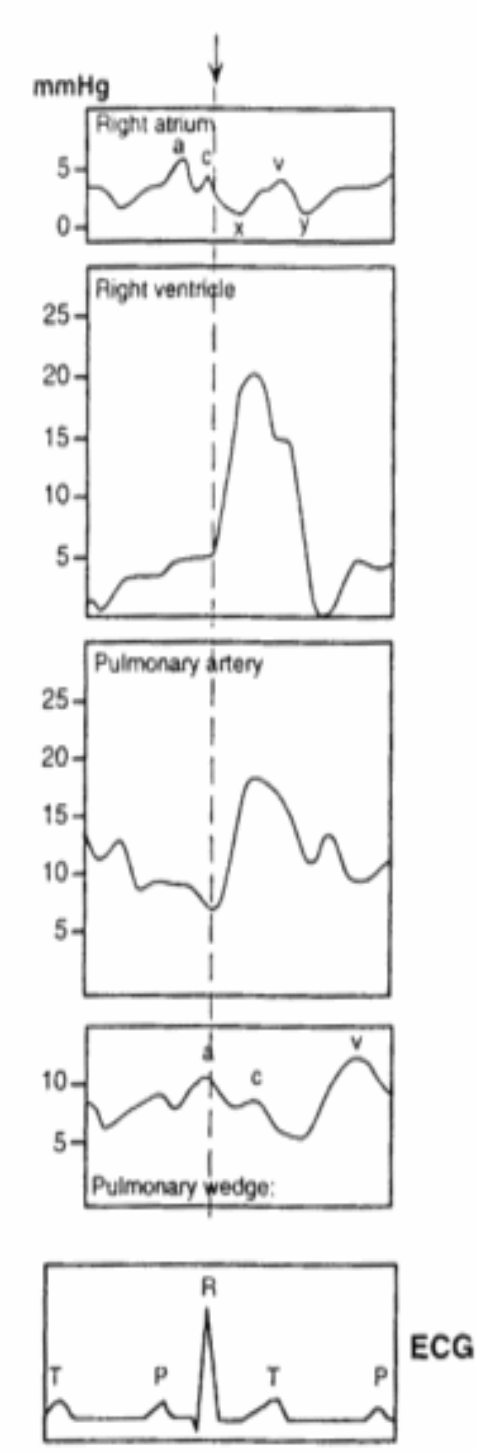
Physiology

PCWP estimates left atrial pressure (LAP): when inflated and in wedge position, the balloon stops flow of blood. The catheter tip senses pressure transmitted backward through the static column of blood from the next pulmonary bed, which for the PCWP would be the pulmonary veins. PAC must be in West Zone 3 or else it will be measuring alveolar pressure instead of pulmonary venous pressures.

- When patient is supine, most of lung is zone 3 – i.e. arterial > venous > alveolar
- Increased zones 1 & 2: hypovolemia, positive pressure ventilation, severe lung disease.
- PCWP > LAP: pulmonary venous occlusive disease (PVOD), pulmonary vein stenosis (i.e., post-pulmonary vein isolation for atrial fibrillation)
- Mean PCWP > LVEDP: MS, MR, atrial myxoma
- Mean PCWP < LVEDP: non-compliant LV, AI
- Always use end-diastolic wedge pressure for more accurate estimation of LVEDP



West Lung Zone 1: PA > Pa > Pv
West Lung Zone 2: Pa > PA > Pv
West Lung Zone 3: Pa > Pv > PA



RA and PCWP tracings

a wave: **a**trial contraction

o Often aligns with QRS (on RA trace)

c wave: **closure** → sudden motion of mitral and tricuspid valves back into atria in ventricular systole

o More visible in 1st degree AV block.

o Often not seen on PCWP, as it may not be transmitted across the pulmonary vasculature.

x descent: atrial rela**x**ation → downward movement of tricuspid valve in early ventricular systole

v wave: → passive atrial filling during systole

o Peaks at the end of ventricular systole.

o Corresponds to end of EKG T wave in RA tracing.

o v wave is smaller than the a wave in RA tracing (unless tricuspid regurgitation is present).

y descent: rapid empt**y**ing of RA into the RV during early ventricular diastole after tricuspid valve opening

Hemodynamic considerations

● All quantitative pressure measurements (especially PCWP) should be made at end expiration when intrathoracic pressure is closest to zero, regardless of whether ventilated or spontaneous breathing

● Positive pressure ventilation inverts respirophasic waveform variation: exhalation is low point instead of high point as during spontaneous ventilation

● Measure RAP & PCWP at the end of diastole (which is at the end of the a wave), to estimate RVEDP and LVEDP. The average PCWP is a good assessment of the overall hemodynamic pressure felt in the pulmonary capillaries and bears on likelihood of cardiogenic versus non-cardiogenic pulmonary edema.

Abnormal RA tracings

● Loss of a waves in atrial fibrillation and flutter.

● Prominent a wave in tricuspid stenosis and RVH due to RA contracting against obstructing valve or stiff RV

● Cannon a waves during CHB, VT (i.e. AV dissociation) and certain forms of SVT (AVNRT) when RA contracts against closed tricuspid valve

● Prominent cV wave in TR due to increased pressure caused by regurgitant flow (this causes effectively a steep y descent)

● Prominent x descent and prominent y descent seen in pericardial constriction

● Blunted y descent seen in cardiac tamponade

● Elevated RA pressures – Some types of pulmonary HTN, RV infarct, left-to-right shunt, tricuspid or pulmonary valvular disease, right heart failure

Elevated PWCP: Hypervolemia, tamponade/restriction/constriction, systolic/diastolic HF; mitral/aortic valve disease
Low PWCP: Hypovolemia, LV underfilling eg PE or RVMI, PVOD (wedge can also be normal)

Troubleshooting
Modified and Revised from Griffin[5]

Arrhythmia	Catheter may be in RVOT. Talk to fellow/attending and consider pulling the catheter back or advancing forward
No PCWP tracing	Catheter tip is not advanced far enough, balloon has ruptured, or the catheter is coiled in the RV. Consider fluoroscopy for guided placement.
Continuous PCWP	Balloon is inflated or the catheter is too far advanced. It may be "overwedged."
Abnormal tracing	Catheter tip may be against a vessel wall or is too far advanced
Dampened tracing	Tubing may be kinked. Air or thrombus is in the catheter or the catheter tip is up against the vessel wall. Flush and/or withdraw the catheter
Change in pressure tracing	Calibration is off. Change in patient position. Patient has had interval intubation or extubation.
Flushes but doesn't draw	Consider clot at the catheter tip

Measurements by PAC

- Direct measure of RA, RV, PAP, PCWP (indirect measurement of LAP).

Location	**Normal range (mmHg)**	**Simplified 'Rule of 5s' [coins]**
RA (CVP)	0-6	5 [nickel]
RV	15-30/0-6	25/5 [quarter]
PAP	15-30/4-12	25/10 [quarter]
mPA	10-20	10-20 [dime]
PCWP (est. LAP)	6-12	10 [dime]

- Direct measure of MVO2 at distal port in pulmonary artery: normally 65–75%.
    - CVO2 (measured in SVC) can be used to approximate MV02
        - CvO2 generally slightly higher than MVO2 (typically 5–8%), since extraction by the myocardium will generally be greater than extraction in the periphery alone, and this is what distinguishes the mixed venous from central venous. The venous return from the coronary sinus empties into the RA and will not be reflected in the SCV saturation.
- Direct thermodilution measure of cardiac output (CO)/cardiac index (CI)
- Indirect measurement of SVR and PVR

Note: PA diastolic pressure (4-12mmHg) is usually within 5mmHg of PCWP. Usually, will use direct PCWP with daily wedging at rounds to assess LAP and volume status. If PCWP and PAD are correlating well, may not need to wedge and can take PAD as a crude estimation of LAP.

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Normal values

- Cardiac Output (CO) 4–7 L/min
- Cardiac Index (CI) 2.8–4.2 L/min/m2
- Systemic Vascular Resistance (SVR) 700–1200 dynes*second/cm5
- Pulmonary Vascular Resistance (PVR) 20–130 dynes*second/cm5

Cardiac output monitoring

Measurement of cardiac output is one of the key uses of PA catheters. The number gained from PA catheters is indirect and calculated from measurements taken with the catheter. This is calculated using one of two main methods: thermodilution or Fick equation (using MVO2).

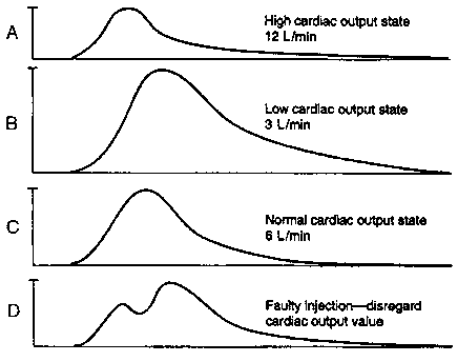
Thermodilution

- Thermodilution uses a thermal indicator - cold saline - to calculate CO.
- A fixed volume of cold saline is injected in the proximal catheter port in RA.
- The change in blood temperature is recorded at the distal catheter port in PA.
- CO is calculated from the area under curve of temperature (y axis) vs. time (x axis).
- Higher CO = rapid Δ temp = smaller area under curve (AUC)
- Lower CO = slow Δ temp = larger AUC
- CO ~ 1/AUC by the modified Stewart-Hamilton equation
- **Inaccurate if**:
    - Very low CO
    - Severe TR or PR: reflux of blood into SVC/RA makes measurement of temperature change inaccurate
    - Intracardiac shunt: fluid will be lost with blood in L → R shunts; blood will add to fluid and augment temperature in R → L shunts

Thermodilution equation

$$Q = \frac{k(Tb-Ti)}{\int \Delta Tb(t)dt}$$

Q = CO (L/min)
Tb = blood temperature
Ti = cold saline temperature



A = High output state. B = Low CO state. C = Normal CO. D = faulty injection.

Fick equation (and other important formulae)

$$\boldsymbol{CO = \frac{VO2}{(CaO2 - CvO2)}}$$

- Where:
    - VO2 = O2 consumption (ml O2 / min)
    - CaO2 = oxygen **content** arterial blood (ml O2/L blood) [not a saturation]
    - CvO2 = oxygen **content** venous blood (ml O2/L blood) [not a saturation]
- O2 consumption (VO2) can be measured (if requested) by calling for the metabolic cart from the CPET lab. Otherwise it is estimated
    - Normally 250–300 ml/min or 3 mL/kg/min at rest.
    - However, note these estimates are based on nomograms and they do not readily apply to critically ill patients. Thus, these errors will be part of any estimated Fick calculation based on an estimated VO2. Please do not use estimated Fick without discussing with your attending.
- CaO2 – CvO2 can be calculated using a simplified formula which does not take into account the dissolved O2 in the blood, only the oxygen that carried by hemoglobin (i.e. saturated oxygen).

  - CaO2 is estimated to **SaO2 –** oxygen saturation in the arterial blood
  - CvO2 is estimated to **MvO2 –** mixed venous oxygen saturation – measured from a VBG pulled from the PAC
  - Hgb is in g/dL; multiplied by 1.34 as an estimate of how many g oxygen each molecule of Hgb can carry

CaO2-CvO2 ≈ (SaO2 – MvO2) x Hgb (g/dL) x 13.4

- MvO2 must be interpreted with reference to the SaO2 and Hb (i.e. not alone).

Thermodilution versus Fick equation

In a large observational study of 12,232 VA patients, there was only modest agreement between thermodilution and Fick cardiac index estimates. Thermodilution cardiac index better predicted mortality and thus could be favored over Fick in clinical practice, unless contraindications to using thermodilution exist.

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4. Vasoactive Medications

The acutely ill cardiac patient may require continuous infusion of medications to augment cardiovascular function. These agents fall into four general categories:

- Vasopressors
- Inotropes
- Chronotropes
- Vasodilators

The physiologic effects of these medications are mediated through their action on catecholamine receptors (generally α1, β1, and β2 adrenergic receptors) or by modulating downstream signaling pathways. Since most agents act on multiple receptors, effects are mixed, resulting in combination agents as inopressors and inodilators. Receptor effects may also be dose-related. Thus, knowledge of drug mechanisms is critical to choosing the appropriate agent at the right dose and interpreting the resulting hemodynamic effects.

Receptor Mechanisms

α receptors

- Predominantly located in the peripheral vasculature
- Binding to the α1 receptor results in contraction of smooth muscle in peripheral arterioles with subsequent vasoconstriction
- Binding to the α2 receptor results in decreased NE release from pre-synaptic terminals causing mild vasodilation and significant CNS-mediated sedation

β receptors

- Predominantly located in cardiac tissue
- Stimulation of the β1 receptor activates adenylate cyclase, leading to an increase in intracellular levels of cAMP, which in turn causes an increase in intracellular calcium concentration through interaction with cAMP protein kinases. Increased intracellular calcium augments the positive inotropic and chronotropic response in cardiac myocytes
- The same cellular process occurs with binding to a β2 receptor expressed in peripheral tissues and the bronchial tree, which results in vasodilation and bronchodilation

Dopamine receptors (D)

- These receptors are predominantly located in the splanchnic and renal circulation, resulting in proportionally increased flow to these vascular beds via vasodilation

Vasopressin receptors (V)

- V1A receptor activation results in vasoconstriction via activation of phospholipase C
- V1B agonism results in ACTH release
- V2 agonism results in water reabsorption in the distal collecting duct via ADH

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Table: Summary of Receptor Mechanisms

	Location	Action/Effect	Effect	Adverse Effect(s)
α1 agonist	Blood vessels, eyes, renal vasculature, GI tract	Vasoconstriction	↑ SVR	Ischemia
α2 agonist	CNS, blood vessels	System vasodilation Sedation		Hypotension
β1 agonist	Heart	Positive inotrope Positive chronotrope	↑ Stroke volume ↑ Heart rate	Tachyarrhythmia
β2 agonist	Lungs, blood vessels	Systemic vasodilation Bronchodilation	↓ SVR	Hypotension
D1 and D2 agonist	Heart, spleen, kidneys	Renal/Splanchnic vasodilation		
PDE-III inhibitor	Heart, blood vessels	Positive inotrope Systemic vasodilation	↑ Stroke volume ↓ SVR	Arrhythmia
V1A agonist	Blood vessels	Vasoconstriction	↑ SVR	
V1B agonist	Anterior pituitary	ACTH release		
V2 agonist	Kidneys	Water reabsorption (ADH)		

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Vasoactive Agents

Class	Drug	Mechanism	Starting Dose	Titration	Max dose
Vasopressor	Phenylephrine	α-1 agonist	10 mcg/min	5-10 mcg/min *q5 min*	1000 mcg/min
	Vasopressin	V-receptor agonist	0.04 units/min	N/A	0.08 units/min
Inopressor	Norepinephrine	α-1 > β-1 agonist	1-5 mcg/min	1-2 mcg/min *q5 min*	100 mcg/min
	Dopamine	Dose-dependent D > β-1, β-2 > α-1 agonist	5 mcg/kg/min	1-2 mcg/kg/min *q5 min*	20 mcg/kg/min
	Epinephrine	α-1, β-1, β-2 agonist	1 mcg/min	1 mcg/min *q2 min*	20 mcg/min
Inotrope	Digoxin*	Na^+/K^+ pump inhibitor	10 mcg/kg♦ of ideal body weight	Split in 2-3 doses at a q6h interval; post load level 6-8h after last loading dose	
Inodilator	Dobutamine*	β-1 > β-2 agonist	2 mcg/kg/min	1-2 mcg/kg/min *q10 min*	20 mcg/kg/min
	Milrinone*	PDE-III inhibitor	0.1 mcg/kg/min	0.05 - 0.1 mcg/kg/min *q4-6 hours*	0.75 mcg/kg/min
Chronotrope	Isoproterenol*	β-1, β-2 agonist	2 mcg/min	1 mcg/min *q5 min*	10 mcg/min
Vasodilator	Nitroprusside*	NO donor	0.5 mcg/kg/min	0.25-0.5 mcg/kg/min *q5 min*	5 mcg/kg/min
	Nitroglycerin*	NO donor	10-20 mcg/min	5-10 mcg/min *q5 min*	200 mcg/min
	Nicardipine	DHP calcium channel blocker	2.5-5 mg/hr	2.5 mg/hr *q15 min*	15mg/hr
	Clevidipine	DHP calcium channel blocker	1 mg/hr	1 mg/hr *q90 seconds*	21 mg/hr

** Can be infused peripherally for extended periods of time*

♦Age, renal function, and drug interactions determine need for full load; goal post-load level: <1.2 ng/mL

Phenylephrine (Neosynephrine)

Pure vasopressor which, via α1 agonism, produces profound arterial vasoconstriction. Overall, the indication for phenylephrine in a CICU patient should be clearly defined, as other medications are likely to be better tolerated.

Clinical use(s)

- **Hypotension due to a vasodilatory etiology such as sedation, narcotics, or sepsis** – although frequently used in the medical ICU at MGH, phenylephrine is generally not recommended for the treatment of sepsis and is indicated for three specific circumstances. These are when (1) norepinephrine is associated with serious arrhythmias, (2) cardiac output is known to be high but blood pressure is persistently low or (3) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve the blood pressure target
- **Uncontrolled atrial fibrillation or ventricular tachycardia with hypotension** – as it produces reflex bradycardia and raises blood pressure
- **HOCM or dynamic LV outflow tract obstruction** – if worsening obstruction or presents with hypotension; in severe cases, phenylephrine (in combination with IV fluids and beta

blockers) can rapidly relieve the obstruction, as increased afterload helps to stent open the outflow tract; agents with β1 activity (i.e. norepinephrine, epinephrine) increase inotropy and worsen outflow tract obstruction

Caution(s)

- **Low cardiac output states** – it produces increased afterload and reflex bradycardia

Vasopressin

Per its name, a vasopressor that acts via V-receptors; usually added to another primary pressor. The use of vasopressin generally allows for lower doses of other vasopressors. Typically, it is not titrated unless going to max dose of 0.08 units/min. It can be stopped immediately our weaned by 0.01 units/min every hour.

Clinical use(s)

- **Septic shock, in combination with norepinephrine** – the VASST trial showed the addition of vasopressin to norepinephrine in septic shock did not affect 28- or 90-day survival compared to norepinephrine alone.[1] However, in the vasopressin arm there was a significant reduction in 28-day mortality (26.5% vs. 35.7%) among the subgroup of patients with less severe septic shock (defined as norepinephrine dose of < 15 mcg/min). There was a trend toward increased digital ischemia in the vasopressin group and a higher rate of cardiac arrest in the norepinephrine group.
- **Hepatorenal syndrome in cirrhotic patients** – it is sometimes used as a preferred agent (as an alternative to terlipressin which is not approved in the US), although data suggest no benefit over norepinephrine

Caution(s)

- **ACS** – can cause dose-related coronary vasoconstriction.[2]
- **Acute mesenteric ischemia**
- **Digital ischemia**
- **RV failure** – some data suggest that it increases pulmonary vascular resistance at doses > 0.03 u/min, but may cause pulmonary vasodilation at lower doses.[3]
- **Hyponatremia** – it's other name is anti-diuretic hormone (ADH)

Norepinephrine (Levophed)

Both a positive inotrope (β1) and a vasopressor (α1); little β2 activity, thus causes much more profound vasoconstriction than dopamine and other agents that affect the β2 receptor; minimal chronotropic effects.

Clinical use(s)

- **Septic shock, cardiogenic shock, undifferentiated hypotension** – a first-line agent
- **Mixed cardiogenic and distributive shock** – it can be used as a temporizing measure while awaiting an IABP for additional circulatory support or a PA line to elucidate the interplay between the types of shock

Caution(s)

- **Arrhythmias**
- **Reflex bradycardia**
- **Digital ischemia**

Dopamine

A biosynthetic precursor to norepinephrine and epinephrine that has dose-dependent activity on multiple receptors ultimately acting as a sympathomimetic. As dose increases, α1 agonism increases, causing vasoconstriction. Note that D receptors preferentially vasodilate renal/splanchnic circulation.

Clinical use(s)

- **Symptomatic bradycardia, septic shock, cardiogenic shock** – multiple trials have demonstrated *no* improvement in renal function with the addition of low-dose dopamine in oliguric patients at risk for post-ischemic ATN. However, low doses are occasionally used in an attempt to augment diuresis
- **Vasodilation of renal and splanchnic vessels** – at infusion rates of 0-2 mcg/kg/min via dopaminergic receptors
- **Chronotropic effects** – at doses of 2-5 mcg/kg/min via β1 agonism.
- **Systemic vasoconstriction** – at doses above 5 mcg/kg/min, it stimulates α1, β1, and β2 receptors; vasoconstriction increases via increasing α1 agonism at doses of 10-20 mcg/kg/min

Caution(s)

- **Arrhythmias** – in a comparison of dopamine vs norepinephrine as first-line agent for patients with shock, arrhythmia incidence was 24.1% vs 12.4%; atrial fibrillation was most common but ventricular arrhythmias also occurred.[4]
- **Higher 28-day mortality in cardiogenic shock** – a pre-defined subgroup analysis showed that patients with cardiogenic shock who were treated with dopamine had higher 28-day mortality than those treated with norepinephrine; there was no difference in those with septic or hypovolemic shock.[4]

Epinephrine

Potent agonist of α1, β1, and β2 receptors, leading to its properties as an inopressor. β-adrenergic effects tend to predominate at lower doses and α1 effects at higher doses.

Clinical use(s)

- **ACLS protocol for cardiac arrest**
- **Anaphylaxis**
- **Symptomatic bradycardia** – when unresponsive to atropine
- **Refractory hypotension** – as a third pressor, not first-line
- **Following cardiac bypass surgery** – as temporary inotropic and pressor support
- **Septic shock** – though this medication is now considered second-line after norepinephrine
- **Cardiogenic shock** – though, compared to norepinephrine in post-acute MI, it resulted in a higher incidence of refractory shock and a trend toward higher mortality.[5]

Caution(s)

- **Arrhythmia**
- **Angina**
- **Sudden death**
- **Cardiac toxicity** – in high-dose, prolonged infusions

Digoxin

A positive inotrope that works by indirectly raising intracellular Ca concentrations with negative chronotropic properties by decreasing AV node automaticity and by slowing nodal conduction velocity. Has a long half-life. Dosing is 10 mcg/kg of ideal body weight split in 2-3 doses at a q6h interval; post load level 6-8h after last loading dose [Note: Male/{Female} IBW: 50{45.5} + 2.3*(height in inches - 60)]. Age, renal function, and drug interactions determine need for full load; goal post-load level: <1.2 ng/mL.

Clinical use(s)

- **Atrial fibrillation** – can be used as a negative chronotropic agent and is commonly used in patients with concomitant heart failure and LV dysfunction; in a post hoc digoxin subgroup analysis of the ARISTOTLE trial, patients with AF with digoxin levels >1.2

ng/ml had a 56% increased hazard ratio of mortality compared with those not on digoxin; When analyzed as a continuous variable, serum digoxin concentration was associated with a 19% higher adjusted hazard ration of death for each 0.5 ng/ml increase.[6]

Caution(s)

- **Symptomatic bradycardia, heart block**
- **Ventricular tachycardia, ventricular fibrillation**
- **Neurotoxicity**
- **Gastrointestinal toxicity**

Dobutamine

β1 > β2 – potent inotropic effects + some chronotropy + varying degrees of vasodilation, therefore it results in an increased cardiac output but a potential decrease in systemic blood pressure, so it should be thought of as an inodilator.

Clinical use(s)

- **Reduced LVEF and diminished end-organ perfusion** – it is used to improve cardiac output and end-organ perfusion, especially in those who have marginal blood pressures or who are unresponsive to vasodilators and diuretics
- **Preload reduction** – by restoring forward flow to the kidneys and decreasing sodium and fluid retention, which ultimately reduces venous return to the heart
- **Afterload reduction** – it can be used in combination with direct vasodilators (i.e. nitroprusside)
- **Periodic "tune-up" infusions in patients with advanced heart failure** – these "tune-ups" can unload the LV and help interrupt the cycle of volume overload by transiently improving renal perfusion and diuresis; most of the evidence is anecdotal, and this practice is generally reserved for patients with refractory heart failure as a bridge to transplant or transitioning to palliative care

Caution(s)

- **Arrhythmias** – can occur at any dose, but especially when >500 mcg/min
- **Myocardial ischemia** – can be induced due to increased cardiac myocyte O2 demand (exercise-mimicking drug)
- **Tolerance** – may develop after several days of continued use due to down-regulation of β-receptors

Milrinone

PDE-3 inhibitor that inhibits the breakdown of intracellular cAMP, which leads to increased cardiac contractility as well as significant arterial and venous vasodilation, granting it an inodilator classification; also improves left ventricular diastolic function.

Clinical use(s)

- **Reduced LVEF and diminished end-organ perfusion** – may be synergistic when used with dobutamine for this indication. Both agents increase cAMP; dobutamine stimulates its production while milrinone inhibits its breakdown
- **RV failure** – it has been shown to improve RV function, pulmonary vascular resistance, pulmonary blood flow, and LV filling.[7]
- **Adrenergic receptor resistant patients** – it has a significantly longer half-life than dobutamine (2 hours)

Caution(s)

- **Arrhythmias**
- **Myocardial ischemia** – can be induced due to increased cardiac myocyte O2 demand
- **Hypotension** – due to the decrease in right-sided filling pressures, left-sided filling pressures, and SVR

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Isoproterenol

Non-selective β-adrenergic agonist, leading to increased inotropy, chronotropy, and potent systemic vasodilation due to its β2 agonism.

Clinical use(s)

- **Bradycardia** – used as a "medical pacemaker"
- **Recurrent, pause-dependent Torsades** – for patients who do not have congenital long-QT syndrome; those with Torsades and congenital long-QT should be treated with a β-blocker and either lidocaine or mexiletine
- **Temporary chronotropic support** – in transplant patients

Caution(s)

- **Arrhythmias**
- **Myocardial ischemia** – can be induced due to increased cardiac myocyte O2 demand

Nitroprusside (Nipride)

NO donor to stimulate the production of intracellular cGMP, resulting in smooth muscle relaxation; potent arterial and venous dilation with a short half-life (1-2 minutes). By reducing afterload, cardiac output is increased. Doses >3 mcg/kg/min increase risk for toxicities. Note that continuous BP monitoring via a-line is necessary.

Clinical use(s)

- **Hypertension** – when rapid titration needed (including hypertensive emergency, aortic dissection, acute valvular dysfunction, and ventricular septal rupture)
- **Cardiogenic shock** – when presenting with elevated SVR
- **Afterload reduction in heart failure** – PCWP and SVR fall, and the cardiac output increases through an augmentation of stroke volume due to decreased afterload, though the agent has no direct inotropic effect

Caution(s)

- **Coronary steal syndrome** – can be precipitated in patients with CAD
- **Cyanide toxicity** – nitroprusside is metabolized to cyanide in the blood stream which decomposes to prussic acid and is converted to thiocyanate for renal excretion. Patients may develop toxicity from cyanide or thiocyanate, especially in the setting of underlying renal insufficiency, high infusions rates, or infusions beyond 24-48 hours. Cyanide toxicity may clinically manifest as altered mental status (in extreme cases leading to coma), cardiovascular instability, and lactic acidosis. Thiocyanate levels and ABGs should be checked routinely in patients treated with nitroprusside for prolonged periods.

Nitroglycerin

Converted to NO by aldehyde dehydrogenase; serves as a potent venodilator, reducing preload and afterload. See "Aortic Dissection" section for additional IV anti-hypertensives, which can be used for acute aortic syndromes as well as hypertensive emergency.

Clinical use(s)

- **ACS** – used acutely as it reduces myocardial oxygen demand via venous (primarily) and arterial vasodilation, which reduces LV preload and afterload; there is also more efficient redistribution of blood flow within the myocardium
- **Hypertension** – when rapid titration needed

Caution(s)

- **Headache** (most common)
- **Reflex tachycardia**
- **Orthostatic hypotension**
- **Tachyphylaxis**

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Nicardipine (Cardene)

Dihydropyridine calcium channel blocker that inhibits calcium ions from entering the L-type calcium channels (aka “slow channels”) or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation as well as a decrease in systemic vascular resistance and mean arterial pressure; increases myocardial oxygen delivery in patients with vasospastic angina.

Clinical use(s)

- **Hypertension** – especially in acute ischemic stroke

Caution(s)

- **Hypotension**
- **Tachycardia**
- **Aortic stenosis** – use with caution in patients with mild to moderate aortic stenosis; use is contraindicated in patients with advanced aortic stenosis
- **Hypertrophic cardiomyopathy with outflow tract obstruction** – decrease in afterload may cause worsening in symptoms
- **Renal impairment** – renally cleared, so generally avoided in those with renal impairment

Clevidipine

Similar to nicardipine; dihydropyridine calcium channel blocker which inhibits calcium ion influx through the L-type calcium channels during depolarization in arterial smooth muscle producing a decrease in systemic vascular resistance and mean arterial pressure.

Clinical use(s)

- **Hypertensive emergency/urgency**
- **Peri-operative to cardiac surgery** – ESCAPE trials compared clevidipine to placebo in peri-operative cardiac surgery; ECLIPSE trial compared it to nitroglycerin, nitroprusside, and nicardipine and found no difference in composite of death, stroke, MI, or renal dysfunction at 30 days.[8]

Caution(s)

- **Hypotension**
- **Atrial fibrillation** – anywhere from 13% to 35% in ESCAPE and ECLIPSE trials, commonly reported incidence is 21%
- **Acute HF** – may cause negative inotropic effects and exacerbate HF
- **Severe aortic stenosis**
- **Hypertriglyceridemia** – since it’s formulated within a 20% fat emulsion (0.2 g/mL), hypertriglyceridemia is an expected side effect with high-dose or extended treatment periods; median infusion duration in clinical trials was approximately 6 hours.[8] Secondary pancreatitis is also a risk, especially when trig >500 mg/dL. Use is contraindicated in patients with defective lipid metabolism (eg, pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia)

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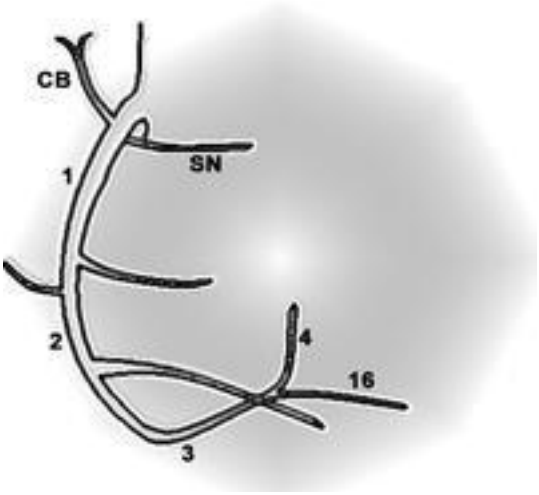
5. Basics in Coronary Anatomy and Catheterization

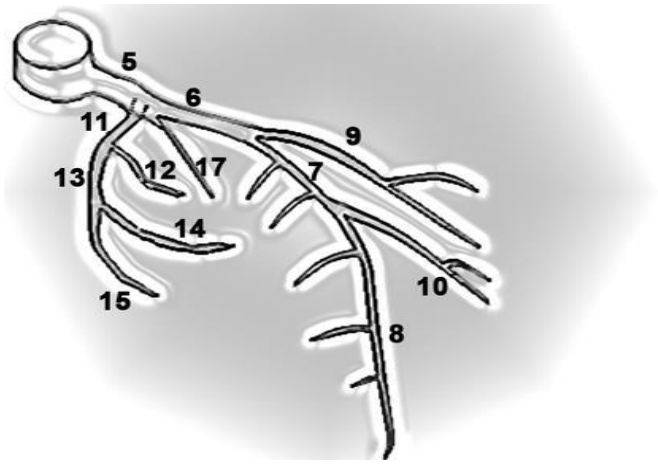
The gold standard for the evaluation of coronary arteries is invasive coronary angiography (often referred to as cath). The goal of coronary angiography is to identify coronary anatomy and atherosclerotic burden. You should review the angiography for each patient in the CICU. It is important to have an appreciation for the relevant anatomy involved in the clinical presentation of each patient. Knowledge of coronary anatomy will also allow you to be more prepared to deal with complications.

Left Coronary Artery: The left main coronary artery (LM) bifurcates early in its course into the left anterior descending artery (LAD) and the left circumflex artery (LCx). The LAD runs on the anterior part of the interventricular septum. It has two sets of branches – the diagonal branches, which feed the anteroapical and lateral wall, and the septal perforators, which branch from the LAD in straight angles and feed the septum. The left circumflex runs in the AV groove, toward the posterior aspect of the heart. Branches off the LCx are called obtuse marginal branches (OMs) and supply the lateral wall. In left dominant systems, the LCx also gives rise to the PDA (in right dominant systems, the PDA branches off the RCA). Some patients have a ramus intermedius branch, which is a 3rd branch arising from the left main artery (in between the takeoffs of the LAD and LCx).

Right Coronary Artery (RCA): The first branch off the RCA is usually the conus branch, which feeds the right ventricular outflow tract. In roughly 50–60% of patients, the next branch of the RCA is the sinus node artery. The next branch off the right coronary artery is the **acute marginal**, which supplies the right ventricle. The right coronary also gives rise to the posterior descending (PDA) in a right dominant system as well as the posterior left ventricular (PLV) branches.

Dominance: Dominance is determined by which artery gives off the PDA (RCA v. LCx). Most individuals (85% of population) are right dominant.





Right Coronary Artery Branches
1 Proximal RCA
2 Mid RCA
3 Distal RCA
4 Posterior descending artery (PDA)
16 Posterior left ventricular branch (PLV)
CB Conus branch (first branch off the RCA)
SN Sinonodal branch (feeds SA node)

Left Coronary Artery Branches
5 Left main coronary artery
6 Proximal LAD
7 Mid LAD (after take off of D1)
8 Distal LAD
9 First diagonal branch (D1)
10 Second diagonal branch (D2)
11 Proximal Left Circumflex
12 First Obtuse Marginal (OM1)
13 Mid left circumflex (after OM1)
14 Second Obtuse Marginal (OM2)
15 Distal Left Circumflex
17 Ramus intermedius

The Views

LAO vs. RAO: Stands for left anterior oblique and right anterior oblique. Left anterior oblique means the camera is on the left side of the patient; right anterior oblique means that the camera is on the right side. In RAO views, the heart is directed toward the right, and the catheter (and spine) are on the left side of the image. In LAO views, the heart is directed toward the left, and the catheter (and spine) are on the right side of the image.

Cranial vs. Caudal: In cranial views, the camera is looking down from the shoulder. In this view, the image looks like a chest X-ray. The **diaphragms are well delineated** and the lung fields look clear. Cranial views are good for visualizing the LAD. Caudal means the camera is looking from the feet up to the head. In this view, the lung fields are not as clear given that the X-ray is going through the abdomen (air, soft tissue, etc). The diaphragms are not well delineated. Caudal views are good for visualizing the left circumflex.

TIMI flow

When reading catheterization reports, you will commonly encounter terms describing the quality of blood flow before and after an intervention is performed. These are defined as follows:

● TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond a coronary occlusion.

● TIMI 1 flow (penetration without perfusion) is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed.

● TIMI 2 flow (partial reperfusion) is delayed or sluggish antegrade flow with complete filling of the distal territory.

● TIMI 3 is normal flow which fills the distal coronary bed completely

Contrast Induced Nephropathy

It is a common fear amongst medicine house staff and a not uncommon phenomenon that patients will develop contrast induced nephropathy after diagnostic catheterization. As such, many risk scores have been devised to determine which patients are at risk of CIN, and their ultimate risk of requiring renal replacement therapy. One such calculator, developed at Columbia and Mount Sinai, can be accessed easily as follows: http://www.qxmd.com/calculate-online/nephrology/contrast-nephropathy-post-pci. Note that this risk score requires the volume of contrast. A well-performed diagnostic catheterization without difficult anatomy generally requires **~25-40cc** of contrast, while PCI can require up to **150cc** of contrast depending on how many interventions a patient requires. For comparison, a PE-CT generally uses **90cc** of contrast, though this is dependent upon the size of the patient.

Vascular Access

While rotating in the CICU and SDU, you will notice patients will have coronary angiograms from either the femoral *or* the radial approach – the radial approach offers many advantages to the femoral approach: 1) Fewer bleeding complications, as the puncture site is easily compressible, 2) the patient is not required to lay flat after the procedure, and 3) it is easier to obtain access in obese patients. It should be noted that many catheters are still not designed for the radial approach, and thus patients with difficult-to-access coronary ostia (i.e. accessing graft vessels in patients s/p CABG) may ultimately require a femoral approach.

QUICK REFERENCE GUIDE: TOOLS IN THE CICU

Pulmonary Arterial Catheter and Hemodynamic Monitoring

- Pulmonary arterial catheters ("PA lines" or "PAC" or "RHC" or "Swan-Ganz") are multi-lumen catheters that terminate in the main pulmonary artery and are used in the CICU to monitor hemodynamics
- A number of studies investigating the use of PACs (ESCAPE, PAC-MAN, 2005 JAMA meta-analysis, 2013 Cochrane systematic review) have failed to demonstrate a benefit in terms of mortality, ICU or hospital length of stay, or hospitalization cost; though of note, no trial has adequately studied their use in the types of patients that tend to have them in our CICU. Given this, it is ultimately thought to be a safe tool when used appropriately
- Common indications for PAC placement include 1) To differentiate types of shock, 2) To differentiate right versus left heart failure, and 3) To facilitate tailored therapy for heart failure and pulmonary hypertension
- PACs allow for direct measurement of chamber pressures, including (most commonly) the RAP/CVP (transduced from the catheter's proximal port via the blue wire, which usually terminates in the right atrium), the PAP (including PA systolic and diastolic pressures, transduced from the catheter's distal port via the yellow wire, which usually terminates in the PA), and the PCWP (transduced from the catheter's distal port when the balloon is inflated, allowing the catheter to advance into wedge position). PACs also allows for direct measurement of MVO2 from the distal/PA port (normal value: 65–75%)
- Using the values above, the following additional parameters can be calculated: Fick Cardiac Output (CO, normal value 4–7 L/min), Cardiac Index (CI, normal value 2.8–4.2 L/min/m2), Systemic Vascular Resistance (SVR, normal value 700–1200 dynes*second/cm5), and Pulmonary Vascular Resistance (PVR, normal value 20–130 dynes*second/cm5; though note that PVR is often reported in Woods units, with pulmonary hypertension defined as PVR>3. Convert to Woods units by dividing by 80)
- In addition to the Fick equation, CO can also be measured using thermodilution. This involves injecting a fixed volume of cold saline into the proximal catheter port in RA and recording the change in blood temperature at the distal catheter port in the PA. CO is calculated from the area under curve of temperature (y axis) vs time (x axis)
- There is only a modest correlation between these methods, and thermodilution may be a better predictor of mortality, though note that it will be inaccurate in patients with tricuspid or pulmonary regurgitation or among patients with intracardiac shunts

Vasoactive Medications

- There are three commonly used classes of vasoactive medications in the CICU: vasopressors, vasodilators, and inotropes. Inotropes increase contractility and usually have either vasopressor or vasodilator effects (and thus may also be referred to as "inodilators" or "inoconstrictors")
- Common vasopressors include norepinephrine (NE, Levophed or "Levo"), vasopressin ("vaso"), and phenylephrine (Neo-synephrine or "Neo"). NE also has some inotropic and chronotropic effects via B1 agonism. These agents are primarily used to maintain MAP goal > 65
- Common vasodilators include nitroglycerin (TNG), nitroprusside, nicardipine, and clevidipine. Afterload reduction is often used to optimize cardiac output.
- Common inotropes include the inopressors dopamine and epinephrine and the inodilators dobutamine and milrinone

Basics in Coronary Anatomy and Catheterization

- The goal of coronary angiography is to identify coronary anatomy and atherosclerotic burden
- Coronary angiogram requires separate assessment of the right and left circulation by separately engaging the right coronary artery (RCA) and left main coronary artery (LM). The LM bifurcates early in its course into the left anterior descending artery (LAD) and the left circumflex artery (LCx)
- Dominance is determined by which artery gives off the PDA (RCA vs LCx). Most individuals (85% of population) have a right-dominant circulation

HEART FAILURE

See Page 69 for Quick Reference Guide

6. Initial Evaluation and Management of Heart Failure

Heart failure is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling and/or ejection of blood. The initial evaluation of patients admitted to the SDU/CICU with heart failure includes a determination of clinical acuity, diagnosis of an etiology for new-onset failure or acute decompensation, and the implementation of appropriate treatment.

Etiologies of Acute Decompensated Heart Failure

The initial assessment of any patient with acute decompensated heart failure (ADHF) should include an evaluation for precipitants of the decompensation in order to identify potentially reversible causes. Common etiologies are listed below:

Primary cardiac issues:

- Ischemic heart disease (acute MI or chronic progressive disease)
- Mechanical complications of MI (VSD, acute MR)
- Uncontrolled hypertension
- Arrhythmias, including atrial fibrillation and conduction system disease
- New or progressive valvular disease

- Acute cardiovascular disorders (endocarditis, myopericarditis, etc)
- Inherited cardiomyopathies (non-compaction, hypertrophic CM, adult congenital disease)

Medications/dietary etiologies:

- Recent addition or titration of medications with negative chronotropic or inotropic properties (beta-blockers, non-dihydropyridine calcium-channel blockers)

- Initiation of drugs that increase salt retention (NSAIDs, steroids)
- Medication or dietary nonadherence (sodium/fluid excess)
- Alcohol or illicit drugs (cocaine, amphetamines, stimulants)
- Dietary deficiencies (selenium, thiamine/B1)
- Systemic infections (including HIV)

Other organ system etiologies:

- Endocrinopathies, including thyroid disorders (hypo- or hyperthyroidism)
- Worsening renal function
- Primary lung disease with RV dysfunction

Signs and Symptoms of Acute Heart Failure

The clinical presentation of acute or worsening heart failure may be heterogeneous and encompass the signs and symptoms of volume overload / fluid congestion and relative hypoperfusion. These include fatigue, SOB, dyspnea, tachypnea, cough, diminished exercise capacity, orthopnea/trepopnea, PND, nocturia, weight gain/loss, edema, abdominal bloating or pain, loss of appetite, somnolence, and reduced UOP.

Physical Exam Findings in Acute Heart Failure
Tachycardia, narrow pulse pressure, pulsus alternans, tachypnea, cool extremities, elevated JVP, diminished breath sounds or fine rales* and wheezing (cardiac asthma), displaced apical impulse, parasternal lift, S3 (highly specific) or S4, MR murmur, hepatomegaly, ascites, presacral edema, anasarca, and pedal edema.

*Rales may be absent in advanced chronic HF, reflecting a compensatory increase in local lymphatic drainage.

Initial Diagnostic Testing
Laboratory:
Initial evaluation (to identify risk severity of decompensation and potential reversible etiologies): BUN/creatinine, electrolytes, CBC with differential, urinalysis, LFTs, hsTnT, NT-proBNP**, iron studies (ferritin, iron, TIBC), TSH with reflex, Hgb A1c, and lipid panel. Consider screening for cardiac amyloidosis (SPEP/SFLC), hemochromatosis (iron studies, *HFE* gene testing), HIV, rheumatologic disease (ANA, Scl-70, ANCA), pheochromocytoma (plasma and urine metanephrines), and nutritional deficiencies (selenium, carnitine, B1) in patients for whom there is reasonable clinical suspicion.

**Measuring NT-proBNP on admission is useful to establish prognosis and disease severity in ADHF. This biomarker reflects ventricular stretch and is highly sensitive and specific for the diagnosis of HF.[1] Note that levels increase with age and renal failure, and obese patients may have lower-than-expected values.

EKG:
May show sinus tachycardia secondary to sympathetic nervous system activation or an atrial arrhythmia. Increased QRS voltage may be indicative of LVH whereas low voltage may suggest an infiltrative disease (e.g. amyloidosis, sarcoidosis, hemochromatosis) or a pericardial effusion. Q waves or ST-T wave changes suggest a history of acute or chronic coronary artery disease as a potential culprit. In some cases, q waves may reflect a pseudoinfarction pattern due to myocardial infiltration (e.g. cardiac amyloidosis).

Imaging:
CXR**, TTE and repeat measurement of EF if there has been a significant change in clinical status, a history of treatment that may affect ventricular function, or for consideration of device therapy.
**The classic CXR appearance in patients with pulmonary edema is a “batwing” pattern of hilar congestion. Other cardinal findings include Kerley B lines, peribronchial cuffing, and cephalization of the vasculature. As with rales, in advanced HF, the CXR may appear clear.

Advanced diagnostic testing:
Right heart catheterization (RHC) should be considered in patients with challenging clinical exams to determine volume status and when there is concern for hypoperfusion necessitating initiation of acute circulatory supportive therapies including inotropes and mechanical circulatory support. Coronary angiography in patients with known ischemic heart disease, new/suspected symptomatic ischemia, or any new HF without other discernable cause. Alternatively, pending clinical assessment, a nuclear imaging study for ischemia / viability may be considered in patients suspected of having an ischemic etiology for their cardiomyopathy. Endomyocardial biopsy should be considered if suspicion for myocarditis in certain scenarios where the risk of native heart biopsy will change urgent diagnosis and management.

General Considerations and Categorization of HF

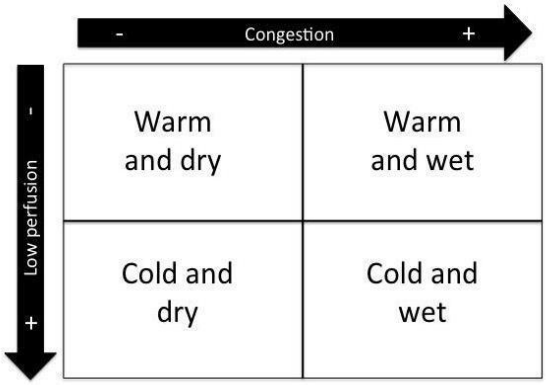
Left-Sided vs. Right-Sided: The most common cause of right-sided HF is left-sided HF. Distinguishing patients in an absolute manner is not always possible nor appropriate. The physiology of predominantly right-sided failure differs from the physiology of predominantly left-sided failure in important ways. For this reason, it is helpful to think about patients along this spectrum and to characterize the function of both ventricles, while remembering that ventricular function is interdependent (i.e. the function of one affects the other).

Left-sided HF typically manifests with symptoms and signs of pulmonary vascular congestion, such as exertional or rest dyspnea, orthopnea, PND, rales and wheezes, displaced and sustained PMI, and CXR findings consistent with pulmonary edema. The PA line is also useful for its ability to measure PCWP as a surrogate for LVEDP in order to better differentiate cardiogenic from non-cardiogenic pulmonary edema.

Right-sided HF is generally characterized by symptoms and signs of systemic venous congestion, including anorexia, bloating, nausea, RUQ pain, early satiety, diffuse abdominal pain, and exam findings of jaundice, JVD, a positive hepatojugular reflux, hepatosplenomegaly, ascites, and lower extremity edema.

Reduced vs. preserved EF: The vast majority of HF patients admitted to the CICU will have systolic heart failure with reduced LVEF and a low cardiac output. The most common causes of systolic dysfunction are coronary (ischemic) heart disease, hypertension, valvular disease, and idiopathic dilated cardiomyopathy. Heart failure with a preserved EF (HFpEF), which is often, but not always, associated with diastolic dysfunction, is most often caused by hypertension, ischemic heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, among others.

Low Output vs. High Output: HF can also be categorized on a spectrum from low to high cardiac output. Cardiac output is most accurately calculated using equations that rely on information obtained during right heart catheterization (thermodilution or Fick equation, as described earlier). Low output heart failure is characterized by an inability to maintain adequate blood flow to maintain vital organ perfusion and can occur in both cases of preserved and reduced ejection fraction. High output states are much less common but are related to diagnoses such as hyperthyroidism, AVMs (e.g. hepatopulmonary syndrome, ESRD patients with AV-fistulas) with high shunt fractions, nutritional deficiencies (e.g. thiamine) and profound chronic anemia.



Wet vs. Dry and Warm vs. Cold

Evaluation for systemic congestion and for reduced cardiac output is useful to separate patients with HF into “wet/warm” (congested with normal perfusion, most common), “dry/cold” (uncongested but hypoperfused; low output), and “wet/cold” (cardiogenic shock). Signs of congestion at rest include, an elevated JVP, rales, S3, edema. Signs of low perfusion include a narrow pulse pressure, cool extremities, hypotension, reduced urine output, and altered mentation.

Defining a patient as warm or cold is often challenging and requires careful attention to the history and exam. Important features suggesting low perfusion and a "cold" patient include the following:
Mental status: Often very sensitive to severe hypoperfusion; altered mental status (drowsiness, decreased attention, obtundation) is a particularly ominous sign that the patient may be rapidly deteriorating.
Urine output: Expected to drop in the cardiogenic shock patient; low UOP typically reflects renal insufficiency and azotemia; a Foley catheter is essential as it allows for the hourly UOP to be measured as a vital sign and to relieve any confounding from urinary retention or a post-obstructive uropathy.
Pulse pressure: Calculated as SBP – DBP. A proportional pulse pressure, defined as (PP / SBP), < 25% correlates highly with a reduction in the cardiac index to less than 2.2 with a sensitivity of 91% and a specificity of 83%.[2] **NB**: this association has been identified in patients with chronic HFrEF, but not HFpEF.

Urgent/Emergent Management of ADHF:
These recommendations are focused on the initial triage and management of ADHF, loosely tailored to the acute stabilization of a tenuous patient, followed by more nuanced management.

1. **Treat hypoxemia**. Administer O2 if SpO2 < 92%, and sit the patient upright. Avoid hyperoxia in patients with COPD to prevent hypercarbia and respiratory depression. CPAP/NIPPV may improve symptoms, and early studies demonstrated a reduction in the need for invasive ventilation and mortality; similar findings were not seen in the 3CPO trial,[3] although use of CPAP/NIPPV was superior in improvement in patient-reported dyspnea and metabolic abnormalities (acidosis, hypercapnia) compared with standard oxygen therapy. CPAP is typically initiated with a PEEP of 5-7.5 cm H2O. Caution in patients with shock, RV failure, severe COPD, or altered mental status (inability to protect airway). Mechanical ventilation is often required, namely in patients requiring post-arrest cooling or severe cardiogenic shock requiring inotropes and/or mechanical circulatory support (MCS), for whom impaired oxygenation may result.
2. **Address cardiac output.** Examine the patient for surrogates of end-organ perfusion (mental status, warm vs cold, peripheral pulses, urine output). Initial labs to triage the severity of shock include K/BUN/Cr, ABG (pH), lactate, CvO2/MvO2. hsTnT should be followed if there is concern for ischemia. In addition to normal hemodynamic findings of low CO (low SBP, narrow pulse pressure), a PA catheter, if present, can provide informatics, including CVP, PCWP, and CO/CI. If signs of cardiogenic shock are confirmed (SBP < 90 mmHg, CI < 2.2 L/min/m2, PCWP > 15-18 mmHg), inotropes and/or MCS will be necessary (e.g. IABP, Impella), see below. Caution with inotropes if concerns for active coronary ischemia, as this will increase myocardial demand. Similarly, avoid pure vasopressors for hypotension (e.g. phenylephrine) due to their deleterious effect on LV afterload.
3. **Treat ischemia.** For ACS, treat according to standard ACS protocols, including antiplatelet therapy, anticoagulation, and emergent revascularization, as indicated. ***Avoid Nipride*** due to risks of coronary steal. If a vasodilator is required, reach for IV TNG.
4. **Urgent diuretic therapy.** Typically starting with loop diuretics (Lasix or Bumex), indicated for rapid relief of dyspnea. Initial therapy typically consists of a bolus injection with a dose of 2-2.5X the patient's oral dose, with a titratable drip if necessary. If the urine output does not augment, consider escalation in diuretic dose, conversion to a different loop diuretic, or addition of a thiazide diuretic (metolazone or

Diuril/chlorothiazide). Intestinal edema may prevent resorption. An infusion may be preferable to IV pushes in patients when hypotension is a concern for ease of titration.

5. **Reduce systemic afterload.** In the absence of hypotension, use IV TNG as a vasodilator over a titratable dose range of 0-300 mcg/min, maintaining a MAP > 65. IV TNG is predominantly a venodilator, but at higher doses, can cause coronary and arterial dilation affecting systemic blood pressure, and in turn, SVR and LV afterload. Caution is advised in patients with suspected RVMI as this is a preload dependant condition and thus TNG should be avoided. Note that afterload reduction has two predominant effects on the ventricular myocardium: (1) reduced myocardial oxygen demand, especially important in the context of known ischemia, and (2) augmentation of cardiac output in dilated cardiomyopathy.
6. **Start GDMT.** After initial stabilization of the patient, management in the following days-weeks should center on diuresis and initiation of guideline-directed medical therapy, including ACE/ARB/ARNi, mineralocorticoid receptor antagonist, and beta-blocker, as indicated by NYHA functional status and LVEF. These therapies are further delineated below.
7. **Address arrhythmias.** If AF with RVR is present, consider cautious use of a beta-blocker. If there is any concern for cardiogenic shock, avoid starting beta-blockers and/or calcium channel blockers. An amiodarone bolus/drip or IV digoxin load can be considered for symptomatic or hemodynamically intolerant AF. Caution with both medications should be taken if there is a suspicion for cardiac amyloidosis, as both chemicals can accumulate in the amyloid fibrils and cause local myocardial toxicity. The QTc should be followed on amiodarone – although amiodarone will not cause TdP, patients are on many QTc-prolonging medications in the CICU. Digoxin should be renally dosed.

- Other In-Hospital care: Optimize the patient's hemodynamics and volume status and initiate or optimize chronic HF therapy.
  - Monitor daily weights, fluid intake and output, vital signs including orthostatic blood pressure.
  - Lab monitoring of daily renal function and electrolytes (increase to BID if aggressively diuresing).
  - Dietary sodium restriction (< 2 g daily) and fluid restriction (to < 2L daily) may be useful.
  - VTE prophylaxis is indicated in all patients without a clear contraindication
  - Most outpatient medications can be continued with the following exceptions: hold ACEi and mineralcorticoid receptor antagonists if worsening renal function is present; hold beta blockers if hypotension or shock is present.
  - Consideration cardiac cath/revascularization and cardiac resynchronization therapy
  - Provide patient education, nutritional counseling, and PT/OT if appropriate
  - Aggressively manage other co-morbidities which can complicate HF management.

Impaired renal function: Some patients have impaired renal function due to chronic kidney disease or cardiorenal syndrome, which makes it challenging to remove fluid and unload the left ventricle with diuresis. Cardiorenal syndrome in which co-existing renal and heart failure accelerate the failure of the other organ in a feed-forward cycle characterized by worsening renal failure during treatment of acute heart failure and resistance to diuretic therapy.[4]These patients may require admission to the SDU or the CICU for therapies such as inotropes to improve end-organ perfusion, ultrafiltration, or renal replacement therapy requiring hemodynamic monitoring.

Clinical course
Most patients who are "warm and wet" will improve rapidly enough to warrant triage to the SDU or a general medicine floor. Some patients, including those with severe surgical disease such as mitral stenosis or severe heart failure-related mitral regurgitation may require closer monitoring or tailored therapy in order to properly manage their volume status. Patients with cardiogenic shock represent the sickest category of heart failure patients, with a 6-month mortality of approximately 40%.[5] Patients with a "cold and wet" profile usually require aggressive tailored therapy with close hemodynamic monitoring. Tailored therapy as it is implemented in our CICU will be discussed below. It may be used as a bridge to definitive therapies, but many of these patients may not be candidates for transplantation or placement of durable mechanical support (i.e. VAD). Patients who are not candidates for these definitive therapies, and for whom no reversible cause of their chronic heart failure is identified, should be considered for referral to palliative care and/or hospice given their overall poor prognosis.

Discharge of the HF patient
The time of discharge is a potentially dangerous and anxiety-provoking transition for a patient that has been admitted with HF. In addition, hospital readmission rates after a HF admission are closely tracked and serve as a quality metric for the hospital. Therefore, standardizing the discharge process for HF patients as much as possible is crucial to improve their comfort level upon discharge and to reduce readmission rates.

- **Pre-discharge consults**: Once a HF patient is admitted to the SDU or CICU, they should be admitted using the E9 or E10/E11 admission template which will standardize their admission orders. Included in that template are **consults for PT, nutrition, cardiac rehab, and smoking cessation (if applicable)**. Please make sure that these are ordered prior to the day of discharge.
- **Medications on discharge:** All HF patients should be discharged on the following medications, unless there are contraindications:

  ACE inhibitor/ARB/ARNi, beta-blocker, diuretic, +/- spironolactone, +/- digoxin. Additional considerations are nitrates +/- hydral and CAD management if they have ischemic cardiomyopathy (ASA, statin, etc).
- **Labs prior to discharge:** There is a large effort to try to reduce re-admissions for HF, including trying to predict which patients are at highest risk for readmission. NT-proBNP prior to discharge has been shown to predict mortality and readmission after discharge.[6] **Therefore consider ordering an NT-proBNP prior to discharge** to triage the intensity of your patient's follow up.
- **Discharge Instructions:** Standardized discharge instructions are important so that patients know how to recognize worsening symptoms or congestion. **Please document the dry weight in the discharge summary and tell the patient their dry weight in the discharge instructions**. Patients need to know when they should go to the ED, however appropriate triage of symptoms to the outpatient cardiologist may save hospital readmissions as well. Below is an example of the instructions that should be provided to patients:

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MANAGING HEART FAILURE AT HOME

- Know your target ("dry") weight. **Your weight leaving the hospital is _____.**
- Check your weight every day after you wake up and after you have gone to the restroom, before eating breakfast, and record it daily
- Avoid salty foods
- Avoid excessive fluid intake and try to adhere to the amount of fluid you drank while in the hospital

WARNING SYMPTOM INSTRUCTIONS
I need to call 911 if I have any of these signs or symptoms:

- Severe shortness of breath
- A **new** feeling that I can't catch my breath at rest
- Fainting or passing out
- A racing heart or very quick heartbeats that don't go away when resting
- Sudden weakness, confusion, or slurred speech
- Chest pain that does not resolve

I NEED TO CALL MY DOCTOR IF I HAVE:

- A **new** feeling that my heart is beating fast or skipping beats
- Weight gain of > 4 lbs despite taking medications as prescribed
- Feeling dizzy or faint
- **New or worsening** swelling in your feet, ankles, hands, or abdomen
- **New or worsening** difficulty breathing when lying flat, difficulty breathing at night, waking up breathless in the middle of the night
- A new dry, harsh cough
- A new feeling of fatigue
- Trouble taking your medications
- Chest pain that lasts longer, happens more often, or is worse than in the past

- **Follow up**: The patient should be scheduled to see a cardiologist or their PCP within one month of discharge. They should also be given a phone number to call for their cardiologist (even if an appointment is not scheduled at the time of discharge) so that they can call if they have symptoms.

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6. Salah K et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: a European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF Score. *Heart.* 2014;100(2):115-25

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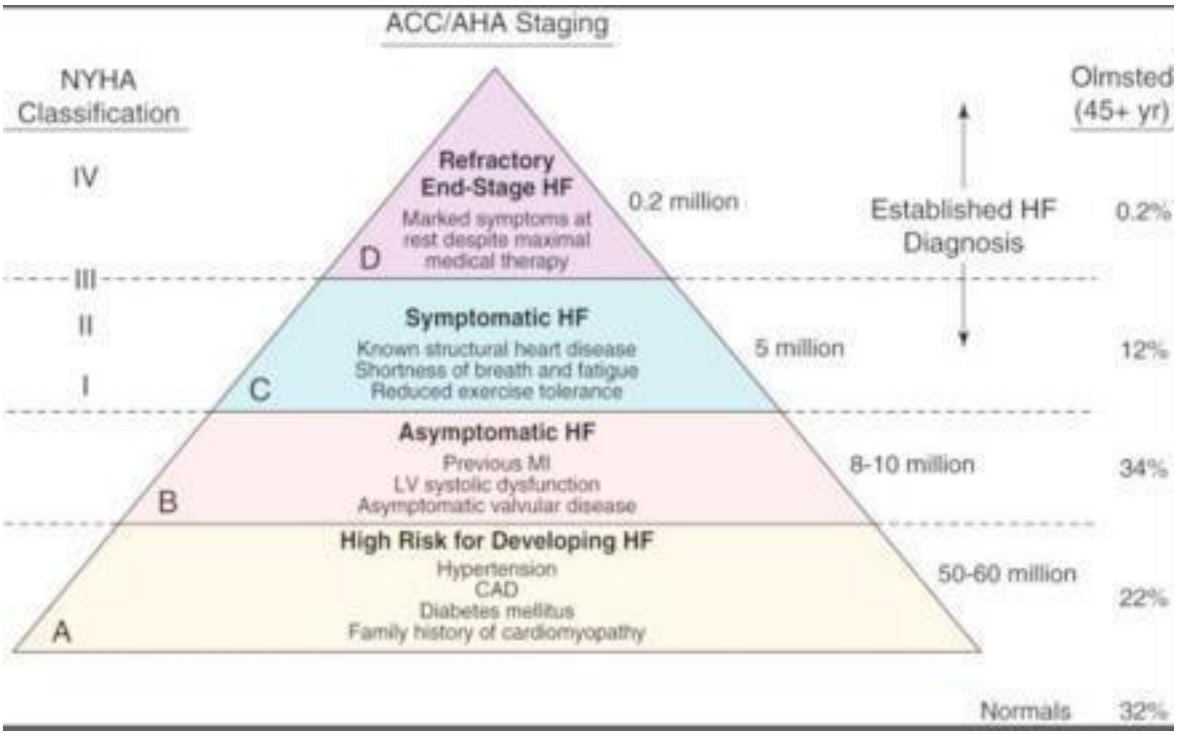
7. Evidence for Medical Therapies

Heart failure is a clinical syndrome in which the heart cannot pump sufficient blood to meet the body's metabolic needs or does so at the expensive of elevated filling pressures. It is a major public health issue in the United States, with a prevalence of ~ 5 million patients and an incidence of >500,000 cases/year. Indeed, the lifetime risk in the US is 1 in 5 at age 40. Heart failure is also one of the most common reasons for hospital admission, accounting for 6.5 million hospital days annually. Further, it carries a higher mortality rate than many cancers with 5-year survival rates of men and women, 25% and 38%, respectively.

Heart failure is classified according to 1) symptoms (functional status) and 2) structure (reviewed in Chapter 22). The two formal categorizations are New York Heart Association classifications (for functional status based on patient-reported symptoms; class I–IV) and ACC/AHA stages (for symptomatic and structural progression; stage A–D).The ACC/AHA staging system allows patients to be stratified for the purposes of targeting therapy. Notably, once structural heart disease develops (i.e. stage B→D), therapy depends on NYHA functional class.



Approach to ACC/AHA CHF stages and progression of disease

Systolic Heart Failure Pharmacology/Therapy: Rapid Literature Reference
The following summary of relevant evidence for chronic HF treatments includes brief descriptions of interventions with, and without, mortality benefits as well as references for corresponding clinical trials. Dose ranges are also provided in parenthesis (beginning with preferred starting dose end ending with target dose at which benefit has been demonstrated in outcomes studies). Medications should be titrated to the target dose unless up-titration is limited by side effects. Many of these medications, however, may need to be held initially for most patients admitted to the CICU with decompensated HF, as most of these medications have not

been evaluated for treatment of acute decompensated HF (ADHF), and some may be harmful if initiated in the setting of ADHF.

AHA/ACC 2017 updates recommend that all patients with HFrEF have an agent to block the renin-angiotensin (ACE-I, ARB or ARNI) plus beta- blocker and aldosterone antagonist in select patients to reduce morbidity and mortality.[1]

ACE inhibitors:

Improve LV function and mortality. Contraindicated if patient has history of angioedema, known bilateral RAS, and symptomatic hypotension or SBP < 90. ACE-I can cause dry cough, angioedema, azotemia, hyperkalemia, and transient renal insufficiency upon initiation of therapy. Reduction in eGFR of **up to** 30 percent in the first six to eight weeks post initiation of therapy is tolerated. Recommended for NYHA classes I through IV. Per AHA/ACC 2017 update ARNIs (angiotensin-neprilysin inhibitor) are superior to ACE-I (decreased mortality and HF admissions); however, ACE-I are still recommended for all classes of HFrEF if ARNIs cannot be tolerated (hypotension, hyperkalemia, angioedema).

Captopril	**SAVE:** NEJM 1992; 327: 669-77 (12.5-25 mg TID)
Enalapril	**CONSENSUS:** NEJM 1987;316: 1429-35 (dose 5-20 mg BID, enhanced effect in patients NYHA class IV) **SOLVD:** NEJM 1991; 325: 293-302 (2.5-10mg BID)
Lisinopril	**ATLAS:** Circ 1999; 100: 2312-8 (32.5-35 mg QD superior to 2.5-5mg QD)
Ramipril	**AIRE:** Lancet 1993; 342: 821-8 (2.5-5mg BID)

Angiotensin-receptor blockers (ARB):

Reduce HF admission and mortality in pts with HFrEF and should be used in patients intolerant to ACE-I (cough, angioedema) have also (rarely) been used in addition to ACE-I, though combination is commonly avoided in practice due to the risk of hypotension, electrolyte abnormalities and renal dysfunction.[2] Avoid ACE-I/ARB combo.[3]

Candesartan	**CHARM-ALTERNATIVE** (ACE-I intolerant): Lancet 2003; 362:772-776 (32 mg daily) **CHARM-ADDED** (+ ACE-I): Lancet 2003; 362: 767-776 (4-32 mg QD)
Valsartan	**VAL-HeFT**: NEJM 2001;345: 1667-1675 (40-160 BID)
Losartan	**HEAAL**: Lancet 2009; 374: 1840-1848 (150 mg QD superior to 50 mg QD)

ARNI (Angiotensin receptor-neprilysin inhibitor):

In patients with NYHA class II-III who tolerate ACE-I or ARB, replacement by ARNI is recommended by ACC/AHA guidelines to further decrease morbidity and mortality. Neprilysin is an enzyme which degrades vasoactive substances such as adrenomedullin, bradykinin, natriuretic peptides. In PARADIGM-HF, valsartan/sacubitril (Entresto) was compared against enalapril in outpatients with symptomatic HFrEF

(NYHA II-IV, LVEF <35-40%). ARNI reduced cardiovascular death and hospital admissions by 20%.[4] Side effects were similar to ACE-I, including hypotension, renal insufficiency, and angioedema. The PIONEER-HF trial compared Entresto with enalapril for inpatients admitted with ADHF (LVEF <40%, NYHA II-IV not on inotropes or IV vasodilators). Entresto met safety endpoints (see above), was superior to ACE in reduction of NT-proBNP, and had reduced rates of readmission for HF.[5]

Four ongoing trials will examine the efficacy, tolerability, and safety of ARNI compared with ACE/ARB in HFpEF (PARAGON-HF, PARALLAX), advanced NYHA IV HF requiring MCS or inotropes (LIFE), and post-AMI (PARADISE-MI). ARNIs should not be administered with ACE-I or ARBs, and the first dose of an ARNI should not occur sooner than 36 hours after or before an ACE-I dose. Omapatrilat, an ACE-I plus neprilysin inhibitor, had no difference in combined endpoint of death and HF admission, but was associated with higher rates of angioedema. Ultimately, omapatrilat was not approved by the FDA due to angioedema safety risk.

Entresto (LCZ696)	**PARAMOUNT:** Lancet 2012; 380: 1387-95 (versus Valsartan) (200mg BID) **PARADIGM-HF:** NEJM 2014; 371:993-1004 (versus Enalapril) (200mg BID) **PIONEER-HF:** NEJM 2019; 380:539-548 (versus Enalapril) (200mg BID) **PARAGON-HF, PARALLAX, LIFE, PARADISE-MI** – clinicaltrials.gov
Omapatrilat	I**MPRESS:** Lancet 2000; 356: 615-620 (versus Lisinopril) (40mg daily) **OVERTURE:** Circulation 2002;106: 920-926 (versus Enalapril) (40mg daily) **OCTAVE:** Am Journal HTN 2004; 17:106-111 (max 80mg daily)

Beta-blockers:

Recommended for NYHA II-IV, with proven mortality benefit and LV remodeling. Carvedilol (non-selective β-blocker with α-blocking capacity) tends to have a greater effect on BP. Limited data on head-to-head comparative efficacy, but carvedilol was superior to metoprolol tartrate in COMET. Contraindicated in severe conduction disease and use with caution in patients with tenuous cardiac index (e.g. immediately post-MI), asthma or bronchospastic COPD; however, meta-analyses reveal that cardioselective β-blockers are safe in bronchospastic disease.[6] Careful with initiation during acute heart failure exacerbation as may result in negative inotropy.

Bisoprolol	**CIBIS-II:** Lancet 1999; 353: 9-13 (1.25-10 mg QD)
Carvedilol	**COPERNICUS:** NEJM 2001; 344: 1651-8 (3.125-25 mg BID)

	COMET: Lancet 2003; 362: 7-13 (3.125-25 mg BID)
Metoprolol XL	**MERIT-HF:** Lancet 1999; 353: 2001-7 (XL:12.5-200 mg QD)
Nebivolol	**SENIORS:** Eur Heart J 2005; 26: 215-25 (1.25-10 mg QD).
Bucindolol	**BEST:** NEJM 2001; 344:1659-1667, no mortality benefit.

Aldosterone antagonists:

Data suggest mortality benefit for patients with at least NYHA II and EF < 35% (or NYHA class I with recent MI). Cannot be given to patients with K > 5 and caution should be exercised in AKI or Cr > 2.0. Spironolactone can cause gynecomastia and breast pain in men; eplerenone has fewer endocrine side effects.

Spironolactone	**RALES:** NEJM 1999; 341: 709-17 (25-50 mg QD)
Eplerenone	**EPHESUS:** NEJM 2003; 348: 1309-21 (25-50 mg QD);
	EMPHASIS-HF: NEJM 2011; 364:11-21 (25-50 mg QD

Hydralazine-isosorbide dinitrate:
Recomm
Recommended for self-identified African American patients with NYHA III-IV HF and LVEF < 35% or LVEF < 45% and LVEDD > 65 or > 29 mm/m^2. This combination was studied as an additional therapy for patients already on an ACE/ARB and BB, not as a replacement for either. The A-HeFT trial demonstrated a 40% reduction in all-cause mortality compared with placebo and 33% reduction in HF hospitalizations.

Hydralazine + Isordil	**V-HeFT:** NEJM 1986;314:1547–52. (split dosing, 25-50 mg TID or QID + 20-30 mg TID or QID [hydral + ISDN] vs placebo)
	A-HeFT: NEJM 2004;351:2049-57 (fixed-dose combination
	37.5/20 mg TID – 75/40 TID [hydral/ISDN] vs placebo)

Vasopressin Antagonists/"Vaptans"

Effects mediated via increased urine volume, decreased urine osmolarity. No effect on mortality but appears to be safe in patients with advanced HF. Conivaptan and Tolvaptan are FDA approved for hypervolemic and euvolemic hyponatremia (Na<125) resistant to fluid restriction in patients with HF.

Tolvaptan	**EVEREST**: JAMA 2007;297(12):1319-1331 (30 mg/day)

Digoxin:

Decreases vagal tone and increases myocardial calcium through Na/K+ pump. No mortality benefit. Decreased HF symptoms (28%) and overall hospitalizations (6%). Post-hoc analysis of DIG trial showed that all-cause mortality was lower than placebo at **0.5–0.8 ng/ml** and higher than placebo at > 1.2 ng/ml; consequently, it is useful to follow digoxin levels in HF. Contraindicated if significant sinus or AV block. Consider for treatment of AF in ADHF. Caution with renal failure.

Digoxin	**DIG:** NEJM 1997; 336: 525-33 (dosing per eGFR/levels)

CCBs:

No absolute morbidity or mortality benefit when used alone or in combination with ACE-I. Subgroup analysis of PRAISE showed that treatment with amlodipine had mortality benefit for patients with HF due to dilated CM (22% vs. 35% placebo), but not ischemic CM. However, these benefits were not recapitulated in the larger double-blind PRAISE-II study. Therefore, amlodipine may be used for treatment of concomitant HTN or angina in patients with systolic HF. In MDPIT (diltiazem in post-MI setting) diltiazem was found to increase late onset HF in patients with EF <40% and to decrease HF in patients with EF >40%. Short acting nifedipine also shown to increase HF related hospitalizations in HFrEF. Generally, it is recommended to AVOID nodally-selective CCB for LVEF < 40%; if SVR/afterload reduction needed, amlodipine appears to be the safest.

Diltiazem	**MDPIT:** NEJM 1988; 319: 385-92
Amlodipine	**PRAISE:** NEJM 1996; 335: 1107-14 (10mg QD + ACE-I)
	PRAISE-II: JCHF 2013; 1: 308-14 (10 mg QD only)
Nifedipine	**Elkayam et al.**: Circulation 1990; 82(6):1954-61

Nesiritide:

Nesiritide (recombinant BNP) has vasodilatory properties and was approved for early relief of dyspnea in HF; however there is no mortality benefit in HF. Of note, nesiritide was not found to worsen renal function or increase mortality, as had previously been proposed, but was associated with increased hypotension.

Nesiritide	**ASCEND-HF:** NEJM 2011; 365: 32-43 (optional 2 ug/kg bolus + 0.01 ug/kg/min infusion)

Dopamine:

Low dose dopamine does not alleviate renal venous congestion (as measured by UOP) or improve renal function in combination with loop diuretics in patients with HF and CKD (eGFR 15-60). Low dose nesiritide (see above) was also tested and also did not improve these endpoints.

Dopamine	**ROSE**: JAMA 2013; 310: 2533-43 (2µg/kg/min infusion + diuretics)

Direct renin inhibitors:

Aliskirin in addition to standard therapy decreases BNP levels but does not improve mortality (ASTRONAUT). In addition, rates of hyperkalemia, hypotension, and renal dysfunction were higher in the aliskirin group. Subgroup analysis of patients with known T2DM showed that aliskirin actually increased mortality (HR 1.64, 95% CI 1.15-2.33).

Aliskirin	**ASTRONAUT**: JAMA 2013; 309: 1125-35
	(150-300 mg QD + standard therapy)
	ALOFT: CIRC Heart Failure 2008: 1(1):17-24.

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ATMOSPHERE: Eur J Heart Fail 2011: 13(1):107-14.

Loop diuretic dosing:

In IV form, functions as a venodilator and decreases RA and PCWP quickly. Typically given as 2-2.5x home PO dose. Bolus vs infusion: no significant difference in sx or in Cr, but infusion→ lower total daily lasix dose. High dose vs low dose: No significant difference in symptoms or in Cr. The high dose group had greater diuresis but transient worsening of AKI. Overall, there were no significant differences in symptoms or renal function among any of these strategies. Can add metolazone/diuril for increased effect. Conversions: 40 mg PO Lasix = 20 mg IV Lasix = 20 mg PO torsemide = 1 mg IV/PO Bumex = 50 mg ethacrynic acid.

Diuretic dosing **DOSE**: NEJM 2011; 364: 797-805

Ivabradine:

Heart rate-lowering agent that acts by selectively blocking the cardiac pacemaker "funny" current (I_f). The magnitude of inhibition is directly related to the frequency of channel opening and therefore is most effective at higher heart rates. Shown to improve outcomes (reduced death and hospitalization) in patients with LVEF <35% (SHIFT); safe for use in heart failure (BEAUTIFUL). Indicated for patients with HR >70bpm at rest. Can be considered once BB therapy is maximized.

Ivabradine: **SHIFT:** Lancet 2010;376(9744):847-9. (max dose 7.5 mg BID)

BEAUTIFUL: Lancet 2008;372(9641):807-16. (5-7.5 mg BID)
SHIFT HF: Am Journal Card 2015; 116 1890-1897 (2.5, 5 or 7.5 BID versus placebo)

Ultrafiltration:

No advantage to stepped pharmacologic care in acute decompensated heart failure but may still have role in those patients unresponsive to diuretic therapy. CARESS trial revealed similar weight loss in patients treated with diuretics vs. UF but increase in severe adverse events (renal failure, bleeding, IV access complications) in the UF group (72% vs. 57%). Patients with cardiorenal syndrome actually had their creatinine rise.

Ultrafiltration **CARESS:** NEJM 2012; 367: 2296-2304

Anticoagulation:

No significant difference in time to first ischemic stroke, cerebral hemorrhage, or death between warfarin (INR 2-3.5) and ASA 325 QD in patients with EF<35% and NSR. Warfarin offered a reduced risk of ischemic stroke but an increased risk of major hemorrhage. Rivaroxaban also did not reduce the risk of all-cause mortality, MI, or stroke in patients with EF <40% and CAD.

Anticoagulation **WARCEF**: NEJM 2012; 366: 1859-69
COMMANDER HF: NEJM 2018;379:1332-1342

Statins:

Reduced hospital admissions in statin-naïve patients with EF<40% and no other indication for cholesterol-lowering therapy; no effect on mortality.

Rosuvastatin	**CORONA:** NEJM 2007; 29;357(22):2248-61.

n-3 Polyunsaturated Fatty Acids:

Three month treatment with n-3 PUFA improved outcomes but small treatment effect.

n-3 PUFA	**GISSI-HF:** Lancet 2008;372(9645);1223-30.

Iron:

Anemia is associated with increased HF symptoms, worse NYHA class, decreased survival, and increased frequency of hospitalization. Correction of iron-deficiency (ferritin 15-100 or 100-299 with Tsat < 20%) in NYHA II-III HF with IV iron improves NYHA functional status, 6-min walk test and several quality of life assessments, as shown by the FAIR-HF trial. The IRONOUT-HF study assessed oral iron repletion in the same patient population, showing no benefit compared with placebo. Supplementing with darbepoetin alfa has not shown any effects and may actually be harmful by increasing the risk of thromboembolic events.

Ferric carboxymaltose	**FAIR-HF**: NEJM 2009;361:2436-48. (Repletion to iron deficit, or approximately 1g)
Iron polysaccharide	**IRONOUT-HF:** JAMA 2017;317(19):1958-66. (150mg BID)
Darbepoetin alfa	**RED-HF**: NEJM 2013;368:1210-19. (target Hgb >13)

Consider influenza and pneumococcal vaccination.

AVOID: NSAIDS, COX-2 inhibitors, CCBs (verapamil, diltiazem), thiazolidinediones

Diastolic Heart Failure (DHF)/Heart Failure with Preserved Ejection Fraction (HFpEF)

In diastolic heart failure (DHF), ejection fraction is preserved, and symptoms occur due to impaired LV relaxation during diastole, which results in impaired LV filling. Heart failure with preserved ejection fraction (HFpEF) refers to the clinical syndrome of heart failure in a patient with an EF >50%. Many, but not all, patients with HFpEF have DHF. No specific pharmacotherapy has been shown to improve mortality in either DHF or HFpEF.

Beta-blockers	**OPTIMIZE-HF Registry:** JACC 2009; 53: 184-92. No benefit.
ACE-I	**PEP-CHF:** Eur Heart J 2006; 27: 2338-45. Non-significant trend toward reduced mortality.
ARB	**CHARM-Preserved:** Lancet 2003; 362: 777-8 **I-PRESERVE:** NEJM 2008; 359: 2456-67

Aldosterone antagonists	**TOPCAT:** NEJM 2014; 37:1383-92. Spironolactone decreased hospitalizations due to HF but no effect on mortality.
	ALDO-DHF: JAMA 2013; 309: 781-791
Sildenafil	**RELAX**: JAMA 2013; 309: 1268-77. No benefit.
Imdur	**NEAT-HFpEF**: NEJM 2015;373:2314-24. Worse outcomes (reduced daily activity).
Digoxin	**DIG**: NEJM 1997;336:525-33. No effect.
CCBs (diltiazem)	**MDPIT subgroup analysis**: Circ 1991; 83: 52-60

Global strategy is aimed at preventing worsening of LV filling pressures, notably:

- Blood pressure control
- Ventricular rate control or rhythm control in atrial fibrillation
- Symptomatic management of pulmonary or right-sided congestion

- Coronary revascularization in patients with CHD/ischemia thought to impair diastolic function

Ambulatory Remote Hemodynamic Monitoring Strategies:

The **CardioMEMS device** is an FDA-approved permanently implantable pressure measurement system that wirelessly monitors PA pressure and heart rate in HF patients. The CHAMPION trial tested the device in NYHA III patients regardless of LVEF and demonstrated a significantly reduced frequency of hospitalizations. While the device is considered safe, its efficacy has been called into question by the FDA due to preferential support of the treatment group during the trial and difficulty separating the efficacy of the device from appropriate HF therapy.

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8. Tailored Therapy

One of the first challenges encountered in the CICU is the evaluation and management of patients with heart failure who have failed—or are likely to fail—maximal aggressive management that can be delivered on the floor (e.g., diuresis based on urine output and clinical assessment of volume status who require escalation of their medical management to include parenteral vasoactive agents, including inotropes or pressors). These can be patients who are too hypotensive to diurese safely on the floor but are clearly still volume overloaded ("cold and wet") or patients whose volume status is difficult to determine clinically (and are potentially "cold and dry").

On admission to the CICU, many of these patients meet the definition of cardiogenic shock, with evidence end-organ dysfunction or failure due to severely decreased cardiac output. Specifically, cardiogenic shock is defined as SBP < 90 mmHg, cardiac index (CI) < 2.2 L/min/m2, pulmonary capillary wedge pressure (PCWP) > 18 mmHg, UOP < 30 mL/h. Blood pressure and urine output can be measured with general ease, but cardiac index and PCWP, among other related complex hemodynamic parameters, require the use of a pulmonary artery (PA) catheter (previously known as the Swan-Ganz catheter).

In this setting, therapy with intravenous medications including inotropes and vaso-venodilators and/or mechanical support such as an intra-aortic balloon pump (IABP) is often necessary to support cardiac function, with management decisions guided by information obtained from the PA line. The previous chapter on "Tools in the CICU" introduced some of the basics regarding the use of the PA line. The PA line offers a direct assessment of filling pressures and cardiac output, as well as calculation of pulmonary and systemic vascular resistance. The approach to tailored therapy, however, requires more discussion regarding the hemodynamic parameters used in the evaluation of end-stage heart failure and the approach to treatment in the CICU based on the integrated data provided by the PA catheter and nursing flow sheets, along with physical exam, labs, and imaging.

In practice, the PA catheter is used to "tailor" real-time adjustment of medications, specifically inotropes and vaso-venodilators, as well as diuretics or renal replacement therapy, in order to optimize cardiac output and end-organ perfusion based on a particular patient's hemodynamics. Ideally, this is accomplished by optimizing LV filling and minimizing LV afterload with the ultimate goal of weaning inotropic support. It is important to realize that treatment strategies have been largely empirically and limited by an incomplete understanding of the pathophysiology.

Indications for Tailored Therapy

- "Cold and wet" or "cold and dry" profile ~ Low output failure
- Multi-factorial shock syndromes including mixed cardiogenic and distributive shock processes requiring hemodynamic tailoring
- Inability to wean inotropes
- Bridge therapy during OHTx evaluation or consideration for long-term mechanical support

Each of the "targets" of tailored therapy is based on the principle that cardiac output is a function of stroke volume (and heart rate): **CO = SV × HR**

HR modification is relatively straightforward: symptomatic bradycardia could be accelerated by positive chronotropic strategies such as dopamine or isoproterenol or pacing) and hemodynamically significant tachyarrhythmias (e.g., that impair LV filling due to a reduction in diastolic time) should be judiciously slowed down (by rate or rhythm control or cardioversion/defibrillation) without negatively affecting myocardial contractitlity (i.e. caution with aggressive up-titration of beta-blockers). **Importantly, any attempt before HR reduction requires an assessment of whether the tachycardia is an appropriate reflexive physiologic strategy to maintain cardiac output.**

Tailored therapy specifically targets the hemodynamic variables that can be modified to improve intra-cardiac filling pressures and augment the cardiac output generated by a given heart rate.

Hemodynamic Variables and Goals of Tailored Therapy
The following is a glossary of relevant hemodynamic variables in the CICU, their normal ranges, and methods of derivation:

Cardiac Output (CO):	4–7 L/min = Fick equation or thermodilution or SV × HR
Fick: CO = VO2 / (CaO2 – CvO2) ~ VO2 / (13.4 x Hg x [SaO2 - SvO2]	
Oxygen Consumption (VO2):	CO × (CaO2 – CvO2) = metabolic cart (cath lab) or ~250 ml/min
Cardiac Index (CI):	2.6–4.2 L/min/m2 = CO / body surface area
Stroke Volume (SV):	60–70 ml/beat = CO (in ml) / HR
Systemic Vascular Resistance (SVR):	770–1200 dynes × sec × cm5 = (MAP – CVP) / CO × 80
Pulmonary Vascular Resistance (PVR):	20–130 dynes × sec × cm5 = (mPAP – PCWP) / CO × 80
Oxygen Content:	oxygen bound to hemoglobin + oxygen dissolved in blood
Arterial Oxygen Content (CaO2):	17–20 ml/dl = (Hg × SaO2 × 1.34) + (PaO2 × 0.0031)
Venous Oxygen Content (CvO2):	12–15 ml/dl = (Hg × SvO2 × 1.34) + (PvO2 × 0.0031)
PaO2, PvO2:	partial pressure of oxygen in arterial and venous blood
SaO2, SvO2:	hemoglobin oxygen saturation of arterial and venous blood
MvO2 (“mixed venous sat”):	SvO2 of mixed venous blood (taken in the PA by PA catheter)
ScvO2 (“central venous sat”):	SvO2 of central venous blood (taken in SVC* by central line) *misses venous return from coronary circulation

Sample calculation:
Known values: VO_2 220 mL/min (from the cath lab report), Hg 11 g/dL, SaO2 98% (finger probe), BSA 2 m^2
From PA line: MvO2 65%, MAP 70, CVP 10, mPAP 20, PCWP 14

CO ~ VO_2 / (13.4 × Hg × [SaO_2 - SvO_2]) = 220 / (13.4 × 11 × [0.98 – 0.65]) = **4.52 L/min**
CI = CO / body surface area = 4.52 / 2 = **2.26 L/min/m^2**
SVR = (MAP – CVP) / CO × 80 = [(70 – 10) / 4.52] × 80 = **1062 dynes · sec/cm^5**
PVR = (mPAP – PCWP) / CO × 80 = [(20 – 14) / 4.52] = **1.33 Woods units** × 80 = **106 dynes · sec/cm^5**

The following are generally accepted hemodynamic parameter goals in most tailored therapy patients, but you should **tailor** these goals based on what you know about the particular patient (eg how dilated or "stiff" the LV is, level of RV function, ambient or normal SBP and MAP for the patient):

- CI 2.0–2.2
- PCWP 14–18, PA diastolic pressure (PAD) 16–20

- CVP 8–12
- SBP > 80 and MAP > 60
- SVR ideally < 800
- PVR ideally < 3 (Wood units)

- MvO_2 > 65

*Oxygen consumption (VO2) is either measured by exhaled breath analysis or estimated from a nomogram that is based upon age, sex, height, and weight.

Limitations
It is critical to remember the limitations of a given cardiac output derivation method. Thermodilution (using the temperature gradient between two points on the PA catheter to assess blood flow) may not adequately reflect cardiac output in the setting of shunt or valvular insufficiency (in particular tricuspid regurgitation). Similarly, derivation of cardiac output via the Fick equation requires an assessment of oxygen consumption (VO_2), which can be measured directly using a metabolic cart in the catheterization lab (using rapidly responding gas analyzers capable of breath-by-breath determination of O_2 and CO_2 concentrations in inspired and expired air) or estimated as a function of body weight. Even when VO_2 is measured directly, it is important to remember that oxygen consumption can vary with physiologic state (i.e., infection) and interpretation of a derived cardiac output should be made in the context of the patient's clinical status (i.e. ambulation). For this reason, the MVO2 should always be considered along with the hemoglobin and ambient SaO2. This is discussed in more detail in the following chapter.

Remember that the normal ranges apply to the afebrile patient at rest. Measurements of these variables can change with changes in temperature, patient activity, or position (CICU nurses are generally strict about "shooting numbers" only when a patient has been still in bed for some time and leveled with the transducer). Also, keep in mind the setting in which the variables are interpreted. For instance, a cardiac index of 2.3 may be acceptable, although abnormal, in a resting, afebrile patient being treated with dobutamine for cardiogenic shock and in this case, further manipulations of the IV medications may cause more harm than benefit. On the other hand, if the peripheral demand is increased by infection or fever, the same cardiac index may in fact be inadequate and lead to low-perfusion end-organ dysfunction.

It should also be noted that vascular resistances (SVR and PVR) are derived variables that should be interpreted with caution. Specifically, SVR is mostly helpful in categorizing the hypotensive patient as vasoconstricted ("clamped down" or "cold") or vasodilated ("warm"). It can be misleading to consider an alteration in SVR as a primary derangement when often it is not. For instance, in a patient with a low cardiac index, elevated SVR, acceptable blood pressure, and large oxygen extraction (CaO2 – CvO2), adding a vasodilator such as nitroprusside to reduce SVR would enhance peripheral perfusion and likely augment CO. On the other hand, in a patient with marginal blood pressure, elevated SVR, and acceptable cardiac index and oxygen extraction, "treating" the SVR independently without considering the

other variables would likely depress blood pressure to a harmful level in a patient who had otherwise been well compensated. Likewise, be careful with pressor use in patients with cardiogenic shock, which have been shown to increase mortality. Only consider if "pseudosepsis" is present (i.e. after over-dose of afterload reducing agents or sedation).

Final Thoughts

There are no data to demonstrate that this management and these goals improve outcomes of either mortality or symptom improvement. Numerous studies of PA catheters used in critically ill ICU patients—generally septic—have shown no mortality benefit.[1] In theory, tailored therapy using PA catheters helps to reduce congestion by providing invasive measurements to help improve the titration of a suite of therapies (including diuretics and inodilators), thereby enabling simultaneous LV "unloading", improvements in cardiac output, and preservation of adequate end-organ perfusion pressure (measured by SBP and MAP).

When inotropes cannot be weaned, there should be consideration for mechanical support (e.g. left ventricular assist device) as well as assessment of candidacy for orthotopic heart transplant. If no definitive intervention is feasible or desired, patients may be discharged from the CICU with plans for destination inotrope therapy (e.g., continuous home infusion) and/or palliative care. Patients who are discharged on continuous inodilator infusions are unlikely to survive for more than six months following discharge.[2]

One final note: Tailored therapy is best learned on the job, and this chapter may be most useful if re-read after or during a CICU month to solidify concepts once one has "learned by doing."

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TOC

9. Physiology of Preload, Afterload, & Contractility

In the CICU, we use physiologic terms such as preload, afterload, contractility, and compliance in our day-to-day description of patient findings. However, many of these variables are actually quite difficult to measure using the PA catheter and one should keep in mind that we are measuring/calculating surrogates and attempting to extrapolate estimates of preload, afterload, contractility and compliance from them. Also, it is important to remember that the interplay of all of these variables is complicated, and they cannot be manipulated independently of each other.

Physiologic Parameter	Measured Surrogate	Associated Possible Interventions
Preload	PCWP, PAD	Diuresis, Ultrafiltration, Hemodialysis, Afterload reduction
Afterload	SVR, Diastolic BP	*Vasodilators*: *Oral*: ACE-I/ARB, hydralazine *IV:* Nitroprusside, Nitroglycerin *Device:* IABP *Vasopressors:* Levophed, vasopressin [phenylephrine rarely used]
Contractility	CO by Thermodilution CO by Fick Equation MVO2, CVO2 Pulse Pressure	*"Inodilators":* Dobutamine, Milrinone *"Inopressors:"* Epinephrine, Dopamine

PCWP pulmonary capillary wedge pressure; PAD pulmonary artery diastolic pressure; SVR systemic vascular resistance; MVO2 mixed venous O2, CVO2 central venous O2; IABP Intra-aortic balloon pump

The Frank-Starling Mechanism

Many of the concepts about management of heart failure patients in the CICU derive from the Frank-Starling mechanism. The physiologists Frank and Starling discovered a basic mechanism of cardiac function in the late 19th and early 20th centuries whereby the heart alters its force of contraction (and therefore stroke volume) in response to changes in venous return (i.e. myocardial stretch or preload) independently of neurohormonal input. This mechanism compensates for differences in venous return with each beat (due to changes in position, respiration, etc.) and thus regulates beat-to-beat stroke volume to match blood return and exit.

Importantly, the ventricle does not operate along a single Frank-Starling curve. Instead, a myriad of curves exist for a ventricle, which are determined by afterload and inotropy (Figure 1).

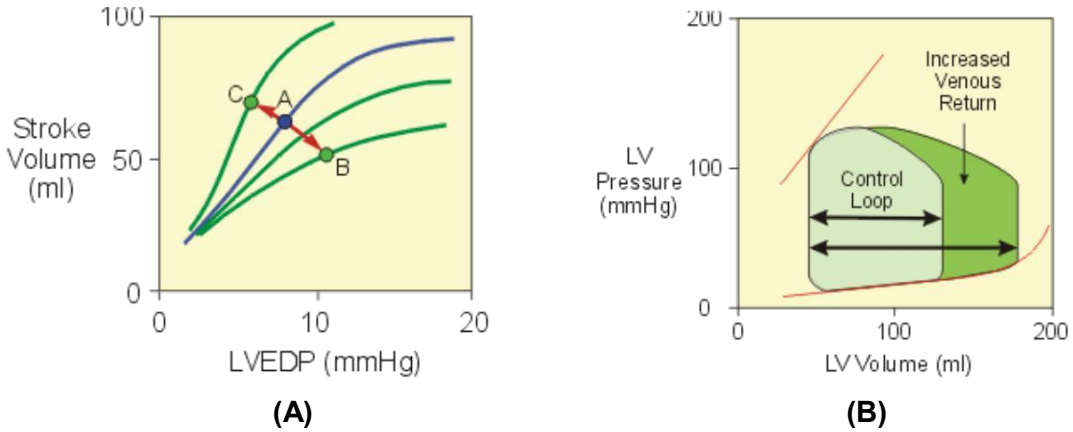

Figure 1 (**A) Starling Curve**: Relationship between preload (LVEDP) and stroke volume. Increases in afterload or decreases in inotropy shift the curve from point A to point B. Decreases in afterload or increases in inotropy shift the curve from A to C. **(B) Pressure-Volume Loop**: Under control conditions, diastolic filling increases LV volume until isovolumic contraction forces the aortic valve open, which decreases LV volume until the end of systole. With increased venous return, LV volume increases more than control, and the end systolic volume does not change from control, therefore stroke volume increases. *cvphysiology.com.*

Preload

Preload refers to the level of myocardial stretch seen by cardiac myocytes. Clinically, preload is equivalent to LV end diastolic volume (LVEDV) and is related to venous return to the heart as well as the LV end diastolic pressure/filling pressure (LVEDP). LVEDP is difficult to measure; therefore we use surrogate measures such as the pulmonary capillary wedge pressure (PCWP) and the PA diastolic (PAD) pressure.

In theory, at the end of diastole, the PAD pressure should reflect the LVEDP because there is an equalized, uninterrupted column of fluid between the pulmonic valve and the LV while the mitral valve is still open (directly before LV contraction). Anything that interferes with flow between the pulmonary artery and the LV cavity can thus prevent equalization of pressure within this column of fluid. It is important to correlate the PAD to the PCWP by looking at the wedge tracing to see the different wave forms represented by the a-wave, c-wave, x-descent, v-wave, and y-descent (reviewed in PA Catheter section). These waveforms can help you troubleshoot and determine if the PAD and PCWP correlate, as well as if either of those measurements are good surrogates of LVEDP. The assumption that preload = LVEDP = LAP = PCWP = PAD can fail for the following reasons:

- LVEDP itself is affected by ventricular interdependence, ischemia, and LV compliance.
- Mean PCWP does not accurately reflect LVEDP with mitral valve disease. For instance, LAP > LVEDP in MS. However, the end-diastolic pressure on PCWP tracing should reflect the LVEDP in MR before systole.
- PCWP will be greater than LAP in veno-occlusive disease, pulmonary vein stenosis or mediastinal fibrosis.

- If PCWP is unavailable (e.g. catheter malfunction), PAD can be used as a surrogate of PCWP if previously correlated.

- Decreased ventricular compliance can increase LVEDP without significant change in LVEDV (i.e. preload).

In the normal heart, Starling curves relate changes in preload (LVEDV) to changes in stroke volume. When venous return increases, the ventricle passively fills to an increased LVEDV. When the ventricle contracts at this point, and the afterload is constant, the ventricle will empty to the same end systolic volume, thereby increasing stroke volume (Figure 1). Therefore, in a NORMAL heart with NORMAL compliance, the ventricle augments stroke volume to match increased venous return.

In the diseased heart, such as in dilated cardiomyopathy, pericardial disease, infiltrative disease, and LVH, compliance is not normal. The LV does not "stretch" appropriately with the same pressure because the dilated heart has decreased compliance (reflected by the decreased slope of the line with point B in the previous figure) and the Starling curve of the ventricle is relatively flat. The goal is to then shift the Starling curve back up and to the left through alteration of afterload and inotropy until the heart becomes more preload responsive. The LVEDP is, therefore, not always a surrogate of preload since one can observe a significant elevation in LVEDP without any change in myofiber stretch in the noncompliant LV.

The goal of "unloading" the LV with diuretics, morphine, or nitrates is to reduce LV diastolic venous return to reduce LVEDP and restore the Starling curve where preload and stroke volume match. Decreasing preload, or LVEDP, also improves mitral valve closure in the dilated ventricle and improves MR.

While many processes can precipitate heart failure, neurohormonal activation—and most notably activation of the renin-angiotensin-aldosterone (RAA) axis—appears to play a crucial role in the pathophysiology of recurrent acute decompensation and disease progression. Briefly, a reduction in cardiac output and intravascular volume stimulates RAA axis activity, adrenergic tone, and non-osmotic vasopressin release.[1] All of these occurrences, in turn, lead to increased sodium and water retention by the kidneys in an attempt to restore intravascular volume. This salt and water retention leads to LV enlargement and dilation, reduction in LV compliance, and worsening of functional MR. Moreover, RAA axis activation and increased adrenergic tone also lead to LV remodeling.

Therefore, improving cardiac output and "forward flow" to the kidneys will improve sodium and water excretion, which will lower LVEDP and venous return. This pathophysiology has been used to justify brief inotropic support to "warm up" the kidneys prior to diuresis.

Estimating preload, and using this estimate to tailor a patient's treatment, can be complicated due to the complex interplay between preload and stroke volume. Additionally, the relationship between cardiac and renal function makes it impossible to conceptualize preload as an isolated variable and requires that the clinician consider preload in the context of other variables such as afterload, contractility, compliance, and renal function.

Afterload
Afterload refers to the load that the ventricle must contract against at the beginning of systole, and consists of the pressure it takes to open the aortic valve (the diastolic BP). However, aortic valve disease can increase afterload markedly above diastolic BP.

Afterload shifts the Starling curve. For instance, increasing afterload will decrease stroke volume independently of preload. As afterload increases, the aortic valve closes earlier, which reduces stroke volume and shifts the starling curve to the right. This decrease in stroke volume will, in turn, increase the preload of the next beat because the blood left in the ventricle at the end of systole (LVEDV) is added to the next beat's venous return. Conversely, if afterload decreases, the same energy expended by the contracting LV will increase stroke volume.

Generally, afterload is reduced by decreasing arterial blood pressure (particularly diastolic BP) and SVR. SVR and blood pressure are reduced through the administration of arterial vasodilators such as nitroprusside and hydralazine, non-selective vasodilators such as TNG (which preferentially dilate the venous system, but also have some effect on the arterial system), or inodilators (e.g. milrinone, and dobutamine), which increase inotropy and cause arterial vasodilation. The inodilators also increase cardiac output by improving stroke volume.

Contractility
Contractility refers to amount by which myofibers shorten in a cardiac cycle. Simply, the more myofibers shorten during systole, the higher the stroke volume. The Starling curve shifts when contractility changes because a separate variable affects stroke volume for a given preload.

Clinically, improving the contractility of the LV will improve the stroke volume and thus cardiac output at any given heart rate. Thus, the terms "contractility" and "inotropy" are often used to refer to cardiac output.

The contractility of a patient's heart can be measured by using trans-thoracic echocardiogram (TTE) to the LVEF, which enables the approximation of stroke volume. However, this tool may be limited by a number of factors, including MR, which leads to retrograde movement of blood back into the left atrium during systole. Even though this blood does not move into the systemic circulation, it is included in calculations of LVEF because it leaves the LV during systole. Thus, in patients with moderate-severe MR, estimates of LVEF may be significantly higher than true forward" LVEF (e.g. the stroke volume that moves through the aortic valve and into the systemic circulation with each beat). It is also important to remember that the TTE provides a "snapshot" of LV function, and does not give us the whole picture on stroke volume at a given moment. TTE is also technically variable.

PA catheter measurements can be used to approximate cardiac output by using either thermodilution at the bedside or the Fick equation in the cath lab. Recall that the Fick equation states that cardiac output can be expressed as:

$$CO = \frac{VO_2}{(CaO_2 - CvO_2)}$$

where VO2 is a measured value of oxygen consumption (measured in the cath lab), and CaO2 and CvO2 refer to the arterial and venous concentrations of O2. Clinically, SaO2 and MvO2 approximate CaO2 and CvO2, respectively. The initial measurement of VO2 (must specifically request) in the cath lab can provide a baseline measurement of cardiac index and the MvO2

utilized at that time can be a reference point. Subsequently, you can follow the SaO2 and the MvO2 to approximate changes in cardiac output. Perhaps one of the most challenging aspects of following patients undergoing tailored therapy is the utilization of the MvO2 and its relationship to the overall clinical picture.

Since VO2 is the measured value of oxygen consumption, it is affected by exercise, fever, **infection**, or any systemic process that increases metabolic demand. The other component of the equation is the difference between arterial oxygen content and venous oxygen content prior to delivery to the LV. This difference in oxygen content is the same as the extraction of oxygen by the tissues.

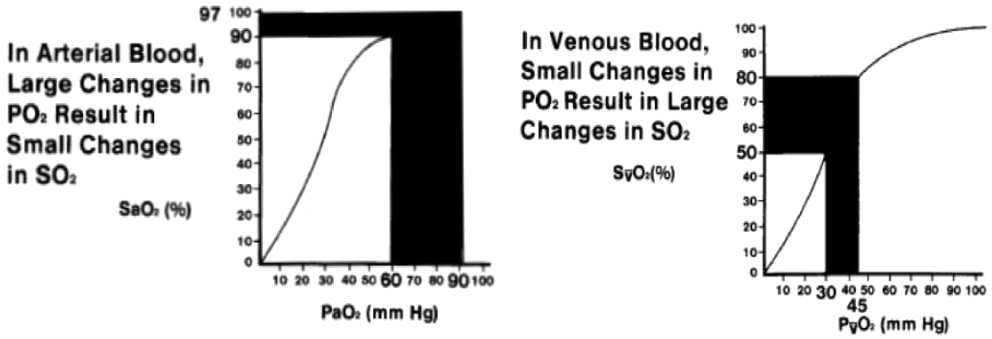

Figure 2. Changes in arterial and venous oxygen saturation with changes in the partial pressure of oxygen.

When cardiac output decreases, flow to the tissues will also decrease, resulting in a decline in oxygen delivery per unit of time. If tissue oxygen remains constant (a major assumption that frequently does not hold true), then tissues extract greater proportions of blood per unit of blood volume, which reduces the oxygen content of venous blood returning to the heart, and MvO2. The ability of tissues to extract more oxygen in the setting of low flow is a compensatory mechanism for reduced cardiac output. Thus, measuring MvO2 to estimate oxygen extraction can serve as a surrogate marker for cardiac output. Changes in MvO2 often signal changes in cardiac output.

Adaptive Measures of Oxygen Extraction in Response to Changes in Cardiac Output

Condition	Oxygen Consumption (ml/min)	Cardiac Output (QT) (L/min)	Oxygen Extraction ($CaO_2 - CvO_2$) (vol%)	(ml/L)
Normal Cardiac Output	250	5	5	(50)
Increased Cardiac Output	250	10	2.5	(25)
Decreased Cardiac Output	250	2.5	10	(100)

Since Cardiac output cannot be measured by the Fick equation for all CICU patients, measuring MvO2, and understanding the meaning of increases or decreases in MvO2 in terms of their

relationship to cardiac output, can help you to answer important questions in the CICU overnight.

Take, for example, a patient who underwent a full right heart cath where MVO2 was 60 and the cardiac index was calculated to be 2.1 using Fick.

Overnight, the patient's MvO2 declines to 45. What do you do? Before calling the heart failure attending to ask if you can increase the dobutamine drip, it is critical that you make sense of the MvO2. Is the patient is having a GI bleed? Does the patient have a fever, or did he just have an argument with his wife? Was he particularly hypoxemic at the time that the MvO2 was drawn? Is the value simply spurious? And how do these variables affect MvO2?

Common Causes of Abnormal MvO2 Values

High SvO_2	↑ Oxygen delivery	↑ FIO_2
		Hyperoxia
	↓ Oxygen demand	Hypothermia
		Anesthesia
		Pharmacologic paralysis
		Sepsis
Low SvO_2	↓ Oxygen delivery	
	↓ Hb	Anemia, hemorrhage
	↓ SaO_2	Hypoxia, suctioning
	↓ CO	Hypovolemia, shock
		Arrhythmias
	↑ Oxygen demand	Hyperthermia, pain
		Shivering, seizures

If the patient's clinical status has not changed since the time that his first Fick cardiac output and index were calculated in the cath lab, then an MvO2 drop from 60 to 45 likely represents decreased tissue perfusion and increased O2 extraction consistent with a decrease in cardiac output. You must then decide which variable (preload, afterload, inotropy) to target to improve the patient's cardiac output. However, variables that the MvO2 frequently do change over time, and these factors may influence tissue extraction without affecting f cardiac output. Common causes of MvO2 alteration are listed above. Moreover, MvO2 is one of many data points that we use in the CICU to assess trends in hemodynamics, and random variation in MvO2 measurements is not uncommon. Thus, it is important to look at the overall trend in MvO2, and to contextualize MvO2 measurements by interpreting them with other markers of tissue perfusion and cardiac output. If you receive an MvO2 measurement that doesn't make sense, or is drastically abnormal, you should repeat it.

A significant increase in MvO2 in a patient who looks critically ill must be investigated. The MVO2 can become highly unreliable during changes in shunting of perfusion, such as in sepsis and/or septic shock. In distributive shock, there is an aberration in arteriolar function and some tissue beds may be receiving insufficient blood flow while other tissue beds may be "clamped off" with no oxygen exchange taking place. Therefore, if oxygen delivery to some tissues is shunted, venous return can achieve high oxygen content despite worsening cardiac function.

Carefully examine the patient for evidence of sepsis and potential sources of infection, evaluate for vasodilation and review the vital signs flow sheet to understand the trend in SVR.

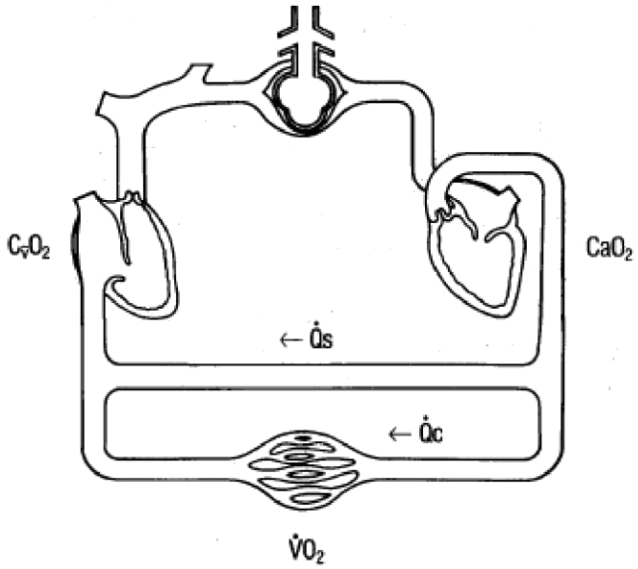

Figure 3. Qs represents shunt of flow from Qc (tissue perfusion) and arterial admixture causing increased venous oxygen content.

Interpreting and making decisions based on MvO2 measurements during tailored therapy can be daunting. To use this data point appropriately, it must be interpreted in the context of the whole patient (not just his/her cardiovascular system) to determine the patient's hemodynamics and what (if any) intervention(s) should be undertaken.

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QUICK REFERENCE GUIDE: HEART FAILURE

Initial Evaluation and Management

- Heart failure is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling and/or ejection of blood
- The initial assessment of any patient with acute decompensated heart failure (ADHF) should include an evaluation for precipitants in order to identify potentially reversible causes (e.g. ischemic heart disease, new or progressive valvular pathology or arrhythmia, addition of medications with negative chronotropic or inotropic properties, primary lung disease with RV dysfunction, etc.)
- If there is evidence of low perfusion as suggested by a narrow pulse pressure, cool extremities, hypotension, reduced urine output (despite appropriate diuretic dosing), and altered mentation, transfer to the CICU for tailored therapy may be needed
- The initial management of pt's transferred to the CICU for ADHF focuses on diuresis with loop diuretics +/- thiazides, reducing afterload, and initiating inodilators if necessary (in addition to investigating/treating the potentially reversible causes above)
- Prior to hospital discharge, all patients should be initiated on guideline directed medical therapy, including ACE/ARB/ARNi, mineralocorticoid receptor antagonist, and beta-blocker, as indicated by NYHA functional status and LVEF

Evidence for Medical Therapies

- Heart failure with reduced ejection fraction (HFrEF) is generally defined as an LVEF <35-40%
- Evidence suggests that in patients with HFrEF, ACEi/ARBs, beta blockers, angiotensin receptor-neprilysin inhibitors (ARNI), and aldosterone antagonists (spironolactone and eplerenone) reduce mortality
- Additionally, hydralazine in combination with isosorbide dinitrate has been shown to reduce mortality in self-identified African American patients with NYHA III-IV HF (e.g. symptoms with less than normal physical activity or at rest) and LVEF < 35% or LVEF < 45% and LVEDD > 65 or > 29 mm/m^2
- Digoxin may reduce readmissions in HFrEF but it does not reduce mortality, though a post-hoc analysis of the DIG trial showed that all-cause mortality was lower than placebo when targeting a serum drug level of 0.5–0.8 ng/ml and higher than placebo at > 1.2 ng/ml
- There is no evidence that calcium channel blockers, anticoagulation, statins, or diuretics reduce mortality in HFrEF
- The following medications should be avoided in HFrEF patients: NSAIDS, COX-2 inhibitors, nodally-selective CCBs (verapamil, diltiazem), thiazolidinediones
- Intravenous iron supplementation (but not oral) may improve symptoms and exercise capacity in HFrEF
- Heart failure with preserved ejection fraction (HFpEF) refers to the clinical syndrome of heart failure in a patient with an EF >50%.
- No medical therapy has been shown to reduce mortality in patients with HFpEF, but ACEi/ARB and aldosterone antagonists appear to reduced HF hospitalizations in this population
- General management strategies in HFpEF patients are aimed at preventing worsening of LV filling pressures, notably: Blood pressure control, ventricular rate control or rhythm control in atrial fibrillation, symptomatic management of pulmonary or right-sided congestion, and coronary revascularization in patients with CHD/ischemia thought to impair diastolic function

Tailored Therapy

- Patients who remain volume overloaded despite appropriate attempts at diuresis and patients with cardiogenic shock may be considered for transfer to the CICU for tailored therapy
- Tailored therapy involves the use of a PA catheter to guide management of therapies targeting preload, contractility, and afterload
- Target parameters will vary from patient to patient but generally, medications are adjusted to target a CI of 2.0-2.2, PCWP 14-18, PAD 16-20, CVP 8-12, MAP >65, SVR <800, and a PVR <3

Physiology of Preload, Afterload, and Contractility

- The management of heart failure patients in the CICU is derived from the Frank-Starling mechanism. Under this mechanism, the heart alters its force of contraction (and therefore stroke volume) in response to changes in venous return (i.e. myocardial stretch or preload) independently of neurohormonal input
- Left ventricular preload is measured in the CICU using either PCWP (or PAD as a surrogate). It may be decreased with diuresis and ultrafiltration (in the CICU, this is generally accomplished via CVVH)
- Left ventricular afterload is most accurately assessed by measurement and calculation of SVR (note: patients in cardiogenic shock may have very low blood pressures but high SVR and therefore, high LV afterload). LV afterload may be reduced using ACEi/ARB, hydralazine, or nitrates
- Contractility is measured via CO using either thermodilution or the Fick equation. Contractility can be increased with agents such as dobutamine, milrinone, epinephrine, or dopamine. CO can also be augmented with mechanical circulatory support

MECHANICAL CIRCULATORY SUPPORT & TRANSPLANT

See Page 105 for Quick Reference Guide

10. Mechanical Circulatory Support Overview

An evolving area of critical care cardiology is the utilization of mechanical circulatory support (MCS): the use of an artificial pump technology to augment native cardiac output. This section is meant to be an introduction to the more commonly used MCS devices one may encounter in the MGH CICU. Although an attending will always be involved in the decision to deploy MCS, residents often guide overnight bedside management of these patients and it is therefore important for us to understand the options, criteria for patient selection, clinical indications, benefits, complications and approaches to device trouble-shooting.

Options for acute MCS:

- Intraaortic balloon pump (IABP)
- Impella (LV: Impella 2.5, Impella CP, Impella 5.0; RV: impella RP)
- Tandem Heart (LV or RV or both)- not currently in use at MGH
- CentriMag or RotaFlow (LV and/or RV)
- ECMO (peripheral or central)

Options for durable MCS:

- Left Ventricular Assist Device (LVAD – e.g. HeartMate III or HeartWare)

Indications for Acute MCS.

MCS can be used in the following clinical scenarios that are all predicated on the need to ensure adequate systemic blood flow that is refractory to medical therapy:

- Refractory end-stage heart failure
- Cardiogenic shock (with or without acute MI)
- Periprocedural support during high-risk procedures such as coronary revascularization, ablation of ventricular arrhythmias, or high-risk percutaneous valve repair or replacement
- Refractory malignant arrhythmias
- Cardiac arrests

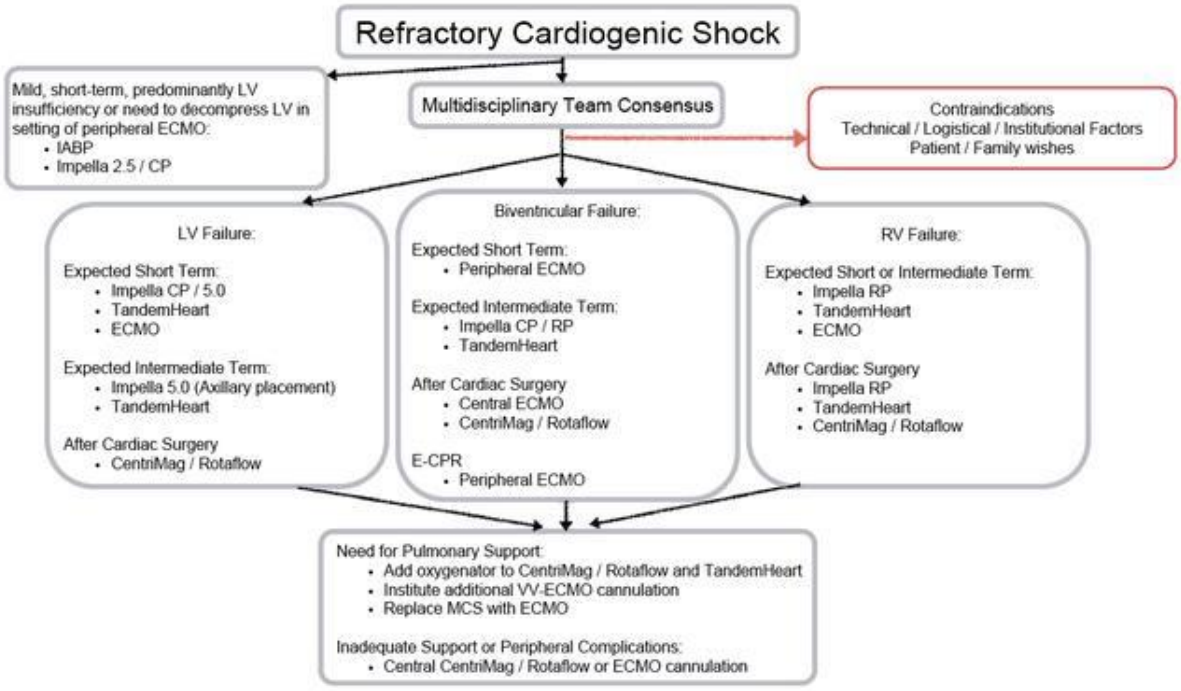
MCS can help to improve end-organ perfusion, decrease filling pressures, LV volume, wall stress and myocardial O2 consumption, and can augment coronary perfusion.[1] When used in the setting of cardiogenic shock, MCS is most effective when the intervention is deployed early, and prompt identification of patients who would benefit is therefore critical. If early intervention is achieved, interruption of the inflammatory cascade and subsequent progression to irreversible end organ damage may occur.[2] Overall, this area of cardiology is still developing with limited clinical trial data; as is often the case in critical care, well designed studies can be difficult to perform. The ultimate question that has yet to be answered is whether improvement in hemodynamics translates to mortality benefit.

Deploying MCS: The Shock Team

The Cardiogenic Shock Team is a resource for the management of acutely decompensating patients with cardiogenic shock. *In general, the shock team should be considered for patients with severe refractory cardiogenic shock with evidence of worsening end-organ perfusion despite escalating doses of inotropes.* After discussion with senior members of the care team (the attending of record must be involved), the current shock team can be paged via 29151. The Heart Center Intensivist will respond, and help assess whether ECMO is required (in conjunction with attendings in heart failure and cardiac surgery); they will also decide whether another MCS option is sensible. For a non-ICU patient, rapid response nursing triage supervisor should also be involved for re-triage and coordinating care.

Device Selection

Once we identify a patient who would benefit from MCS, the team must choose the appropriate device. Device selection can be challenging with considerations for the acuity and severity of the shock and requisite hemodynamic support requirements, univentricular vs. biventrcular support needs, oxygenation requirements and presence of arrhythmia. One potential algorithm to consider is as follows:[3]



Brief Overview of Device Selection (each device discussed in detail thereafter):[3-5]

Device	Max Support Provided	Peripheral or Central Cannulation	BiV support	Device Advantages	Device Disadvantages
IABP	0.5 L/min	Peripheral	LV only	•Bedside insertion possible •Wide familiarity with device •Least cost prohibitive	•Requires stable cardiac rhythm •Short duration of support (days) •Minimal hemodynamic support •No direct RV or pulmonary support •Prohibits patient mobility
Impella	Options: 2.5 L/Min; CP (3-4L/min); 5.0 (5L/min) or RP (4L/min from RV)	Peripheral	LV only	•Ventricular decompression •Allows patient mobilization with axillary approach (surgical cutdown only) •Longer term support (days to weeks)	•No direct RV or pulmonary support •Requires anticoagulation •Placement in cath lab/hybrid OR •Hemolysis common
Tandem Heart	5 L/min	Peripheral	Individual devices for LV and/or RV	•Ventricular decompression •Permissive breaks in anticoagulation •Addition of oxygenator possible •Longer term support (weeks)	•Technical expertise required for trans-septal puncture •Requires anticoagulation •Immobilization of patient
CentriMag /RotaFlow	10 L/min	Central	Individual devices for LV and/or RV	•Ventricular decompression •Allows patient mobilization •Forgiving anticoagulation requirement •Addition of oxygenator possible •Longer term support (weeks/months)	•Central cannulation required •Less familiarity with devices
ECMO	10 L/min	Both	Individual devices for LV and/or RV	•Bedside and urgent insertion possible •Short term support (days/weeks)	•Higher anticoagulation requirement •Immobilization unless central cannulation •Overloads LV and may require venting •Bedside perfusionist required

Abbreviations: IABP = Intraaortic balloon pump; ECMO = Extracorporeal Membrane Oxygenation; RV = right ventricular; Bi-V = biventricular

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11. Intra-Aortic Balloon Pump (IABP)

Intra-aortic balloon pumps (IABPs) are a commonly used method of circulatory assist at MGH. The device is an intravascular 30–50cc balloon positioned in the aorta. At MGH, it is usually placed in the catheterization lab via percutaneous femoral access. The device can also be placed using an axillary approach via a surgical cut-down, although this technique is rarely employed. The balloon is connected to a console that synchronizes inflation and deflation to the cardiac cycle using either surface EKG or aortic pressure. The balloon inflates with helium during diastole and deflates during systole.

Unlike a ventricular assist device (VAD) or impella, the IABP does not generate cardiac output; rather it improves left ventricular unloading by the following two hemodynamic effects:

Increased coronary artery blood flow during diastole: during diastole, the IABP inflates, which increases the pressure in the proximal aorta. This higher pressure (called the "augmented diastolic" pressure) increases coronary artery perfusion, and therefore increases oxygen supply to the myocardium.

Decreased left ventricular afterload during systole: during systole, the IABP deflates, decreasing systolic pressure in the aorta. The drop in afterload decreases wall tension in the LV and reduces myocardial oxygen demand.

Expected hemodynamic changes in a patient with IABP:

- Decrease in systolic blood pressure
- Increase in diastolic blood pressure (on the nursing flow-sheet, the higher number in the BP log is actually this augmented diastolic pressure)
- Decrease in pulmonary capillary wedge pressure
- Increase in cardiac output

It is important to appreciate that IABPs have not been shown to increase flow distal to a critical coronary stenosis before revascularization, but it does so after. This explains the finding that patients in whom IABP is placed for cardiogenic shock, but who do not undergo revascularization or reperfusion therapy, have a mortality rate approaching 85%. The RCT (IABP-SHOCK II) did not demonstrate a 30-day mortality benefit from IABPs in patients with acute MI and cardiogenic shock.

Indications
Based on the updated ACC/AHA 2013 STEMI guidelines, there are no class I indications for IABP placement.[2]

Class IIa indication

- Cardiogenic shock and hemodynamic instability after STEMI refractory to pharmacologic management

Other indications

- Mechanical complications of MI: VSD, papillary muscle rupture leading to severe MR
- Refractory ischemia: intractable angina with impaired LV function or large territory
- Refractory polymorphic ventricular tachycardia after AM

Prophylactic placement in certain situations

- Prior to high-risk percutaneous coronary intervention (e.g. in patients with a low left ventricular ejection fraction) → augments perfusion
- Prior to high-risk coronary artery bypass grafting (CABG), such as with a left main coronary artery stenosis or diffuse coronary disease, low ejection fraction, or a redo CABG. This indication is controversial.
- For inability to wean from cardiopulmonary bypass after CABG
- Following failed thrombolysis for AMI

Contraindications

- Severe aortic regurgitation
- Severe bilateral peripheral arterial disease (including patients who have undergone revascularization)
- Aortic dissection, aneurysm or intramural hematoma
- Sepsis
- Severe coagulopathy

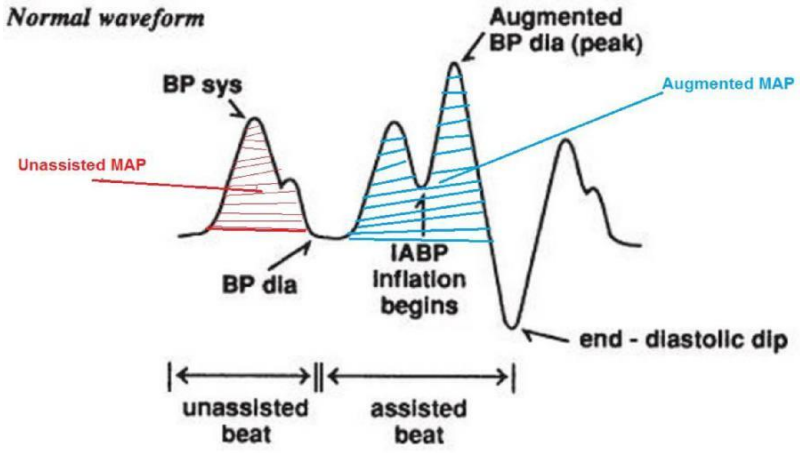
IABP Daily Assessment

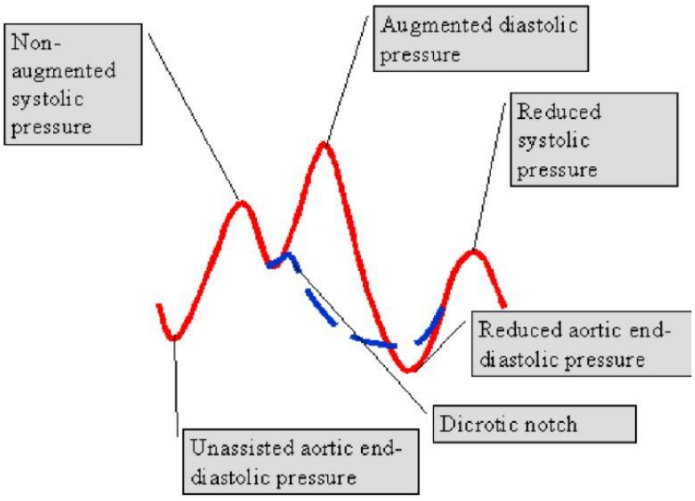
- Placement of IABP must be assessed daily by chest radiograph. The tip of the catheter must be 1–4 cm below the aortic arch. This is to ensure that it does not occlude branches of the aortic arch proximally or the splanchnic or renal arteries distally. If the IABP appears to have migrated, consider repeating the X-Ray to ensure patient is appropriately positioned.
- The insertion site must be checked daily for hematoma or infection; a full pulse exam must be conducted; the distal lower extremities must be examined for evidence of ischemia. The patient cannot sit up or bend legs with IABP in place. This can be a challenge for the awake patient.
- The IABP waveforms should be assessed at least daily on rounds and during hemodynamic or ECG changes (see below for more details).

Evaluation of IABP Waveforms

Problems related to the timing of inflation and deflation can be detected by analyzing the waveform. Currently available devices have the capability to do automated waveform analysis and auto correct. Inflation starts at the aortic valve closure (dicrotic notch). Deflation starts before the end of diastole. If the balloon inflates before the aortic valve closes or deflates after the left ventricle begins to contract (i.e. if it is inflated for any portion of left ventricular systole) a dangerous situation exists. Analysis of the waveforms is undertaken with the balloon inflation set to 1:2 so that assisted waveforms can be compared to unassisted (native) waveforms. There should be a deep, symmetric “V” at the start of inflation; if this is lost the balloon may be inflating too early, thus impeding ventricular emptying. Similarly, there should be a second deep, symmetric “V” at the end of inflation; if this is delayed or blunted the start of left ventricular ejection may be impeded. Both of these situations require immediate attention. The other problems in timing decrease the utility of the IABP but are not dangerous; these include late inflation (resulting in a “W” when the balloon inflates at the start of diastole) and early deflation (causing the normally sharp and symmetric “V” at the start of systole to appear more like a “U”).

Normal Waveforms

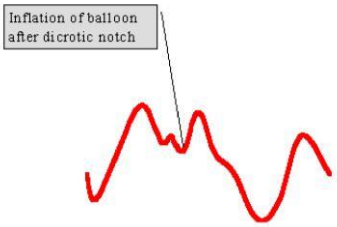




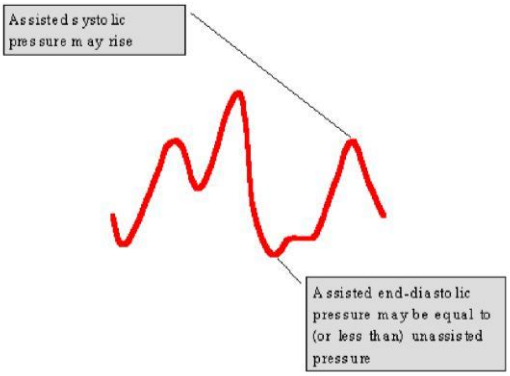
Dotted line represents normal unassisted waveform as seen above (balloon must be set to 1:2 in order to check for normal waveforms).

Solid line represents actual pressure tracing with an initial systolic waveform followed by a pump generated waveform (making an early “v” appearance) and then the systolic waveform seen following a balloon waveform with reduced systolic pressure

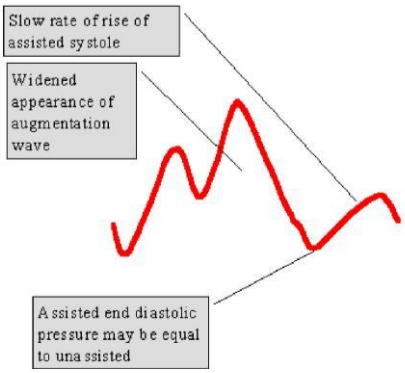
Early Inflation: “Loss of early deep V.” This may result in premature closure of aortic valve, incomplete LV emptying, aortic insufficiency, increase in LVEDV and LVEDP, increased afterload, and increased myocardial oxygen demand. This requires immediate attention.



Late Inflation: “V becomes a W.” This results in decreased augmented coronary perfusion, decreased O2 supply to coronaries and reduced overall benefit of the IABP.



Early Deflation: “Second ‘V’ waveform looks like a deep-broadened ‘U.”. This occurs because when the balloon deflates prematurely, the aortic arch “fills up” and aortic pressure increases prior to the isovolumetric contraction, causing increased afterload and increased myocardial demand. Notice the sharp drop following diastolic augmentation. Diastolic augmentation also becomes sub-optimal. This results in sub-optimal coronary perfusion, potential for retrograde coronary and carotid blood flow, suboptimal afterload reduction and increased myocardial oxygen demand.



Late Deflation: “Loss of the deep even-sided second ‘V’ waveform. ” In this case, the balloon remains partially inflated during isovolumetric contraction.

Thus the LV is contracting AGAINST an inflated balloon leading to significantly increased afterload. This requires immediate attention.

Prophylaxis

Antibiotics: cefazolin x 1gm IV q8H or vancomycin 1gm IV q12H (PCN allergy or known MRSA colonization) is the practice at MGH for most patients while IABP in place. It should be noted that patients in whom the IABP is being used for prolonged use (i.e. awaiting transplant with IABP in for weeks) continuous antibiotics is not used.

Therapeutic anticoagulation: unfractionated heparin with a goal PTT 60–85. This is particularly important if the IABP is set to any inflation ratio other than 1:1 (balloon assisted beat: native beat) as increased stasis of the balloon increases the risk of thromboembolism.

Weaning

The standard MGH weaning protocol involves decreasing the inflation ratio to 1:2 (1 balloon assisted beat for every 2 total heartbeats), then to 1:4, and finally 1:8. The rapidity of the wean is per the attending and/or fellows recommendations. During this time the patient is monitored for hemodynamic instability and for signs or symptoms of ischemia.

Weaning Protocol

- Heparin should be off for about 4 hours before pulling balloon (verify PTT)
- Must be at 1:1 when off heparin to reduce thromboembolism risk
- Check symptoms/exam, EKG and PA hemodynamics with each IABP setting change for evidence of ischemia
- **Fast wean** (UA, MI or s/p PCI and EF > 40%): 1:2 x 1h → 1:4 x 1h → 1:8 x 1 h → 1:1 x 4h → OUT
- **Medium wean** (UA, MI or s/p PCI and EF < 40%): 1:2 x 2h → 1:4 x 2h → 1:8 x 2h → 1:1 x 4 h → OUT
- **Slow wean** (cardiogenic shock): 1:2 x 4h → 1:4 x 4h →1:8 x 4h → 1:1 O/N (rest) → in am 1:2 x 1h→ 1:4 x 1h→ 1:8 x 1h → 1:1 x 4h →OUT

Contact fellow or balloon tech (6-3693) at least one hour before anticipating ultimate IABP pull.

Complications of IABP

- Mild anemia and thrombocytopenia
- Injury related to the site of insertion
- Limb ischemia → requires device removal
- Vascular injury: dissection or pseudoaneurysm
- CVA
- Hemorrhage
- Balloon rupture (rare) → suspect if blood is seen in the helium line. The device can detect a rupture, and will attempt to aspirate helium from the aorta to prevent gas embolism.

Any suspected complication should prompt an immediate call to the fellow/attending and to the balloon technician.

The incidence of vascular complications ranges from 12% to 40%. Most patients in whom limb ischemia occurs after placement of IABP have resolution of ischemia after IABP removal and do not require intervention (such as thrombectomy, vascular repair, fasciotomy, or amputation). The risk of limb ischemia is greater in patients with a post-insertion ankle-brachial index of < 0.8. Use of smaller catheters also reduces risk of vascular complications.

Note we have in MGH a protocol for balloon rupture. If this occurs, immediately contact the HCICU intensivist and vascular surgery.

References:

1. Thiele H et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet.* 2013;382(9905):1638-45
2. O'Gara et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013; 61(4):e78-14

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12. Impella

The Impella is a percutaneous temporary ventricular support device (Figure 1). There are three approved versions for percutaneous left ventricular support, Impella 2.5, Impella CP, and Impella 5.0, as well as one for right ventricular support, Impella RP. All of the devices act as microaxial flow pumps that work on the principle of the Archimedes screw. For the purposes of this chapter, Impella use will be in default reference to LV support devices (2.5, CP, 5.0), unless otherwise indicated.

Typically, the device is placed via the femoral artery or axillary arteries (the latter via a surgical cut-down) and advanced in a retrograde fashion such that the Impella inflow cannula crosses the aortic valve (Figure 2). The blood inflow cage sits within the left ventricle, while the outflow cage rests within the ascending aorta. The pump revolves at high speed and draws blood out of the LV into the aorta with continuous flow. Rotatory speed is in set ''P'' levels, with higher values indicating higher support. With increasing speeds and unloading of the LV, the Impella has the ability to improve systemic blood pressure (improves MAP but may reduce systolic BP), reduce LV wall stress, and improve coronary flow.

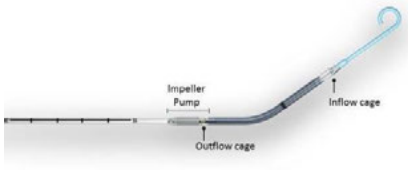

Figure 1. Impella 2.5

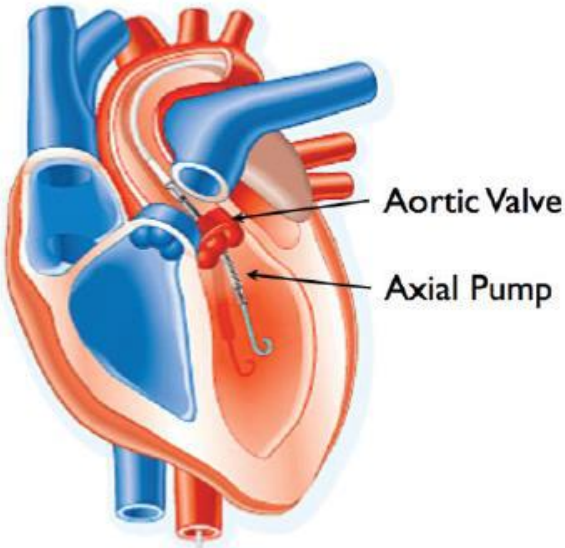

Figure 2. Impella 2.5 (Cove et al); Video at http://www.abiomed.com/products/impella-2-5

The Impella is FDA-approved for the treatment of cardiogenic shock, specifically occurring within 48 hours following acute myocardial infarction or open heart surgery "as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures with or without an intra-aortic balloon pump." While intended for short-term use (between 4-6 days), it is often left in beyond this time. As it volumetrically unloads the LV, the Impella may also facilitate myocardial recovery, be used as an adjunct to ECMO to "vent" the LV or act as a temporary bridge to durable LVAD or cardiac transplantation if myocardial recovery is not anticipated.

Daily checklist for Impella devices

- ❒ Daily labs:
  - ❒ Assess for hemolysis:
    - CBC, LDH, total and direct bilirubin
  - ❒ Assess adequacy of anticoagulation:
    - ACT: goal 160-180
    - PTT: goal 70-100
- ❒ Daily CXR for device position
- ❒ On rounds –
  - ❒ Run telemetry for arrhythmias
  - ❒ Look at speed (P setting [2-9] and RPM); calculate CO [using Fick or TD – the true CO will be a function of native LV function and Impella flow]
  - ❒ Check history for alarms
  - ❒ Check catheter mark – is it at same position?

- ❒ Look at placement and pulsatility signals (below)
- ❒ Neurovascular exam of limb (high risk of limb ischemia due to catheter size and risk of thromboembolism; **check PVRs**)

Available Impella Devices

Impella type	Indications	Access site	Size	Max. flow (L/min)	Notes
Impella 2.5	• <48h post AMI or open cardiac surgery •Hemodynamic support in refractory cardiogenic shock (incl. IABP)	Percutaneous via femoral artery	13 Fr	2.5	**PROTECT II:** Impella 2.5 vs IABP: no difference in mortality at 30d, trend towards superiority at 90d[1]
Impella CP	As above	Percutaneous via femoral artery	14 Fr	3-4	**IMPRESS:** CP vs. IABP: No difference in 30d mortality[2]
Impella 5.0	As above	Surgical placement with graft via femoral or axillary artery	22 Fr	5	**RECOVER I:** Impella 5.0 for post cardiotomy shock – 94% 30d survival[3]
Impella RP	• HD support for max 2 weeks in pts w BSA >1.5m2 • Acute RV failure • RV decomp post LVAD, MI, HTx	Femoral vein → pulmonary artery	22 Fr	3-4	**RECOVER RIGHT:** Impella RP for RV failure after LVAD placement; 73% 30d survival[4]

Contraindications

Left-sided (2.5, CP, 5.0) Impella –

1. LV or LA thrombus
2. Mechanical aortic valve
3. ≥ Moderate AS or AI
4. ASD and/or VSD
5. Significant RV dysfunction
6. Cardiac tamponade
7. Severe PAD *(relative CI)*

Right-sided (RP) Impella –

1. PA wall pathology precluding correct placement or positioning
2. Mechanical valve replacements
3. Severe valvular dysfunction
4. Mural thrombus in vena cava, RA/RV
5. Presence of IVC filter unless documented clear access that would allow passage of 22 Fr catheter

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Complications

- Hemolysis:
  - Less common with Impella 5.0 – larger inflow
  - Requires regular monitoring of labs and urine (as above)
  - *How to avoid:*
    - Optimal impella positioning
    - Use lowest RPM (speed) required [NB: P9 setting rarely used]
- Thromboembolism
- Injury to aortic or mitral valve
- Device migration
- Suction events
  - Due to device migration, improper positioning or decreased preload (eg RV dysfunction)
- Ventricular arrhythmias
  - Due to device-myocardial contact, decreased preload or unmasking of RV dysfunction
- Distal limb ischemia
  - Risk similar across left-sided Impella devices

Alarms and what to do with them:

- *"Pump position wrong"*
  - Get TTE to assess device placement
- *"Suction likely"*:
  - Three main differentials: 1) Low LV preload, 2) malposition, 3) thrombus
  - *LV preload*:
    - Assess volume status → if low, give IVF if down
    - Assess RV (Is the RV failing? PAP, PVR, SvO2) → if down, titrate RV support
  - *Malposition:*
    - Assess for possibility of migration → **always** on differential – obtain TTE
  - *Thrombus*:
    - If none of above, consider thrombus in device
- *"Impella flow reduced"*
  - See "Suction likely"
- "*Pump outlet blocked"*
  - Device is too deep and obstructing AoV
    - Turn down speed
    - Get TTE to see if needs to be withdrawn slightly
- *"Low purge flow"*
  - Check for kinked tubing
  - Check for leaks
  - If none of above, consider reducing dextrose concentration in purge solution to reduce viscosity (20% → 5%)

Emergencies:

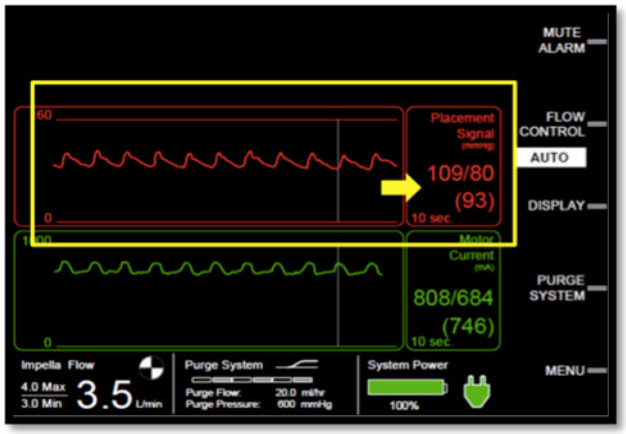
- *Ventricular tachycardia*
  - Assess for intrinsic reversible causes:
    - Electrolytes, ischemia, documented patient history
  - If none –
    - Consider device-driven: device-myocardial contact
    - Consider RV failure as cause, unmasked by LV support from Impella
    - Perform the usual treatments: amiodarone, lidocaine, ventilation/sedation, EP consult
- *Cardiac arrest*

- *i.e. no flow or flat arterial line tracing on pVAD monitor*
- **If a patient with an Impella *in situ* arrests –**
  - Change power setting to P2 during chest compressions
  - ACLS algorithm as usual otherwise
  - After ROSC, return flow to previous level (using prior P level and RPMs)
  - Assess placement signal carefully to assess for device migration

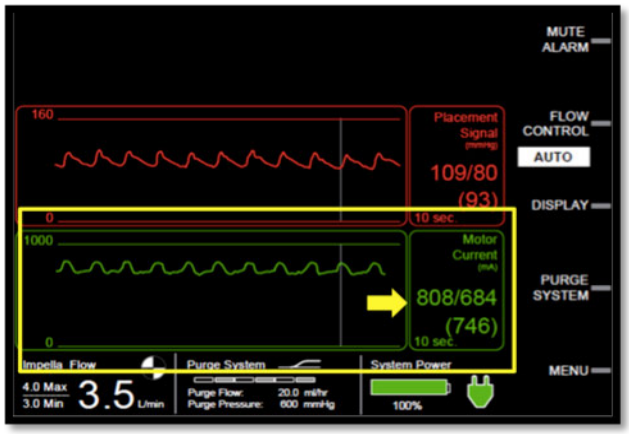
Placement Signals *(Section adapted from Dr Kaavya Parurchi MD, with thanks. Images used from Abiomed instruction manual)*

Impella 2.5 and CP

Correct signals:

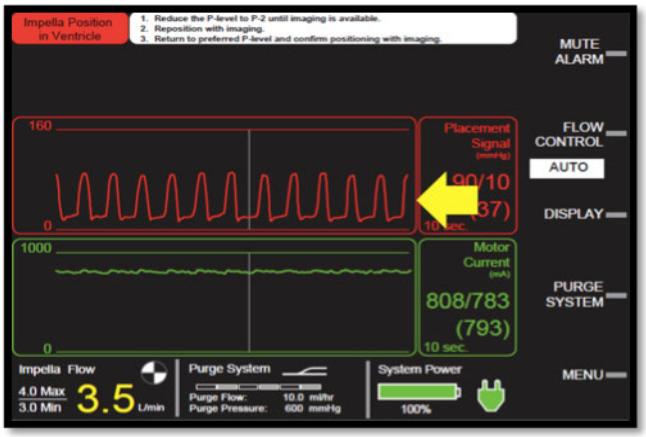


Look at placement signal: waveform should be aortic

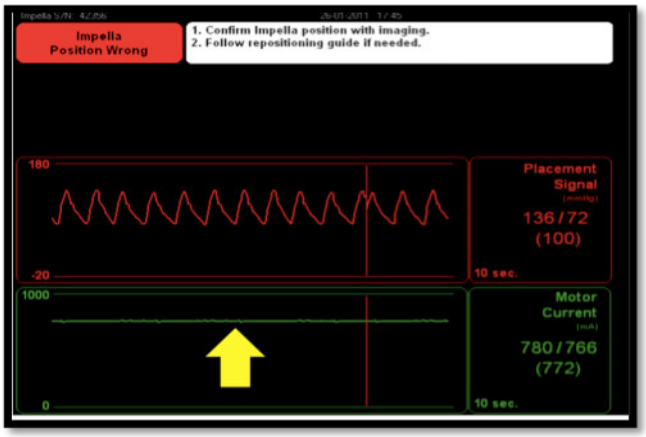


Look at motor current signal: waveform should be pulsatile

Incorrect signals:

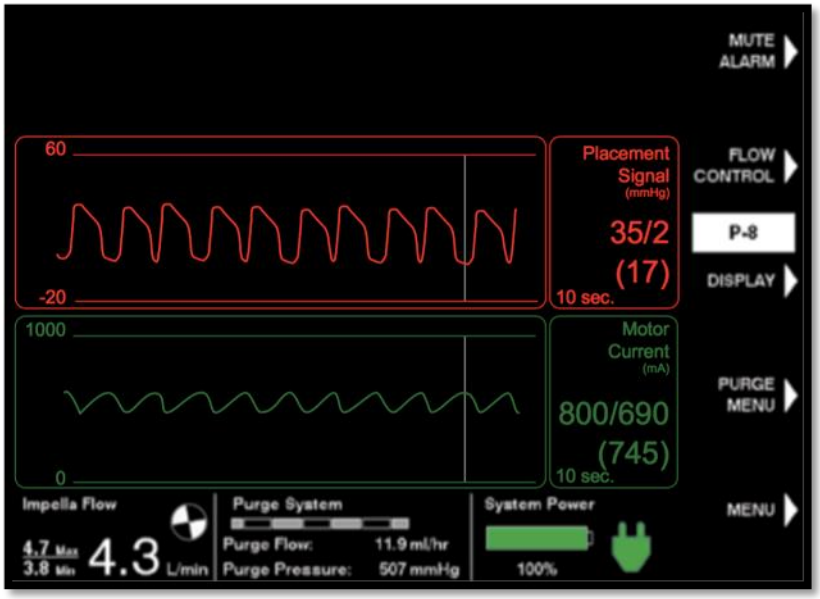


Placement signal: ventricular
Motor current: waveform flat
Fix: withdraw by interventional fellow or HCICU intensivist



Placement signal: aortic
Motor current: waveform flat
Fix: advance under fluoro/TTE guidance by interventional fellow or HCICU intensivist

Impella 5.0



Correct Placement

Look at placement signal:

- Waveform is neither aortic nor ventricular – it is the differential between the two
- This is different to the Impella 2.5 and CP
- Numerical measure has no clinical significance

Look at motor current signal:

- Does not change across devices
- Pulsatile, reflecting native heart function

Incorrect Placement

Look at placement signal:

- Flat - pressures are same inside and outside catheter (fully in aorta or fully in ventricle) throughout cardiac cycle
- Impella needs adjustment with imaging guidance

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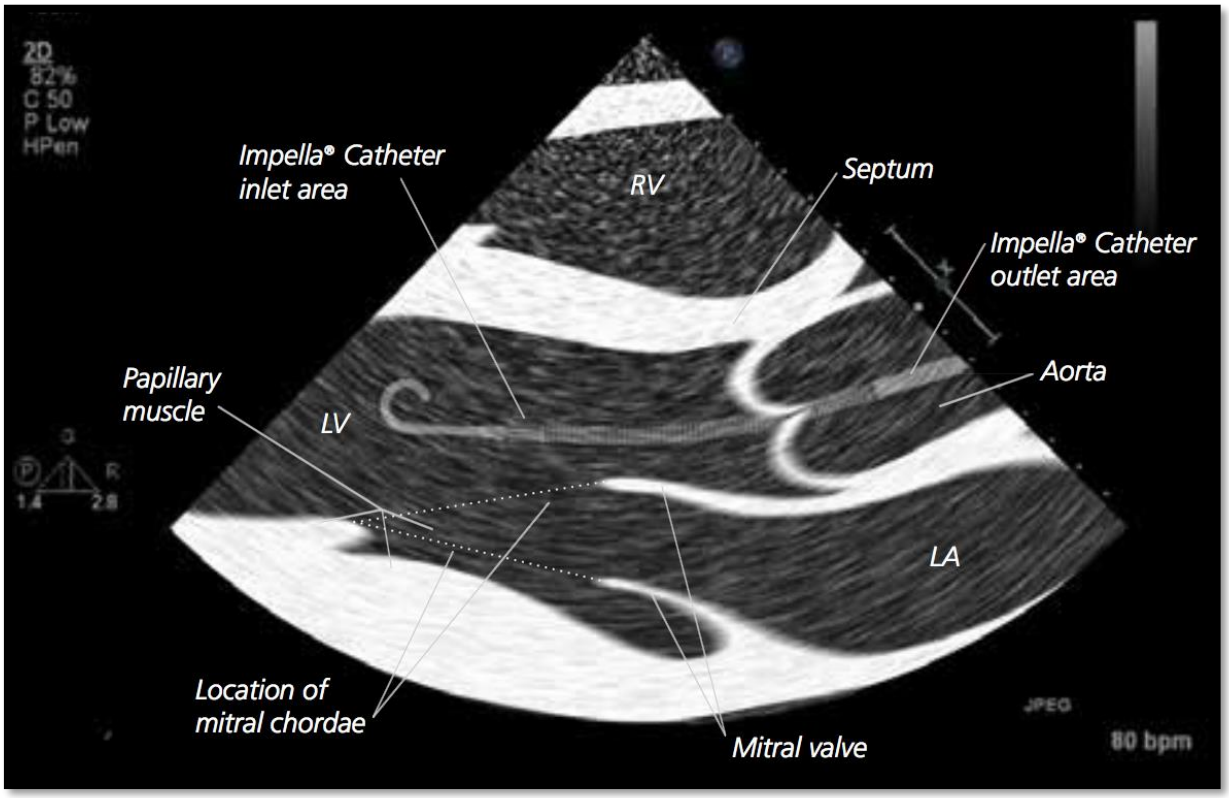
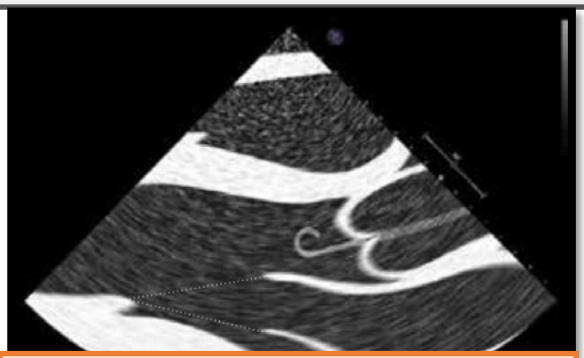
Impella Placement: Echo



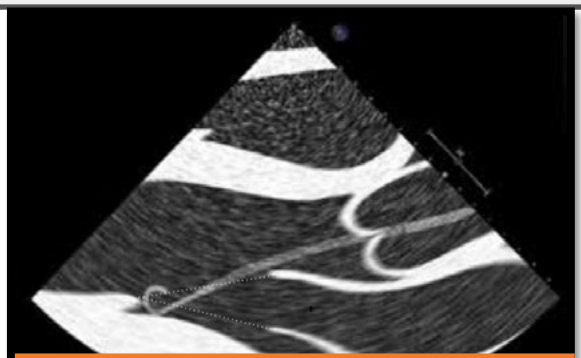
Correct placement on TTE:

- Distance from inlet (inflow) to aortic valve should be 3.5-4.0 cm
- Note measurement is from the inflow, NOT the pigtail. Thus be careful unless you have experience with ultrasound and Impella.
- Outlet area is well above the aortic valve
- Catheter angled toward the left ventricular apex (away from myocardium and mitral valve)



Incorrect:

- Inlet is in aorta/near AoV
- Pigtail too close to mitral valve



Incorrect:

- Pigtail in papillary muscle
- Inlet more than 4 cm below AoV
- Outlet too close to AoV

References:

1. O'Neill WW, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation.* 2012. 2;126: 1717–27.
2. Ouweneel et al. Impella CP Versus Intra-Aortic Balloon Pump in Acute Myocardial Infarction Complicated by Cardiogenic Shock: The IMPRESS trial. *J Am Coll Cardiol.* 2016: 23127.
3. Griffith BP et al. The RECOVER I: a multicenter prospective study of Impella 5.0/LD for postcardiotomy circulatory support. *J Thorac Cardiovasc Surg. 2013.* 145(2): 548-554.
4. Anderson MB et al. Benefits of a Novel Percutaneous Ventricular Assist Device for Right Heart Failure: The Prospective RECOVER RIGHT Study of the Impella RP Device. *J Heart Lung Transplant.* 2015;34(12):1549-560.

13. Durable Ventricular Assist Devices

Implanted ventricular assist devices, or durable VADs, are devices which support the function of one or both ventricles in the failing heart. These devices contrast with the previously discussed temporary and percutaneous mechanical circulatory devices. Durable VADs typically support the left ventricle (LVAD), and much less commonly the right ventricle (RVAD) or both ventricles (BiVAD).

LVADs pump blood from the left ventricle to the ascending aorta, while RVADs pump blood from the right ventricle to the pulmonary artery. All generations of LVADs connect the apex of the left ventricle to the ascending aorta and are connected to an external power source and system controller by a percutaneous lead.[1]

At MGH, the most common devices used are the Heartmate 3 and the Heartware HVAD, which are placed by cardiac surgeons and managed by the heart failure service. It is important however to be aware of the several generations of VADs, discussed below:

> **First Generation:** Perform via a pulsatile system, providing pulse pressure. These devices were less durable and have more complication rates then second generation devices. Examples include: Heart Mate I, Thoratec PVAD, and Novacor. None of these devices are currently being used at MGH.
>
> **Second Generation:** Rely on a rotary pump with helical blades powered by an electrical motor to provide continuous flow from the LV apex to the ascending aorta. There are no inflow or outflow valves, and the only moving part is the blade. Linear flow is encouraged by pieces called flow straighteners and diffuser blades reduce turbulence, driving blood forward. These devices are smaller, lighter, more durable and associated with improved survival, quality of life and less frequency of adverse side effects than their pulsatile flow predecessors.[1] Examples of second generation VADs include: **Heartmate II** (used at MGH), Jarvik 2000, Berlin Heart INCOR, Micromed DeBakey.
>
> **Third Generation:** Third-generation LVADs have more efficient electronics and are designed for longer duration of use. They use continuous flow pumps (centrifugal flow), but in contrast with second-generation devices, the internal rotor uses magnetic levitation, which eliminates contact with bearings and the resulting wear. Examples include **Heartware HVAD**, **Heartmate 3**, and DuraHeart. The Heartware HVAD is FDA approved for bridge to transplant (BTT) and destination therapy (DT). The DuraHeart is only available in in the US through clinical trials. The **Heartmate 3** was approved for BTT in 2017 and as a destination therapy in 2018.

Of note, MOMENTUM 3 (2016) trial data demonstrated that the Heartmate 3 (a fully magnetically levitated continuous centrifugal flow pump) was both non-inferior and superior to the Heartmate II (a mechanical-bearing axial continuous flow pump) in terms of the primary study outcome, which was a composite of survival free of disabling stroke or survival free of reoperation to replace or remove the device at 6 months after implantation. The Heartmate 3 centrifugal flow pump had significantly lower rates of pump malfunction, which was the main driver in differences in outcomes. Significantly fewer pump thrombosis events occurred with the centrifugal flow pump.[2]

Additionally, there is a BiVAD called The SynCardia temporary Total Artificial Heart (TAH) that is FDA approved, but not used at MGH.

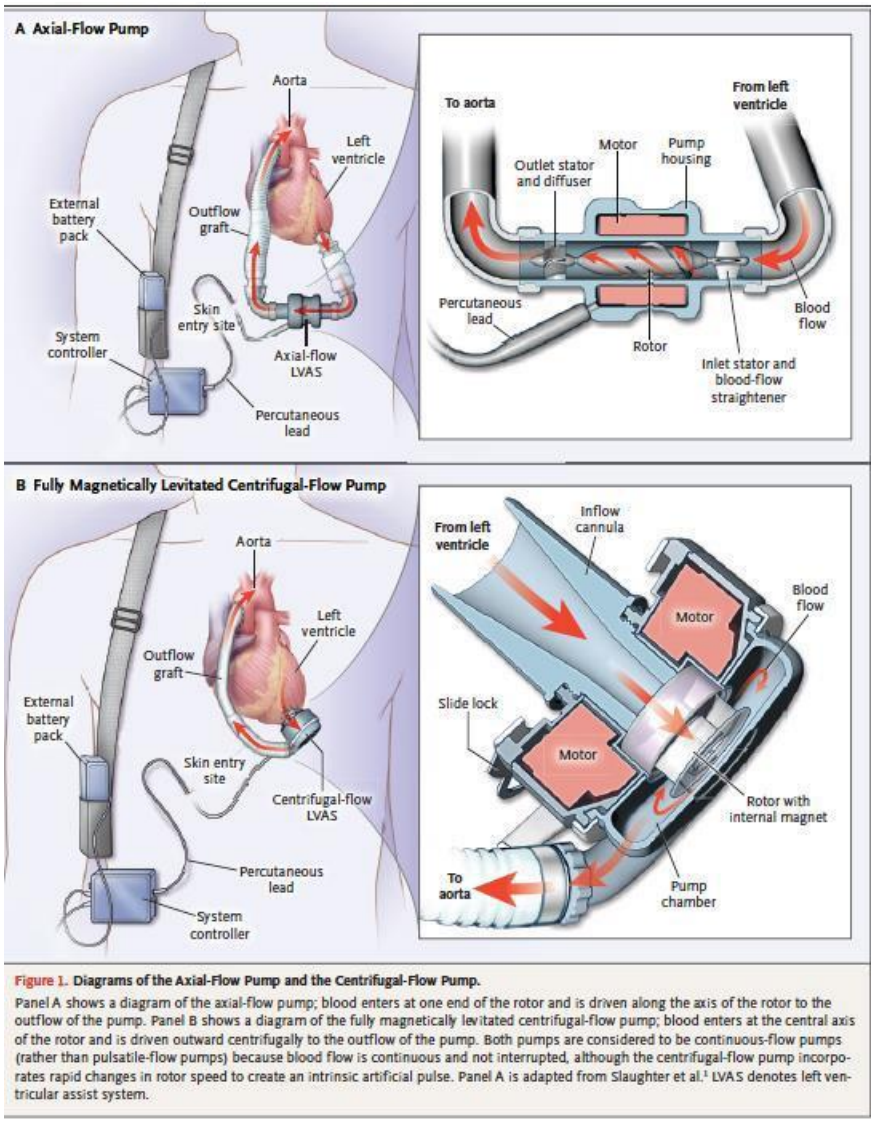


Figure 1. Diagrams of the Axial-Flow Pump and the Centrifugal-Flow Pump.

Panel A shows a diagram of the axial-flow pump; blood enters at one end of the rotor and is driven along the axis of the rotor to the outflow of the pump. Panel B shows a diagram of the fully magnetically levitated centrifugal-flow pump; blood enters at the central axis of the rotor and is driven outward centrifugally to the outflow of the pump. Both pumps are considered to be continuous-flow pumps (rather than pulsatile-flow pumps) because blood flow is continuous and not interrupted, although the centrifugal-flow pump incorporates rapid changes in rotor speed to create an intrinsic artificial pulse. Panel A is adapted from Slaughter et al.[1] LVAS denotes left ventricular assist system.

Patient Selection: Who Gets a VAD?

VADs are approved for two main indications:

(1) Bridge to transplant (BTT; the VAD will remain *in situ* until transplant, then it is explanted)

(2) Destination therapy (DT; the VAD will remain *in situ* indefinitely)

Other uses one may see include:

(3) Bridge to decision (BTD; a decision on transplant candidacy unable to be made at the time of VAD placement, but the patient cannot survive without durable MCS).

(4) Bridge to recovery (BTR: anticipated heart recovery with eventual VAD explant)

Patients are considered for a **bridge to transplant (BTT)** when they have advanced heart failure and deteriorating clinical status on maximal medical therapy, require durable mechanical circulatory support (MCS), and are appropriate transplant candidates. In this

setting, LVADs have been shown to prolong survival and improve secondary end organ dysfunction prior to transplant, which improved post-surgical outcomes. Due to organ shortages and long wait times for transplant, approximately 43% of all listed heart transplant recipients receive durable MCS prior to transplant. It is ideal if patients are referred for LVAD placement prior to onset of severe end-organ dysfunction (e.g. renal failure) due to lower perioperative risk. A **bridge to decision (BTD)** strategy exists for patients who require durable MCS but in whom a temporary contraindication to transplant exists (e.g. substance use) or additional data is needed. These patients may be reconsidered by a transplant committee at a later time for full listing.

For patients with end-stage heart failure not deemed to be transplant candidates, destination VADs (termed, **"destination therapy", or DT**) have been shown to improve quality of life and survival, as shown in the REMATCH trial, which compared first generation devices to medical therapy alone. Second generation devices improved upon these results, showing more than triple the one-year survival and almost twice the rate of survival at 2 years than first generation devices, as well as decreased adverse events and rehospitalizations[1,3]. The 3rd generation VAD Heartware HVAD has also been shown to have >86% survival with significantly improved quality of life measures at 12 months.[3,4]

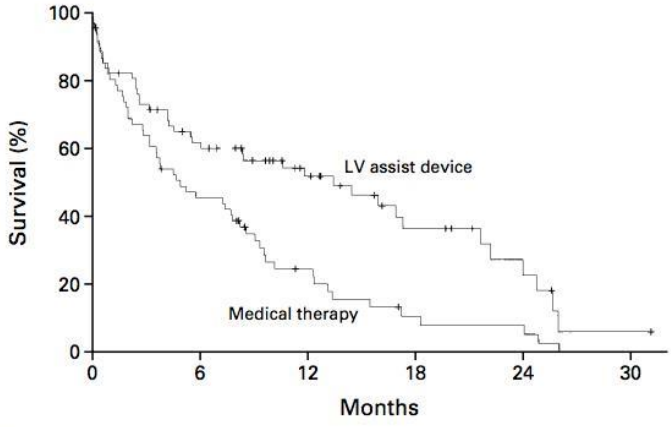


Figure 2. Kaplan–Meier Analysis of Survival in the Group That Received Left Ventricular (LV) Assist Devices and the Group That Received Optimal Medical Therapy.
Crosses depict censored patients. Enrollment in the trial was terminated after 92 patients had died; 95 deaths had occurred by the time of the final analysis.

There is an emerging body of evidence suggesting that "resting" the heart with VADs in combination with maximally tolerated medical therapy (such as ACE inhibitors, beta blockers and mineralocorticoid receptor antagonists) allows for the recovery of myocardium, improved hemodynamics[5], and can lead to eventual explanation of the device. This strategy has been studied in patients with dilated cardiomyopathy (such as acute infectious myocarditis) and has been sometimes called "bridge to recovery".[6]

Important considerations to take into account when assessing candidacy for a VAD placement include: age, severity of heart failure, poor baseline RV function or risk for developing right heart failure, risks of long term anticoagulation, and other severe comorbidities.

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Management:
VADs are carefully monitored in the outpatient setting by heart failure specialists. The principles of monitoring VADs are a physical exam, labs (including measures of hemolysis, INR), electrocardiogram, echocardiography, and device interrogation.

A. Physical exam: Conventional BP monitoring for current generation devices may be unreliable as these patients typically lack palpable pulses due to lower pulse pressures. Doppler ultrasound and brachial sphygmomanometer are generally used, aiming for mean arterial pressures of 65-80 mmHG. ***Doppler measurements of MAP >90 mmHG require immediate intervention***.

B. ECGs can be useful to evaluate for arrhythmias, as ventricular arrhythmias can be subclinical, result in new-onset RV failure, or present with nonspecific symptoms such as shortness of breath, fatigue, and malaise.

C. Echocardiogram is useful in assessing VAD position relative to the interventricular septum as well as aortic valve opening as a measure of native cardiac output. Special "ramp studies," are performed under echocardiographic guidance in the days after initial placement to determine the optimal VAD speed based on septal position, aortic valve opening, and cardiac output. Additional measures include assessment of RV function, degree of aortic regurgitation, and thrombus formation. Echo should be obtained if there are unexplained symptoms of fatigue, device alarms, defibrillator discharges, dizziness, or signs of right heart failure.

D. Mechanical function of the device is assessed by interrogating the device controller. Variables assessed include pump speed, flow estimates, power, and pulsatility index. Numerical ranges of these variables may be device specific. For the HM3 (third generation device):

- **Flow estimates** range from 3-10 liters/minute.
- **Pump speed** is a fixed, numerical value in rotations per minute (rpm) set by the clinician during a ramp study. This is the value that we adjust that modifies device-assisted cardiac output. Flow estimates (L/min) that the device reports are estimate calculations, not measured, and should be correlated with standard measurements of CO/CI (ie Fick/TD). The speed should be set to allow adequate filling of the LV without the development of suction from underfilling. The interventricular septum should be midline and the aortic valve should open occasionally. If the pump speed is too high, suction induced arrhythmias may arise[6]. During a suction event, the device speed drops to the "low speed limit," and then ramps up to the fixed speed unless another pulsatility index (PI) event (see below) is detected. If another PI event is detected, the device drops to the "low speed limit" again and then ramps back up. This cycle repeats as long as PI events are detected.
- **Power** is a direct measurement of pump motor voltage and current. Changes in pump speed, flow, or physiological demand (e.g. afterload) affect power. Note that increases in power without changes in volume status, speed or systemic afterload could indicate development of pump thrombosis. ***Abrupt changes in power should be evaluated***.
- **Pulsatility index** (PI) is a dimensionless measure that represents intrinsic cardiac pulsatility: when the LV contracts, the increased ventricular pressure causes an increase in pump flow during cardiac systole; the magnitude of these flow pulses are measured and averaged to produce a pulsatility index. PI values typically range from 1 to 10. Higher values indicate more ventricular filling and higher pulsatility (ie, the pump is providing less support to the LV). Lower values indicate less LV filling and lower

pulsatility (ie, the pump is providing greater support and further unloading of the LV). Under otherwise stable conditions, a significant drop in PI value may indicate a decrease in ventricular filling or circulating blood volume.

Given the risk of thrombus formation with continuous flow devices, VADs mandate anticoagulation. After surgical implantation, patients are usually anticoagulated with unfractionated heparin as a bridge to definitive therapy with warfarin and aspirin. Further medical therapy includes standard heart failure medications, including beta-blockers, ACE/ARB, diuretics and aldosterone antagonists. MAP goals are **imperative** for device function, prevention of thrombus formation, and reduction of stroke risk.

Complications: Patients with VADs must be monitored for a myriad of potential complications. These complications are discussed below but are generally grouped into categories. Aside from structural complications that result in device failure, these extend to include hematologic, hemodynamic, and infectious complications that ultimately lead to sequelae such as acquired VWF deficiency, pump thrombosis, hemolysis, RV failure, aortic regurgitation stroke, and device infections.

Hematologic Concerns

Patients with VADs are at chronically elevated risk of **thrombosis** and **bleeding**. Hemorrhagic risk with VADs is attributed to requisite need for anticoagulation and acquired von Willebrand Factor deficiency, which occurs due to destruction of VWF by shearing in the pump.

Hemolysis: Monitor with daily LFTs, Hgb, and LDH with vigilance for clinical signs of hemolysis including jaundice and darkened urine. If present, measure plasma-free hemoglobin, haptoglobin, and U/A. Pump speed may need to be adjusted accordingly.

In addition to hemorrhage, another ominous complication is thrombus formation. Thrombus formation in a VAD is known as **pump thrombosis**. Hemodynamic changes associated with pump thrombosis include the appearance of power spikes, which are abrupt increases in power consumption, as well as a gradual increase in power requirement without changes in other variables. Additionally, pump thrombosis can lead to outflow tract obstruction. When this occurs pump flow decreases, and power increases to maintain speed. In addition to unexplained changes in device mechanics, clinical evidence of **hemolysis (*i.e. abrupt rise in LDH*) can suggest pump thrombosis and merits emergent consultation with the advanced HF service**. Early pump thrombosis is treated with pump exchange or heart transplant, whereas late pump thrombosis can sometimes be treated with IV heparin.

Strokes are another dreaded complication and are the leading cause of long-term mortality. VAD patients are at risk of both ischemic and hemorrhagic stroke. Ischemic stroke occurs as a result of emboli from pump thrombosis, while hemorrhagic stroke occur due to the need for chronic anticoagulation with the superimposed risk of hemorrhagic conversion. A non-contrast head CT should be emergently pursued for all patients in VADs with acute mental status or neurologic changes.[7]

Hemodynamic Concerns

Right ventricular failure is a serious complication associated with left ventricular mechanical support, and a patient's risk of developing right heart failure is an important consideration in assessing candidacy for LVAD. Right heart failure can occur after LVAD placement by the exacerbation of pre-existing right heart failure, or by changes to RV structure (septal bowing)

due to off-loading of the left ventricle.[8] The development of right heart failure while on LVAD support is associated with a significant increase in morbidity and mortality. Risk factors associated with the development of right heart failure include preoperative intracardiac balloon pump placement, increased pulmonary vascular resistance prior to LVAD support, and the use of an LVAD for destination therapy.[8]

Another potential hemodynamic complication observed in patients with LVADs is **aortic regurgitation** (AR). AR is observed in approximately 25% of patients with LVADs and is be related to the degree of aortic pulsatility.[9]

Infectious Concerns

Patients are at risk of **infection**. The percutaneous driveline requires meticulous care to ensure appropriate healing and device maintenance. Driveline infections and blood stream infections may mandate chronic antibiotic therapy, device exchange or emergent transplantation depending on the clinical severity. Patients receive extensive pre-discharge counseling by the VAD team for device home-care and driveline maintenance.

LVAD Reference Guide

LVAD type	Heartware HVAD	Heartmate 3
Speed range (rpm)	2400-3200 (>3200 risk of suction events)	3000-9000
Maximal device-assisted flow (L/min)	10	10
Power range (watts)	3-7	4-8 (>10 suggestive of thrombosis)
Daily diagnostics	EKG, CXR (defer if clinically stable), LFTs, LDH, PTT (heparin), INR (warfarin); if concern for thrombosis or hemolysis, U/A, plasma-free Hgb, haptoglobin.	
MAP goal (mmHg)	65-80	
Anticoagulation	INR goal 2-3 on warfarin + ASA 325	

LVAD Alarms

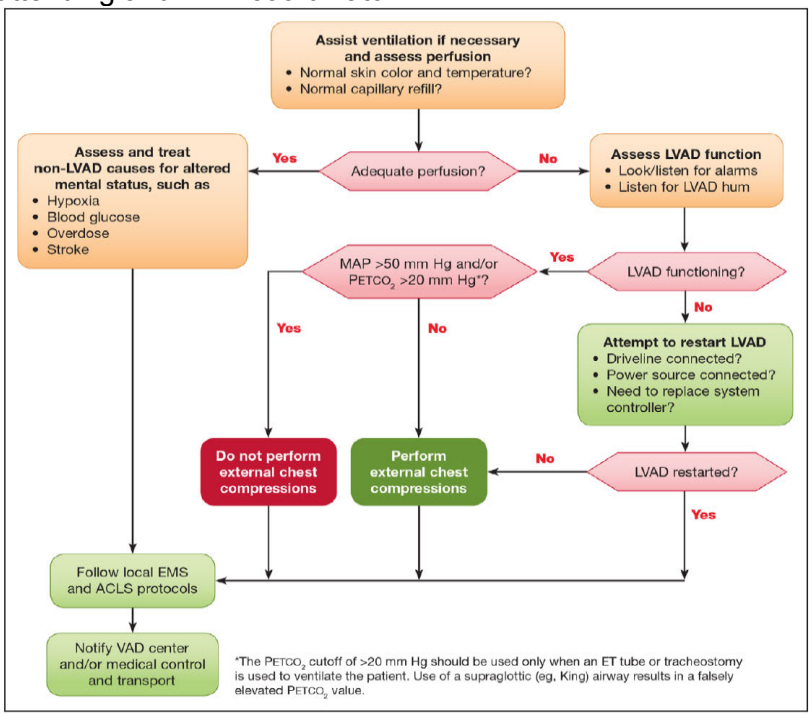
- Two alarm types exist: advisory (intermittent audible alarms, yellow-light, non-emergent) and critical (red light warnings, require immediate assessment/action)
- If advisory alarm is associated with clinical changes or changes in pump parameters, notify HCICU attending, consult VAD coordinator if needed, and treat as you would for a critical alarm.

Alarm type	Advisory (non-critical)	Critical	Evaluation and Management
Low flow or suction	• Speed to high or low • Hypovolemia • RV dysfunction • Tamponade • Hypertension	• Same differential as advisory alarm, but associated with extremely low flow	• Obtain MAP, ECG • TTE • Trial of volume (eg albumin) if suction events

	• Inflow/outflow obstruction • Arrhythmia		• Manage HTN • Treat VT • Page HF or VAD pager (11045)
Low power	• Power source disconnected • Low battery power • System controller internal battery disrupted	• Driveline disconnect • Depleted batteries • Power module disconnect	• Examine driveline • Replace batteries • Page HF or VAD pager (11045)
High power	• Pump thrombosis • Poorly-controlled HTN • Electric fault	• Same as advisory column.	• STAT LDH, LFTs, INR/PTT, U/A, CBC. • **Treat HTN** • Page HF service or VAD pager (11045)

Need-to-know for ACLS with VADs[10]

- Patients may be in a state of pseudo-PEA and may not have a pulse or manual BP despite appropriate perfusion.
- If the patient is unresponsive or hypoperfusing clinically, check connections and exchange controller if still not functioning. Ensure driveline and power sources are connected.
- If PETCO2 < 20, start external chest compressions and progress through standard ACLS protocol.
- If PETCO2 > 20, and MAP > 50, withhold external compressions and notify HCICU attending and VAD coordinator.



References:

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2. Mehra MM et al. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med.* 2017; 376:440-450.
3. Birks EJ et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacologic therapy. Circulation. 2011;123(4):381-90.
4. Strueber M et al. Multicenter evaluation of an intrapericardial left ventricular assist system. *J Am Coll Cardiol.* 2011; 57:1375.
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6. Drakos, et al. Magnitude and Time Course of Changes Induced by Continuous-Flow Left Ventricular Assist Device Unloading in Chronic Heart Failure. *J Am Coll Cardiol.* 2013:1985-994.
7. Transplantation Guidelines for Mechanical Circulatory Support: Executive Summary. *J Heart Lung Transplantation*. 2013: 157-87.
8. Drakos SG et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. *Am J Cardiol.* 2010;105(7):1030-5.
9. Jorde et al. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. *Circ Heart Failure.* 2014;7(2):310-9.
10. Peberdy MA et al. Cardiopulmonary Resuscitation in Adults and Children with Mechanical Circulatory Support: A Scientific Statement from the AHA. *Circulation.* 2017;135(24): e115-e1134.

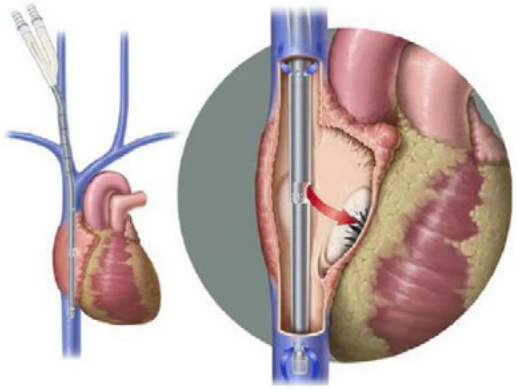
14. Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is a form of paracorporeal life support that provides either respiratory or combined respiratory and circulatory, support. There are two types of ECMO:

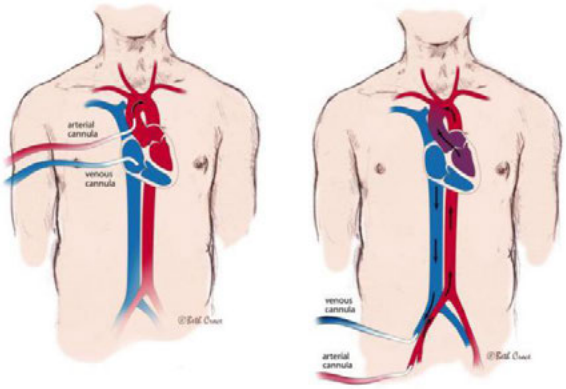
- Veno-Venous (VV) is used for patients with respiratory failure
- Veno-Arterial (VA) is used for patients with combined respiratory and circulatory failure

ECMO circuits consist of a centrifugal blood pump, a membrane oxygenator, and inflow (from the patient to the oxygenator) and outflow cannula (from the device back to the patient). There are multiple cannulation techniques depending on the type of ECMO chosen for each patient. In VV-ECMO, the inflow cannula is usually placed in the R femoral vein up to the junction of the IVC and RA and outflow cannula in the right IJ down to the SVC-RA junction. In the newer Avalon VV-ECMO catheter, both inflow and outflow cannula are contained within one catheter placed in the right IJ. In VA-ECMO, the inflow cannula is inserted into the right atrium via either the IJ or femoral vein and outflow cannula is inserted into the femoral artery. There is often an anterograde catheter placed on the ipsilateral femoral artery to provide perfusion to the distal leg.

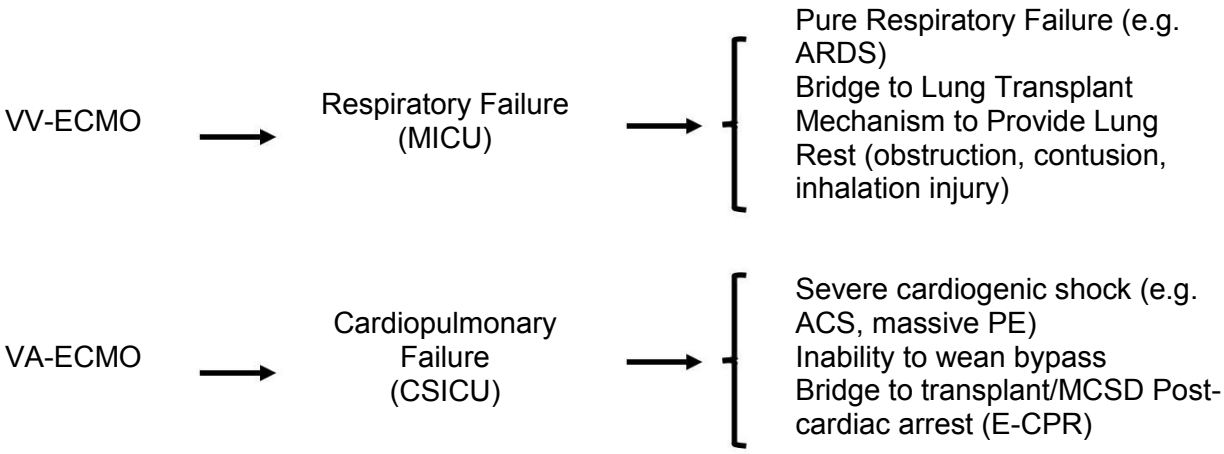
VV-ECMO



VA-ECMO



Catheters are placed by the ECMO team either at the bedside in the ICU, the cath lab, or in the OR, and can provide >6 L/min of cardiac support. At present, VV-ECMO and VA-ECMO are managed in the MICU and CSICU, respectively, but not currently in the CICU.



E-CPR is a particularly new and exciting area, whereby individuals in cardiac arrest are placed on ECMO for cardiopulmonary support. In a small, prospective study of people with in or out of hospital cardiac arrest, 96% of individuals placed on ECMO achieved ROSC, 54% of patients were weaned from ECMO successfully, and 54% survived to hospital discharge with full neurologic recovery (CHEER trial).[1] A meta-analysis of observational studies evaluating ECMO-CPR found survival to discharge to be 40%.[2]

In severe cardiogenic shock secondary to STEMI, Sheu and colleagues compared survival prior to and after ECMO was instituted as salvage therapy over a 17-year period, and found a mortality rate of 39% in patients on ECMO versus 72% without.[3] ECMO can also be used as a bridge to recovery for acute myocarditis or as a bridge to transplant or durable LVAD in decompensated cardiomyopathies. It is also used in patients with circulatory collapse after PE as a bridge to thrombectomy or lysis.

Management and Complications

Flow - There are three phases to flow in an ECMO circuit:

1. Immediately after cannulation, flow is gradually increased to promote mixing of the priming fluid with the patient's blood.
2. Blood flow is then increased until maximum flow is achieved. This is critical to determining the maximum flow permitted by the patient's circulatory system and the natural resistance of the ECMO circuit.
3. Blood flow is decreased to the lowest level necessary to support the patient based upon specific physiologic goals set by the ECMO team (MAP, venous and arterial saturation).

Oxygen Parameters - Target oxyhemoglobin saturation > 95%. Typically, SaO2 will be 100% with PaO2 of > 200. If outlet saturation falls below 95%, it may indicate a defective membrane lung (e.g. due to clotting, irregular flow). Maintaining Hct > 40% optimizes oxygen delivery. Only measure from right atrial line. Remember to have a right radial arterial line in the VA ECMO patient, as the right radial arterial line will be the best available proxy of cerebral perfusion and oximetry (unless there are tissue oxygen monitors available).

Sweep Gas - This is a countercurrent flowing gas that is responsible for delivering O2 and removing CO2 from flowing blood. Typically, sweep flow rate will equal the blood flow rate.

Increasing sweep flow **will increase** CO2 clearance but **will not affect** O2 uptake. Occasionally water vapor will accumulate on the membrane lung; this can be cleared by temporarily increasing sweep flow rate.

Anticoagulation – Necessary for VA-ECMO. Heparin is the primary anticoagulant, and its infusion rate should be titrated to maintain an ACT of 1.5x the upper limit of normal. PTT can be used as well, however this is less reliable. Common complications of anticoagulation include:

Antithrombin Deficiency - This can reduce heparin efficacy and should be first area of investigation if ECMO clotting occurs. It is optimal to maintain AT3 levels between 80-120%; replete with FFP.

Thrombocytopenia - ECMO use is typically associated with platelet counts < 150K. Platelet activation due to circulation through ECMO circuit can result in substantial thrombocytopenia.

HIT - It is very difficult to diagnose with ECMO use as PF4 antibodies and serotonin release assays can be falsely positive. If platelets are < 10K despite transfusion, suspect HIT and switch to a different anticoagulant. Argatroban is the second line agent.
Fibrinogen - Goal to maintain fibrinogen in the 250-300 mg/dL range.

Increased LV afterload - Retrograde blood flow from femoral arterial cannulation can lead to ventricular distention and increased LV afterload, decreasing LV outflow and worsening myocardial ischemia and wall stress. Temporary LVAD placement (i.e. the Impella) may be used in addition to ECMO to volumetrically unload the LV and allow for myocardial recovery, particularly in post-myocardial infarct patients.

Venting - The goal of ventilation on ECMO is to maintain pulmonary air flow while permitting lung rest. Common vent parameters for rest include low rates with long inspiratory times, low tidal volumes, low plateau pressures (< 25 cmH2O), and low FiO2 (30%). Alternatively, the patient can be extubated and allowed to undergo spontaneous respiration (preferable for bridging patients to lung transplant).

Differential Tissue Hypoxemia – “North-South Syndrome” is a complication of VA-ECMO that is a consequence of the existence of two circulations, the patient’s native circulation and the one imposed by VA-ECMO. If the patient has severe ARDS, there is effectively a right to left shunt, and the native cardiac output consists of deoxygenated blood. Highly oxygenated blood from the VA-ECMO circuit mixes with this deoxygenated blood in the middle of the aorta, creating a situation of differential hypoxemia, whereby poorly oxygenated blood perfuses the upper body (North) and highly oxygenated blood perfuses the lower body (South), leading to cerebral and cardiac ischemia. Altering cannula location can fix this issue.

Limb Ischemia - Also a complication of VA-ECMO with cannula placed in femoral arteries, whereby oxygenated blood flows retrograde up the aorta, and perfusion of the limb distal to the cannula site is reduced. Address by inserting a second anterograde arterial cannula to perfuse the ipsilateral limb.

Weaning - Typically, this is an automatic process that occurs as organ recovery progresses and ECMO blood flow is reduced. When ECMO provides less than 30% total support, a trial off is indicated to determine if the patient should be decannulated. Adjust vasopressors, inotropes, and ventilator settings appropriately, and then begin as below:

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VV - Continue normal blood flow through ECMO circuit, but stop sweep gas flow and cap the oxygenator. Follow serial SaO2 and pCO2. If lung function is adequate to regulate these variables for 1 hour, the patient is ready for decannulation.

VA - Clamp off the entire ECMO circuit and follow perfusion and gas exchange (SaO2, SvO2, pCO2). Echocardiography can be useful to monitor cardiovascular function during a trial. If the patient is capable of maintaining cardiopulmonary status for 1 hour, cannula can be clamped, and the patient can be decannulated.

There is an ECMO team for consultation and monitoring of the system. At the bedside, there are always specialized respiratory therapists and perfusionists to assist with troubleshooting.

Contraindications

Absolute:

Unrecoverable heart (if not a candidate for transplant or VAD)
Disseminated malignancy
Severe CNS injury
Unrepaired aortic dissection or severe aortic regurgitation
Severe chronic organ dysfunction (e.g. emphysema, cirrhosis, renal failure)
Unwitnessed cardiac arrest or prolonged CPR w/o adequate tissue perfusion

Relative:

Inability to tolerate required high levels of anticoagulation
Advanced age
Obesity
Financial, cognitive, psychiatric, or social limitations in patients w/o social support

References:

1. Stub D et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation.* 2015: 88-9
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15. Orthotopic Heart Transplant (OHTX)

Heart transplantation is the treatment of choice for many patients with end-stage heart failure (HF), including acute fulminant myocardial injury (e.g. a large myocardial infarction or myocarditis) or progressive heart failure leading to cardiogenic shock or NYHA class IV symptoms refractory to maximal medical and device therapy. Advances in management have increased survival after transplant; median life expectancy, conditional on survival for the first year post-transplant, is now 13 years.

Donor hearts are allocated according criteria set out by the United Network for Organ Sharing (UNOS), which were recently updated in 2018 as follows:

- **Status 1:** VA-ECMO, non-dischargeable BiVAD, MCS with life-threatening ventricular arrhythmia.
- **Status 2:** Non-dischargeable LVAD, MCS with device malfunction/mechanical failure, percutaneous endovascular MCS, IABP, VF/VT.
- **Status 3:** Dischargeable LVAD for discretionary 30-days, ≥2 inotropes or single high-dose inotrope with continuous hemodynamic monitoring, VA-ECMO (after 7-days), IABP (after 14-days), percutaneous endovascular MCS (after 14d), MCS with device infection/hemolysis/AI/RV failure/pump thrombosis.
- **Status 4:** Dischargeable LVAD without discretionary 30-days, inotropes without HD monitoring, congenital heart disease, ischemic heart disease with intractable angina, re-transplant, amyloidosis/HCM/restrictive CM.
- **Status 5:** Awaiting dual-organ transplant.
- **Status 6:** Adult candidate suitable for transplant.
- **Status 7:** Temporarily inactive.

Peak oxygen consumption (VO_2) thresholds measured by CPET can also inform listing and prognosis but are not used as the sole criteria for listing -- peak VO_2 ≤14 mL/kg/min (intolerant of β-blockers), or ≤12 mL/kg/min (on β-blocker) correlate strongly with 1-year mortality.[1] For young patients in particular, peak VO_2 <50% predicted can be an alternative criterion. In cases of sub-maximal effort CPET study (where respiratory exchange ratio [RER] <1.05), a ventilation (V_E) / V_{CO2} slope >35 can be another criterion. Poor blood pressure and heart rate response to exercise and exercise oscillatory ventilation (EoV) are also poor prognostic indicators.

MGH has implemented a program for the transplantation of organs from HCV positive donors, which was created to expand the donor pool with an ever-growing wait list. Organ recipients receive an 8-week course of Mavyret (glecaprevir/pibrentasvir), as it has pan-genotypic coverage and is highly effective at eradicating HCV infection.

Transplant evaluation at MGH: (*Orders are placed by transplant coordinators*)

- **Labs:** ABO blood typing (2 samples on separate days), second sample for PRA (check with tissue typing x63722; **NB** PRA samples must be sent again 2 weeks after any blood transfusion), BMP, LFT, amylase, CBC with differential, PT-INR/PTT, TSH, lipids, PTH, 25-OH-D, 1,25-OH-D, HIV, CMV, EBV, VZV, Toxo IgG, MMR, RPR, hepatitis serologies, IGRA, U/A, 24h urine CrCL (and 24h urine protein if diabetic), PSA in men.
- **Vaccines:** Please consult with the transplant team before administration of any vaccines, as live vaccines may confer risk given anticipated high-dose immunosuppression.
- **Consults:** Psychiatry (Dr John Purcell), SW (Kathryn Tsagronis), Tx coordinators (Sally Keck, Coral Haggan, Karen Turvey – can all consent patient), dental clearance (panorex and inpatient consult), nutrition, transplant ID, palliative care (if DT-VAD; please confer with HF team before consulting).

- **Diagnostics:** RHC to measure filling pressures, CO/CI, and evaluate for presence/reversibility of pHTN with vasodilator challenge; if unsuccessful vasodilator challenge, note that PVR often declines after 24-48h of treatment (e.g. diuretics, inotropes, vasoactive agents), +/- LHC, level 1 CPET (Paul Pappas, x47825), abdominal US, carotid US, TTE, ECG, colonoscopy or CT colon, CT chest (if former smoker), CXR, DXA, PAP smear/mammogram for women, ABIs +/- angiography.

Post-transplant care:

1. Immunosuppression

The principle of immunosuppression is to administer robust suppression in the early post-transplant phase when the risk for rejection is highest, followed by gradual tapering to a lifelong maintenance regimen. A balance must be navigated between rejection and risk of opportunistic infection and malignancy. Chronic immunosuppression typically consists of a 3-pronged approach: corticosteroids, a calcineurin inhibitor (CNI; tacrolimus, or less commonly cyclosporine), and an anti-metabolite (mycophenolate, or less commonly azathioprine). An mTOR inhibitor such as sirolimus or everolimus can be added in place of the anti-metabolite in patients who develop coronary allograft vasculopathy (CAV). mTOR inhibitors are typically not used in the immediate post-transplant phase as they impair wound healing. Younger patients tend to require higher target immunosuppressive drug levels and a more intense regimen due to an intrinsically more robust immune system and higher risk of rejection; conversely, older patients have higher risk of infections.

Anti-thymocyte globulin (ATG) and basiliximab are the 2 most commonly used induction agents.

- ATG
  - Indications: dual transplant (heart-kidney) or highly sensitized recipients
  - Polyclonal antibody that depletes multiple lymphocyte subsets (CD2, 3, 4, 8, 20 and 56) by complement-dependent cell lysis
  - Dose: 1-1.5 mg/kg/dose, rounded to the nearest 25 mg
  - Usually monitor response using CD3 counts (flow cytometry)
  - Pre-medicate with steroids, acetaminophen and diphenhydramine
- Basiliximab
  - Typically used in recipients with renal failure precluding use of a CNI
  - Monoclonal antibody directed against IL2 receptors
  - Dose: 20 mg on day 0 and day 4
  - No pre-medication needed

<table>
<tr><th colspan="5">Calcineurin inhibitors (CNI)</th></tr>
<tr><th>Drug</th><th>When to draw trough</th><th>Goal trough (by time since HTx)</th><th>Caveats</th><th>Side-effects</th></tr>
<tr><td>Tacrolimus</td><td rowspan="2">▪ 10-12h after evening dose (AM lab draws allow same day result)
▪ Can be added to a CBC sample if timing appropriate</td><td>▪ <1 yr: 10-12
▪ 1-2 yr: 7-8
▪ 3+ yr: 4-7</td><td rowspan="2">▪ ↑ target trough if recent history of graft rejection
▪ ↓ target trough if recent history of infection, renal dysfunction, or malignancy</td><td rowspan="2">▪ Nephrotoxic
▪ HTN
▪ HLD
▪ ↑ K+
▪ ↑Glu, DM
▪ Peripheral neuropathy</td></tr>
<tr><td>Cyclosporine</td><td>▪ 0-6 mo: 200-250
▪ 6-12 mo: 150-200
▪ 1-5 yr: 100-150
▪ 5+ yr: 50-100</td></tr>
</table>

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Anti-metabolites			
Drug	**Target dose (by time since HTx)**	**Caveats**	**Side-effects**
Mycophenolate mofetil (MMF, *Cellcept*)	▪ <1 yr: 1500mg BID ▪ 1-3 yr: 1000-1250mg BID ▪ 3+ yr: 500-1000mg BID ▪ *Note:* PO to IV conversion is 1:1 Cellcept 1500mg x1 intra op	▪ ↑ dose if recent history of graft rejection ▪ ↓ dose if recent history of infection or GI upset ▪ If profound GI upset, can switch MMF to mycophenolate sodium (*Myfortic*) which can be TID/QID dosed ▪ Conversion: 180mg Myfortic = 250mg Cellcept	▪ GI upset ▪ Leukopenia
Azathioprine (*Imuran*)	Typically 50-150 mg daily	▪ Avoid xanthine oxidase inhibitors (allopurinol, febuxostat) which potentiate myelosuppression ▪ Patients with low or absent TPMT activity may require ↓ dose or discontinuation	▪ Leukopenia ▪ Hepatotoxic ▪ Pancreatitis

MGH steroid weaning protocol		
First week post-op: <u>Methylpred 500mg IV x2 intraop</u> POD 1: methylpred 125mg IV Q8h x6 doses POD 2: prednisone 80mg BID POD 3: prednisone 60mg BID POD 4: prednisone 40mg BID POD 5: 40mg AM / 30mg PM POD 6: 40mg AM / 20mg PM POD 7 (Bx #1): 40mg AM / 10mg PM POD 8: 40mg QD (remain on this dose until Bx #2)	**Biopsy at week*:**	**If normal Bx, reduce pred to:**
	Week 2	35mg
	Week 3	30mg
	Week 4	25mg
	Week 6	20mg
	Week 8	17.5mg
	Week 10	15mg
	Week 12	12.5mg
	Week 15	10mg
	Week 18	10mg / 7.5mg QOD
	Week 22	7.5mg QD
	Week 26	7.5mg / 5mg QOD
	Week 34	5mg QD
	Week 42	5mg QD
	Prednisone may variably be stopped in patients at low risk for rejection 1 year post transplant or with complications of steroids, especially bone-related	

*Biopsy scheduled may be altered depending on clinical situation.

Allograft rejection:
Aside from hyperacute rejection, which occurs within minutes of organ reperfusion, allograft rejection comprises acute cellular rejection (ACR) and antibody-mediated rejection (AMR), also known as humoral rejection.

Acute cellular rejection (ACR) is a T-cell mediated inflammatory response that can occur any time after heart transplant, but most commonly in the first 6 months (hence coinciding with the most intense schedule of endomyocardial biopsies (EMBx)). Up to 24% of patients experience at least 1 episode of rejection within 12 months. The signs and symptoms are often non-specific and may manifest late. Notably the LVEF is often preserved in early ACR. Unlike kidney or liver transplant recipients, there is no biomarker available to identify ACR, meaning patients must undergo biopsy. ACR is graded according to the International Society of Heart and Lung Transplantation (ISHLT) 2004 guidelines as Grade 0 (no rejection), Grade 1R (mild), Grade 2R (moderate) or Grade 3R (severe), according to histologic findings from EMBx of the right ventricle, which remains the gold standard for diagnosis. At MGH, we also continue to use the 1990 ISHLT histologic criteria, which includes the following grades: 0 (no evidence of ACR), 1A (focal infiltrate without myocyte damage), 1B (diffuse infiltrate without myocyte damage), 2 (one focus of infiltrate with associated myocyte damage), 3A (multifocal infiltrate with myocyte damage), 3B (diffuse infiltrate with myocyte damage), 4 (diffuse injury with extensive myocyte damage). The 2 criteria are combined to give a score (for example 3A/ 2R). Treatment of ACR involves pulse high-dose steroids (typically IV methylprednisolone 1000mg QD x3 doses), or alternatively ATG 1-1.5 mg/kg QD x 3-5 doses. Patients should be pre-medicated with steroids, acetaminophen and diphenhydramine prior to ATG. Finally, alemtuzumab (*Campath*) can be used as salvage therapy (30mg IV x1 dose) in those who fail to respond to the above.

Antibody-mediated rejection (AMR) occurs more commonly in those who have positive panel reactive antibodies (PRA), often a result of prior blood transfusions, transplants or pregnancy. Of note, patients with PRA-measured sensitization *can* undergo pre-transplant desensitization protocol involving rituximab, and plasmapheresis (PLEX). IVIG (1g/kg QD x2 doses) is then given to replete lost antibodies.

2. Infectious prophylaxis:
Antimicrobial regimens are based upon donor and recipient serology status, as follows:

- **CMV**
  - Highest risk for CMV infection with donor+ and recipient-.
  - Prophylaxis for D+/R-, D+/R+, D-/R+ is valganciclovir 900mg QD x3 months.
  - Prophylaxis for D-/R- is famciclovir x 3 months.
- **HSV**
  - Should be given to those who are not on valganciclovir due to leukopenia or cost.
  - Prophylaxis: acyclovir 400mg BID or famciclovir 500mg QD
- **Pneumocystis**
  - Bactrim x1 year
- **Toxoplasmosis**
  - D+/R- : double strength Bactrim x1 year, then single strength lifelong
  - D+/R+, D-/R+ or D-/R- : single strength Bactrim x1 year
- **Candida**
  - Nystatin 500,000 units TID x6 months

3. **Cardiac allograft vasculopathy:**
Cardiac allograft vasculopathy (CAV) remains the Achilles' heel of long-term survival after heart transplant; one-third of patients develop CAV by 5 years, and it causes 1 in 8 deaths beyond a

year. Endothelial inflammation, injury and dysfunction occurs due to either immune or non-immune insults, causing diffuse intimal hyperplasia and vascular fibroproliferation. Rather than focal eccentric plaques as seen in atherosclerotic coronary disease, CAV causes diffuse circumferential thickening to which coronary angiography is often insensitive in the early stages, also affecting the microvasculature. Additionally, **classic anginal symptoms of myocardial ischemia are often absent due to myocardial denervation – the predominant symptom post-transplant patients may endorse with acute allograft ischemia may be dyspnea**. Diagnosis is therefore challenging in early CAV, and adjuncts such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) allow for higher resolution (10-20μm in the case of OCT), or non-invasive approaches, including SPECT/PET or dobutamine stress echo.

ISHLT Staging of CAV		
Stage	**Severity**	**Definition**
CAV_0	Non-significant	No detectable angiographic lesion
CAV_1	Mild	LM <50% or Single primary vessel <70% or Branch stenosis <70%
CAV_2	Moderate	LM <50%, Single primary vessel ≥70% or Isolated branch stenosis in 2 systems ≥70%
CAV_3	Severe	LM ≥50% or ≥2 primary vessles ≥70% or Isolated branch stenosis in all 3 systems ≥70% or CAV_1 or CAV_2 with LVEF <45%

Management:

- **Aspirin:** Not well studied, but used empirically on the basis of presumed microthrombi formation.
- **Statin:** Standard post-transplant care, may also reduce inflammatory and immune response. A landmark trial (N = 97) studied pravastatin initiated 2 weeks post-HTx, showing reduction in severe rejection, CAV and mortality.[2] The preferred statin is pravastatin.
- **Vasodilators:** Small studies of diltiazem or ACEi suggest possible benefit.[3,4] Not generally used unless additional BP control needed.
- **Immunosuppression:** MMF reduces progression of intimal thickening compared with azathioprine and is the preferred anti-metabolite in most patients. mTOR inhibitors (sirolimus or everolimus) have been shown to reduce incidence and progression of CAV. mTOR inhibitors are generally started >6-12 months post-transplant due to their inhibition of wound healing.
- **Revascularization:** May be considered on a case-by-case basis, as no trials have shown a benefit for PCI over medical management. One single-center study (N = 105) showed a high ISR rate (31%) and lower freedom from a composite of death, MI or retransplantation at 7 years follow-up (28% v 63%), driven primarily by reduced survival.[5] The suspected physiologic basis to these observations is that CAV tends to manifest as diffuse, narrowing disease rather than focal, eccentric plaques, which may be more amenable to stenting.

References:

1. Mancini DM et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83(3):778-86
2. Kobashigawa JA et al. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med.* 1995;333(10):621-7
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4. Erinc K et al. The effect of combined Angiotensin-converting enzyme inhibition and calcium antagonism on allograft coronary vasculopathy validated by intravascular ultrasound. *J Heart Lung Transplant.* 2005;24(8):1033-8
5. Lee MS et al. Long-term outcomes of heart transplantation recipients with transplant coronary artery disease who develop in-stent restenosis after percutaneous coronary intervention. *Am J Cardiol.* 2012;109(12):1729-32

QUICK REFERENCE GUIDE: MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Mechanical Circulatory Support Overview

- MCS support options include intraaortic balloon pump (IABP), Impella (LV: Impella 2.5, Impella CP, Impella 5.0; RV: Impella RP), Tandem Heart (LV and/or RV; not currently in use at MGH), CentriMag or RotaFlow (LV and/or RV), LVAD/RVAD/BiVAD, and ECMO
- Acute MCS (all of the above minus VADs) may be considered in the following scenarios: refractory end-stage HF, cardiogenic shock, periprocedural support, refractory malignant arrhythmias, and cardiac arrest
- When considering MCS for acute indications, the current MGH shock team can be paged at 29151

Intra-Aortic Balloon Pump (IABP)

- The IABP is a 30-50 cc intravascular balloon that is placed in the proximal descending aorta (just below the origin of the left subclavian artery)
- The balloon is connected to a console that synchronizes inflation and deflation to the cardiac cycle using either surface EKG or aortic pressure. Thus, proper synchronization requires a stable cardiac rhythm
- Unlike a ventricular assist device (VAD) or Impella, the IABP does not generate cardiac output (max support provided = 0.5L/min); rather it improves left ventricular unloading by the following two hemodynamic effects: Increased coronary artery blood flow during diastole and decreased LV afterload during systole
- IABP placement is indicated in cardiogenic shock and hemodynamic instability after STEMI refractory to pharmacologic management (class IIa), though the use of IABP may be declining with the emergence of Impella devices
- IABP should be avoided in patients with severe AR, severe bilateral PAD, aortic dissection, aneurysm, and hematoma
- Proper IABP placement should be assessed daily by CXR (the tip of the catheter must be 1–4 cm below the aortic arch) and waveform, as should the insertion site (for hematoma or infection)
- Patients receive prophylactic antibiotics (usually cefazolin) and anticoagulation with heparin while the device is in place. They are prohibited from getting out of bed while the IABP is in place
- Complications of IABP include: Anemia, thrombocytopenia, limb ischemia, dissection, CVA, and balloon rupture. Any suspected complication should prompt an immediate call to the fellow/attending and to the balloon technician (6-3693)

Impella

- The Impella is a percutaneous temporary ventricular support device. There are three approved versions for percutaneous left ventricular support, the Impella 2.5, Impella CP, and Impella 5.0, as well as one for right ventricular support, the Impella RP
- For LV support, the Impella is FDA-approved for the treatment of cardiogenic shock, specifically occurring within 48 hours following acute myocardial infarction or open-heart surgery. While intended for short-term use (between 4-6 days), it is often left in well beyond this time
- The Impella RP is indicated in acute RV failure or decompensation following: LVAD, MI, OHTx, or CT surgery
- Anticoagulation is required while the Impella device is in place, typically using systemic heparin with a goal PTT 50-60

- Daily assessment to ensure proper/safe device functioning includes: CBC, LDH, PTT/ACT, LFTs (bilirubins), CXR, device alarm history, and placement/pulsatility signal
- In the event that a patient with an Impella requires ACLS: Place the power on setting P2 for duration of chest compressions. Once ROSC is achieved: Return to previous settings and carefully assess placement signals given the risk for device migration
- In an emergency, the HCICU attending should be available. Another resource is the cardiac access fellow

Durable Ventricular Assist Devices

- Implanted ventricular assist devices, or durable VADs, are devices which support the function of one or both ventricles in the failing heart
- All generations of LVADs connect the apex of the left ventricle to the ascending aorta and are connected to an external power source and system controller by a percutaneous lead
- At MGH, the most common LVADs used are the third-generation devices, the Heartmate 3 and the Heartware HVAD
- VADs are approved for two main indications: Bridge to transplant (BTT; the VAD remains *in situ* until transplant, at which time the device is explanted) and destination therapy (DT; the VAD remains in situ indefinitely). BTT VADs may optimize surgical candidacy and have been shown to improve post-surgical outcomes. In destination therapy, LVADs have been shown to improve quality of life and survival compared with standard medical therapy
- Other uses one may see include: Bridge to decision (BTD; a decision on transplant candidacy is unable to be made at the time of VAD placement, but the patient cannot survive without durable MCS) or bridge to recovery (anticipated recovery of cardiac
- VADs are carefully monitored in the outpatient setting, involving regular assessment of: Physical exam, labs (including measures of hemolysis, INR), electrocardiogram, echocardiography, and device interrogation. VAD patients require AC with Coumadin and an INR goal of 2-3 as well as full dose ASA
- Note that conventional BP monitoring for current generation devices may be unreliable (as these patients typically lack palpable pulses due to lower pulse pressures). Instead, BP is assessed via Doppler ultrasound using a brachial sphygmomanometer and is reported as a mean arterial pressure, with goal range of 65-80 mmHg
- Complications of VAD include hematologic (hemolysis, bleeding, stroke, thrombosis), hemodynamic (e.g. aortic regurgitation is observed in approximately 25% of patients with LVADs and is be related to the degree of aortic pulsatility), and infectious (e.g. driveline infection)
- Regarding ACLS, note that VAD patients may be in a state of pseudo-PEA and may not have a pulse or manual BP despite appropriate perfusion
- However, if the patient is unresponsive or hypoperfusing clinically, first assess LVAD functioning (look/listen for alarms, listen for LVAD hum). If the device does not appear to be functioning, ensure the driveline and power sources are connected and consider controller exchange
- If the device does appear to be functioning and/or if PETCO2 < 20, start external chest compressions and progress through standard ACLS protocol
- If PETCO2 > 20 and MAP > 50, withhold external compressions and notify the HCICU attending and VAD coordinator ASAP

Extracorporeal Membrane Oxygenation (ECMO)

- ECMO is a form of extracorporeal life support that provides either respiratory (veno-venous ECMO) or combined respiratory and circulatory support (ven-arterial ECMO)
- In general, the ECMO circuits consist of a centrifugal blood pump, a membrane oxygenator, an inflow cannula (from the patient to the oxygenator), and an outflow cannula (from the device back to the patient)
- Veno-Venous (VV) ECMO is used for respiratory support and may be considered in cases of pure respiratory failure (e.g. ARDs) or as a bridge to lung transplant. It may also be employed as a mechanism to provide lung rest (e.g. in cases of obstruction, contusion, and/or inhalation injury). In VV-ECMO, the inflow cannula is conventionally inserted via the R femoral vein and advanced up to the junction of the IVC and the RA, while the outflow cannula is inserted via the RIJ and advanced down to the junction of the SVC and the RA (though in the newer Avalon VV-ECMO catheters, both inflow and outflow cannulas are contained within one catheter that is placed in the RIJ)
- Veno-Arterial (VA) ECMO is used for combined respiratory and circulatory support and may be considered in cases of severe cardiogenic shock (e.g. AMI, massive PE), inability to wean from cardiopulmonary bypass post-cardiac surgery, or as a bridge to recovery/transplant/MCS (particularly post cardiac arrest). In VA-ECMO, the inflow cannula is inserted via either the femoral vein or the IJ and advanced into the RA, while the outflow cannula is inserted into the femoral artery
- Absolute contraindications include: Unrecoverable heart (if not a candidate for transplant or VAD), disseminated malignancy, severe CNS injury, unrepaired aortic dissection or severe AR, severe chronic organ dysfunction, and unwitnessed cardiac arrest or prolonged CPR w/o adequate tissue perfusion

Heart Transplant

- Heart transplantation is the treatment of choice for many patients with end-stage heart failure, including acute fulminant myocardial injury (e.g. a large myocardial infarction or myocarditis) or progressive heart failure leading to cardiogenic shock or NYHA class IV symptoms refractory to maximal medical and device therapy
- Advances in management have increased survival after transplant and median life expectancy (conditional on survival for the first year post-transplant) is now ~13 years
- Transplant evaluation is largely driven by the advanced HF/transplant team, and all non-trivial management decisions should be made in discussion with this team or the attending on call
- For patients listed for transplant who have an indication for blood product, FIRST discuss with the HF team given risk of sensitization; a PRA should be repeated 2-weeks after the last transfusion
- Post-transplant considerations include maintenance of immunosuppression (the first routine EMBx to evaluate for allograft rejection is typically performed on POD7 #1), infectious prophylaxis, and close hemodynamic monitoring (new arrhythmia in the post-transplant setting should prompt consideration of rejection
- All new medications should carefully be reviewed by a transplant pharmacist, as many drug-drug interactions exist with commonly-used immunosuppressive agents (e.g. tacrolimus, cyclosporine) and aberrant drug levels pose a risk of acute rejection

ACUTE CORONARY SYNDROMES AND ISCHEMIC HEART DISEASE

See Page 178 for Quick Reference Guide

16. Classification and Pathogenesis

UA	NSTEMI (Type 1)	STEMI
ECG Δs or hx; (-) biomarkers	ECG Δs; (+) biomarkers	ECG Δs; (+) biomarkers
- Subtotal-occlusive thrombus + platelet activation + cross-linking on pre-existing plaque - No myocardial necrosis - In the era of hs-cTn testing, there is an argument that UA will become extinct. Although, higher sensitivity testing will capture more NSTEMIs, there is still a proportion of patients that will have the right history of ACS but without hs-cTn elevation.	- Subtotal-occlusive thrombus + platelet activation + cross-linking on pre-existing plaque - Myocardial necrosis	- Typically a **completely occlusive** thrombus or thromboembolism, usually arising on a disrupted or eroded plaque - ≤ 7% of STEMIs have no critical lesion - 3% have *normal* coronaries (see MINOCA section)

Figure 1: Joint ESC/ACCF/AHA/WHF Task Force Fourth Universal Definition of MI

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure–related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5 or >10 fold increase and manifest a change from the baseline value of >20%. In addition with at least 1 of the following:

- New ischemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the prespecified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology.
- Patho-anatomical findings of a prior MI.

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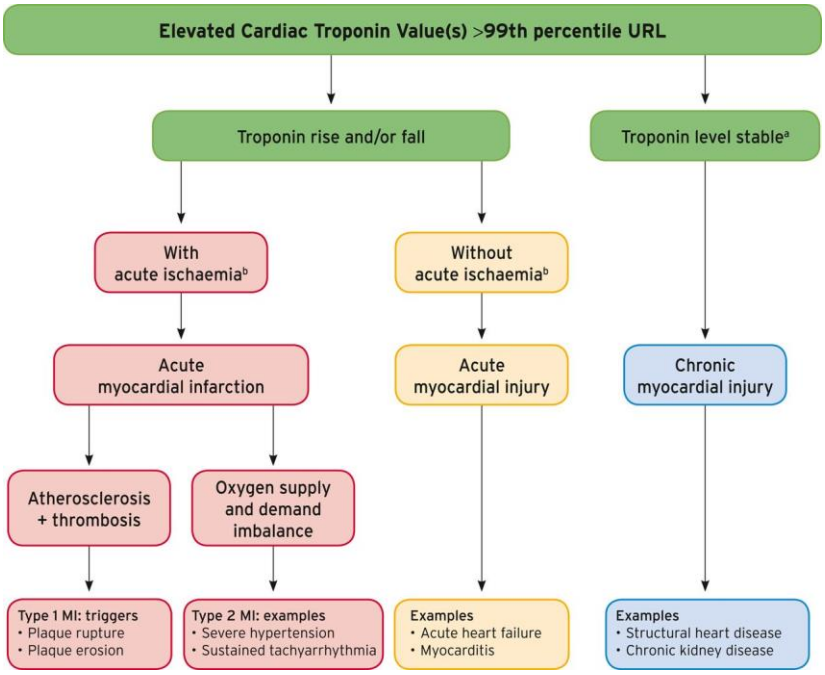
One of the most important updates in the 4th Universal Definition of MI is how to interpret hsTnT. The following figure addresses these challenges (also see *Cardiac Biomarkers* section).

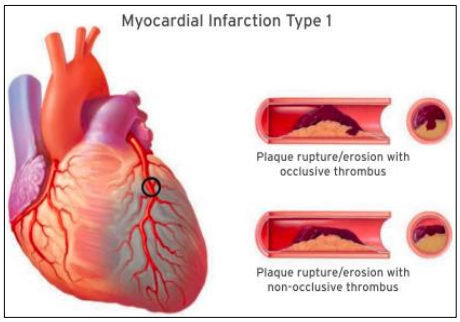
Figure 2: Schema for Interpreting Myocardial Injury[2]

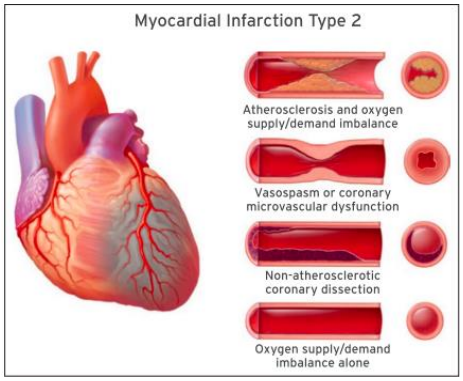


Joint Task Force Classification of MI:

1. **Spontaneous MI (*Type 1 MI*)**: Atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection causing intraluminal thrombus in 1+ coronary arteries. These lead to decreased myocardial blood flow or distal platelet emboli and myocyte necrosis.

2. **MI related to an ischemic imbalance (*Type 2 MI*)**: The so-called **"demand MI",** this classification includes instances of myocardial injury *with* necrosis in which a condition *other than CAD* contributes to an imbalance between myocardial O_2- supply and demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy- or brady- arrhythmias, anemia, respiratory failure, hypotension, HTN +/- LVH. Type 2 MI should be differentiated from *myocardial injury*. The former must have evidence of ischemia i.e. ECG changes, ischemic symptoms, or new regional wall motion abnormalities on echocardiography; if not present then the diagnosis is myocardial injury.





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3. **MI resulting in death but biomarkers unavailable (*Type 3 MI*)**: with symptoms suggestive of MI including new ischemic ECG changes or new LBBB

4. **MI related to PCI (*Type 4a MI*)**: arbitrarily defined by cTn values >5x the 99th percentile of the ULN in patients with normal baseline values.

5. **MI related to stent thrombosis (*Type 4b MI*)**

6. **MI related to CABG (*Type 5 MI*)**: arbitrarily defined by cTn values >10x the 99th percentile of the ULN in patients with normal baseline values.

References:

1. Thygesen, K., et al. "Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018)." *J Am Coll Cardiol* 72.18 (2018): 2231-2264
2. Thygesen, Kristian, et al. "Fourth universal definition of myocardial infarction (2018)." *Journal of the American College of Cardiology* 72.18 (2018): 2231-2264

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17. Diagnosis

HPI, **PE**, and **12-lead ECG** can identify 92-98% patients with MI and 90% of patients with UA.

A. History

Typical chest pain is defined by the following features:
1) Substernal
2) Worsened with exertion
3) Relieved by rest or nitroglycerin

Typical chest pain is classically described as substernal pressure (squeezing, burning or tightness) and radiates to the shoulder, neck, jaw, or either arm (may also be inter-scapular or epigastric). The pain is associated with nausea, vomiting, and diaphoresis and is provoked by exercise, stress, excitement, or cold weather. Those with stable CAD may have a phenomenon known as "**ischemic walkthrough**" whereby their **pain improves with exercise** secondary to recruitment of collateral circulation, thereby reducing the sensitivity of this historical item for the evaluation of CAD. Ischemic CP typically lasts minutes and resolves with rest or nitroglycerin, though the latter is not specific to cardiac etiologies (e.g. esophageal spasm). Ischemic pain is typically stuttering in onset, and those presenting with acute onset of tearing CP should be considered for aortic dissection. Angina occurs more commonly in the morning due to increase in sympathetic tone (higher resting HR and BP, putting more stress on the heart).

UNSTABLE ANGINA: Unstable angina should be differentiated from stable angina based on history. Three important features of unstable angina can help distinguish ACS from stable CAD.
1) Rest angina, which is usually more than 20 minutes in duration
2) New onset angina that markedly limits physical activity
3) Angina that is more frequent, longer in duration, or occurs with less exertion than previous angina

ATYPICAL CP: Atypical chest pain falls short of meeting all three criteria above. These presentations are common, with 10% of individuals with ACS reporting **dyspnea alone**. Other presentations include **fatigue**, **lethargy**, **syncope**, **AMS**, **CVA/TIA**, or **GI distress**. Atypical presentations are more common in **women**, **elderly** (who may be also be asymptomatic), **inferior MIs**, and **diabetics** (absence of CP due to neuropathy).

NON-ISCHEMIC CP:
Quality: Pleuritic, sharp, or reproducible with palpation
Timing: Occurring with cessation of exercise or lasting only seconds or >6 hrs
Context: Without evidence of myocardial damage by biomarkers. Chest pain that is not ischemic may represent other life-threatening etiologies of chest pain, such as aortic dissection, PE, or pneumothorax. Alternative diagnoses should be ruled out before disregarding chest pain.

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Figure 3: Value of Specific Components of the Chest Pain History for the Diagnosis of Acute Myocardial Infarction[1]

Pain Descriptor	Reference	No. of Patients	Positive Likelihood Ratio (95% CI)
Increased likelihood of AMI			
Radiation to right arm or shoulder	29	770	4.7 (1.9-12)
Radiation to both arms or shoulders	14	893	4.1 (2.5-6.5)
Associated with exertion	14	893	2.4 (1.5-3.8)
Radiation to left arm	24	278	2.3 (1.7-3.1)
Associated with diaphoresis	24	8426	2.0 (1.9-2.2)
Associated with nausea or vomiting	24	970	1.9 (1.7-2.3)
Worse than previous angina or similar to previous MI	29	7734	1.8 (1.6-2.0)
Described as pressure	29	11 504	1.3 (1.2-1.5)
Decreased likelihood of AMI			
Described as pleuritic	29	8822	0.2 (0.1-0.3)
Described as positional	29	8330	0.3 (0.2-0.5)
Described as sharp	29	1088	0.3 (0.2-0.5)
Reproducible with palpation	29	8822	0.3 (0.2-0.4)
Inframammary location	31	903	0.8 (0.7-0.9)
Not associated with exertion	14	893	0.8 (0.6-0.9)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval.

B. Physical Exam

Although few exam findings predict ACS reliably, physical examination may indicate a high pre-test probability for CAD (e.g. PAD, Frank's sign).

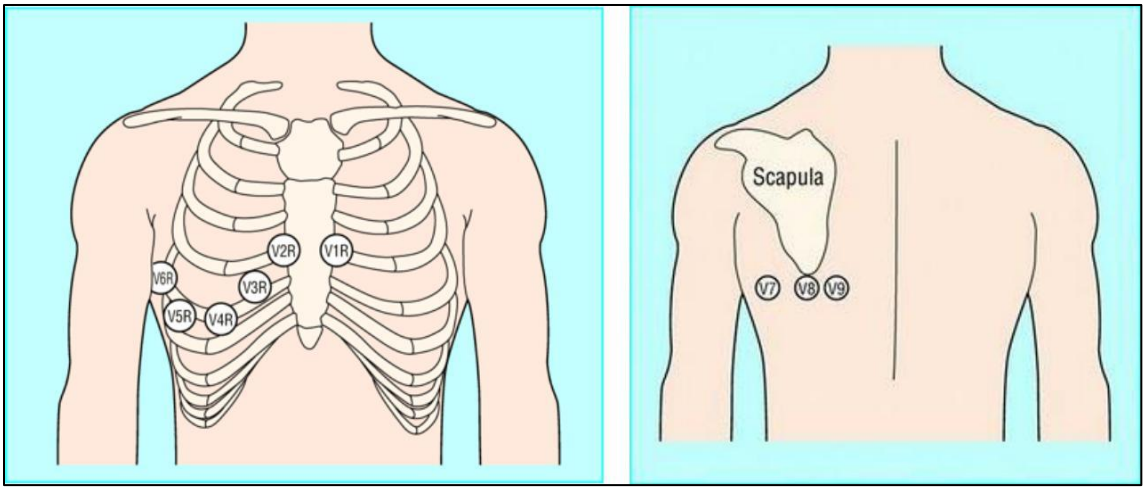
Additional findings in presumed ACS may signify high-risk features such as new HF (S3 gallop, rales, or elevated JVP) or a mechanical complication such as papillary muscle or ventricular septal rupture (sinus tachycardia, hypotension, elevated JVP, or new systolic murmur).

C. 12-lead ECG

Obtain **ECG within 10 minutes of CP onset** and **during active CP**. Roughly 50% of patients with MI have a normal or non-diagnostic ECG on presentation to the ED. Therefore, the finding of a normal ECG does not exclude ACS and should prompt **serial ECGs (every 10-15 min and with any changes in chest pain)** to evaluate for dynamic changes. Ischemic changes present during CP should rapidly normalize on resolution of CP.

When to ask for right-sided or posterior leads:

- Obtain right-sided leads in ANY patient with inferior STEMI to evaluate for RV involvement
- Obtain posterior leads in any patient with a good story for ACS but normal ECG, STDs in V1-V3, or R/S ratio >1 in V1-V2



(*Left*) Right-sided precordial lead placement, (*Right*) Posterior lead placement

NSTEMI ECG CRITERIA:

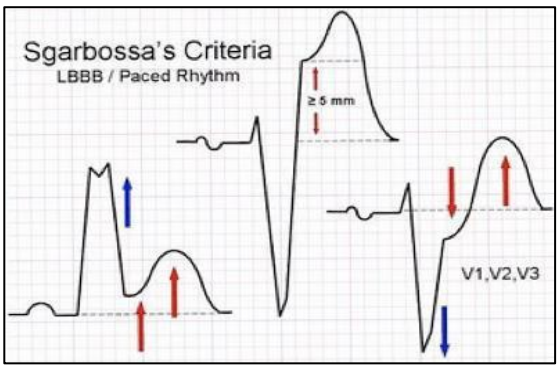
- New horizontal or down-sloping **STD of ≥ 0.5mm**
- **TWI ≥ 0.1mm** with a **prominent R-wave or R/S ratio > 1** in ≥ 2 contiguous leads

Findings typically resolve with symptom improvement, which is highly suggestive of underlying CAD. Findings on ECG do not tend to correlate with a vascular territory in NSTEMI.

STEMI ECG Criteria: (≥1 of the following)

1. **New STE** just distal to the J-point and in 2 contiguous leads (defined by coronary territory, see below)
    a. Evaluate the ST segment 80ms (2 small boxes) from the J-point, which is the inflection point between the S wave and the ST segment
    b. Pathologic elevations are ≥1mm in all leads, with the exception of V2-V3
    c. For leads V2-V3, the following cut-points apply*
        i. M < 40 yr: ≥2.5mm
        ii. M≥ 40 yr: ≥ 2mm(M < 40 yr)
        iii. F (all ages): ≥ 1.5mm

    **Patients may demonstrate elevations in the anterior precordial leads (V1–V3) which is NOT pathologic*[2]
2. **New LBBB** (see Sgarbossa's criteria below for criteria for those with prior LBBB)
3. **"True" posterior MI** defined by STD in ≥2 precordial leads (V1–V4) (not to be confused with inferior MI, which historically was called the posterior wall). Check posterior leads V7-V9 (as above)



Sgarbossa Criteria: Used to diagnose AMI in LBBB/Paced Rhythm

- ST segment should be discordant with the QRS complex. Any **QRS-ST concordance** or **exaggerated discordance** should raise suspicion of ischemia.
- Sgarbossa criteria:

- STE > 1mm concordant with QRS in any lead = 5 points
- STD > 1mm concordant with QRS in V1, V2 or V3 = 3 points
- STE > 5mm *discordant* with QRS in any lead = 2 points

Total Sgarbossa criteria point score ≥ 3 yields 90% specificity and 88% PPV for MI, but notably only a sensitivity of 20%.[3]

Localization of Injury
Contiguous STE may indicate which vessel is involved. This information helps plan subsequent cardiac catheterization. In general, STE correlate better with a vascular territory than STD or TWIs.

INFERIOR-POSTERIOR MI (**RCA**): When ST/T wave changes are seen in II, III, and/or aVF, there may be involvement of the infero-posterior wall of the LV. Often, this represents an occlusion of the RCA. If the occlusion is proximal to the acute marginal branches that supply the RV free wall, there may also be an RVMI.

- Important to identify before nitrate or diuretic therapy, which can decrease preload (as RV infarct is a preload-dependent state).
- Associated with arrhythmias, including high-grade AVBs and can often require temporary pacing. RVMIs are associated with a worse prognosis than isolated inferior MIs.
- STE in lead III>II and STD are suggestive of RCA occlusion.[4] This is because the ST segment vector is pointed to the right (III)
- To evaluate for RVMI in the setting of inferior STE, **obtain right sided leads (V4R–V6R)**. STE >1 mm in V4R is the most predictive of RV infarct. STE in V1 is also suggestive of RV involvement.

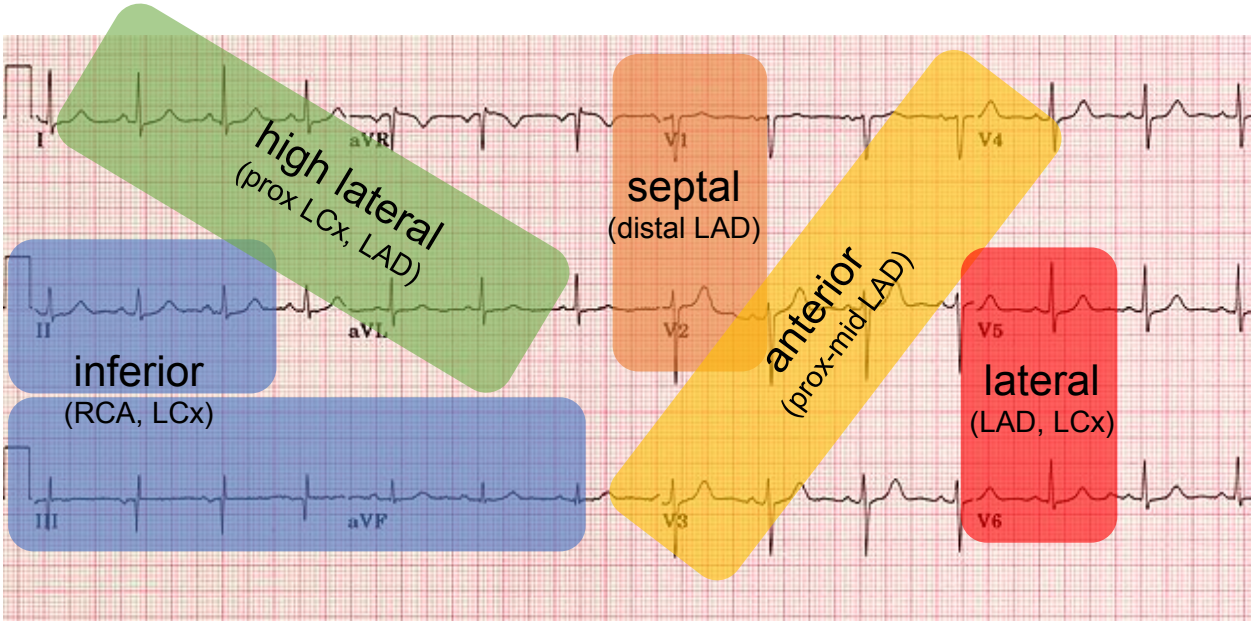
POSTERIOR MI (**LCx, PDA**): A posterior MI may be electrically silent. It should be suspected in any ECG with **ST depressions in V1-V3** (posterior MI or anterior ischemia) or **R/S ratio >1 in V1-V2** and should prompt **posterior lead (V7-V9) evaluation** (see diagram above).

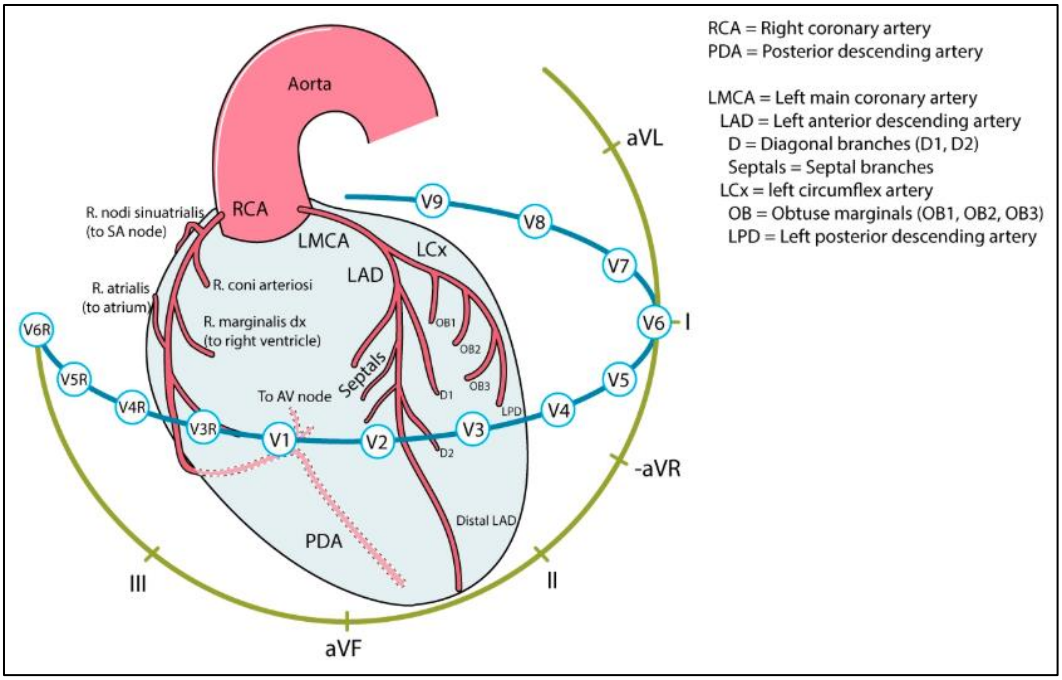
- STE in V7-V9 have 90% specificity and 50% sensitivity for posterior wall STEMI.
- >1 mm STE in V7–V9 is diagnostic of a true posterior STEMI. >0.5mm are suggestive and should raise concern

CRITICAL LMCA/PROXIMAL LAD**: STE >1 mm in aVR** AND **STE in aVR > V1** OR **widespread STD** (most prominent in I, II, and V4–V6). A high index of suspicion is required since some of these will be labeled as NSTEMI due to the dominant feature of multi-lead STD (note also that LMCA occlusion will often result in out-of-hospital cardiac arrest, so this may be a relatively rare ECG/ACS phenotype).

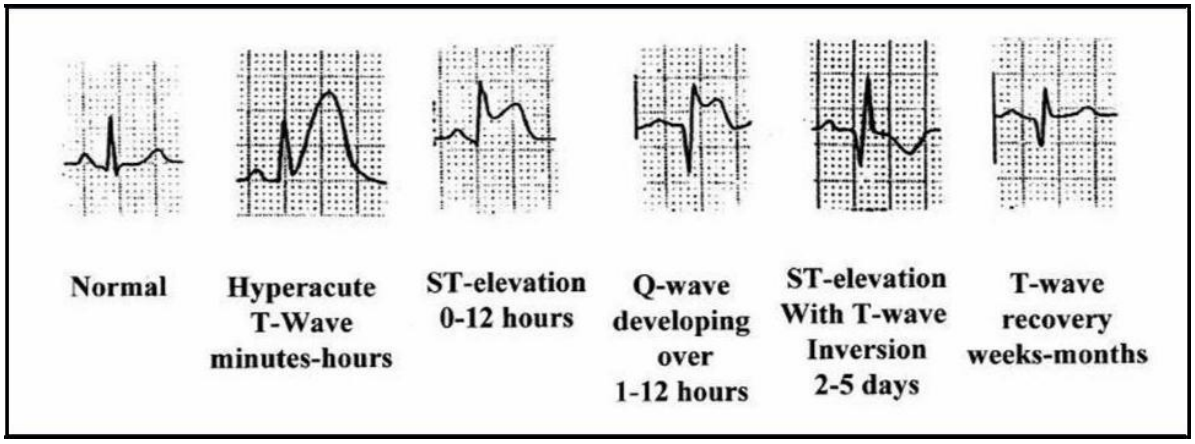
Culprit Vessel and ECG Findings[5]

CATEGORY	ANATOMY OF OCCLUSION	ECG FINDINGS
Proximal LAD (antero-lateral MI)	Prox to 1st septal perforator	STE V1–6, I, aVL +/– BBB
Mid-LAD (antero-lateral MI)	Distal to 1st septal perforator, prox to 1st diag	STE V1–6, I, aVL
Distal LAD/Diag (apical MI)	Distal to diagonal or diagonal itself	STE V31–6 or I, aVL, V5–6
High Lateral MI	Proximal LCx	STE I, aVL +/– V5, V6
"Low" Lateral (apical MI)	Distal LCx	STE V5, V6
Large IMI	Proximal RCA (90%) or LCx (10%)	STE II, III, AVF *and:* 1. V1, V3R, V4R *(RV)* 2. V5-V6 *(lateral/apical)* 3. R>S V1-2, STD V1-V3, STE V8 *(posterior)*
Small IMI	Distal RCA, LCx branch	STE II, III, aVF





Evolution of the ECG in ST Elevation MI[6]



A subset of patients who initially present with STE do not develop Q-waves. This subset of patients typically has a better prognosis (as this may indicate vasospasm rather than plaque rupture as the primary driver of injury).

Other Notable ECG patterns:
Pre-existing RBBB: Interpret ECG as if no BBB. If deep discordant STD in V1-V3, check posterior leads.
deWinter's T-waves (2% of STEMIs): Tall symmetric T-waves + >1mm STD at J-point in precordial leads + 0.5-1mm STE in aVR, may evolve to STEs, consistent w/ acute LAD occlusion.
Wellen's Pattern: Biphasic T waves (25%; Type A) or symmetric, deeply inverted T waves (75%; Type B) in V2, V3
Wellen's Syndrome: Wellen's pattern in patients with resolved CP → indicates reperfusion of myocardium consistent with **LMCA or prox LAD stenosis**. 75% of pts will have anterior MI in

days to weeks if not treated. Should proceed to cath lab WITHOUT stress testing. *DDx*: apical HCM, coronary vasospasm, elevated ICP (long QTc), MI, PE, post-tachycardia/pacing, BBB, WPW, idiopathic.

NOTE: Not all STE or STD indicate myocardial ischemia. The following is a differential for ECG changes:

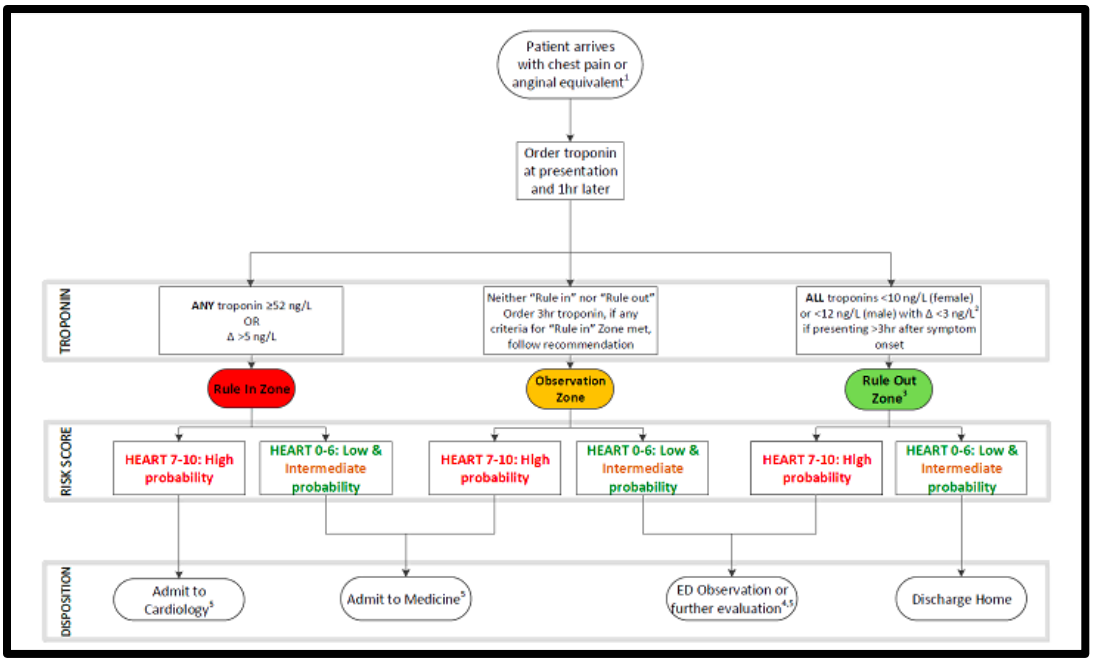
DDx ST Elevations		DDx ST Depressions
Acute MI	Takotsubo/stress cardiomyopathy	Ischemia, NSTEMI
Vasospastic Angina	Massive PE (V1, V2 occasionally)	Posterior wall MI
Benign Early Repolarization	Brugada pattern (V1–V3 with RBBB)	Digoxin effect
Acute Pericarditis	Tumor or Trauma	Pericarditis
LVH or LBBB	V-paced rhythms	LVH or LBBB
LV Aneurysm	Hypothermia (Osborn/J wave)	LV Aneurysm
Myocarditis	Post-DC cardioversion (rarely)	Myocarditis
Hyperkalemia (V1, V2)	Hypercalcemia (rarely)	Hypokalemia

D. Cardiac Biomarkers

The presence of myocardial injury is defined by an elevation in cardiac troponin >99% ULN. Myocardial injury may be acute (with a rise and/or fall in troponin concentration) or chronic (with a stable elevation in troponin). If there is evidence of myocardial injury PLUS clinical signs and symptoms of ischemia then a diagnosis of *myocardial infarction* is made. There are many different biomarkers that are currently in use or have been used historically.

Troponin: Troponin-I and troponin-T are both biomarkers of cardiac injury. Either biomarker can be detected using high-sensitivity assays. At MGH, we now use a hsTnT assay. An elevated troponin is defined as: hsTnT ≥10 ng/L (in F) and ≥12 ng/L (in M).

- High-Sensitivity Troponin (hsTnT):
  - Advantages: Rapid rule-out of MI in the ED, facilitating earlier discharge
  - Caveats:
    - Troponin concentration will be detectable in >50% of healthy adults
    - Numbers are now expressed in ng/L (previous ng/mL)
    - A single troponin value does not tell the mechanism of injury
  - Converting numbers between assays (4th generation to current hsTnT assay):
    - For values > 0.1 in the 4th generation assay, multiply by 1000 to get hsTnT
    - For values < 0.1, the following are important values to remember
      - A 4th generation cTnT value of 0.01 ng/ml = hscTnT value of 30 ng/L
      - A value of 0.03 ng/ml = hscTnT value of 53 ng/L
  - How to Use:
    - In the ED (or CP onset ≥ 3hr): See MGH ED algorithm below (NOTE: **This is a triage algorithm; i.e. not an algorithm to diagnose MI)**
    - On the Floor (or CP onset < 3hr): **Baseline** + **3hr repeat**. A rising *OR* falling value ≥ 5 AND symptoms or ECG changes → consider ACS. If baseline troponin >99th percentile, a rise and fall of 20% is suggestive of MI. You can also check in 1-hour if you are worried



- In ESRD/CKD, cardiac troponin will be elevated in many patients, especially with the high sensitivity assays. The mechanism is not completely understood, **but decreased clearance of troponin is not thought to be the main mechanism**. Rather, elevated troponin levels in this population are thought to represent microvascular ischemia. In addition, patients with CKD often have LVH, which is associated with troponin release. As with the general population and hsTnT, the "delta" in troponin values is critical to determine the likelihood of an acute coronary syndrome

CK-MB: CK-MB peaks within 24 hrs and normalizes within 48-72 hrs, while TnT peaks within 12-48 hours and returns to normal within 5-14 days. Theoretically, this makes CK-MB an optimal marker for re-injury or re-infarction. At MGH, CK and CK-MB are no longer used routinely except post-PCI to evaluate for infarct size or when reinfarction is suspected.

References:

1. Swap, Clifford J., and John T. Nagurney. "Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes." *Jama* 294.20 (2005): 2623-2629
2. Rautaharju, Pentti M., Borys Surawicz, and Leonard S. Gettes. "AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology." *Journal of the American College of Cardiology* 53.11 (2009): 982-991
3. Sgarbossa, Elena B., et al. "Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block." *New England Journal of Medicine* 334.8 (1996): 481-487
4. Zimetbaum, Peter J., and Mark E. Josephson. "Use of the electrocardiogram in acute myocardial infarction." *New England Journal of Medicine* 348.10 (2003): 933-940

5. Zimetbaum, Peter J., and Mark E. Josephson. "Use of the electrocardiogram in acute myocardial infarction." *New England Journal of Medicine* 348.10 (2003): 933-940
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18. Risk Stratification

A. Risk Scores

There is a Class IIa recommendation that risk-stratification models (e.g. TIMI, GRACE, PURSUIT, HEART) be used to assist with decision making in patients with UA/NSTEMI. The purpose of risk stratification is first to assist with triage decisions (e.g. discharge with follow-up, 24-hr observation admission, general ward, SDU/CCU) and next to determine the timing of intervention.

The most well-validated risk scores are the TIMI and GRACE. The MGH ED uses the HEART score in their algorithm. At MGH, the TIMI Risk Score is most often used.[1]

Table 1: TIMI Risk Score

Predictor Variable	Point Value of Variable	Definition
Age ≥65 years	1	
≥3 risk factors for CAD	1	Risk factors • Family history of CAD • Hypertension • Hypercholesterolemia • Diabetes • Current smoker
Aspirin use in last 7 days	1	
Recent, severe symptoms of angina	1	≥2 anginal events in last 24 hours
Elevated cardiac markers	1	CK-MB or cardiac-specific troponin level
ST deviation ≥0.5 mm	1	ST depression ≥0.5 mm is significant; transient ST elevation >0.5 mm for <20 minutes is treated as ST-segment depression and is high risk; ST elevation ≥1 mm for more than 20 minutes places these patients in the STEMI treatment category
Prior coronary artery stenosis ≥50%	1	Risk predictor remains valid even if this information is unknown

Calculated TIMI Risk Score	Risk of ≥1 Primary End Point* in ≤14 Days	Risk Status
0 or 1	5%	Low
2	8%	
3	13%	Intermediate
4	20%	
5	26%	High
6 or 7	41%	

*Primary end points: death, new or recurrent MI, or need for urgent revascularization.

TIMI Score of ≥3 or GRACE score of >140 and high clinical suspicion for a Type 1 MI warrants an early invasive strategy (catheterization ≤ 48hrs), though notably, the TIMACS study showed that early intervention (≤24 hrs) did not differ from delayed intervention (>36 hrs) in preventing death, MI, or stroke in NSTEMI patients.[2]

The decision for angiography in patients with NSTEMI should always be made *while considering the underlying pathophysiology of a particular acute coronary event* (e.g. coronary angiography may not be necessary in Type 2 MI), as well as the patient's baseline risk profile. For instance, elderly women have *worse* outcomes with an aggressive up-front interventional strategy. In general, these patients experience benefit from a routine invasive strategy though the timing of angiography remains somewhat controversial.[3]

B. Stress Testing
In general, there is no role for stress testing when true ACS is suspected. It is a diagnostic tool utilized most appropriately for CAD/stable ischemic heart disease (see section in SIHD).

C. Coronary CTA
CCTA uses iodinated contrast and multidetector CT scanning to evaluate the coronary anatomy. The imaging is highly sensitive and specific (85/95% respectively) for identifying coronary stenosis. It has a high NPV for ruling out coronary artery stenosis (99% in low-risk individuals).[4] CCTA is less useful in individuals with extensive calcifications or stented vessels due to "blooming artifact". It should NOT be used to screen asymptomatic individuals. Common uses include:

- **Low to intermediate risk patients** in the ED **who present with new CP (i.e. to rule out ACS)**
- Assess patency of CABG
- Assess anatomy (e.g. detect anomalous coronaries)
- Map CTO prior to catheterization

CTA for the evaluation of stable chest pain significantly reduces non-fatal MIs and deaths from CAD (2.3% vs 3.9%) at 5 years, without resulting in a significantly higher rate of coronary angiography or coronary revascularization.[5]

Fractional flow reserve (FFR) can be computed on CCTA to determine the hemodynamic relevance of stenosis. FFR derived from CCTAs closely mimic invasive FFR (obtained by conventional angiography) and may provide some functional data. Unlike stress imaging, CCTA (and cMRI) are *not* functional tests (e.g. they cannot discern ischemia) and they can only identify the degree of stenosis. Of note patients with renal dysfunction will NOT be able to receive iodinated contrast.

References:

1. Antman, Elliott M., et al. "The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making." *Jama* 284.7 (2000): 835-842
2. Mehta, Shamir R., et al. "Early versus delayed invasive intervention in acute coronary syndromes." *New England Journal of Medicine* 360.21 (2009): 2165-2175
3. Mehta, Shamir R., et al. "Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials." *Jama*293.23 (2005): 2908-2917
4. Budoff, Matthew J., et al. "Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial." *Journal of the American College of Cardiology* 52.21 (2008): 1724-1732
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19. Triage Decisions

Directly to Cath Lab:

- STEMI
- UA/NSTEMI accompanied by high-risk features, including:
  - Cardiogenic shock
  - CP that is refractory to anti-ischemic and anti-anginal therapies
  - Electrical instability (frequent NSVT, unstable SVT, or sustained VT)

CICU Admission: Any patient in cardiogenic shock, having refractory chest pain, or electrical instability. Ideally, these patients will go to the catheterization lab first. Some of these patients will need mechanical support (IABP or Impella) +/- RHC. If patients are very high-risk and *cannot* proceed directly to cardiac catheterization, they should also be considered for CICU admission.

SDU/CAU Admission: Those with evidence of ischemia by history, ECG, or initial (or early repeat troponin) provided **that their pain has resolved** and has not recurred. In general, patients with evidence of UA/NSTEMI will be admitted to the SDU/CAU to await an expedited angiogram. However, clinical deterioration, rapidly rising troponin, marked/developing ECG changes, dysrhythmia, etc. should prompt consideration for more urgent catheterization.

EDOU: Those with a *non-diagnostic* history and initial ECG (as well as negative troponin) should have alternative causes of CP sought. If no cause is identified, a troponin and ECG should be repeated in 3 hours, often through admission to an EDOU. If suspicion remains after this time for ACS but data suggests low objective risk, a **stress test** could be performed to evaluate for inducible ischemia or the presence of stable CAD (as is the case with coronary CTA).

> **Exercise stress testing** may be safely performed in those at low risk for MI with a normal or non-diagnostic ECG and negative cardiac biomarkers at 6-12 hrs after presentation, with no active CP for the prior 24 hrs. For certain individuals at low risk (age ≤ 70, no prior CAD, CVD, PAD, or angina at rest) with good expected follow-up, stress testing may also be performed as an outpatient within 72 hrs.
> In addition to evaluation in ACS (patients presenting with CP but with a low pre-test probability), **coronary CTA** may also be used to evaluate for stable CAD in **low-risk patient** or those with an **equivocal** stress test. If the results of stress test or CTA indicate the person is **no longer low risk**, the patient should be considered for catheterization (cardiology input should be sought in questionable cases).

Bigelow Admission: Those with cardiac risk factors but an equivocal history for ischemia may be considered for admission to the Bigelow. In general, these patients should have a negative ECG and negative early and repeat troponins (6-8 hrs after the onset of symptoms). Generally speaking, if the patient has a high probability of needing coronary angiography for definitive diagnosis or management or has ongoing CP that is likely to be ischemic in origin (no better/alternative diagnosis), they should be considered for admission to a dedicated cardiac floor.

STEMI in Admitted Patients: For patients who develop a **STEMI** while already on an MGH inpatient floor. The number to call is 6-8282. While any provider may initiate this process, it is generally preferred to first call a **Rapid Response.** This will bring the Senior-On (among others) to evaluate the patient and to determine the need to notify the on-call interventional attending.

Note that calling 6-8282 **DOES NOT** activate the cath lab but puts you in touch with the interventional attending (if after hours) or the cath lab charge RN (if during business hours). The decision to activate the cath lab will then be made by the attending interventionalist. If there is uncertainty about the ECG meeting STEMI criteria, STAT page the general cardiology fellow on call.

On-call cardiology assignments can also be viewed through amion.com, password mghcard.

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20. Medical Treatment

If concerned for ACS, all patients at MGH (*without contraindications*) should receive the following medications up front:

1) ASA 325 mg, chewed/crushed
2) Atorvastatin 80 mg
3) Beta blocker (usually metoprolol tartrate) for HR goal of around 60 bpm
4) Heparin (ACS protocol)
5) Nitroglycerin (attempts should be made to relieve chest pain)
6) Blood pressure control (reduce afterload)

Decisions regarding P2Y12 inhibitors and other medications should be had in conjunction with cardiology. See below for contraindications and more information regarding medical therapy in ACS.

A. Anti-Platelet

ASA

- Indication: All patients with suspected ACS
- Dose: 325 mg, non-enteric coated, chewed/crushed (onset of action 20 min); 81 mg daily thereafter for lifetime
- Mechanism of action: Irreversibly inhibits prostaglandin H synthase (cyclooxygenase-1) in platelets; prevents the formation of thromboxane A2, a potent vasoconstrictor and platelet aggregator.
- Evidence/Benefit:
    - Mortality reduction: Associated with 23% relative risk reduction in 5-week mortality (9.4% in ASA vs 11.8% in placebo).[1]
    - Non-fatal reinfarction: 50% RR reduction (2.0% vs 1.0%)
    - Maintenance dose: there is likely no benefit (w/ some potential for harm with increased GIB) for chronic therapy with ASA 325 mg PO daily over ASA 81 mg PO daily when administered as part of a dual-antiplatelet regimen after ACS (with or without PCI).[2] In patients receiving ticagrelor, ASA 81 mg PO daily is explicitly recommended instead of 325 mg PO daily. (US centers did not show mortality benefit in the PLATO Trial, which was felt to be driven by the increased ASA dose in US centers relative to European sites).
- Aspirin allergy, limited data exists but recommendations include 1) **substitution of a P2Y12 inhibitor** 2) cilostazol instead of aspirin, 3) vorapaxar instead of aspirin. In all cases, when patient is stable, aspirin desensitization with Allergy/Immunology is recommended.

P2Y12 Inhibitors

- Indication: STEMI, Type I NSTEMI/UA (regardless of if medical management or an invasive strategy is chosen)
- Dose: See below for different agents
- Mechanism of action: These drugs inhibit the G-protein couple receptor P2Y12 that interact with ADP in the process of platelet activation; see notes below for different agents
- Evidence/Benefit: See below for different agents
- Timing: No clear evidence that before angiography is better than in-lab administration. **Discuss with cardiology fellow or attending regarding timing of administration.**

Clopidogrel:

- Dose: 300-600 mg loading dose + 75mg daily

    - 600 mg dose vs 300 mg dose: Maximal platelet inhibition is reached within 2 hrs w/ a 600 mg loading dose vs. 15-24h w/ a 300 mg loading dose. This correlates with better outcomes both in those with STEMI (HORIZONS-AMI, CURRENT-OASIS) and NSTE-ACS (ARMYDA 2) who underwent PCI.[3-5]
- Pharmacokinetics: requires conversion to active metabolite, irreversible binding, platelet functions returns to baseline around ~5 days after last dose
- Evidence/Benefit:
    - CURE (NSTEMI): Decrease in the primary end point of CV death, non-fatal MI, stroke in patients that received clopidogrel + ASA vs ASA alone (9.3% vs 11.4%, driven mostly by recurrent MIs) that presented with NSTEMI. Increased risk of major bleeding (3.7% vs 2.7%), but not life-threatening or hemorrhagic stroke.[6]
    - PCI-CLARITY (STEMI): at 30 days post-PCI, clopidogrel therapy was associated with decrease in combined primary end point of CV death, MI, stroke (3.6% vs 6.2%).[7]
- Important considerations:
    - CYP2C19 genotype variants: poor metabolizers of clopidogrel with decreased response based on high platelet reactivity (unclear relationship to CV events and bleeding). These individuals are at higher risk of in-stent thrombosis with clopidogrel. Most studies have not shown benefit of increasing dose of clopidogrel in these patients. Switch to another agent.
        - Consider genetic testing if patient presents for in-stent thrombosis.
    - Clopidogrel is a generic drug and is much less expensive than most of the other anti-platelet choices; thus, it remains the treatment of choice for many cardiologists despite trial benefit of increased efficacy of newer agents

Ticagrelor:
- Dose: 180 mg load followed by 90 mg BID maintenance
- Pharmacokinetics: Reversible binding = faster acting, shorter duration, BID dosing. Does not require activation by CYP450 system
- Evidence/Benefit
    - PLATO: Compared ticagrelor to clopidogrel. Improved primary end point of MI, stroke, vascular death (9.4 vs 10.8%) without significant increase in non-CABG related bleeding. Also reduced mortality alone (HR 0.82)[8]
    - First anti-platelet agent since aspirin therapy to show a mortality benefit in ACS
    - PLATO trial showed a reduction in stent thrombosis. Thus, ticagrelor is used in many circumstances for those individuals who have had in stent thrombosis on clopidogrel ("nonresponders")
- Important considerations:
    - Side effects: Associated with the development of dyspnea and more rarely, heart block, potentially related to inhibition of adenosine metabolism. Higher bleeding risk than clopidogrel.

Prasugrel:
- Dose: 60mg loading dose, followed by 10mg daily
- Pharmacokinetics: Prodrug with more potent inhibitor of platelet aggregation than clopidogrel
- Evidence/Benefit:
    - TRITON TIMI 38: Reduction in CV death, MI, stroke compared to clopidogrel but high major and life-threatening bleeding[9]

    - PRAGUE-18: compared ticagrelor to prasugrel with no significant difference in outcomes[10]
- Important considerations:
    - Contraindicated if prior TIA/CVA, weight < 60 kg, or >75 years old
    - Timing: No role in upstream use (prior to coronary anatomy known in the cath lab) or in NSTEMI/UA[11]

Cangrelor:
- Dose: 30 mcg/kg bolus followed by 4 mcg/min/kg for PCI
- Pharmacokinetics: Intravenous, fast-acting; half-life of ~3–5 minutes. Ability to restore platelet function approximately one hour after infusion
- Evidence/Benefit
    - CHAMPION-PHEONIX: More effective in patients prior to undergoing urgent or elective PCI than clopidogrel in reducing death, MI, and ischemia-driven revascularization at 48 hours; also, less in stent thrombosis compared to clopidogrel; similar rates of severe bleeding[12]
- Use: Expensive, so use is limited. Consider in a patient that cannot take oral P2Y12 (critically ill in the CCU where there is concern for absorption)

Switching between P2Y12 inhibitors: Either for cost or bleeding risk (de-escalation, switching to clopidogrel) or need to switch to a more potent agent (escalation, switching to ticagrelor), switching between P2Y12 is sometimes necessary. The most common switches are:
- Switching from ticagrelor to clopidogrel: Some differences in opinion on timing of loading dose (12 vs 24 hours). Based on the PK of ticagrelor (BID dosing), giving loading dose of clopidogrel (usually 600 mg) 12 hours after last dose of ticagrelor seems logical. However, the most recent consensus statement says 24 hours after ticagrelor dose.[13] The pharmacokinetic studies have shown there are no differences in platelet activity between 12- and 24-hour initiation.[14] MD clopidogrel started the following day after LD.
- Switching from clopidogrel to ticagrelor: When in the acute/early phase (<30 days), 180 mg ticagrelor irrespective of when the last clopidogrel dose was, ticagrelor maintenance dose given ~24 hours after last clopidogrel dose. If switching after 30 days, 90 mg ticagrelor 24 hours after maintenance dose

Glycoprotein IIb/IIIa inhibitors
- Indication: If used, typically initiated in the cath lab and may be continued for 12–24 hours after PCI, especially in those with persistent thrombus. Usually not needed in patients who have received DAPT and no evidence of ongoing ischemia.
- Drugs: Eptifibatide, abciximab, and tirofiban. Eptifibatide (Integrilin) most often used at MGH
- Mechanism of action: These drugs block the glycoprotein IIb/IIIa receptor, the binding site for fibrinogen, von Willebrand factor and other ligands critical to platelet aggregation. Inhibition of this final common receptor reversibly blocks platelet aggregation and prevents thrombosis.
- Evidence/Benefit:
    - There has been evidence of mortality benefit in patients presenting with STEMI. A meta-analysis of 11 trials showed that apiciximab lowered rate of death at 30 days (2.4% vs 3.4). However, these patients were NOT treated with P2Y12 inhibitors[15]
    - More contemporary trials have suggested lack of benefit when used with P2Y12 inhibitors.

- Data to suggest benefit of of IIb/IIIa inhibition in high-risk patients such as those with elevated troponin biomarkers, those with diabetes, and those undergoing revascularization who are not treated up-stream with bivalirudin
- Early use of eptifibatide associated with increased risk of bleeding in patients who had already received clopidogrel[16]

B. Lipid Lowering Therapy

Statins

- Indication: All patients who present with ACS
- Dose: During ACS, typically atorvastatin 80 mg with data showing superiority to moderate dose pravastatin, though rosuvastatin 20 or 40 mg PO is a reasonable alternative; data supports that high intensity statin therapy rather than the specific agent used is associated with mortality benefit[17]
- Mechanism of action: 1) LDL-C lowering through hepatic upregulation of LDL receptors secondary to inhibition of cholesterol biosynthesis, 2) plaque stabilization and prevention of plaque rupture (this may be a relevant mechanism during an ACS event), 3) anti-inflammatory, anti-thrombotic and endothelial stabilization effects (incompletely understood).
- Evidence/Benefit:
  - For immediate high intensity: PROVE IT TIMI suggests benefit of high intensity statin (vs pravastatin) seen as early as 15 days post MI.[18] This argues for early initiation of high intensity rather than gradual up titration
  - Before or after PCI: SECURE-PCI trial evaluated initiation of statin therapy before planned PCI or 24 hours after. At 30 days, there was no difference in primary composite outcome. However, in a subgroup analysis the population that underwent PCI, there appeared to be benefit to administering statin prior to PCI[19]
  - Overall Benefit: Associated with reductions in death, adverse cardiac events, readmission for recurrent angina, atherosclerosis, and reduction in infarct size[20-21]

Ezetimibe

- Indication: Not typically given in ACS (as most patients given high intensity statin). Reasonable to start in someone who cannot tolerate high intensity statin or who has failed statin therapy (see discharge planning for more information). Recommended for patients with MI who have an LDL >70 despite high dose statin.
- Dose: 10 mg daily
- Mechanism of action: LDL-C lowering through inhibition of an intestinal enterocyte cholesterol transporter thus reducing dietary cholesterol uptake and ultimately promoting hepatic LDL uptake
- Evidence/Benefit: IMPROVE-IT demonstrated that in patients with recent ACS (prior 10d), addition of ezetimibe to a moderate intensity statin is associated with a reduction in CV mortality, major CV event or non-fatal stroke when compared to statin therapy alone (34.7% vs 32.7%, p=0.016). There was no reduction in all-cause mortality or stroke. *Of note, patients already on a high-potency statin were excluded*[22]

C. Beta Blockers

- Indication: Oral beta-blocker therapy should be initiated within 24 hours of STEMI/NSTEMI in patients without contraindications
- Dose/Route: In general, we usually start with metoprolol tartrate PO q6h and titrate up for goal HR 55–60. IV beta blockers should not be routinely given to patients with NSTEMI as

this may lead to increased risk of cardiogenic shock, though they may be considered for treatment of hypertension if there are no contraindications.[23]

- Mechanism of action: Beta-blockers reduce the magnitude of infarction, rate of reinfarction, and frequency of life-threatening ventricular tachyarrhythmias by decreasing myocardial oxygen demand and sympathetic tone. This occurs by decreasing heart rate, systemic arterial pressure, and myocardial contractility. In addition, prolongation of diastole secondary to the reduction in heart rate may augment perfusion to ischemic myocardium, particularly to the sub endocardium.
- Evidence/Benefit: Has been relatively well studied in STEMI patients, not so in NSTEMI patients. Has also been studied under certain revascularization approaches:
    - No reperfusion: 25% reduction in mortality at 1 year. However, these patients did not receive statin or P2Y12 therapy
    - Fibrinolysis: No high-quality evidence
    - PCI: No RCTs, just observational studies. One observational study showed significant mortality benefit, 2.8% vs 4.1%, while other meta-analyses have not[24,25]
- Contraindications: Signs of HF and evidence of low output state. Relative contraindications include the following: active asthma or reactive airways, PR interval > 0.24 seconds, or second- or third-degree heart block.

D. Nitroglycerin

- Indication: Patients with ongoing ischemic discomfort should receive nitroglycerin. IV nitroglycerin is indicated within the first 48 hours after NSTEMI for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. IV nitroglycerin should not preclude other mortality-reducing interventions, such as beta-blockers and/or ACE-I
- Dose: Sublingual 0.4 mg every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin
- Mechanism of action: Nitroglycerin forms nitric oxide, which in smooth muscle induces relaxation and vasodilation in peripheral veins and arteries. This reduces cardiac oxygen demand by decreasing preload, with modest effects on afterload and dilation of coronary arteries
- Contraindications: Nitrates should not be administered to patients with SBP < 90 or ≥ 30 mm Hg below baseline, suspected RV infarction (V4R elevation), or patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the preceding 24 hours

E. ACE-I and ARBs

- Indication: An ACE inhibitor should be administered orally within the first 24 hours of (N)STEMI to patients with any of the following:
    - Anterior infarction
    - Diabetes
    - LVEF less than 40%
- Dose/Agent: At MGH, we generally start with short-acting captopril and titrate to BP, with conversion to a long-acting agent prior to discharge. An ARB should be substituted in patients who are intolerant of ACEi
- Mechanism of action: The primary mechanism of benefit in ACS is attenuating the remodeling of the myocardium. Additional protective mechanisms include preservation of ischemic preconditioning, reduction of recurrent MI and ischemia (through reducing afterload and mitigating vasoconstriction induced by angiotensin II) and reduction in sudden cardiac death through decreased sympathetic activity and reduced ventricular remodeling

- Evidence/Benefit: Use in early MI is supported by several trials (ISIS-4, GISSI-3, CONSENSUS-II, AIRE, SAVE). In a meta-analysis, the absolute benefit was greatest in certain high-risk groups (Killip class 2 to 3 and HR > 100 bpm) in anterior MI[26-31]
- Contraindications: Hypotension (SBP < 100 mm Hg or > 30 mm Hg below baseline)

F. Anticoagulation

- Indication: All patients with NSTEMI/STEMI without contraindication. If on warfarin, do not start until INR < 2. If on a DOAC, consult with pharmacy regarding the best time to start anticoagulation.
- Agent/Dose:
    - Heparin: Agent of choice at MGH. Unfractionated heparin (at a dose of 60 U/kg bolus followed by 12 U/kg/hr drip, titrating to goal PTT 50–70) is the anticoagulant of choice, especially if the patient will proceed to catheterization as the activated clotting time (ACT) can be followed during the procedure, leading to lower bleeding rates
    - Bivalirudin: Reserved for patients with HIT
        - Compared to heparin: Ongoing debate, but most recent evidence (MATRIX) is that there may be a modest reduction in bleeding, but a slight increase in in-stent thrombosis with bivalirudin. Overall there was no difference in primary ischemic endpoint of death from any cause, MI or stroke at 30 days[32]
    - Enoxaparin: For patients in whom a conservative strategy is selected, it is a Class IIa recommendation to select enoxaparin or fondaparinux over UFH. This is based on evidence of decrease in primary composite end-points as compared to heparin (ESSENCE, TIMI11B, and Phase A to Z trials).[33,34] Of note, enoxaparin resulted in higher rates of bleeding in patients age > 75 years, though the rate of bleeding was greatest when patients were transitioned from LMWH to UFH or vice versa (SYNERGY).[35] Dose is 1 mg/kg BID, no loading dose necessary
- Mechanism of action: Treat intra-coronary thrombus and thrombogenesis that leads to acute reduction in coronary blood flow. There are two pathologically distinct types of thrombus that typically form: the platelet laden “white clots” (more often seen in NSTEMI specimens), and erythrocyte rich “red clots” (more often seen in STEMI specimens). Anticoagulants have been shown to be effective in both types of clots and in both types of MI, as they target fibrin. Fibrin provides the non-cellular matrix (or “mesh”) upon which platelet cross-link in Type 1 NSTEMI, and furthermore represent the scaffold upon which erythrocytes accumulate in Type 1 STEMI. In addition, fibrin itself is involved in platelet activation, and therefore anticoagulants may themselves additionally demonstrate antiplatelet properties.
- Length of therapy:
    - After PCI: Stop
    - If PCI is *not* performed (but CAD seen on angiography): Continue intravenous UFH for at least 48 hours or until discharge; continue enoxaparin or fondaparinux for duration of the hospitalization, up to 8 days; either discontinue bivalirudin or continue at a dose of 0.25 mg/kg per hour for up to 72 hour
    - Medical management: UFH should be continued for 48 hours OR enoxaparin or fondaparinux should be administered for hospital duration, up to eight days
    - Of note: Discontinuation of heparin can sometimes cause a “heparin rebound” syndrome, or a brief period of hypercoagulability during which patients may experience worsening angina.[36] Heparin rebound is effectively managed through the use of aspirin alone, although progressive weaning of UFH drip is another method to ameliorate transient hypercoagulability. In patients who cannot receive aspirin,

another antiplatelet should be utilized and consideration for UFH wean can be considered

G. Oxygen

- Indication: O2 should be used to maintain SaO2 > 90%. Routine use of supplemental O2 in cardiac patients without hypoxemia is not beneficial and may be harmful (AVOID).[37]
- Evidence/Benefit: The best evidence regarding harms and benefits of supplemental O2 in ACS comes from the DETO2X-AMI trial. This was a registry-based randomized trial in over 6,600 patients with suspected MI and SaO2 > 90% were randomized to either supplemental O2 (6L/min for 6-12 hrs) or ambient air. This study found no difference in rate of all-cause mortality within 1 year and no difference in rehospitalization with MI in 1 year or hospitalization for heart failure[38]

H. Morphine

- Indication: First, attempt to reduce pain with nitroglycerin drip. Reasonable to consider if patient either cannot tolerate nitroglycerin drip or pain is severe on high doses of a nitroglycerin drip
- Dose: Morphine sulfate (1 to 5 mg IV repeated at 5- to 30-minute intervals) is recommended as the analgesic of choice in patients with STEMI and is reasonable for management of pain associated with NSTEMI, which is not relieved with TNG (Class IIb)
- Mechanism of action**:** Reduction in pain**,** which is often severe in the acute phase of the event, contributes to increased sympathetic activity
- Of note: Morphine in acute MI significantly delays antiplatelet effect of clopidogrel due to direct effects on plasma levels of clopidogrel active metabolite and delays and attenuates ticagrelor exposure and action.[39,40] Additionally, morphine has been associated with increased mortality in NSTEMI patients (based on a large retrospective analysis[41,42]

I. Fibrinolysis

- Indication: Fibrinolysis is recommended by the 2013 ACC/AHA guidelines for STEMI for patients with symptom onset within 12 hours who cannot receive primary PCI within 120 minutes of first medical contact
- Timing: Time from hospital arrival to initiation of fibrinolysis should be < 30 min. Fibrinolysis has not improved outcomes in patients who present > 12 hrs after symptom onset and thus is not recommended for patients who are stable or asymptomatic. But it can be considered up to 24 hrs after symptom onset if the patient has ongoing angina symptoms (constant or intermittent) and PCI is not available
- P2Y12 inhibitors: Patients receiving fibrinolysis benefit from pretreatment with clopidogrel but not GpIIb/IIIa inhibitors
- Ticagrelor and prasugrel have not been evaluated as initial P2Y12 inhibitor therapy in STEMI patients treated with fibrinolysis and therefore they are not currently recommended in part due to increased bleeding risk over clopidogrel
- The TREAT trial showed that early use of ticagrelor may be safe with regard to bleeding. In this trial almost 3800 patients treated with fibrinolysis were randomly assigned to clopidogrel vs ticagrelor after fibrinolysis and there was no difference in both groups in the primary outcome of TIMI major bleeding in 30 days. Based on the results of this trial, it is considered reasonable to switch from clopidogrel to ticagrelor 12-24 hrs after fibrinolytic therapy, and also continue ticagrelor for 1 year, based on extrapolation from the PLATO trial[43]

Cocaine-induced myocardial infarction

- Aspirin should be used at a dose of 325 mg unless suspicion of acute aortic dissection
- Sublingual nitroglycerin is commonly also given at a dose of 0.3-0.4 mg q5min until chest pain is relieved up to 3 doses
- Calcium channel blockers are adjunctive treatments for ongoing/recurrent symptoms of ischemia despite optimal therapy with nitroglycerin. Usually IV diltiazem 5-20 mg or verapamil 2.5-5 mg is used
- For agitation 2/2 cocaine, benzodiazepines (diazepam 5-10 mg IV q3-5 min) is also used (Grade 2C recommendation)
- Beta blockers are NOT recommended for cocaine-associated MI or ischemia prior to elimination of cocaine from patient's body based on theoretical considerations of coronary artery vasoconstriction and systemic hypertension from unopposed alpha adrenergic stimulation. However, this is not universally accepted and some still give beta blockers. If beta blockers are to be used, mixed alpha/beta blockers such as labetalol and carvedilol are favored over nonselective beta blockers
- Reperfusion is an important early part of management

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TOC

21. Catheterization, PCI, and CABG

A. Indications for Percutaneous Coronary Intervention (PCI)

PCI can be used in:
1. Treatment of STEMI
2. UA/NSTEMI
3. Stable CAD refractory to OMT

- STEMI: Primary PCI in STEMI (including true posterior MI) or presumed new LBBB who can undergo PCI within 12hrs of symptom onset
  - If patient arrives in the ED, ED staff activates cath lab with optimal door-to-balloon time of 90min
  - If patient has STEMI while on inpatient floor, activate **MGH STEMI protocol: Call Rapid Response (x6-3333**) → will activate Senior On to evaluate patient and determine need to call on-call interventional cardiologist (x6-8282) and decide whether to activate cath lab

- UA/NSTEMI: Management less clear-cut. If severe-refractory angina or high-risk features (HD instability, cardiogenic shock, malignant arrhythmias), patient likely benefits from early invasive strategy (PCI within 24h of presentation). Intermediate-low risk patients do not show similar benefit. See risk-stratification section for more information.

- Stable CAD refractory to OMT: Electively for refractory or severe symptoms, change in symptom severity, high-risk coronary anatomy, LV dysfunction (PCI or CABG as appropriate)

B. Access

- Commonly used access for cardiac catheterization includes transradial (TRA) and transfemoral (TFA) approaches
- The RIVAL trial demonstrated that TRA was non-inferior to TFA in terms of death, MI, stroke, and non-CABG related bleeding; in STEMI subset, TRA was associated with a 30-d all-cause mortality benefit[1]
- Strong evidence to suggest ↓ rates of bleeding and ↓ vascular complications with TRA vs TFA
- AHA endorses a "radial-first" strategy for PCI in ACS[2]

Radial Access:
1. After catheterization, a clear plastic band (TR Band) with an inflatable pressure pad is secured around the access site. The sheath is withdrawn and the inflatable pressure band is adjusted to a pressure just above that which produces leakage from the access site, allowing sufficient blood flow to transport hemostatic factors to the area. The site can be checked 1-2 hours later and if hemostasis is achieved, the band can be removed.

Femoral Access:
1. After catheterization, the FA sheath can be removed when the activated clotting time is <180-200. Gentle downward pressure is applied and the sheath is removed. This is followed by 15-20 mins of application of manual pressure. Vascular closure devices (e.g. Angio-Seal) may be indicated in fully anticoagulated patients, patients who have difficulty

lying flat and other select scenarios to achieve faster hemostasis. The size of the sheath should be noted post-catheterization as it may correlate to bleeding risk.

C. Identifying Significant Lesions

Fractional Flow Reserve (FFR):

- Evaluates if a stenosis visualized on angiography is functionally significant. Useful for decreasing unnecessary intervention + achieving complete revascularization.
- FFR is the ratio between coronary pressure distal to stenosis/aortic pressure with maximum myocardial hyperemia (usually using adenosine); traditionally cutoff value of 0.75 was used but increased to 0.80 to improve sensitivity.
- In general, FFR is useful when 1) evaluating lesions in stable ischemic heart disease and 2) non-culprit lesions in ACS to determine their ischemic significance.
- Stable Ischemic Heart Disease: reasonable to use FFR to evaluate functional significance of intermediate-severe coronary stenosis (50-90%).
    - DEFER was an RCT that found that in patients with stable CAD with no evidence of objective ischemia on non-invasive tests and FFR ≥ 0.75, deferral of PCI was not associated with worse outcomes or symptoms[3]
    - FAME: lower costs and improved outcomes in FFR-guided PCI v Angiography-guided PCI in revascularization of multivessel CAD[4]
    - FAME II compared FFR-guided PCI v OMT and found for patients with FFR <0.80 PCI > OMT and in FFR negative lesions OMT alone was sufficient[5]
- ACS: FFR is not used in evaluating culprit lesion, however there is evidence that demonstrates utility in using FFR to revascularize non-culprit lesions in ACS.
    - Stenting of non-infarct related lesions significant by FFR to achieve complete revascularization reduces subsequent revascularization (DANAMI-3-PRIMULTI, Compare-Acute)[6,7]
- See Fig. 1 for algorithm: https://www.acc.org/latest-in-cardiology/articles/2017/05/25/08/34/ffr-in-2017-current-status-in-pci-management

Instant Wave Free Ratio (iFR):

- Alternative to FFR with benefit of avoiding adenosine
- Cutoff is </= 0.89 when clinical/non-invasive testing c/w ischemia, </= 0.86 if clinical/non-invasive testing not c/w ischemia
- iFR-SWEDEHEART trial demonstrated that iFR is non-inferior to FFR to guiding revascularization in stable ischemic heart disease/ACS. Demonstrated to be non-inferior to FFR for MACE at 1yr in RCTs.[8]
- See Fig. 2 for algorithm: https://www.acc.org/latest-in-cardiology/articles/2017/05/25/08/34/ffr-in-2017-current-status-in-pci-management

PCI of Non-culprit Lesions

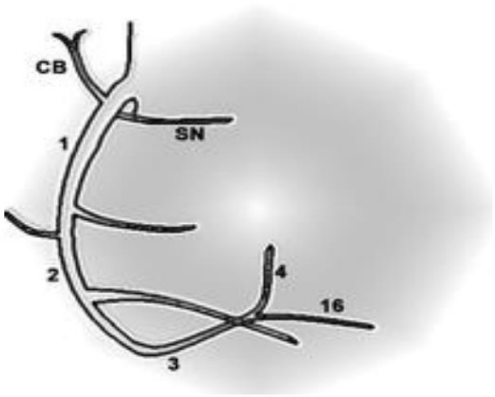
- NSTEMI/UA: Controversial. No RCTs, only observational studies. Most studies support complete revascularization.
    - A 2018 observational study of >20,000 patients, all-cause mortality was lower in the complete revascularization group at a follow up of 4 years (22.9 vs 25.9), however there were higher rates of initial hospital mortality in complete revascularization group[9]
- STEMI: There are 4 options in the management of non-culprit lesions in STEMI 1) CABG in those that have clear indications 2) no revascularization 3) PCI at time of primary PCI 4) PCI before discharge. In contrast to NSTEMI, there are RCTs addressing this question.

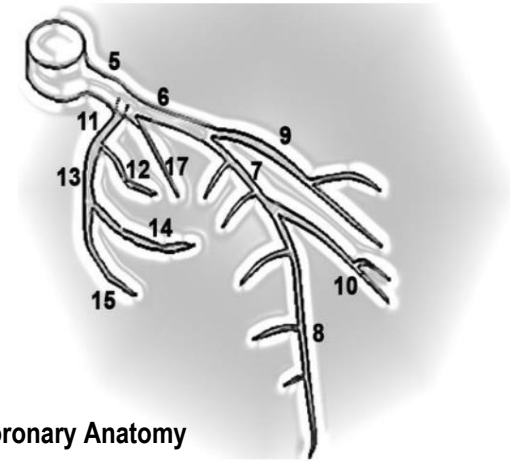
    - Evidence that PCI of non-culprit lesions leads to better outcomes (especially need for repeat revascularization):
        - PRAMI, CvLPRIT, DANAMI-3-PRIMULTI: Three of the largest RCTs addressing this issue suggested that complete revascularization was associated with better outcomes in STEMI. All three had a decrease in the primary composite outcome (mortality, non-fatal MI, and repeat revascularization).[10-12]
        - Meta-analysis of 10 RCTs showed complete revascularization was associated with a lower risk of MACE (RR 0.57, CI 0.42-0.77). The composite end-point was driven by need for urgent revascularization, but there were trends to improved mortality and recurrent MI.
        - 2015 ACC/AHA guideline: IIb recommendation for PCI to non-culprit lesions.
    - There is still uncertainty on the best time for PCI to non-culprit lesions.
    - May be harmful in STEMI with cardiogenic shock: CULPRIT-SHOCK was RCT that randomized patients with STEMI and cardiogenic shock to preventative multi-vessel PCI vs. culprit-only PCI and found increased risk of death with multivessel PCI (culprit only PCI preferred in cardiogenic shock)[13]
- Which non-culprit lesions? Any lesion that looks unstable, stenosis ≥ 70%, use FFR in lesions ≥ 50%. If there is a question regarding viability of the tissue to the area, viability imaging is reasonable prior to PCI.
- CTO (chronic total occlusion): Optimal management of non-culprit CTO in STEMI is not known. Observational studies have suggested improved outcomes in PCI to CTO before discharge, however there are no RCTs.

Viability Testing:
Up to 20-40% of patients with CAD and LV dysfunction may demonstrate improved function after revascularization. This is thought to be due to viable myocardium that lacks adequate perfusion (so-called “stunned” or “hibernating myocardium”). In contrast, necrotic myocardium is unlikely to benefit from reperfusion. The following modalities are used to differentiate stunned/hibernating myocardium from necrotic myocardium. This information is critical in prognostication and in the decision of whether, how, and where to revascularize (though notably this is still somewhat controversial since myocardial viability did not identify patients with a differential survival benefit from CABG compared with medical therapy alone in the STITCH trial).[14]
- Dobutamine echocardiography
- FDG PET
- Technetium MIBI
- Thallium SPECT rest with redistribution
- cMR (~95% sensitive using LGE)

TOC

D. Coronary Artery Anatomy





Right Coronary Anatomy
1 Prox RCA
2 Mid RCA
3 Distal RCA
4 PDA
16 PLV
CB Conus branch
SN Sinonodal branch

Left Coronary Anatomy
5 LM
6 Prox LAD
7 Mid LAD (After take off of first diag)
8 Distal LAD
9 First Diag (D1)
10 Second Diag (D2)
11 Prox LCx
12 First OM (OM1)
13 Mid LCx (after OM1)
14 Second OM (OM2)
15 Distal LCx
17 Ramus intermedius

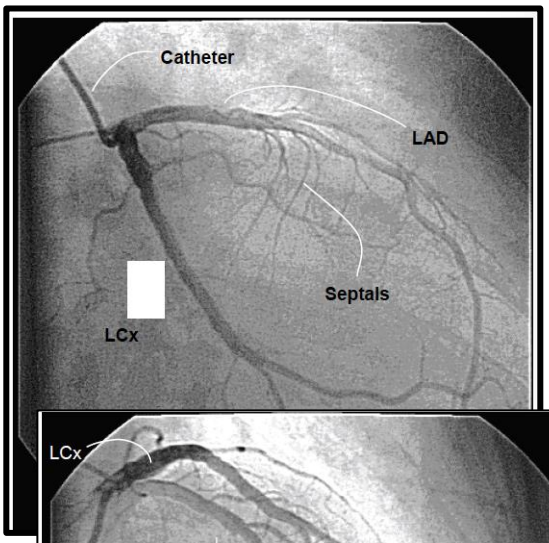
The Views:
RAO v LAO

- Right Anterior Oblique (RAO): Camera is on the R side of patient, and the catheter (and spine) are on the L side
- Left Anterior Oblique (LAO): Camera is on the L side of patient, heart is directed towards the left and the catheter (and spine) are on the R side

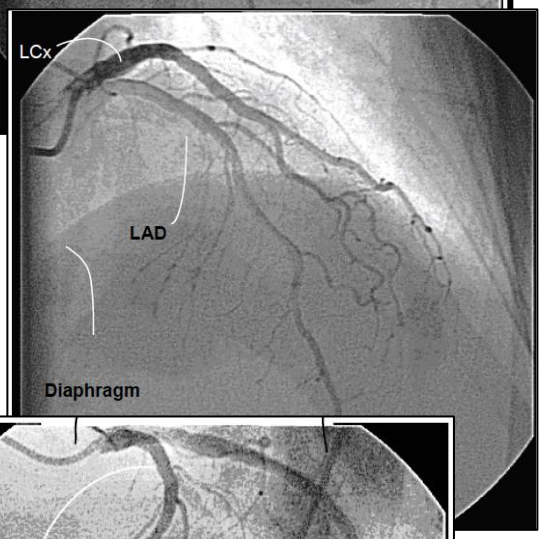
Cranial v Caudal

- Cranial View: Camera looks down from shoulder, diaphragms are well delineated and the lung fields are clear, good for visualizing the LAD
- Caudal View: Camera looks from feet to head, good for visualizing the LCx

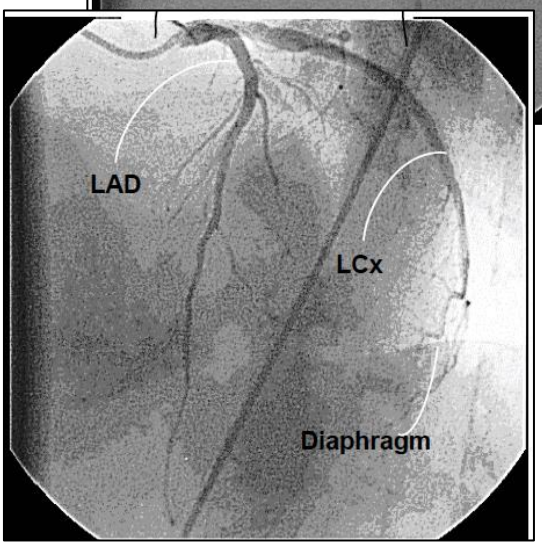
RAO Caudal (L Cor View): Camera is on the R side of patient, looking up from abdomen. Heart is screen right and catheter is left. LCx is clearly delineated.



RAO Cranial (L Cor View): Camera is on the R side of patient, looking down from shoulders. Heart is screen R and catheter is L. Diaphragm is seen LAD runs down apex of heart and ends in a shape that resembles “Salvador Dali’s mustache.” Septal perforators come off the LAD.



LAO Cranial (L Cor View): Camera is on the L side of the patient, looking down from shoulders. Heart is screen L and catheter is R. Diaphragm is seen. LAD runs down to apex of heart.



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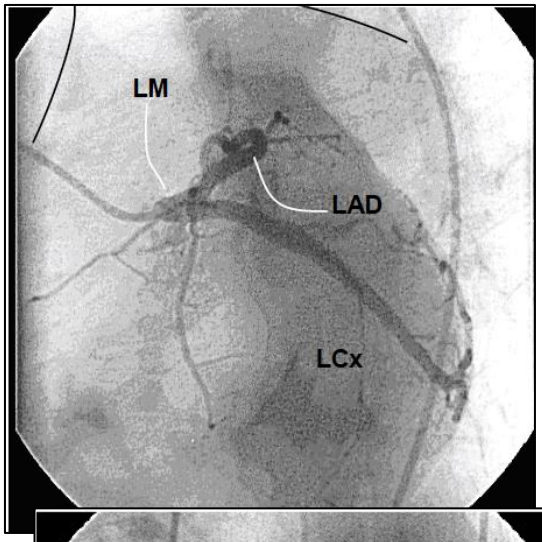
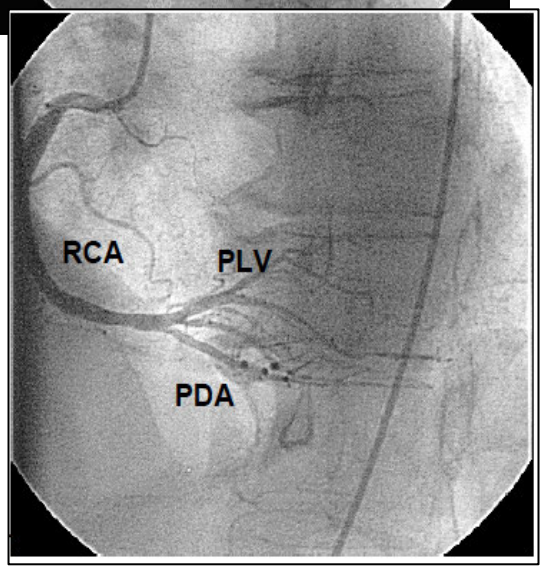
LAO Caudal (L Cor View, Spider View): Camera on the L side of the patient, looking up from the abdomen. Heart is screen left and catheter is R. “Spider view” is good for visualizing LM and Prox LCx disease.



LAO Cranial (R Cor View): Heart is directed to screen L and catheter is R. Acute marginal branch descends toward R side of heart, supplying RV. The PDA (lowest artery on film), runs in the inferior portion of the interventricular and supplies the posterior portion of the RV, LV and septum. PDA has septal perforators.



E. Aspiration Thrombectomy

2015 ACC/AHA guidelines recommend against aspiration thrombectomy in patients undergoing PCI for STEMI. This is based on three large trials (TOTAL, TASTE, TAPAS) and the subsequent meta-analysis, that did not find improved outcomes with this strategy.[15-18] Given the above, aspiration thrombectomy use has declined.

F. BMS vs DES

- BMS:
  - More likely to develop early in-stent restenosis due to re-epithelization within the first 30 days
  - Requires DAPT for at least 1 month (preferred 1 year)
- DES:

  - Contain anti-proliferative drug and polymer that serves as vehicle for the drug and controls the rate of release. The drug inhibits the growth of the neointima, which is the major cause of restenosis.
  - Associated with increased rate of late (>30 day) stent thrombosis due to prolonged foreign body exposure
  - Requires DAPT for at least 6 months (preferred 1 year) so theoretically increases bleeding risk
- The NORSTENT trial comparing 2nd generation DES vs. BMS found no significant difference in mortality, but noted ↓ repeat revascularization in DES group[19]
- High bleeding risk, need for invasive procedures, or difficulty with adherence to 1yr DAPT are considerations for BMS, however emerging evidence suggests that newer generation DES with shorter DAPT may be considered
  - LEADERS FREE II: Prospective single-arm trial evaluating biolimus coated stent in patients with high risk of bleeding receiving ultrashort DAPT for 1mo found that DES was associated with ↓ cardiac death + MI and ↓ target lesion revascularization at 12mo[20]
  - ZEUS: Randomized zotarolimus coated stent vs BMS, 52% of enrolled had high bleeding risk and in this group DES had ↓ in MI, stent thrombosis and target lesion revascularization compared to BMS[21]

Bioresorbable Stents

- Drug delivery and mechanical support similar to DES, but designed to be absorbed to mitigate stent-related adverse events; ABSORB-II compared bioresorbable scaffold with everolimus DES found ↓ angiographic and clinical outcomes[22]

Quality of Blood Flow Before & After Intervention:

- TIMI 0 Flow (no perfusion): Absence of any antegrade flow beyond a coronary occlusion
- TIMI 1 Flow (penetration w/o perfusion): Faint antegrade flow beyond the occlusion, with incomplete filling distal to the coronary bed
- TIMI 2 Flow (partial reperfusion): Delayed or sluggish antegrade flow with complete filling of the distal territory
- TIMI 3 Flow: Normal flow fills the distal coronary bed completely

G. Post-Cath Care

Pass-off Essentials in SDU/CCU:

- Pass-off from interventional cards or EP fellow
- Type of access used for procedure (Arterial v Venous, Femoral v Radial v Jugular)
- Sheaths: What sheaths are in place, whom they should be removed by, removed in post-cath holding area vs. if closure device used
- Medications in cath lab (ex. Anti-platelet loads)
- Drips (heparin, integrilin, etc) and parameters to stop
- Planned course for anti-platelet agents
- Findings of procedure and devices/stent details (DES v BMS, size, location)
- Complications of procedure

Post-Cath Orders/Vascular Access Questions:

- Interventional/EP fellow will place some post-cath orders (IVF, AC); always clarify AC with fellow
- Day questions/issues about procedures directed to procedural fellow during day

- Night questions/issues
    - Re vascular access: Direct to moonlighting fellow on Cardiac Access Unit (Ellison 11, call floor ask for fellow)
    - Other issues are not responsibility of access fellow (ex if patient unstable and needs to return to cath lab, notify day time cards attending or on-call PDW cards fellow)

Sheaths and Removal:
- When FA sheaths in place, patients must strictly lie flat, after removal need to remain flat for 4-6hrs (reverse trendelenburg used if patient needs to sit forward to eat, take meds, or reduce aspiration)
- Arterial sheaths removed by interventional fellow (or Access Fellow on E11 at night) and require 30min manual pressure)
- Vascular closure devices occasionally used to remove sheath despite an elevated PTT (otherwise heparin gtt needs to be off and PTT checked)
- PTT goals vary but achieving near normal PTT ↓ bleeding complications
- SBP goal <140 if possible, to reduce pressure on platelet plug
- If radial access, TR band used for hemostasis there are few activity restrictions (removal is nursing protocol driven)

Vascular Closure Devices (VCD):
- Gold standard is manual compression for hemostasis
- VCDs placed in cath lab to continue AC, shorten bedrest, and reduce manual pressure time
- Most common femoral devices in MGH lab: Angio-seal (endovascular pad with extravascular collagen plug), PerClose (uses sutures), StarClose (extravascular clip)
- TR band used for radial access, removal on floor/unit per nursing protocol

H. PCI Complications:

Vascular Access Complications
If any of below complications, consider Vascular Medicine consult (pager 11589)

Hematoma**:**
- More common with femoral access
- Management:
    - Application of pressure is key (arteriotomy site is 2 fingerbreadths proximal to skin puncture), Fem-Stop device can be used to apply constant pressure if uncontrolled bleeding or unable to interrupt anti-platelets (carefully monitor distal perfusion with help of fellow)
    - IVFs, control blood pressure, and consider reversing AC (after discussing with attending
    - Escalate: vascular medicine consult first, then consider vascular surgery
- Bottom line: HOLD PRESSURE and ask someone to call the appropriate fellow who can help make next decisions

RP Bleed:
- May present with HD instability, ipsilateral flank pain and ecchymosis; up to 20% mortality
- Risk ↑ in females with very low or high BMIs
- Management includes immediately notifying attending and STAT non-contrast CT if patient is stable enough to go to scanner, consider stopping/reversal of antiplatelet/anticoagulant agents, IVFs, blood products

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Pseudo-aneurysm
- Presents as pulsatile masses with systolic bruits, diagnosis by US
- Treatment of small pseudoaneurysms (<2cm) is compression (may be US guided), larger pseudoaneurysms may need surgical interventional/injection
- Wide-necked pseudoaneurysms less amenable to thrombin injection given risk for thrombin run-off

AV Fistula
- Presents as systolic bruit with no pulsatile mass
- Management options include conservative, US guided compression or surgical intervention if unresolving (cannot inject thrombin)

Limb Ischemia
- Due to thrombus, dissection or mal-position of closure device
- Evaluate distal pulses with Doppler and consider PVRs to further assess location of compromise
- Contact attending and fellow immediately if new limb ischemia

Infection
- More common (and potentially devastating) with vascular closure devices

Neuropathy
- Affects lateral cutaneous nerve in femoral cath and resolved with supportive management
- Late sequel of radial artery cath, self-limited

Stent Thrombosis
- Definition
    - Angiographic evidence of thrombus originating in the stent or within 5mm of the stent with ischemic symptoms at rest or EKG signs of ischemia or rise and fall of cardiac biomarkers within 48 hours of angiography
- Mechanism
    - Prior to re-endothelization of the stent, platelet aggregation over exposed struts causing acute thrombus formation
- Timing
    - Most occur within 30 days after placement[23]
    - Risk decreases overtime as stents reendothelialize
- Risk factors
    - Considering the mechanism of ST, risk factors amplify the Virchow's triad with conditions that reduce blood flow, promote thrombotic pathway, or slow re-endothelization via inflammation
    - DAPT cessation or resistance to Clopidogrel
    - ACS
    - Diabetes
    - CKD
    - Inflow/outflow obstruction
    - Vessel geometry (small vessel caliber, long stent length)
- Stent Platforms

    - 1st generation DES were developed to reduce ISR risk but at the cost of higher late ST. Most DES used today are second generation (Xience, Synergy, Resolute) have lower rates of ST at 2 years compared to BMS (<1%)[24]
- Diagnosis
    - The majority (>60%) present as STEMI, rest as either NSTEMI or UA[25]
    - 12-lead EKG – look for STE in coronary distribution of previously stented vessel
    - Early ST (<1 month of implantation) more likely to present in cardiogenic shock
    - Diagnosis requires emergent angiography showing thrombotic occlusion (TIMI 0 flow) of culprit vessel[26]
- Management
    - Recanalization
    - Thrombus aspiration
    - OCT/IVUS for stent apposition
    - Switch to more potent P2Y12 blocker (e.g. ticagrelor or prasugrel), although there are no studies this is common practice
- Prognosis:
    - One year mortality is between 10-20%
    - 30-day rate of MI is 60%
    - Compared to de novo STEMI, ST patients have a higher risk of MACCE (23% vs 9%) and in-hospital mortality (17% vs 7%)[27]

Coronary Artery Perforation

- Definition
    - Class I – Intramural crater without extravasation
    - Class II – pericardial or myocardial blushing (staining)
    - Class III – perforation ≥1 mm in diameter with contrast streaming or cavity spilling
- Risk factors
    - Atherectomy
    - Imaging
    - Oversizing stent/high post-dilation pressure
- Management
    - Most are visualized and immediately treated in cath lab
    - Inflation of balloon at site of perforation for short period of time can be enough to seal off small perforation
    - Pericardiocentesis to drain hemodynamically significant hemopericardium
    - Covered stent deployment at site of perforation

In-Stent Restenosis (ISR)

- Definition
    - Gradual re-narrowing of the stented segment (vs abrupt occlusion in stent thrombosis) due to neointimal tissue proliferation
    - Both clinical definition (recurrent symptoms and signs of ischemia) and angiographic definition (>50% luminal narrowing at follow-up angiography)
- Clinical presentation: usually angina without ACS but ACS is possible (mostly UA, small fraction 5-11% is AMI)[28]
- Management
    - Intravascular imaging to look for stent under-expansion or mal-apposition
    - Consider deployment of DES on top of old stent or drug coated balloon

Renal Complications

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Contrast Induced Nephropathy (CIN)

- Diagnostic Cath ~25-40cc of contrast, PCI 150cc of contrast depending on # of interventions (PE-CT 90cc of contrast)
- ↑ Cr ≥ 0.5 or more than 25% within 28-72h of contrast exposure
- Cr usually peaks 2-3d after contrast and returns to baseline at 2wks
- On the other hand, atheroembolic disease occurs wk-mo after intervention (assoc skin mottling)
- If renal impairment, pre-hydrate 1cc/kg/hr of NS 6hr pre- and post-procedure
- ACC/AHA 2012 recommend against use of N-acetylcysteine for CIN, coordinate with nephrology for patients at ↑ risk for CIN
- Risk calculator:[29] https://qxmd.com/calculate/calculator_47/contrast-nephropathy-post-pci

I. Cardiopulmonary Bypass Grafting (CABG)

Indications for CABG

Class I

- Significant (>50%) L Main Disease
- 3VD
- Significant LAD Disease with 1-2VD and EF<50%
- 1-2VD without LAD involvement but large area of at-risk myocardium
- L Main Equivalent Disease:
    - >70% Proximal LAD Disease
    - >70% Proximal LCx Disease

Class IIa Indication: Significant proximal LAD Disease with 1-2VD without high risk features
Class IIb Indication: 1-2VD without LAD and without high risk features

By-Pass Grafts

Arterial**:** Arterial grafts >> long-term survival compared to vein grafts: >90% patency rate at 10 years, ↑ survival, ↓ MI, ↓ less recurrent angina, ↓ reoperations; arterial ↑ grafts difficulty to harvest compared to SVG so may not be used in emergent situations

- Internal Thoracic Arteries (ITA) *[LIMA/RIMA]:* Native take off from the subclavian with end-to-side anastomosis to coronary, limited by vessel length to proximal touchdown on coronaries (for bypassing proximal stenosis)
    - ITA grafts confer 20 yr survival benefit compared to SVGs alone
    - LIMA anatomically favorable for LAD, so most common graft
    - RIMA technically challenging, increases pump time; can be used to bypass RCA w/ critical stenosis (>90%) or in Y-graft with LIMA to other target vessels
    - ART Trial: Randomized bilateral versus single ITA, intention-to-treat analysis at 5yr, 10yr intervals with no difference in death from any cause; Limitations: 22% in ITA arm received radial artery grafts, 14% in bilateral arm received single ITA, and ↑ rates of GDMT may have narrowed inter-group differences; Internal analysis suggests that patients receiving more arterial grafts may have meaningful difference in mortality compared to those with fewer[30]
- Radial Arteries: 80-85% patency at 5yrs; ↑ patency and ↓ adverse cardiac events compared to SVGs[31]
    - Can bypass severe (>70%) L sided stenosis or critical (>90%) R sided stenosis

    - Safe harvest, sometimes with numbness and tingling in hand ipsilateral to harvest but generally no motor compromise
- Gastroepiploic Arteries: 15 yr patency rate >92%, rarely used

Venous: SVG 5-7 yr patency ~50%, most commonly used vessel in 1970s
- Requires ASA within 48hrs s/p CABG, continued indefinitely
- Smoking, HTN, HLD, DM ↑ risk for graft failure

Key Points:
- Arterial grafts ↑ patency compared to SVGs; may not be limited to RIMA/LIMA with increased radial artery grafting
- Arterial grafts ↑ difficulty to harvest compared to SVGs, so may not be conducive in emergencies

Concomitant Medical Therapy

- ASA 81-325 mg/day (clopidogrel 75mg/day if intolerant/allergic to ASA): Aspirin is associated with decrease in-hospital mortality, MI, stroke, and renal failure. Mortality benefit seen in patients who received ASA within first 48 hours. No increase in bleeding. ASA should be continued pre-operatively.[32]
- P2Y12 therapy: CABG s/p ACS, reasonable to admin ASA + prasugrel/ticagrelor/clopidogrel. Controversial and practice-dependent. Subset of the CURE trial suggested a non-significant decrease in CV death, MI, stroke.[33]
- Statin: High intensity statin for all <75 unless drug-drug interaction or intolerance
- Beta-blocker starting peri-operatively to reduce post-operative AF. However a 2014 review, there was no mortality benefit in beta blocker seen in patients undergoing CABG without ACS in the past 21 days.[34]
- Anticoagulation: COMPASS-CABG Study demonstrated that rivaroxaban 2.5mg BID + ASA 100 daily or rivaroxaban 5mg BID vs ASA 100 alone did not reduce graft failure, but rivaroxaban 2.5mg BID + ASA 100 associated with ↓ MACE.[35]

Cardiopulmonary Bypass Machine

On Pump Cardiopulmonary Bypass CABG (CAB)
- Requires cross-clamping of the aorta, blood is diverted from the RA → Bypass Machine → Cross-clamped aorta → systemic circulation
- Cardioplegia achieved with potassium/ice
- Associated with more significant inflammatory response, requires high doses of heparin, extensively calcified aorta may not be amenable to cross-clamping
- Contraindicated in severe GIB, ICH, and recent CVA

Off Pump CABG (OFCAB)
- Associated with decreased inflammatory response, does not require cross-clamping of aorta, reduces risk of microemboli from bypass filter, may be preferred in high risk patients
- Conflicting clinical data on whether OFCAB truly associated with equivalent clinical outcomes to CAB

CABG Complications

Early	Late
• AF (25%) • MI (5-10%) • Bleeding (5%), assess within 24h for continued bleeding, ↑ risk with pre-op plavix • Death (1-4%), usually from MI • Stroke (1-2%), usually emboli related to aortic cross clamping • Mediastinitis or surgical site infection • Lower extremity edema related to SVG harvest • Graft Failure	• Neurocognitive impairment: "pump brain" frequently described, but limited controlled studies • Recurrent Angina: 95% have improvement or complete relief immediately after surgery; 80-90% remain angina-free at 1-3yrs, 75% angina-free at 5yrs

CABG vs PCI

Syntax Score[36]

- Developed for SYNTAX Trial, which randomized patients with 3VD or LMCA to CABG vs PCI
- Syntax Score is a semi-quantitative tool based on coronary angiography that grades anatomic complexity
- ↑ Syntax Score tends to have better out comes with CABG, while ↓ Syntax Score tends to have non-inferior outcomes compared to PCI

Specific Considerations:

- CABG vs PCI in LMCA Disease: Historically CABG was standard for LMCA disease, based on comparison of CABG v OMT trials conducted in 1970-1980s with some recent randomized trials showing PCI with DES is suitable for certain patients but the data are mixed.
  - SYNTAX Trial: LMCA sub-group of trial showed no significant difference in MACE, death or MI between PCI or CABG, ↑ rates of revascularization with PCI but ↓ stroke risk; in low Syntax Score PCI had lower mortality but in high Syntax Score (>33) PCI had higher mortality[36]
  - PRECOMBAT Trial: LMCA-specified RCT comparing DES v CABG, found that PCI and CABG were similar in rates of MACE, MI, or stroke at 5yr, rates of target vessel revascularization more common with PCI v CABG[37]
  - SYNTAX and PRECOMBAT did not use second-generation DES, may have been insufficiently powered
  - NOBLE Trial: LMCA-specified RCT comparing DES (1st gen) v CABG found ↑ MACE, nonprocedural MI and any revascularization with PCI, 5yr death rate was CABG = PCI[38]
  - EXCEL Trial: LMCA-specified RCT comparing DES (2nd gen) v CABG found ↓ primary composite end point of death, stroke, or MI at 3yrs but ↑ revascularization with PCI[39]
  - MAIN-COMPARE: retrospective cohort of patients with > 50% LM stenosis of PCI v CABG found no significant difference in mortality, MI or stroke after 5yrs with PCI v CABG but noted ↑ repeat revascularization in PCI group over 3yr[40]

Bottom Line: PCI vs. CABG for LMCA is a complex decision with discordant data for which a heart team approach taking patient specific risk factors into account is essential.

- CABG vs. PCI in Diabetes with limited overall CAD

- BARI-2D Trial: RCT that randomized patients with stable CAD + DM to OMT v Revascularization (PCI v CABG), which found no difference in 5yr survival, but rate of MACE was lower in CABG v OMT[41]

Bottom Line: CABG added to medical management reduced the rate of CV events in DM patients compared to medical management alone. There was no difference in adding PCI.

- CABG vs. PCI in Diabetes with advanced CAD

  - FREEDOM Trial*:* RCT that randomized patients with multivessel CAD with stenosis of >70% in two or more major epicardial vessels and no significant LMCA stenosis, found ↑ death, MI, and/or stroke occurred more frequently in the PCI group[42]
  - Benefit of CABG driven by differences in rates of both MI and all-cause mortality
  - Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group

Bottom Line: CABG is superior to PCI in the management of patients with DM2 and multivessel disease with respect to prevention of MI and death, although at a cost of a higher risk of stroke.

- CABG + OMT vs. OMT alone in Ischemic Cardiomyopathy

  - STICHES*:* RCT that randomized patients with EF 35% or less and CAD amenable to CABG randomized to CABG + medical therapy v medical therapy alone, found ↓ all-cause mortality and all secondary outcomes in CABG group[43]

Bottom Line: In patients with ischemic cardiomyopathy eligible for CABG, all-cause mortality, cardiovascular mortality and hospitalization for cardiovascular causes were significantly lower in patients who underwent CABG + medical therapy than those who received medical therapy only

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22. Post-MI Complications

A. Mechanical Complications of MI

Cardiogenic Shock

Definition: Persistent (>30min) SBP < 80 mmHg, CI < 1.8 L/min/m^2, and PCWP > 18 mm Hg
Epidemiology:

- Approx. 7% incidence following AMI
- Risk Factors: older age, prior MI or CHF, anterior MI
- Large infarct size (usually >40% LV mass) accounts for 80% of post-AMI shock
- 30d mortality = 50%; accounts for 60% of 30d mortality following acute MI
- 67% patients have 3VD, usually including the LAD

Dx: STAT TTE to ensure there has not been an alternative mechanical complication (ie papillary muscle rupture)
Treatment:

- **Reperfusion** with PCI (fibrinolytic therapy if unsuitable PCI candidates) or CABG (Class I recommendation)
    - Emergent PCI or CABG reduces 6 month mortality from 63% to 50%, particularly in patients < 75yo and those with previous MI.[1]
- **Diurese** for goal PCWP < 18 mmHg (decreases pulmonary edema and myocardial oxygen consumption).
- **Vasopressors to keep MAP > 60 mmHg**. Typically norepinephrine is chosen, although there is insufficient evidence to recommend a first line vasopressor. Keep in mind that vasopressors increase the workload of the heart so a mechanical support device might be the better option in these patients.
- **Augment LV function to keep CI > 2 L/min/m^2** (increases SV and CO)
    - Inotropes: Dopamine, dobutamine, and/or milrinone. SOAP II suggests increased 28d mortality with dopamine versus norepinephrine.[2]
    - IABP: Available evidence does not support routine use of IABP. IABP might be beneficial in patients with further mechanical complications such as acute MR or VSD or in a patient that is clinically deteriorating. (Class IIa recommendation)
        - IABP-SHOCK II showed no difference in 30d mortality in patients whom early revascularization was planned. At 6 year follow-up of the SHOCK II cohort, there was no effect on all-cause mortality with the iuse of IABP. The trial also highlighted the incredible mortality (2/3rds of patient died) despite therapy.[3]
    - Mechanical LV support (Impella, LVAD, ECMO) – outcome evidence is lacking, but these devices are being used with more and more frequency. Class IIb recommendation that MCS can be considered in this population.
        - Comparison of LVAD to IABP: LVAD reversed hemodynamics more than IABP, but with more complications (ie limb ischemia).[4] Mortality rates similar, although not powered to assess mortality.
        - Delaying reperfusion by offloading the LV: 2018 feasibility/safety trial showed no difference in MACE at 30 days w/ unloading LV w/ Impella CP prior to revascularization in STEMI patients w/ a 30 min delayed as compared to no delay.[5] Appropriately powered superiority trial is needed.

Rupture of Ventricular Free Wall

Timing: Occurs within the first 5 days after MI in about 1/2 of cases and within 2wks in >90% of cases
Epidemiology: Relatively common in those dying of AMI: 14–26% of patients who die from acute MI have LV free wall rupture with decreased incidence and case-fatality (95% to 75%) from 1977 to 2006.[6] Incidence much lower when considering all patients with AMI (<1-4%). This number has also declined in the past 50 years with increased perfusion and effective medical therapy.
Risk Factors:

- Fibrinolytic therapy in patients > 70 (Eur Heart J. 2005;26(17):1705)
- Absence of collateral blood flow (no prior MI)
- Size of the infarct (transmural/STEMI, large enzyme peak CK-MB > 150IU/L)
- Other: Age > 70, female sex

Effect of Reperfusion**:** LV rupture after MI is less common after successful reperfusion, especially PCI
Pathophysiology:

- Early Rupture (<72 hrs) vs Late rupture (>3 days): early rupture is an abrupt slit-like tear in the infarcted myocardium (usually anterior). Late Rupture is due to infarct expansion, occurring at junction of infarct and normal myocardium (usually anterior / lateral walls).
- Complete vs Incomplete: Incomplete occurs when organized thrombus and the pericardium seal the perforation, can progress to frank rupture and formation of an LV false aneurysm or diverticulum.

Clinical Presentation:

  - Can present as sudden death in an undetected or silent MI
  - Complete Rupture: leads to hemopericardium, shock, PEA arrest
  - Incomplete/Subacute Rupture: Clinical presentation varies by can include pericardial pain, nausea, hypotension, EKG changes with localized pericarditis.

Dx: TTE
Management: Survival depends on recognition and immediate therapy

- Pericardiocentesis: if fluid is blood, indication for immediate surgery
- Medical therapy aimed at hemodynamic stabilization (fluids, inotropic support, vasopressors, pericardiocentesis, IABP)
- Surgical repair is indicated for LV false aneurysms

Mortality:

- Acute: Wide ranging, 40-100% in case series
- Subacute: in one study, 76% survived surgical procedure, 48% were long term survivors[7]

Rupture of Intraventricular Septum

Timing: Typically occurs 3–5 days after an acute MI, but can occur within 24 hours-2 weeks
Epidemiology: Half that of free wall rupture, decreasing with reperfusion therapy from 2->0.2% after fibrinolytic therapy[8]
Risk Factors:

- Single-vessel disease (especially the LAD artery) - "wrap around" LAD (when LAD extends beyond LV apex and supplies the entire septum), EKG with inferior STE during a large anterior MI
- Poor septal collateral circulation
- Higher prevalence with first MI's
- Increased in patients with RV infarction

Effect of Reperfusion:
- IVS rupture much lower in those tx with fibrinolytic therapy, 0.2%
- However, fibrinolytics may lead to earlier breakdown of the IVS and earlier rupture

Pathophysiology: Rupture develops at the margin of the necrotic and non-necrotic myocardium. It may be a direct hole or more irregular and serpiginous. The size of the defect determines the magnitude of L-R shunting, which affects survival. IVS rupture is seen with equal frequency in anterior and non-anterior infarctions. Anterior MI: defect is found in the apical septum. Inferior MI: defect is found at base of the heart

Clinical Presentation: Acute hemodynamic compromise (hypotension, BiV failure, a new murmur (harsh, loud, and holosystolic, best heard at LLSB, 50% with thrill) and RV heave

Dx:
- PA line: left->right shunt and large PCWP "V" waves (left->right shunt leads to increased pulmonary blood flow and return to the left atrium which given the acuity is not compliant to handle the increased blood flow)
- TTE w/ doppler flow

Management:
- In pts with cardiogenic shock, operate immediately
- Delayed elective surgical repair is feasible in patients with HF without shock, but the potential for unpredictable and rapid deterioration is always present
- Medical stabilization involves vasodilators and IABP (which reduce afterload and left to right shunt), inotropic agents (which may increase CO), diuretics

Mortality: Surgical 47%, medical 94%[8]

Acute Mitral Regurgitation

Timing: 2-7 days for acute papillary muscle rupture

Epidemiology:
- In AMI: 14% had mild MR (transient and typically no adverse events). 3% had mod-severe MR w/ high mortality (24% at 30d, 52% at one year)[9]
- In patients with AMI + cardiogenic shock: 39% had mod-severe MR . these pts had poorer survival at 1 yr – 58% vs 31%[10]

Pathophysiology: Three causes of Acute MR in setting of MI.
- Ischemic papillary muscle displacement
- LV dilatation or true aneurysm
- Papillary muscle or chordal rupture: Occurs 2-7 d post-infarct. Because of differences in blood supply, posterior-medial papillary muscle (supplied by PDA) is 6-12x more likely to rupture than anterolateral papillary muscle (dual blood supply by LAD, LCx)

Risk Factors for Papillary Muscle Rupture
- Poor collaterals and single vessel disease (in 50% of cases)
- Infarct supplying the posteromedial papillary muscle (PDA)
- First MI

Clinical Manifestations

- Acute onset of **hypotension and pulmonary edema**
- Hyperactive precordium and a mid-, late-, or holosystolic murmur with widespread radiation.
- Intensity of the murmur does not necessarily correlate with the severity. Severe MR may create early equalization of LV and LA pressures, resulting in silent MR or soft/short murmur

Dx: TTE showing flail section of mitral valve. May need TEE. PA line: PCWP tracing usually shows giant V waves (nonspecific, a/w acute VSD or L sided HF). No O2 step up (as seen in IVS rupture)

Treatment:
- Medical therapy: Aggressive afterload reduction with nitrates, sodium nitroprusside and IABP (decreases MR fraction, thereby increasing forward flow)
- Surgery: Mitral valve repair rather than replacement should be attempted in centers experienced in performing this procedure

Mortality: with surgery – 50% ; medical therapy - 75 % at 24h and 95% within 2w after complete papillary muscle rupture

Right Ventricular Infarct

Clinical Manifestations: Hypotension, jugular vein distention, +Kussmaul's, heart block (20% as RCA often supplies AV node), RA/PCWP >0.8, and occasionally shock, all in the presence of clear lung fields

Diagnosis
- STE noted in II, III, aVF (specifically, lead III > II is suggestive of RV involvement)
- R-sided leads (V4R, V5R, V6R); 1mm V4R STE 88% sensitive/78% specific DDx: PE, pericarditis, anteroseptal MI

Treatment
- Preload: optimize w/ IV fluids to increase filling pressures (CVP goal 10–14) and AVOID preload reducing medications (diuretics, nitrates)
- Decrease RV afterload (High PEEP can increase RV afterload; hypoxia leads to pulmonary artery vasoconstriction; can consider pulmonary vasodilators such as inhaled nitric oxide)
- Inotropes: dobutamine, milrinone
- Pacing as necessary to maintain AV synchrony
- Mechanical Support: IABP or RV assist device

Mortality:
- RVMI + cardiogenic shock: ~25-50%[11,12]
- Prior to PCI, the mortality rate was high due to cardiogenic shock and arrhythmias (OR 3.2 compared to patients with inferior MI without RV involvement)[13]
- In the PCI era, the mortality has improved. In a study that evaluated the mortality in patients with RVMI, the mortality was 2% in those with successful revascularization vs 58% in those without successful reperfusion[14]
- Now, long term prognosis is related to the extent of LV involvement since the RV recovers much of its function shortly after MI

Left Ventricular Thrombus

Timing: Most occur days to weeks post-MI, although some earlier studies (i.e. before PCI or thrombolysis) demonstrated dynamic appearance and resolution of thrombi weeks to months after MI regardless of anticoagulation

Incidence 3-15% of ant. MI which has decreased with reperfusion therapies

Risk Factors: Anteroapical MI, w/ EF < 30%, apical dyskinesis, LV aneurysm

Dx**:** TTE (ACC/AHA Class I indication, Sn 95%, Sp 86%); cMRI if index of suspicion

- TTE Cardiac MR

Risk of systemic embolization: Estimated to be between 10-15% in those not treated with AC.15 Most often occurs within the first 3-4 months

Treatment: If LV thrombus on imaging, AC with warfarin is reasonable (Class IIa, Level C in 2016 AHA/ACC guidelines). Duration 3-6 months due to the observation that most embolic events occur within the first 3-4 months. DOACs have not been tested

- Evidence: Meta-analysis of 7 observations studies (n=270), AC (vs no AC) was associated with an 86 percent reduction in the rate of embolization in patients with confirmed LV thrombus (odds ratio 0.14, 95% CI 0.04-0.52)[16]

Prophylaxis (no documented thrombi): Controversial. Historically, argument that those at highest risk for development of left ventricular thrombus should be anticoagulated. However, there is no definitive evidence that this is beneficial and might be harmful.
Guidelines: Anticoagulant therapy may be considered for patients with STEMI and anterior apical-akinesis or dyskinesis (Class IIb, level C).

- Evidence
  - Prophylactic AC with warfarin for apical akinesis or dyskinesis on TTE was associated with increased risk of stroke, death, and major bleeding (on top of DAPT)[17]
  - In patients in normal sinus rhythm and a low EF, anticoagulation with coumadin versus treatment with aspirin did not reduce the composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause as the reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage[18]

True Left Ventricular Aneurysm

Timing: days-weeks post MI
Epidemiology: 8–15% incidence after STEMI (incidence is decreasing with improvements in management of acute MI; past incidence was as high as 30%)
Pathophysiology: "True" LVA is a well-delineated fibrotic area of wall that is either akinetic (no movement) or dyskinetic (paradoxical ballooning) during systole. Most of the time this occurs in the **anterior or apical wall** (70-85%) due to occlusion of LAD. The tissue is usually white, thin fibrinous scar. Majority are 1-8cm in diameter
Risk Factors

- Large, anterior MI
- Absence of collateral flow
- Absence of PCI or thrombolytics for acute MI or inability to achieve patent infarct-related

Clinical Manifestations:

- CHF: Decreased SV due to LVA leads to LV volume overload
- Angina: Increased wall stress leads to increasing oxygen demand
- Thromboembolism: Up to 50% in autopsy studies
- Ventricular arrhythmias
- Unlike pseudoaneurysms, true LVA have very low risk of rupture
- Physical Exam: 3rd, 4th heart sounds, diffuse apical impulse, holosystolic murmur if LVA causes MR. Palpate all patients along their chest wall post MI. LV aneurysms cause dyskinesis which is easy to appreciate (and impressive) as separate from the apical impulse

Diagnosis

- Persistent STE on ECG reflects scar only and is not specific for LVA
- Confirm diagnosis with TTE, contrast ventriculography during cath or cardiac MRI

Treatment

- Standard Post-ACS care with afterload reduction, anginal therapy
- Anticoagulation (see "LV thrombus)
- Indications for aneurysmectomy: VT, CHF, refractory angina

Left Ventricular Pseudoaneurysm

A “false” or “pseudo-” aneurysm occurs when a ventricular free wall rupture is contained by local pericardial adhesions. This “aneurysm” is actually a cavity of blood contained by the pericardium only; it contains no endocardium or myocardium. Blood in the LV cavity communicates with the contained cavity through a narrow neck. Pseudoaneurysms have a high rate of expansion and rupture and are **a surgical emergency**.

B. Pericardial Complications

Three major types of pericardial complications can occur in patients following MI, all are related to infarct size and all have seen declining incidence with the availability of revascularization.

Early infarct-associated pericarditis (often termed peri-infarction pericarditis)

Timing: Often early and 1–4d post-MI
Incidence: 10–20%, this is decreasing with reperfusion therapy
Clinical Manifestations/Dx: PIP is suggested by pericardial friction rub, pleuritic chest pain, and diffuse STE w/ persistent upright T waves in the setting of recent MI (<1 week). These patients should undergo TTE to evaluate for pericardial effusion
Management:

- High dose (650mg) ASA (Class I). There is no established relationship between use of ASA and subsequent development of hemorrhagic pericardial effusion in patients with PIP. Duration for 7-10d
- Second-line therapy includes colchicine, acetaminophen, narcotics (class IIa recommendation)
- Avoid NSAIDS and steroids as they have the potential to cause harm after STEMI (Class III, LOE B)

Pericardial effusion (with or without tamponade)

Timing: Days after MI
Incidence: Serial echocardiographic studies have shown pericardial effusion occurs in approximately one-third of cases of transmural MI. In a review of 330 patients with an acute ST elevation MI, 83 (25 percent) had a pericardial effusion by day 3[19]
Size: Most are often minimal or mild
Clinical manifestations: Usually asymptomatic, rarely develops into tamponade
Prognosis: Moderate to large (>10mm) post MI effusions are associated with higher morbidity and mortality at 30 days (43%) when compared to those with smaller or no effusions (10% and 6% respectively)[20]
Management: usually the presence of a pericardial effusion does not alter management. This of course changes if the patient develops signs of tamponade

Postcardiac injury/Dressler's syndrome

Timing: Weeks to months post-MI
Incidence: < 4% incidence
Pathophysiology: Late onset pericarditis secondary to release of cardiac antigens from initial injury with subsequent antibody formation and immune complex deposition in the pericardium with resultant inflammatory response (i.e. fever, leukocytosis).
Diagnosis/Clinical Manifestations

- Pleuritic chest pain and friction rub similarly to PIP
- Additional symptoms of fever (high grade up to 104F), leukocytosis, and pleural effusion/pericardial effusion/pulmonary infiltrates can be identified

Management:

- NSAIDS or Aspirin
- Colchicine
- If refractory, steroids. However, can delay post-MI healing.

C. Peri-MI Arrhythmias and Conduction Abnormalities

Ventricular Tachycardia/Ventricular Fibrillation

Timing: early (within the first 24 hrs) vs late (>24-48 hrs)
Incidence:

- STEMI: 10.3% in fibrinolytic therapy; 5.6% in PCI (~85% occur in the first 48 hrs)[8,21]
- NSTEMI/UA: 2.1%
- Underestimates because excludes time prior to hospital and SCD

Pathophysiology: Multifactorial but include 1) damaged myocardium which promotes re-entrant circuits or enhanced automaticity 2) arrhythmia triggers (such as HR variability) 3) other contributing factors such as electrolyte imbalances & increased catecholamines

- Acute phase (30m): come in two types[22]
  - 2-10 min (phase 1a): Re-entry is the dominant mechanism due to acute electrical changes (decrease in resting membrane potential, decrease in conduction velocity, increase in refractory period in ischemic tissue while the surrounding healthy tissue has the opposite properties). This tissue heterogeneity increases re-entry.
  - 10-30 min (phase 2b): Abnormal automaticity (due to catecholamine surge) and re-entry
- Delayed (6-48 h): One possible trigger for these arrhythmias is likely abnormal automaticity in surviving Purkinje cells in the infracted or ischemic tissue, which have increased sensitivity to catecholamines.
- Chronic (>48h): Usually scar-mediated, re-entry mechanism. Anchors of sustained monomorphic VT

Treatment: See Arrhythmias chapter for details on medical therapy

- ICD placement: in patients who have sustained VT/VF >48 hours after MI during hospitalization (Class I, LOE B)

Prevention:

- Revascularization
- Replete K+ and Mg: In one trial, the likelihood of VF among patients with a serum potassium <3.6 mEq/L was almost twice as high as among patients with a normal potassium[23]
- Beta blockers in all patients w/o contraindications
- Wearable cardiac defibrillator: Has been proposed in patients with high risk of VT/VF post MI (EF < 35%). Data are conflicting

  - VEST trial: Randomized patients with AMI and EF < 35% to wearable cardiac defibrillator or standard medical therapy within 7 days of hospital discharge. No difference in the primary outcome (arrhythmias) in the follow up of 84 days. However, compliance with the vest was lower than expected (median 18hrs/day) and over half not wearing it by the end of the study. Only 25% of patients in the WCD were wearing the vest when they died[24]
  - Reasonable to consider in highly motivated patients with a low EF who would be a candidate for ICD

Prognosis:

- Acute:
  - In patients with VF within the first 48h, there is a higher in-hospital mortality (12% vs 2%), however long-term mortality was not increased[25]
  - Similarly, there is similar data in patients with early VT. In one series, the in-hospital mortality was significantly higher in patients with early VT alone (18.6 %) compared to those without ventricular arrhythmia (4.2%). The data for long-term mortality is not clear
- Chronic (>48h): the in-hospital mortality is significant, 57% for VT/VF and 37.5% for sustained VT alone. Further, the one-year mortality of the 30-day survivors was almost ten times higher than those without arrhythmia (24.7% v 2.7%)

Accelerated Idiopathic Ventricular Rhyhm (AIVR)

This is a primarily monomorphic ventricular rhythm occurring at a rate of 50–100 (or 120). Typically gradual onset and will self terminate.

Timing: Some studies have associated it with reperfusion
Incidence: Occurs in up to 50% of patients with AMI, though often not documented
Pathophysiology: Abnormal ectopic focus below AV or escape rhythm due to pacemaker failure
Treatment: Typically, does not require treatment. However, in some patients with compromised cardiac function, loss of atrial synchrony can result in further deterioration. In this case, can attempt atropine to try to increase the sinus rate and abolish the rhythm
Prognosis: While AIVR does not seem to be associated with increased mortality, it appears to be associated with increased myocardial damage and delayed microvascular perfusion. There is no convincing evidence that it is linked to sustained VT or VF

Ventricular Premature Beats

VPBs are common peri-MI, occurring in ~93% of cases.[26] Early VPBs (< 48hrs) have no impact on morbidity/mortality. However, late frequent multiform VPBs (occurring for greater than 48–72hr post MI) predicts long-term arrhythmia risk. Treatment of VPBs is not recommended, unless they cause hemodynamic compromise.

Atrial Fibrillation

Atrial fibrillation occurs commonly after acute MI, with an incidence of 6 to 8%.[27] As expected, it is most commonly seen in older individuals with symptoms of heart failure and left atrial enlargement. It is associated with a worse prognosis, increasing in-hospital and long-term mortality. It is still unclear if a-fib is truly an independent causal risk factor for mortality or if it is a marker for other high-risk complications such as heart failure or shock.

Sinus Bradycardia

Timing: Trransient, usually occurs within 6 hours and resolves at 24 hours
Incidence: Up to 40% of patients presenting with inferior MI within the first two hours,
Pathophysiology: RCA infarcts, usually attributed to increased vagal tone in the first 24 hours after infarction due to diaphragmatic irritation, rarely sinus node infarction
Treatment: If the bradycardia is symptomatic, atropine can be used. Temporary pacing can also be instituted if atropine is ineffective or if symptomatic bradycardia is persistent (see ACLS and temporary pacing sections). If bradycardia is a problem during revascularization, or if the RCA is the artery that is revascularized, patients will often come from the cath lab with a temporary pacing wire in place

AV Block

Incidence: For high degree AV block, in the PCI era, the incidence is ~2% for STEMI and < 1% for NSTEMI[28]
Pathophysiology:

- 1st degrees and 2nd degree type I: Result of inferior MIs as RCA supplies the AV node in 90% of people. Ischemia or increased vagal tone are two mechanisms
- 2nd degree type II: Occurs more often in anterior MIs. Variable clinical course with CHB developing without warning
- Complete heart block: Can occur in the setting of inferior or anterior MIs. More common in RCA infarcts compared to others (5.8 vs 1.5%)[29]
    - Inferior MI: the lesion is commonly intranodal lesion. It develops in progressive fashion from 1st→2nd→complete heart block. Typically transient. Usually has a narrow QRS complex
    - Anterior MI: less frequent, but more serious. Usually occurs abruptly within the first 24 hours. May be preceded by RBBB and LAFB or LPFB. Usually has wide complex QRS and is unstable. Represents complete necrosis of bundle branches in the septum

Treatment: See Pacing Section in Arrhythmias.
Prognosis:

- 1st or 2nd degree (Type I) typically resolve in 5-7 days and are benign
- High degree AV block:
    - Inferior MI: typically transient, but associated with a two-fold increase in hospital mortality[30]
    - Anterior MI: increases in-hospital mortality four-fold

Bundle Branch Blocks

Incidence: In patients presenting with MI, ~6% have RBBB and 6% have LBBB present on initial EKG, however the chronicity of the BBB was uknown.[31] Documenting a new BBB during the first 60 min of presentation for MI is rare (<1% for each).[32]
Pathophysiology: RBB is supplied mostly by septal perforators of LAD proximally with some contribution from LCx or RCA distally. LBB is divided into left anterior fascicle, which is supplied by septal perforators of the LAD and the AV nodal artery in about ½ of patients, and the left posterior fascicle, which is supplied by AV nodal artery and at times septal perforators of the LAD. The distal portion of the LPF is supplied by anterior and posterior septal perforators.

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Prognosis: There is not great data regarding LBBB/RBBB in prognosis given the difficulty in discerning when a BBB developed (new or old?). In patients that developed a LBBB within 60 min of presentation, mortality was higher (OR 2.97).[32]

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23. Discharge Planning and Outpatient Management

Standardizing the discharge process for post-AMI patients as much as possible is crucial to improve their comfort level upon discharge and to reduce readmission rates. The section's purpose is to review necessary diagnostic tests and adjunct medicines that should be considered for any patient being discharged from MGH with AMI during their hospitalization. The most salient references for this information are: ACC/AHA guidelines for management of STEMI, as well as the ACC/AHA/SCAI Focused update on primary PCI for patients with STEMI.[1,2]

A. Pre-discharge consults

Once an ACS patient is admitted to the SDU or CCU, they should be admitted using the E10/E11 admission template, which will standardize their admission orders. Included in that template are consults for:

- PT (all post-cath patients must be seen by PT; make sure this order is in early so PT eval doesn't hold up discharge!)
- Nutrition
- Cardiac rehab (it is cost effective and associated with improvement in clinical outcomes; 20-26% lower mortality rates in modern era of secondary prevention; Am J Med. 2004; 116:682–92)
- Smoking cessation (if applicable; meta-analysis has shown smoking cessation to convey ~50% reduction in subsequent cardiac mortality; Arch Intern Med 2000; 160: 939-44)
- Influenza vaccination (All patients with CVD should receive annual flu vaccination).
- Pneumococcal vaccination (All patients with CVD, regardless of age, should receive PSV23. For patients previously vaccinated, a minimum 5-year interval is recommended)
- ***Please make sure that these are ordered prior to the day of discharge.***

B. Assessment of LV function

- Class I recommendation: All patients should have a TTE performed pre-discharge in order to evaluate LV function if they did not have a ventriculogram performed during catheterization.
- In patients with significant LV systolic dysfunction, a post-discharge plan for re-evaluation ≥ 40 days later should be made, especially to address potential need for ICD therapy after allowing for recovery from myocardial stunning.

C. Adjunctive Medications on discharge

All AMI patients should be discharged on the following medications, unless there are contraindications:

- Aspirin: 81 mg daily for lifetime ** send in a prescription to convey the importance of this medication to patients **
- Second anti-platelet agent (clopidogrel, ticagrelor, prasugrel): *Please submit the prescription to the patient's pharmacy as soon as this decision is made as many patients require prior authorization for these medications (ticagrelor and prasurgrel) and this can hold up their discharge. If the cost of the medication is too expensive, the patient may have to be switched to plavix prior to discharge (see switching between P2Y12 inhibitors)*
- PPI/H2 blocker: if sending home on triple therapy, hx of GIB, or high risk. Consider in other patients as well.
    - COGENT trial tested whether PPI therapy would decrease the rate of GIB in patients on DAPT. Primary outcome of GI bleeding was significantly reduced (1.1 vs 2.9%) in patients that were treated with omeprazole 20 mg daily compared to placebo. Of note, there was no increased rate of ischemic events in patients

treated with omeprazole (there have been some observational studies that have raised concern of interaction between clopidogrel and PPI)[3]

- ACE-I/ARB if anterior MI, DM, or LVEF < 40%
- High intensity statin
- Beta-blocker
- PRN sublingual nitro: Of all of the adjunct medications, sublingual nitro is the most likely to be forgotten on discharge. Below is an example of the instructions to give to patients regarding how to take nitroglycerin:

    - Sit or lie down if you can.
    - Place one tablet under your tongue and wait 5 minutes.
    - If you still feel chest pain, take a second tablet, and wait 5 more minutes.
    - If you still feel chest pain, take a third tablet and wait 5 more minutes.
    - If you feel chest pain 5 minutes after taking the third pill, call 911.
    - Always tell your doctor if you had to take this medicine.
    - Keep medicine in the original bottle in a dark, dry place and check the expiration date often.
    - If you need to open the bottle, write the date you opened it in permanent marker.
    - The bottle is good for only **6 months** after it is opened.

- NSAIDs: Patients who routinely took nonsteroidal anti-inflammatory drugs (except for aspirin) before NSTEMI should ***discontinue*** these agents because of increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture (*Class III Recommendation: Harm*)

D. Discharge Instructions

Standardized discharge instructions are important so that patients know what to do when they have symptoms. Patients need to know when they should go to the ED, however appropriate triage of symptoms to the outpatient cardiologist may save hospital readmissions as well. Below is an example of the instructions that should be provided to patients:

WARNING SYMPTOM INSTRUCTIONS

I need to call 911 if I have any of these signs or symptoms:

- Chest pain (or symptoms I had with my admission) that is not helped with 3 doses of nitroglycerin (see below for instructions)
- A new feeling that I can't catch my breath at rest
- Fainting or passing out
- A racing heart or very quick heartbeats that don't go away when resting
- Sudden weakness, confusion, or slurred speech
- A lot of bleeding or swelling from my procedure puncture site

I need to call my doctor if I have these signs or symptoms:

- A **new** feeling that my heart is beating fast or skipping beats
- Feeling dizzy or faint
- New swollen ankles
- Chest pain that lasts longer, happens more often, or is worse than in the past
- Some bleeding or swelling from puncture site
- Fever of 100.5° F or higher

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E. Follow up

- Appointments: The patient should be scheduled to see a cardiologist or their PCP within one month of discharge. For patients who do not have a primary cardiologist, they should be referred to the MGH MI clinic or will be set up with the PDW fellow on service. They should also be given a phone number to call for their cardiologist (even if an appointment is not scheduled at the time of discharge) so that they can call if they have symptoms.
- PCI of non-culprit lesion: Approximately 50% of patients with STEMI have multi-vessel disease. The 2015 ACC/AHA/SCAI Focused Update on Primary PCI for Patients with STEMI put forth an upgraded *Class IIb* recommendation that "PCI of a non-infarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure." (see evidence in Non-culprit lesions in PCI section). Accordingly, a plan for PCI of non-culprit lesions should be addressed during the hospitalization and detailed on the discharge summary.

F. Duration of DAPT

- Minimum:
    - BMS: DAPT should be continued for at least 1 month (preferably 1 year)
    - DES: DAPT should be continued for **at least 12 months in patients who underwent PCI for ACS** and **6-12 months for patients who underwent PCI for stable ischemic heart disease (SIHD)**
    - Medical management: at least 1 year
    - Post-fibrinolysis: 1 year
- Aspirin should be continued indefinitely
- Rationale for Continuing DAPT beyond 1 year: In all patients who have tolerated recommended minimum course of DAPT after PCI (for SIHD or for ACS) without a bleeding complication and who are not at high bleeding risk (e.g. prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of clopidogrel for longer may be reasonable (Class IIb, LOE A).
    - The DAPT Trial randomized 10 thousand patients who had completed 12 months of DAPT after DES placement to either continue DAPT for an additional 18 months or receive placebo and found that continued DAPT reduced rates of stent thrombosis (0.4% v 1.4%) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%), but increased the rate of moderate or severe bleeding (2.5% vs. 1.6%). Benefit greater in those with MI[4]
    - The PEGASUS-TIMI 54 trial found that in patients with MI in the prior 1-3 years, an extended regimen of ticagrelor plus ASA significantly reduced the risk of CV death, MI or stroke compared to placebo[5]
    - Consider calculating a DAPT score to help guide decision-making. The DAPT Score (http://tools.acc.org/DAPTriskapp/#!/content/calculator/) is a decision tool to guide practitioners on deciding whether DAPT should be continued for more than 6-12 months. This uses data from >11,600 patients from the DAPT trial to identify which patients would likely benefit from continuing DAPT from 12-30 months. The DAPT Score predicts the combined ischemic and bleeding risks and includes the following factors: age, cigarette smoking within the last two years, prior MI or PCI, history of heart failure or left ventricular ejection fraction <30 percent, MI at presentation, stenting of a vein graft, type of stent, diabetes, or stent diameter <3 mm. Of these, age ≥75 years was the most important determinant of a worse outcome with longer therapy
    - Usually no reason to continue DAPT beyond 36 months

- Shorter duration of DAPT: Some trials have attempted to assess the safety of a shorter duration of DAPT. This includes the SMART-DATE trial in which >2700 patients with ACS (38% STEMI) who underwent PCI were randomly assigned to 6 or 12 months or longer of DAPT (80% of which were treated with clopidogrel as their P2Y12 inhibitor). Both groups had a similar incidence of the primary end point of all cause death, MI or stroke in 18 months but the 6-month group had a significantly higher incidence of the secondary endpoint of spontaneous MI.
- **When considering stopping an antiplatelet agent, always reach out to their cardiologist for guidance.**

G. Triple Therapy

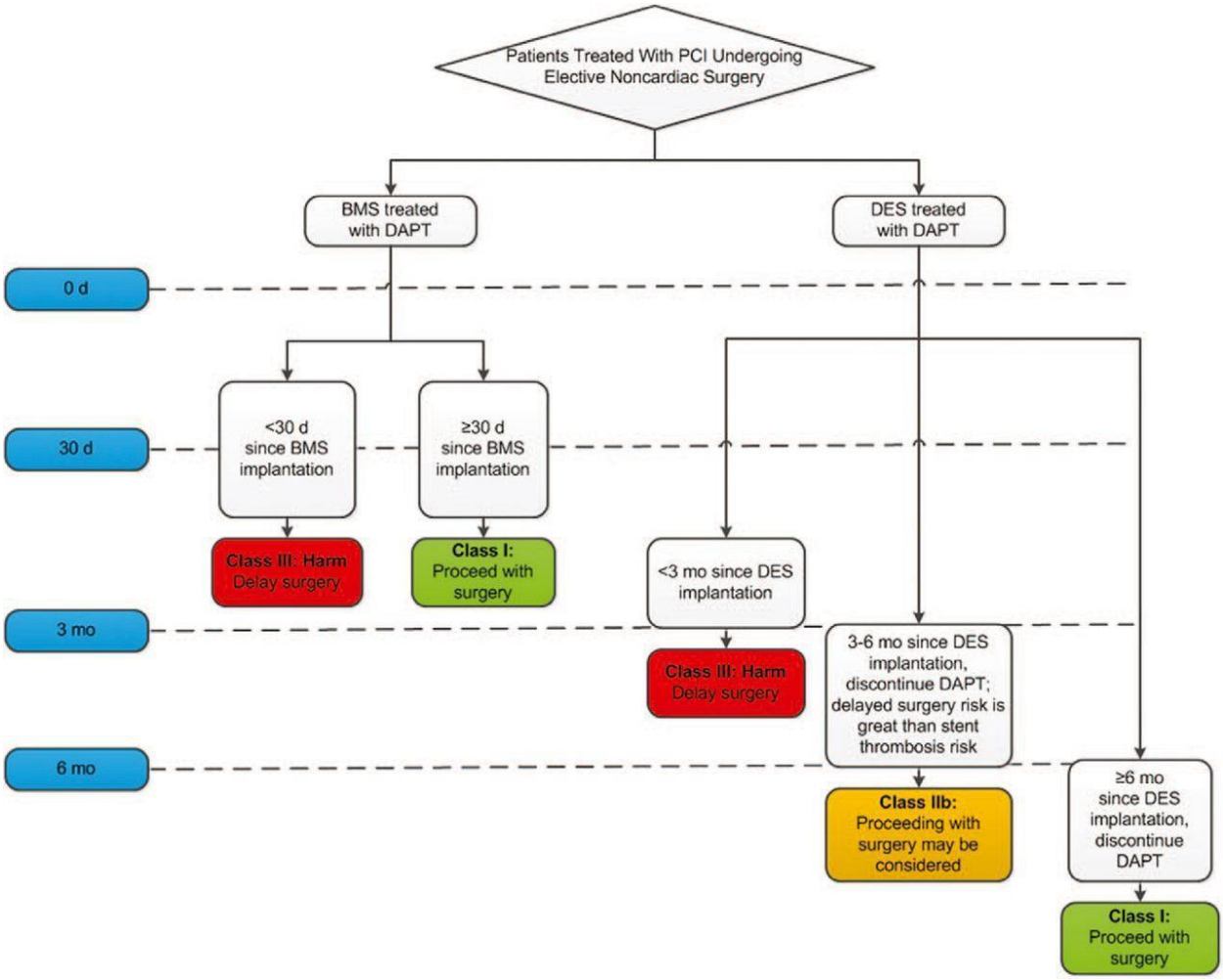
While both DAPT and oral anticoagulant therapy are necessary to reduce risks of stent thrombosis and thromboembolism respectively, the additive therapies increase the risk of bleeding. Recently, several studies have been completed to address this issue in patients with AF and recent ACS. The results of these studies have widely changed practice, **however many of these trials were not powered to assess for ischemic events.**

- A common practice for patients on oral anticoagulation who undergo PCI is to treat with triple therapy (ASA/clopidogrel/AC) for 1 month and subsequently discontinue aspirin, continuing oral anticoagulation and clopidogrel only. If a patient is on triple therapy, they should be treated with clopidogrel over ticagrelor/prasugrel due to increased bleeding risk.
- Evidence:
    - WOEST trial randomized patients on oral anticoagulation to clopidogrel alone (double therapy) vs. clopidogrel plus aspirin (triple therapy) after PCI. The primary endpoint of bleeding episode within 1 year of PCI was significantly lower in the double therapy group and there was no increase in rate of thrombotic events in this group compared to the triple therapy group[6]
    - ISAR-TRIPLE randomized patients on warfarin and aspirin who underwent DES implantation to 6-week vs. 6-month clopidogrel therapy. There was no significant difference in the primary outcome of cardiac death, myocardial infarction, definite stent thrombosis, stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding at 9 months[7]
    - PIONEER-AF-PCI RCT trial randomized participants with nonvalvular atrial fibrillation undergoing PCI to receive low dose rivaroxaban 15 mg daily plus P2Y12 inhibitor monotherapy for 12 months (Group 1), very low dose rivaroxaban 2.5 mg twice daily plus DAPT for 1, 6, or 12 months (Group 2) and warfarin plus DAPT for 1, 6, or 12 months (Group 3). The primary outcome, incidence of clinically significant bleeding, was lower in the two groups receiving rivaroxaban than the group receiving standard therapy (group 3). The rates of death from CV causes, MI, or stroke were similar in the three groups. The fact that the trial was not powered to assess efficacy outcomes such as stent thrombosis or stroke rates is a common criticism[8]
    - RE-DUAL trial showed similar results. Randomized to either aspirin + P2Y12 + warfarin or dabigatran + clopidogrel[9]
- Has not been studied in apixaban or edoxaban.
- Prevention of GI bleeding: Give PPI/H2 blocker in patients on triple therapy (some data suggests interaction between some PPIs and clopidogrel, but more data is needed)
- Mechanical heart values: More challenging, with NOACs deemed contraindicated due to an association of worse outcomes in this cohort (RE-ALIGN trial).[10] Furthermore, <10% of the patients included in both the WOEST and ISAR-TRIPLE studies had mechanical heart valves. The CATHAR trial which is currently investigating the safety of rivaroxaban in patients with mechanical aortic valves may provide more clarity and could open the door for

investigation of a similar antiplatelet/antithrombotic regimen in this cohort as was used in the PIONEER trial.[11]

H. Perioperative Management (DAPT)

The recommendations on the timing of elective noncardiac surgery in patients treated with PCI and DAPT are outlined in the figure below and arise from the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease.



I. Lipid Lowering For Secondary Prevention

- Background: In general, many practitioners support a rationale that lower LDL-C is better for reduction of secondary CV events.
- Goal LDL levels: While evidence does not clearly identify a threshold below which further LDL-C lowering yields limited benefit, lowering < 70 mg/dl should be made in most patients with CAD for prevention of secondary events. Those with the highest risk should have even lower targets. All trials of LDL-C lowering have shown better outcomes in the groups that have the most aggressive LDL-C lowering.
- Evidence:

  - Statins: Many studies have looked at statins effect on outcomes in patients with CVD. While there has been consistent benefit in reducing non-fatal MI and stroke, mortality benefit has been variable. A subgroup of a 2011 meta-analysis of patients with prior ACS did show mortality benefit (HR 0.74, 0.59-0.94)[12]
  - Addition of Ezetimibe: Improved LDL on average from 69->54. Associated with reduction in compositive outcome of CV mortality, major CV event, coronary revascularization or non-fatal stroke when compared to statin therapy alone (high intensity statin use excluded)[13]
  - PCSK9 inhibitors: The FOURIER trial showed that patients with LDL > 70 treated with both high intensity statin and PCSK9 inhibition had a decrease in composite endpoint (CV death, MI, stroke, revascularization, unstable angina), non-fatal MI and stroke. ODESSEY OUTCOMES had similar results, but also had a significant reduction in death (3.5 vs 4.1%)[14,15]
- Bottom line: In patients that have had ACS, lipids should be aggressively managed. In a patient that was not on a high intensity statin prior to the event, they should be placed on a high intensity statin. Recheck LDL in 6-8 weeks and if not ≤ 70, then start ezetimibe. If persistently elevated after ezetimibe, consider PCSK-9. In a patient who was reliably taking a high intensity statin prior to ACS event or cannot tolerate statin therapy, consider adding ezetimibe.

Management of Diabetes

It is well appreciated that aggressive glycemic control decreases likelihood of adverse cardiac events in patients with CAD and DM or PAD and DM. Two classes of drugs have been shown to improve outcomes in patients with established CV disease or at high CV risk.

- Goal: HbA1c is < 7%. Less stringent goals may be appropriate for some patients.
- SGLT-2 inhibitors: SGLT2-inhibitors empagliflozin and canagliflozin decrease cardiovascular mortality and morbidity in T2DM patients who have CAD/high CVD risk factors while Dapagliflozin did not show such efficacy but did reduce hospitalization for heart failure (less patients had documented CVD in the Dapagliflozin trial, which may explain the difference).
  - CANVAS: Among 10,142 patients with DM and high CV risk (65% had documented CV disease) randomized to placebo or canagliflozin, there was a significant reduction in the composite end-point (CV death, MI, stroke). The individualized components of the composite outcome were not significant. Rate of hospitalization for heart failure was lower[16]
  - EMPA-REG OUTCOME: Among 1461 patients in this trial with CVD at baseline, empagliflozin had significant reductions in cardiovascular and all-cause mortality and in composites of major adverse cardiovascular outcomes without differences in major amputations compared with placebo. Patients also had lower A1Cs and greater reductions in weight[17]
  - Adverse events: Increased risk of amputations, which occurred more often in those with prior history of PAD or prior amputation. It remains unclear if this observation extends to all members of the SGLT2-i class. Similar data has not been seen in the Empaglifozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), which collected amputation cases as well[16,17]
- GLP-1
  - The LEADER study of >9,300 patients showed that compared to placebo, liraglutide lowered cardiovascular mortality and all-cause mortality within 3.8 years with nonsignificant lowering of nonfatal MI, stroke or heart failure leading to hospitalization in the treatment group[18]

Inflammation

Inflammation is a critical risk factor for CVD and an important contributor to residual vascular risk beyond other traditional risk factors such as LDL-C, DM, smoking and HTN.

- Evidence: The CANTOS trial of >10,000 patients with recent ACS and elevated hsCRP (>2 mg/L) treated patients with one of 3 doses of canakinumab, a monoclonal antibody to IL-1beta, a component of the inflammsome pathway of macrophage activation, or placebo. Primary end point was nonfatal MI, stroke or cardiovascular death. Compared to patients treated with placebo, treatment with higher doses of canakinumab reduced the primary end point compared to placebo. However, canakinumab was also associated with higher incidence of fatal infection than placebo. Importantly, it had no effects on lipids but did cause a dose-dependent reduction in hsCRP. A secondary analysis showed that patients who achieved on-treatment hsCRP levels < 2 mg/L had significant mortality benefit over those on-treatment with less-improved hsCRP. This was the first study to show that an anti-inflammatory drug with no effect on lipids could improve outcomes in ACS patients and provided therapeutic evidence for the inflammation hypothesis as a causal contributor to ACS risk. However, given modest effect and higher risk of fatal infections, ultimately canakinumab was not approved by the FDA as a treatment for secondary prevention in 2018[19]

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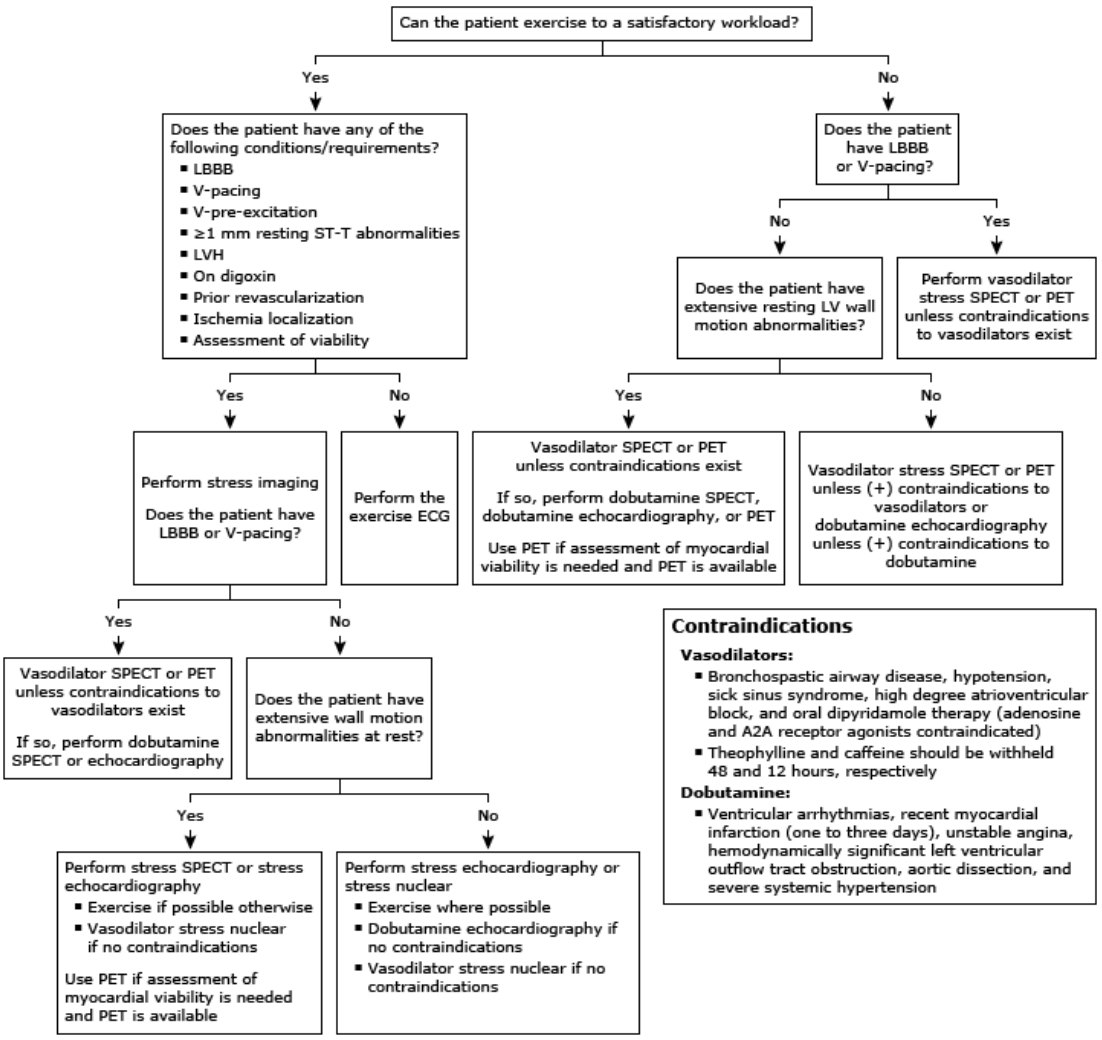
24. Other Issues in Ischemic Heart Disease

A. Stress Testing

Cardiac stress testing can be used to 1) diagnose CAD in patients with intermediate probability of ischemic disease 2) assess known CAD 3) risk stratify/offer prognostic information. Stress testing can be categorized by 2 characteristics: the method used to **induce increased myocardial stress (stress modality)** and the method used to **assess the adequacy of perfusion (imaging modality).** The stress modalities include exercise, vasodilator, and inotrope (dobutamine). The imaging modalities are ECG, TTE, MPI, cardiac MRI and cardiac PET. At MGH, cardiac MRI and PET are not frequently used, but will likely be used increasingly. An approach to choosing the appropriate test and a list of the most common combinations are listed below.



UptoDate. Approach to choosing stress test.[1]

Logistics of Stress Testing:

- Beta Blockers: **Should be held** when trying to **diagnose CAD** and/or with stress modalities that **rely on chronotropy** (exercise and dobutamine) because they may interfere with reaching 85% max HR. **DO NOT need to be held** in known CAD when attempting to assess the quality of medical management.
- Caffeine: No caffeine 12-24 hours before *adenosine* stress testing
- NPO: 6 hours prior to test (if imaging or adenosine) otherwise 3 hours prior for all others
- Control BP and make sure electrolytes (K+) normal
- Weekend: **p38363** (EDOU has 1st priority)
- DNR/DNI needs to be reversed

Prognostic Information:

- Exercise capacity and extent of ischemia (based on imaging) are the two strongest predictors of cardiac events.
    - Exercise events (not limited to the following):
        - Exercise capacity: for each MET of exercise capacity, there is a 12% improvement in survival
        - Exertional hypotension and hypertension are also predictors of adverse cardiac outcomes
        - Chronotropic incompetence (failure to achieve 85% MPHR, not on nodal blockade): Generally thought to increase the risk of all-cause mortality (RR 1.5-2.0 in two studies). However, another study did not show this increase risk, although these patients were asymptomatic and younger[2-4]
        - Induced LBBB: RR of death or major cardiac events – 2.78[5]
    - Duke Treadmill Score: Based on exercise time, magnitude of ST depressions, and exercise angina. Utility has been validated in determining likelihood of significant CAD[6]
        - Of the 36% who had a low risk score, 60% had no stenosis > 75%, 16% had single vessel disease, 9% had MVD, and 5-year survival was 97%
        - Among the 9% that had high risk score, 74% had 3VD or left main disease, 5-year survival was 65%
        - Better in women than men at excluding disease.[7] Also, not as good in older patients (>75 y/o) at excluding significant disease.
    - MPI: Can distinguish those at high (>5% annual mortality) vs intermediate (1-5%) vs low risk (<1%). Exercise and pharmacologic are comparable in their ability to risk stratify
        - Normal MPI: < 1% of cardiac events per year. Normal MPI can even offer prognostic information in patients with abnormal ECG stress. In patients that had an intermediate Duke Treadmill Score, but a normal or near-normal MPI CV survival was 99% and MI-free CV survival was 97%.[8] This is not true at patients with older age or high risk Duke score.
        - High risk features: Extensive ischemia (ischemia in more than one vascular territory, ischemia in multiple segments), large fixed defects, LVEF < 45%, transient or persistent LV dilation, lung uptake of thallium
    - Stress TTE: Exercise wall motion index has a strong association with outcome
        - Normal: 1 and 3 year survival 99 and 97% respectively[9]
        - Compared to exercise ECG alone, TTE provides incremental information in providing a risk assessment in the elderly and DM[10,11]

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B. Stable Ischemic Heart Disease (SIHD)

Definition: Angina that occurs predictably at a certain level of exertion and is relieved with rest or nitroglycerin

Diagnosis:

- **Stress Testing:** Most patients with suspected SIHD should undergo stress testing. Used to determine prognosis/risk of ischemic heart disease and need for coronary angiogram.
- **Coronary Angiogram:**[12]
    - Strong recommendations
        - When noninvasive testing and symptoms suggest to possibility of severe ischemic heart disease (i.e. someone who might meet criteria for CABG where there is a clear mortality benefit to re-vascularization)
        - Initial test in those that survive SCD, ventricular arrhythmias, or develop signs and symptoms of heart failure
    - Weak recommendations
        - Angina significantly interferes with lifestyle despite maximal medical therapy.
        - Equivocal stress testing or contraindications to stress testing
        - Depressed EF (<50%) and at least moderate risk criteria on stress testing

Treatment:

Anti-Anginal Therapy

- Beta-blockers: 1st line therapy to reduce anginal episodes and improved exercise intolerance. BB relieve anginal symptoms by decreasing O2-demand (reduce HR and contractility). All beta-blockers are effective. Additionally, improve survival in patients who have had MI or impaired LV (why BB are first-line). Should NOT be used in vasospasm induced angina (may induce un-opposed alpha activity).
- CCB: Add-on therapy when BB alone are not effective. Work by causing coronary artery dilation and reducing contractility. Diltiazem, verapamil, or amlodipine are preferred. Short acting dihydropyridines (nifedipine) should be avoided unless using with a long acting BB due to the increase in mortality seen in patients after MI or increase in MI in those treated for hypertension
- Nitrates: SL nitro should be provided for patient for acute episodes. A long-acting nitrate can be added for anginal therapy.
- Ranolazine: Works by inhibiting the late sodium channel (which frequently fails to inactivate in many myocardial diseases and results in disturbances of ion homeostasis). Initial dose is 500 mg BID but can be increased to 1000 mg BID. Evidence for ranolazine in SIHD has shown this drug is effective.[13-16] This issue with this drug is expense.

Usually start with monotherapy (BB) then add nitrate or CCB if angina persists. Combination therapy has been shown to improve symptoms (specifically exercise tolerance).[17] In patients that still have symptoms with combination therapy, a third drug can be added. However, often a coronary angiography will be the next step.

Preventative therapy:

- ASA
- Risk factor reduction: weight loss, glycemic control, stress reduction
- Exercise therapy
- Flu vaccine

PCI:

- *Mortality*: No convincing evidence that revascularization improves mortality in patients with SIHD who do not meet criteria for CABG.

  - The landmark 2007 COURAGE trial randomized ~2000 patients with SIHD (+ significant CAD in at least one coronary) to aggressive medical therapy alone or medical therapy + PCI w/ BMS. Most of the patients were symptomatic (87%). At a follow up of 5 and 15 years, there was no significant difference in mortality or non-fatal MI[18]
  - Subsequent meta-analysis (95 trials, n=95,000) showed that PCI with newer DES may be associated with improved mortality (everolimus-eluting: rate ratio [RR] 0.75, 95% CI 0.59-0.96; zotarolimus-eluting RR 0.65, 95% CI 0.42-1.00). However, when restricting to contemporary data (88 trials, 1990 or later), the confidence intervals moved closer to the null effect line. There have been other meta-analyses that have come this conclusion as well (small RR reduction with CI near 1).
  - Ongoing studies are needed. There may be a subset of patients that might benefit.
- *Symptoms*: Studies have shown different effect of PCI on symptoms depending on if there was MVD or single vessel disease
  - MVD (benefit): 2004 MASS II trial randomized patients with MVD + stable angina to CABG, PCI, or medical therapy. PCI (and CABG) showed an improvement in symptoms. At one year, 79% of patients who underwent PCI were symptom free compared to only 46% in the medical therapy[19]
  - Single vessel disease (no benefit): 2017 ORBITA randomized 230 patients with single vessel disease and symptomatic angina to sham-procedure or PCI with DES. There was no difference in primary outcome of incremental exercise improvement nor was there a difference in patient reported symptoms.[20] Of note, we only have the data from 6-week follow up. More data is needed.

CABG:

- *Mortality:* Improved in patients who meet criteria for CABG (left main, 3VD, 2VD with prox LAD lesion)
- *Symptoms*: In 2004 MASS II trial, nearly 90% had relief of their symptoms (compared to 46% in medical therapy group)[19]

C. Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA)

Definition: Rise & fall of troponins with symptoms suggestive of ischemia, but with coronary angiography demonstrating normal or near normal coronaries (≤ 50% stenosis)
Epidemiology: 1-14% in patients presenting with MI
Risk Factors: Traditional risk factors (DM, HTN) similar in MINOCA and obstructive CAD, except for hyperlipidemia. More likely to be younger (mean age=55) and female[21]
Treatment: Should depend on etiology. For patients that have some evidence of CAD and no evidence of alternative etiology, reasonable to assume ACS and medically manage with ASA, P2Y12, beta-blocker, and statin

- SWEDEHEART: >9000 consecutive patients with MINOCA. During > 4 year follow up, the HR for MACE was 0.77 (0.68-0.87), 0.82 (0.73-0.93), 0.86 (0.74-1.01) for patients on statins, ACE-I, and beta blockers respectively. For patients treated with DAPT, HR was 0.90 for MACE at 1 year (CI 0.74-1.08). This was all-comers with MINOCA. Certain etiologies of MINOCA likely derive more benefit from these therapies than others[22]

Prognosis: Meta-analysis of 8 studies showed in-hospital mortality of 0.9% with 12-month mortality of 4.7%.[23] Generally, the mortality is lower than in patients with MI with obstructive CAD

TOC

D. Spontaneous Coronary Artery Dissection (SCAD)

Definition: Separation of the coronary arterial wall, which can lead to myocardial infarction. Non-traumatic and non-iatrogenic.
Epidemiology:

- Accounts for 1-4% of all MIs
- May account for up to 35% of MIs in women ≤ 50
- Most common cause of ACS in pregnancy 43%; 1.81 events per 100,000 pregnancies
- Average age of women 45-53

Risk Factors:

- Female gender
- Pregnancy: usually third trimester, early post-partum
- FMD and other arthropathies
- May be associated with physical or emotional stress

Pathophysiology: Creation of a false lumen with intramural hemorrhage either by intimal tear or bleeding of the vasa vasorum. The enlarging hematoma then encroaches on the true lumen causing myocardial ischemia. The LAD is the most commonly effective artery (32-46%). The mid-distal sections are most commonly affected.
Clinical Manifestations: Vast majority present with ACS with STE, 2-5% present in cardiogenic shock
Diagnosis:

- Coronary Angiography: angiographic classification due to the different appearances of SCAD on angiography. Coronary angiography carries more risk of iatrogenic coronary artery dissection than in other cases (3.4% vs 0.2%)

Treatment:

- Conservative management (no revascularization): Generally recommended in patients that are hemodynamically stable without high risk anatomy. Angiographic healing has been shown to occur in patients that had repeat angiography in the weeks to months after (70-97%). Early complications may occur in these patients – 5-10% develop recurrent MI within the first 7 days. These patients commonly need urgent angiography with PCI. Monitor inpatient for 3-5 days for signs and symptoms of ongoing ischemia.
- PCI: Several observational studies have noted increased complications in patients with SCAD that underwent PCI due to the risks of complications that occur with stent placement (extension of dissection, etc). So generally, only considered if ongoing ischemia or hemodynamic instability.
- CABG: Consider if left main or proximal 2-vessel dissection or if complication of PCI.
- Medical therapy: There is a general lack of data surrounding medical therapy in SCAD. The following is from the 2017 AHA Expert Opinion on SCAD. There is wide practice variation, so it is important to discuss with cardiology.
    - Anticoagulation: Once SCAD is diagnosed, reasonable to stop heparin given concern for propagation (although could reduce thrombus formation).
    - Anti-platelet: Wide variation in use and recommendations of DAPT. Generally, aspirin is prescribed.
    - Beta-blockers: Should be considered in patients with low EF or arrhythmias. The use of a BB was associated with a HR 0.36 of mortality in a 327-patient cohort strengthening the argument for its use.[24] Low HR decreases shear stress on arteries.
    - Statins: Not recommended routinely after SCAD but is indicated if have concomitant hyperlipidemia. In a retrospective cohort of patients (n=87), statin use was associated with a higher risk of recurrence.[25] However, in the 327-patient cohort listed above, there was no association of statin use and recurrence.

- Activities after SCAD: patients should be referred to cardiac rehab (SCAD-specific if available). Target HR during exercise should generally not exceed 50-70% of HR reserve and systolic blood pressure should generally be < 130. Avoid lifting heavy weights (W < 20-30 lbs, M < 50 lbs). A dedicated SCAD rehab program was shown to be beneficial in patients (reduced chest pain, improving exercise capacity, and reducing CV events)[26]

Prognosis:

- Pregnancy-related SCAD has worse prognosis than non-pregnancy related SCAD
- In-hospital mortality: 4.2%[27]
- Recurrent in-hospital MI: 4.6%, unplanned revascularization: 4.3%
- At intermediate follow up (2-3 years), recurrent MI reported in 10-30%
- At long term follow up (10 years): MACE in ~50%, most commonly recurrent SCAD

E. Microvascular Angina

Definition: Symptoms of angina + signs of ischemia on non-invasive testing, but on evaluation of epicardial coronary arteries, no obstructive coronary disease
Epidemiology: More likely to be younger and female, more likely to have CV risk factors than the general population
Clinical Presentation: Some patients present with ACS and then are diagnosed with MINOCA. Others have stable coronary disease that get the diagnosis after persistent and severe symptoms lead to coronary angiography without evidence of obstructive CAD
Pathophysiology: Various mechanisms proposed, but it has been shown that these patients have higher sensitivity to vasoconstrictor stimuli and less ability to vasodilate.[28] Other mechanisms include endothelial dysfunction, luminal obstruction (microthrombi), vascular remodeling, extramural compression, pain sensitivity. Can coincide with other CV conditions, such as HCM, LVH, aortic stenosis due to one of the many mechanisms proposed
Diagnosis: These patients will get stress testing and coronary angiography as described above. The focus here will be on supplemental tests that can be used to diagnose MVA
During angiography:

- Coronary Flow Reserve (CFR): Measured at the time of angiography. Administer intra-coronary vasodilator and measure the flow reserve. If the CFR is low (<2-2.5) and there is no epicardial disease, microvascular dysfunction can be diagnosed
- Provocative testing with Ach: diagnostic if have symptoms + EKG changes without evidence of epicardial disease

Non-invasive

- Fractional flow reserve using CT, PET, or CMR

Treatment:

- Risk factor modification
- Aspirin and statin if have any evidence of atherosclerotic disease
- Anti-anginal: as listed in SIHD
- ACE-I: There is some evidence of benefit. For example, in the WISE trial, women who had received quinapril had improved CFR after 16 weeks. They also had improved symptoms of angina[29]
- Imipramine: Small study showed 50% reduction in chest pain[30]

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QUICK REFERENCE GUIDE: ACUTE CORONARY SYNDROMES AND ISCHEMIC HEART DISEASE

ACS Classification and Pathogenesis

- ACS is a term used to refer to three major clinical syndromes, including unstable angina (UA, by definition biomarker-negative), non-ST elevation MI (NSTEMI, specifically Type I), and ST elevation MI (STEMI)
- Note that in the era of hs-cTn testing, there is an argument that UA will become irrelevant. Although, higher sensitivity testing will capture more NSTEMIs, there is still a proportion of patients that will have a clinical syndrome consistent with ACS but without hs-cTn elevation and will go on to have a significant flow-limiting lesion on coronary angiography (that will benefit from coronary revascularization)

Diagnosis

- History, physical exam, and 12-lead ECG alone will identify ~92-98% patients with MI and ~90% of patients with UA
- The history should be focused on identifying typical features of cardiac chest pain. Although limited in certain populations, these include: Substernal pressure-like CP, lasting >20 minutes and provoked by exercise or emotional stress and relieved by NTG or rest
- In addition, history should aim to differentiate UA from stable angina, with UA defined as:
    - Rest angina (which is usually more than 20 minutes in duration)
    - New-onset angina that markedly limits physical activity, or
    - Angina that is more frequent, longer in duration, or occurs with less exertion than previous angina
- In cases where ACS is suspected, an ECG should be obtained within 10 min of symptoms/presentation then Q10-15 minutes (to evaluate for dynamic changes). Remember that there is ddx for STE and STD (see Diagnosis section)
- STEMI criteria include ≥1 of the following:
    - New STE, evaluated 80ms (2 small boxes) from the J-point (the inflection point between the S wave and the ST segment) in 2 contiguous leads with the cut-point of ≥1mm in all leads other than V2-V3. Patients may demonstrate elevation in the anterior precordial leads (V1–V3) which are NOT pathologic, so for leads V2-V3, the following cut-points apply ≥ 2mm (M ≥ 40 yr), ≥2.5mm (M < 40 yr), or ≥ 1.5mm (F)
    - New LBBB (see Sgarbossa's criteria in Diagnosis section)
    - Evidence of a "true" posterior MI, defined by STD in ≥2 precordial leads (V1–V4) (not to be confused with inferior MI, which historically was called the posterior wall). If posterior MI is suspected, obtain posterior leads (V7-V9). STE >1 mm in V7–V9 is diagnostic, but STE >0.5mm raises pre-test probability for posterior wall MI
- Obtain right-sided leads in the case of ANY STE in inferior (II, III, aVF) leads or V1 to evaluate for RV involvement. An STE >1 mm in V4R = most predictive of RVMI
- Obtain posterior leads if strong suspicion for ACS but normal ECG OR, as above, if posterior STEMI is suspected (e.g. STD in V1-V3 or R/S ratio >1 in V1-V2)
- Consider critical left main and/or proximal LAD disease in the setting of:
    - STE >1 mm in aVR with STE in aVR > V1 or widespread STD (most prominent in I, II, and V4–V6)
    - Wellen's syndrome, in which the ECG reveals deep inverted or biphasic T-waves in V2-V3. Pt's with true Wellen's syndrome will be CP free, but 75% will have an anterior MI in days to weeks if not treated. In these cases, proceed directly to coronary angiography, as stress testing is contraindicated

- NSTEMI criteria:
    - New horizontal or down-sloping STD of ≥ 0.5mm or
    - TWI ≥ 0.1mm with a prominent R-wave or R/S ratio > 1 in ≥ 2 contiguous leads
- When suspecting ACS, obtain hsTnT immediately + 3hr (1 hr if worried). A rise OR fall in hsTnT ≥ 5 AND symptoms or ECG changes/concerning imaging raises the pre-test probability of ACS

Risk Stratification

- The purpose of risk stratification in ACS is first to assist with triage decisions (e.g. discharge with follow-up, 24-hr observation admission, general ward, SDU/CICU) and next to determine the timing of intervention.
- There is a Class IIa recommendation that risk-stratification models (e.g. TIMI, GRACE, PURSUIT, HEART) be used to assist with decision making in patients with UA/NSTEMI
- In general, there is no role for stress testing when true ACS is suspected, as this is a diagnostic tool utilized most appropriately for CAD/stable ischemic heart disease (see section in SIHD)
- Coronary CTA has a high negative predictive value for ruling out coronary artery stenosis (up 99% in low-risk individuals) and should be considered for ruling out ACS in low-to-intermediate risk patients

Triage Decisions

- Patients who present to the emergency department with signs/symptoms suggestive of ACS should undergo appropriate risk stratification to inform triage to the following locations:
    - Directly to the cath lab: Appropriate in STEMI and UA/NSTEMI accompanied by high-risk features, including: Cardiogenic shock, CP that is refractory to anti-ischemic and anti-anginal therapies, and electrical instability (frequent NSVT, unstable SVT, or sustained VT)
    - To the CICU: Any post-PCI patient in cardiogenic shock or with refractory chest pain or electrical instability as well as high-risk patients as above who cannot proceed directly to the cath lab
    - SDU/CAU: Patients with a high pre-test probability of UA/Type 1 NSTEMI needing expedited coronary angiography, provided that their pain has resolved and has not recurred
    - EDOU: Those with a non-diagnostic history and initial ECG (as well as negative troponin)
    - General Medicine/Bigelow: Those with cardiac risk factors but an equivocal history for ischemia. In general, these patients should have a negative ECG and negative early and repeat troponins (and therefore a low probably of needing cor angio/revascularization)
- For triaging ACS in admitted patients:
    - If concern for STEMI: Call Rapid Response immediately (x6-3333). Senior-on will then notify the on-call interventional cardiologist/cath lab RN via x6-8282. Decisions of whether or not to activate the lab will be made by the med senior and attending interventionalist. If uncertain if ECG meets STEMI criteria, the on-call cardiology fellow may serve as another a resource (STAT page the general cardiology pager “Suspect Acute MI”)
    - If NSTEMI: The patient can stay on the floor if chest pain resolves with SL nitro, and there are no concerning features that would prompt immediate catheterization (i.e. high risk features described above)

Medical Treatment of ACS

- If suspecting ACS, first assess overall stability (airway, breathing, circulation; review O2 monitor and tele). Establish IV access and provide supplemental O2 to maintain SpO2>90%
- Upfront medical management includes ASA 325 mg (non-enteric coated chewable tablet or rectal suppository if unable to take PO, unless worried about aortic dissection) and atorvastatin 80 mg
- Simultaneously, evaluate for signs of left heart failure (while continuously assessing hemodynamic stability). Lab workup should include troponin, electrolytes, Hct/Hgb, coags
- For STEMI, consider PCI immediately; if NSTEMI, risk stratify to help determine optimal timing
- Anticoagulation is indicated in all patients with NSTEMI/STEMI without contraindication
    - Unfractionated heparin (at a dose of 60 U/kg bolus followed by 12 U/kg/hr drip, titrating to goal PTT 50–70) is the anticoagulant of choice. See chapter for further discussion on bivalirudin (reserved for patients with HIT) and enoxaparin
    - If on warfarin, do not initiate AC unless INR < 2; if on a DOAC, consult with pharmacy regarding the best time to start anticoagulation
    - UFH can be stopped after revascularization; if medical mgmt only, UFH should be continued for at least 48 hours or until discharge
- Beta-blocker therapy should be initiated within 24 hours of STEMI/NSTEMI in patients without contraindications
    - They can be initiated in the acute setting as metoprolol tartrate PO q6h, uptitrated for a goal HR of 55-60
    - BBs are contraindicated if the patient exhibits signs of HF/evidence of low output state (absolute). Additional relative contraindications include: active asthma or reactive airways, PR interval > 0.24 seconds, or second- or third-degree AV block
- At MGH, the policy is to defer administration of P2Y12 inhibitors prior to catheterization (discuss with cardiology first)
- For pain, in addition to SLNG (as above), give morphine sulfate (IV 2-4 mg slow push q5-15 min); if cocaine-induced MI, also give benzodiazepines (e.g. lorazepam 2-4 mg IV q15 min, NO beta blockers)
- An ACE inhibitor should be administered orally within the first 24 hours of (N)STEMI to patients with any of the following:
    - Anterior infarction
    - Diabetes
    - LVEF less than 40%

Catheterization, PCI, and CABG

- Indications for PCI
    - STEMI: With optimal door-to-balloon time of 90 minutes
    - NSTEMI/UA: Management less clear-cut. If severe-refractory angina or high-risk features (HD instability, cardiogenic shock, malignant arrhythmias), patient likely benefits from early invasive strategy (PCI within 24h of presentation). Intermediate-low risk patients do not show similar benefit.
    - Stable CAD refractory to OMT
- FFR/iFR: Evaluate if a stenosis visualized on angiography is functionally significant. Not recommended for use in evaluating culprit lesions in ACS

    - FFR is the ratio between coronary pressure distal to the stenosis relative to aortic pressure with maximum myocardial hyperemia (usually using adenosine); traditionally cutoff value of 0.75 was used but increased to 0.80 to improve sensitivity
    - iFR is an alternative to FFR with benefit of avoiding adenosine. The cutoff is </= 0.89 when clinical/non-invasive testing c/w ischemia and </= 0.86 if clinical/non-invasive testing not c/w ischemia
- PCI of non-culprit lesions: Based on available evidence, the ACC/AHA assigns a class IIb recommendation for PCI of non-culprit lesion in ACS, with timing at the discretion of the interventionalist
    - However, there is data to suggest that this may be harmful in cases complicated by cardiogenic shock
- Views during angiography: Cranial views (looking down from shoulder) optimal for viewing LAD, caudal views (looking up from feet) optimal for viewing LCx. LAO means the camera is on the left side of the patient and the heart is directed to the left; RAO means the camera is on the right side of the patient and the heart is directed to the right
- BMS vs DES: The NORSTENT trial (comparing BMS to 2nd generation DES) found no significant difference in mortality, but noted ↓ repeat revascularization in DES group
    - BMS: More likely to develop early in-stent restenosis due to re-epithelization within the first 30 days. Requires DAPT for at least 1 month (preferred 1 year)
    - DES: Associated with increased rate of late (>30 day) stent thrombosis due to prolonged foreign body exposure. Requires DAPT for at least 6 months (preferred 1 year), so theoretically increases bleeding risk; however, emerging evidence suggests that newer generation DES with shorter DAPT may be considered
- Post-catheterization complications: If during the day, call the procedural fellow who did the case. If at night, call the access fellow on Ellison 11
    - Hematoma: HOLD pressure PROXIMAL to the puncture site and have someone call the appropriate fellow. Support patient with IVFs and blood products. Consider stopping/reversal of antiplatelet/anticoagulant agents
    - RP bleed: If suspected and pt stable, evaluate with STAT non-contrast CT. Mgmt as above
    - Pseudoaneurysm: Treatment of small pseudoaneurysms (<2cm) is compression (may be US guided), larger pseudoaneurysms may need surgical interventional/injection
    - AV fistula: Management options include conservative (US-guided compression) or surgical intervention if unresolving (cannot inject thrombin)
    - Limb ischemia: Evaluate distal pulses with Doppler and consider PVRs to further assess location of compromise. If concerned, consult attending/fellow immediately
- Stent thrombosis (ST): Angiographic evidence of thrombus originating in the stent or within 5mm of the stent with ischemic symptoms at rest, EKG signs of ischemia, or rise and fall of cardiac biomarkers within 48 hours of angiography
    - Management involves recanalization, thrombus aspiration, OCT/IVUS for stent apposition and consideration of switching to more potent P2Y12 blocker (e.g. ticagrelor or prasugrel)
- In-stent restenosis (ISR): Gradual re-narrowing of the stented segment (vs abrupt occlusion in stent thrombosis) due to neointimal tissue proliferation with both a clinical definition (recurrent symptoms and signs of ischemia) and angiographic definition (>50% luminal narrowing at follow-up angiography)
    - Management involves intravascular imaging to look for stent under-expansion or mal-apposition. Consider deployment of DES on top of old stent or drug-coated balloon

- Indications for CABG
  - Class I: Significant (>50%) L Main Disease, 3VD, or significant LAD disease with 1-2VD and EF<50%, 1-2VD without LAD involvement but large area of at-risk myocardium, and L main equivalent disease (including >70% proximal LAD OR proximal LCx disease)
- Class IIa: Significant proximal LAD disease with 1-2VD without high-risk features
- Class IIb: 1-2VD without LAD and without high-risk features
- Grafts: Arterial grafts have ↑ patency compared to SVGs; may not be limited to RIMA/LIMA with increased radial artery grafting, but arterial grafts ↑ difficulty to harvest compared to SVGs, so may not be conducive in emergencies
- Concomitant medical therapy: ASA 81 daily, beta blocker, statin; ± P2Y12 inhibitor

Post-MI Complications

- Many post-MI complications present as hypotension. Upfront diagnostics should include STAT TTE (to evaluate for mechanical and pericardial complications) as well as ECG/telemetry (to evaluate for per-MI arrhythmia and conduction abnormalities
- Mechanical complications include those below. See corresponding chapter for bulleted mgmt
  - Ventricular free wall rupture
  - Rupture of intraventricular septum
  - Acute MR
  - RV infarction
  - LV thrombus
  - LV aneurysm and pseudo-aneurysm
- Pericardial complications include:
  - Peri-infarction pericarditis
  - Pericardial effusion (w/ or w/o tamponade)
  - Postcardiac injury/Dressler's syndrome
- Common peri-MI arrhythmias and conduction abnormalities include:
  - VT/VF
  - AIVR
  - VPBs
  - AF
  - Sinus bradycardia
  - Blocks (AVB, BBBs)

Discharge Planning and Outpatient Management

- Key medications:
  - Aspirin 81 mg daily for lifetime (unless otherwise indicated for specific cases)
  - Second anti-platelet agent (clopidogrel, ticagrelor, prasugrel)
  - ACE-I/ARB (if LVEF < 40%, DM, or anterior MI)
  - High potency statin (see below)
  - Beta-blocker
  - PRN sublingual nitro
- Duration of DAPT:
  - S/p BMS: At least 1 month (preferably 1 year)
  - S/p DES for stable ischemic heart disease: At least 6-12 months
  - S/p DES for ACS OR s/p fibrinolysis: At least 12 months
  - Use DAPT Score (http://tools.acc.org/DAPTriskapp/) to assess risks/benefits of continuation past 1 year.

    - ASA indefinitely
- Triple therapy:
    - For patients on oral AC for non-valvular AF, reasonable to discontinue aspirin after 1 month and continue on P2Y12 and oral AC
    - DOAC such as dabigatran or rivaroxaban preferred over edoxaban or apixaban
    - Farther out from index event (>1 year), continue switching P2Y12 to aspirin as anti-platelet
    - When on triple therapy, choose clopidogrel over ticagrelor or prasugrel given bleeding risk
- Lipid Guidelines (secondary prevention):
    - Discharge on high-intensity statin (atorva 80 mg preferred, but atorva 40-80 mg or rosuvastatin 20-40 mg are also considered high-intensity therapy)
    - Recheck LDL in 6-8 weeks and if not ≤ 70 start ezetimibe
    - If persistently elevated after ezetimibe, consider PCSK-9 inhibitor

Other Issues in Ischemic Heart Disease

- Stable ischemic heart disease (SIHD) is defined as angina that occurs predictably at a certain level of exertion and is relieved with rest or nitroglycerin
- Most patients with suspected SIHD should undergo stress testing, which is used to determine prognosis/risk of ischemic heart disease and need for coronary angiogram
- More generally, indications for cardiac stress testing include: Diagnosis of CAD in patients with intermediate probability of ischemic disease, assessment of known CAD, and risk stratification/prognostication
- Stress testing can be categorized by 2 characteristics:
    - Method used to induce increased myocardial stress (stress modality). These include exercise (always preferred), vasodilator, or inotrope (dobutamine)
    - Method used to assess the adequacy of perfusion (imaging modality). These include ECG, TTE, and MPI (as well as cardiac MRI and cardiac PET at other institutions)
- Logistics of stress testing
    - Beta Blockers + Nitrates: HOLD >24h (>48h for atenolol) if *t*rying to diagnose CAD and/or stress modality relies on chronotropy (exercise, dobutamine). DO NOT HOLD if known CAD/attempting to assess quality of medical management
    - Caffeine: Hold for 12-24 hours before adenosine stress testing
    - NPO: x6 hours if imaging/adenosine and x3 hours for all others
- Refer to chapter for discussion of entities that can mimic ischemic heart disease, including:
    - Myocardial Infarction with Non-obstructive Coronary Arteries (MINOCA)
    - Spontaneous Coronary Artery Dissection (SCAD)
    - Microvascular angina

ARRYTHMIAS AND ELECTROPHYSIOLOGY

See Page 238 for Quick Reference Guide

25. Narrow Complex Tachycardias (NCT)

By definition, a narrow complex tachycardia (NCT) implies a supraventricular origin (although some VT arising from the conduction system can be relatively narrow, and SVT with aberrancy/pre-excitation can be wide). NCTs can be organized by or classified in different ways:

- Electrocardiographic appearance ("short RP" versus "long RP")
- Anatomic origin (sinus node, atria, AV node)
- Mechanism (automaticity versus re-entry)

Therapeutically, it is important to consider whether the NCT is dependent on the AV node as a critical component of the tachycardia circuit.

Pathophysiology

For a NCT to exist, there must either be abnormal impulse conduction or abnormal impulse formation (either enhanced automaticity or abnormal triggered activity).

Abnormal impulse conduction

Re-entry is the most common mechanism of NCT (e.g. atrial flutter, AVNRT, AVRT). Re-entry can be "set up" by scar and/or ischemia that produce areas of tissue heterogeneity. Most commonly, this occurs when the following 3 criteria are met:
1. There are 2 distinct pathways with different conducting properties
2. There is a unidirectional block in 1 pathway
3. There is the formation of slow anterograde conduction down the unblocked pathway, which must exist in time for the blocked pathway to recover, allowing for retrograde conduction

Abnormal impulse formation

Abnormal impulse formation occurs in both enhanced automaticity and triggered activity.

Enhanced automaticity can result from increased firing from either a normal or aberrant pacemaker.

- Normal automaticity: A normal pacemaker focus (SA or AV node) fires at an accelerated rate (e.g. sinus tachycardia and accelerated junctional rhythm)
- Abnormal automaticity: A non-pacemaker focus becomes automatic and takes control of the cardiac rhythm. This can occur as a result of ischemia, drugs, or metabolic disturbances (e.g. accelerated idioventricular rhythm)

Triggered activity occurs when there is interruption of normal cardiac repolarization by afterdepolarizations, i.e. depolarizations that attend (early) or follow (delayed) cardiac action potential. This leads to extrasystoles and tachyarrhythmias. In early afterdepolarization, an impulse triggers the myocardium before repolarization is complete (e.g. long QT syndrome, Torsades). In delayed afterdepolarization: an impulse triggers the myocardium after repolarization is complete (e.g. digitalis toxicity due to enhanced calcium influx).

Tachycardia by Site of Origin

Sinus Node: NCTs involving the sinus node include sinus tachycardia and sinus node re-entry tachycardia.

- Sinus tachycardia

  Presentation
  - HR 100–150 in older pts. Can be as high as 200 in young patients (maximum HR ≈ 220 − age)
  - Initiation is gradual (heart rate trend on telemetry increases over seconds)
  - P wave axis and morphology unchanged compared to baseline ECG

  Pathophysiology
  - Secondary causes (physiologic): Due to an underlying process (pain, fever, hypovolemia/shock, CHF, PE, anemia, hyperthyroidism, AV fistula) or drugs (intoxication of caffeine, anticholinergics, catecholamines, nicotine, or withdrawal from EtOH, benzos, opiates). May be seen in roughly one-third of patients with acute MI (Circulation 1972;45:681)
  - Idiopathic (primary):
    - Inappropriate Sinus Tachycardia (IST) is idiopathic resting sinus tachycardia, typically with very high sinus rates on exertion
    - Paroxysmal Orthostatic Tachycardia Syndrome (POTS) is a separate diagnosis characterized by marked sinus tachycardia upon standing
    - Both IST and POTS are diagnoses of exclusion after physiologic ST is ruled out

  Treatment
  - Treat the underlying cause
  - If IST or POTS: treatment is primarily for symptoms (tachymyopathy is exceedingly rare). BB is the most common treatment vs less often non-dihydropyridine CCB, catheter ablation of SA node, ivabradine (off label but can be effective)

- Sinus node re-entry tachycardia

  Presentation
  - Can occur in the absence of other known heart disease
  - Initiation and termination are abrupt (paroxysmal) and can be brought on by pacing
  - P wave axis and morphology are unchanged compared to baseline (sinus) ECG

  Pathophysiology
  - Re-entry within or adjacent to the SA node

  Treatment
  - Vagal maneuvers, modified Valsalva (passive leg raise after Valsalva terminated SVT 43% of time vs 17% of time with Valsalva alone, Lancet 2015; 386: 1747), adenosine, rapid atrial pacing
  - BB, non-dihydropyridine CCB and digoxin can be used to prevent recurrence (although evidence for benefit still lacking); catheter ablation

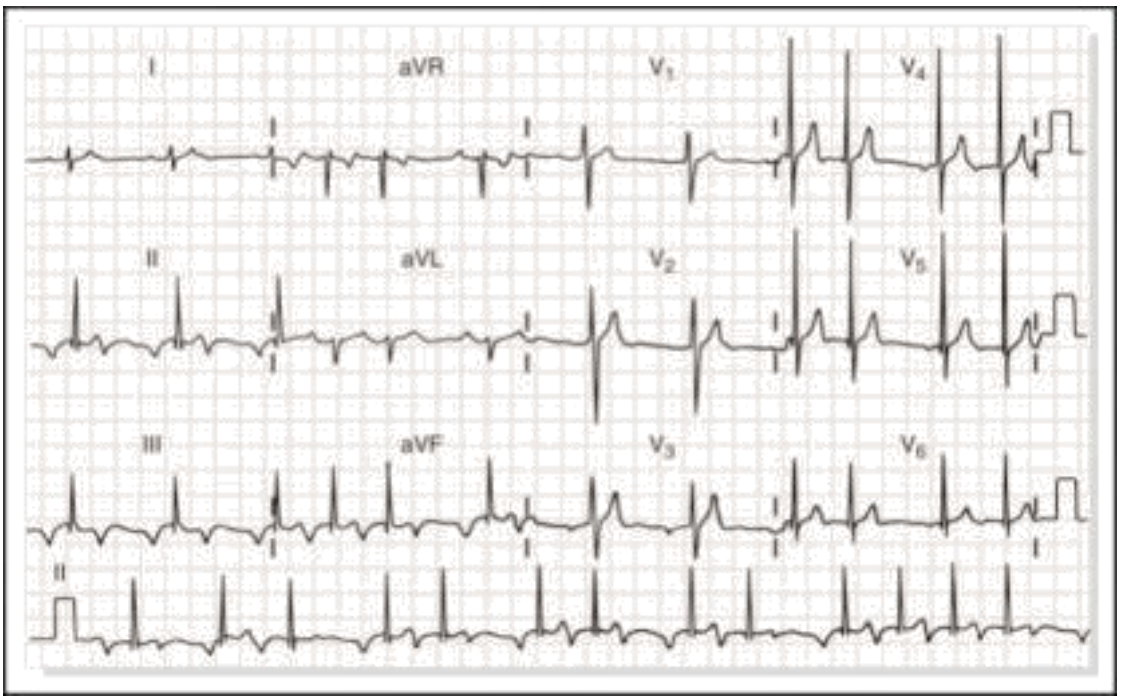
Atrium: These include atrial tachycardia (can be both focal or multifocal), atrial flutter, and atrial fibrillation. These encompass the three primary irregular NCTs: multifocal atrial tachycardia, atrial flutter with variable block, and atrial fibrillation.

- Atrial tachycardia (AT): Either focal or multifocal

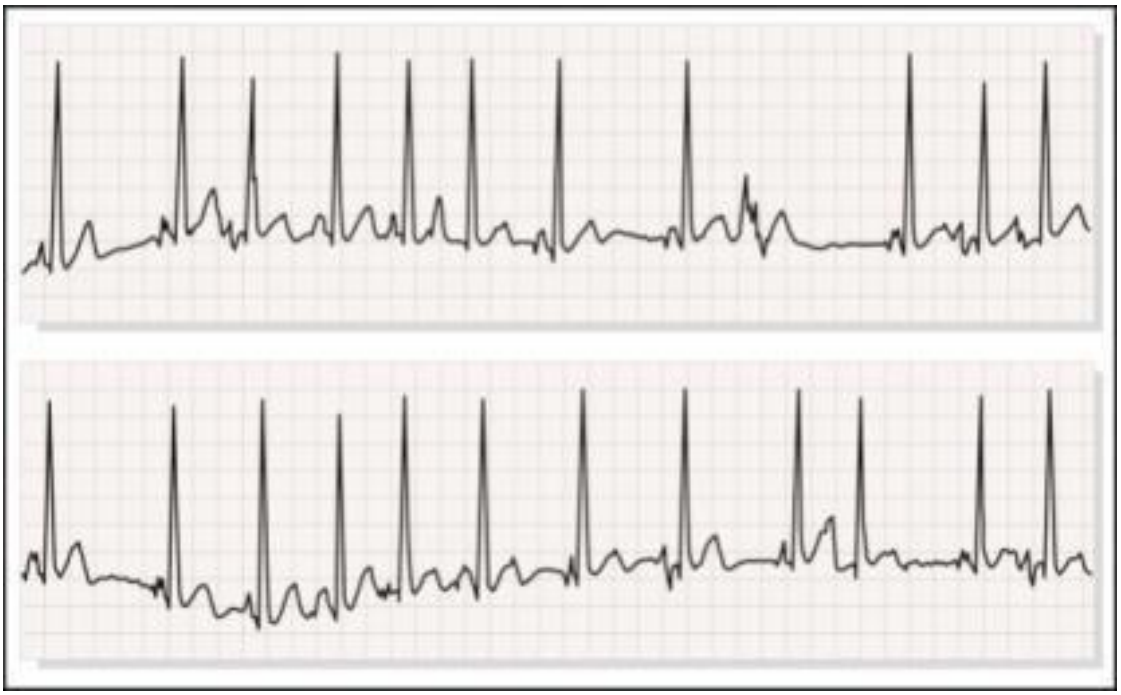
  Presentation
  - Atrial rate 100–250. Ventricular rate typically 90–150 (due to variable block).
  - P different from baseline sinus P. If MAT: 3 different P morphologies, different R-P and P-R intervals
  - When AV block present, baseline between P waves is isoelectric in all leads.

  Pathophysiology
  - Focal AT: Seen in structural heart disease, dig toxicity (which can be exacerbated by hypokalemia)
  - MAT: Seen in older patients with chronic lung disease. Often preceded or followed by atrial fibrillation/flutter, paroxysmal AT, or frequent PACs (Am Heart J 1988;115:680)

  Treatment
  - Focal AT: Stop digoxin if suspect toxicity. Rate control with BB, CCB (can be difficult to achieve). Radiofrequency ablation if AT is incessant and medically refractory.
  - MAT: Goal is to treat underlying pulmonary disease. If lung disease is severe, avoid BBs. Moderate success seen with CCBs. Usually no role for anti-arrhythmic, DCCV, or ablation.



AT with variable block. When P's are consecutive, RP > PR.



MAT with variable Ps and PR, RP intervals.

- Atrial flutter

Presentation

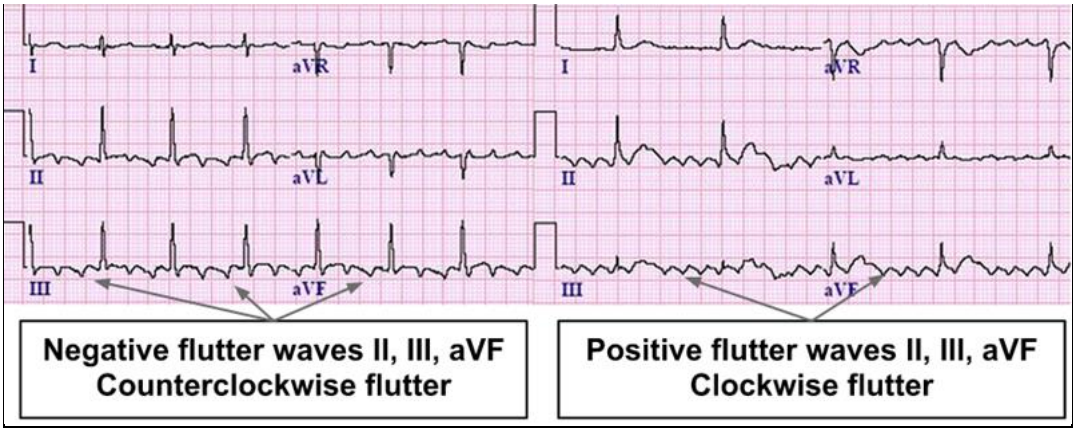
- Atrial rate 250–350, often 300. Ventricular rate can be around 150 bpm if there is 2:1 A-V conduction.
- Typical ("CTI"): 90% of patients have typical flutter with counterclockwise reentry around the tricuspid valve. Sawtooth "F" waves are negative in the inferior leads based on counterclockwise conduction down the right atrial anterolateral free wall, across the cavotricuspid isthmus, and more slowly up the interatrial septum
- Atypical forms of atrial flutter also exist, with a wide variety of atrial rates and p wave morphologies. These are more common after catheter/surgical ablation of atrial fibrillation

Pathophysiology

- Macro-reentrant circuit

Treatment

- If 2:1 block, can first trial vagal maneuvers. Adenosine may also be trialed and generally will transiently slow A:V conduction and the ventricular rate but will not terminate atrial flutter (6mg rapid IV push, followed by 12mg push if no response; if administered through a central line, the doses are 3mg-->6 mg).
- Medical management: Anticoagulation and rate/rhythm control, similar to AFib
- Always rate control first with BB, CCB, and/or digoxin before attempting rhythm control with class IA or IC agents (because these anti-arrhythmics can facilitate 1:1 ventricular conduction if used by themselves). Amiodarone 200mg QD can be used to prevent recurrence. DCCV can be considered if atrial flutter is associated with hypotension or decompensated heart failure. Typical flutter is most amenable to catheter ablation



- Atrial fibrillation: See chapter on atrial fibrillation

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AV Node: These include non-reentrant junctional tachycardias, AV nodal re-entrant tachycardia (AVNTR), and AV reciprocating tachycardia (AVRT).

- Non-reentrant junctional tachycardia
  Presentation
  - These generally include junctional ectopic tachycardia (JET) and accelerated junctional rhythm (which is known as non-paroxysmal junctional tachycardia of NPJT). Junctional tachyardiacs can be difficult to distinguish from other arrhythmias, particularly AVNRT. Retrograde P waves can be observed, and incomplete A-V dissociation is frequent with intermittent capture of sinus beats by the AV node leading to irregular ventricular rates that can also mimic atrial fibrillation
  - Junctional ectopic tachycardia (JET):
    - Rare and relatively benign in adults; more commonly associated with, and often incessant in infants after cardiac surgery for CHD
    - Rapid, occasionally irregular NCT, with rates typically 120 to 220
  - Non-paroxysmal junctional tachycardia (NPJT):
    - More common in adults than junctional ectopic tachycardia
    - Also referred to as accelerated junctional rhythm, rates typically 70 to 130

  Pathophysiology
  - Junctional ectopic tachycardia: Arises from an accelerated, ectopic focus in the AV junction (including the His bundle)
  - Non-paroxysmal junctional tachycardia: Most often due to digitalis toxicity (digitalis can enhance phase 4 depolarization of the His-Purkinje fibers) but a lso seen in acute MI

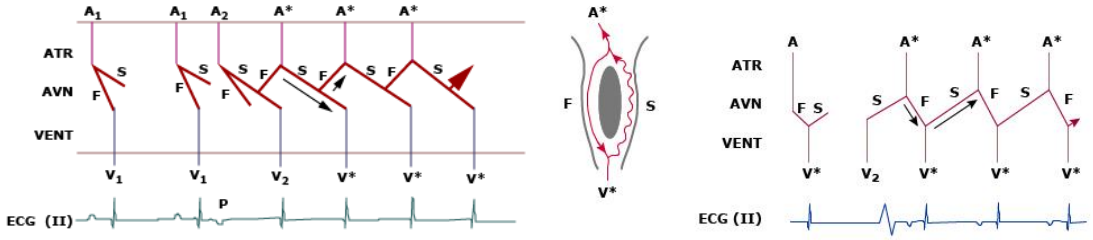
  Treatment
  - Junctional ectopic tachycardia: IV nodal blockade in the acute setting, PO for ongoing management; ablation can be considered if symptomatic and resistant to medical therapy, but is very risky (can result in AV block)
  - Non-paroxysmal junctional tachycardia: Treatment of underlying condition (digitalis toxicity, MI)
- AV nodal re-entrant tachycardia (AVNRT)
  Presentation
  - Initiated by a PAC or PVC and onset and initiation are abrupt
  - There is always a 1:1 AV relationship, generating a regular rhythm with ventricular rates typically between 150–220
  - Ps usually buried within QRS, or found immediately before or after QRS.

  Pathophysiology
  - Re-entry circuit within the AV node with dual pathway physiology
    - Typical (“slow-fast”): Represents >90% of AVNRT in which the impulse travels antegrade down the slow pathway and retrograde up the fast pathway. This classically generates a short RP tachycardia
    - Atypical (“fast-slow”, “slow-slow”): In these cases, the impulse travels initially via the fast pathway, then returns via the slow. This usually generates a long RP tachycardia

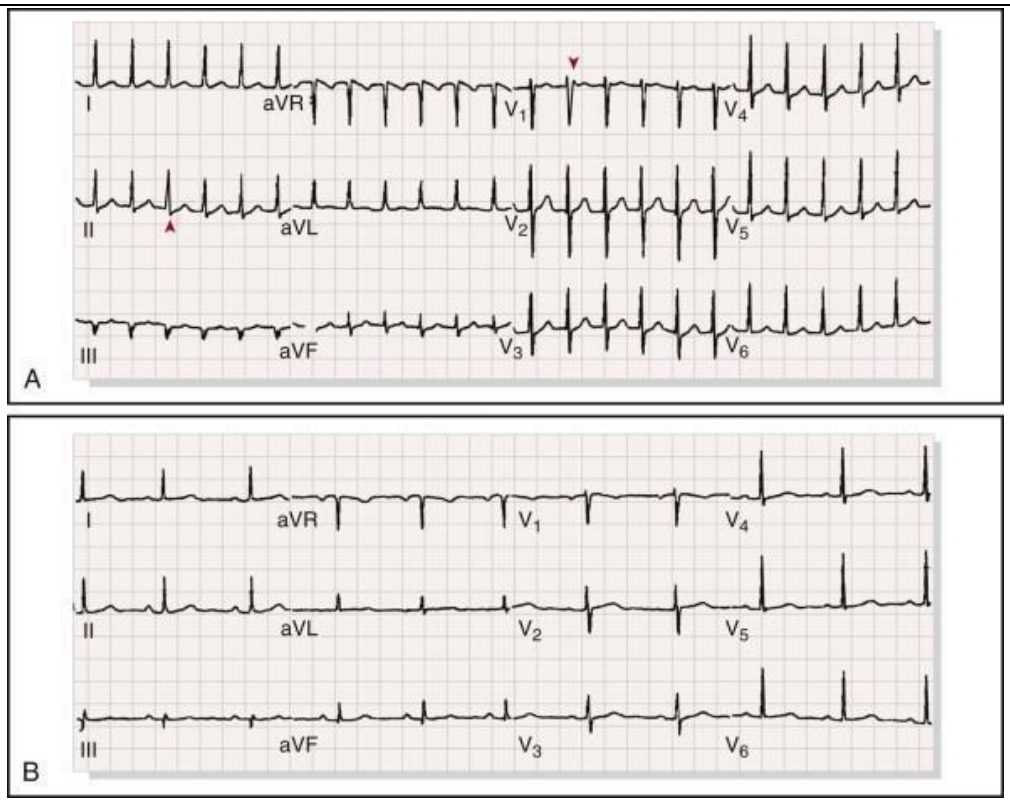
  Treatment
  - Acute: Initial management usually involves vagal maneuver and/or adenosine to terminate, but if the patient is unstable, DCCV should be attempted upfront. To increase the chance of success with vagal maneuvers, have the patient strain (e.g. blow into a syringe) in a semi-recumbent position (60 seconds) and then perform a passive leg raise (45 degrees, 60 seconds) which increases

the chance of success from 17% to 43% compared to standard Valsalva (REVERT RCT in Lancet, 2015)

- Additional effective therapies involve medications that block the AV node, such as BBs and CCBs
- Definitive Tx involves radiofrequency catheter ablation, which has a cure rate > 95%



Ladder diagrams of typical (slow-fast) AVNRT (left) and atypical (fast-slow) AVNRT (right). In typical AVNRT, a PAC triggers re-entry that beings anterograde along the slow pathway (while the fast pathway is refractory). Retrograde conduction occurs along the fast pathway, generating a "short RP." In atypical AVNRT, a PVC triggers re-entry with anterograde conduction via the fast pathway and retrograde atrial depolarization via the slow pathway, generating a "long RP.". A = atrial depolarization, V = ventricular depolarization, F = fast pathway, S = slow pathway, ATR = atrium, AVN = AV node, VENT = ventricle.



AVNRT with retrograde P forming a pseudo r' in V1 and pseudo-S in II, III, aVF (A). These are absent in NSR (B).

- **AV reciprocating tachycardia**

Presentation

- Similar to AVNRT in that there is a 1:1 AV relationship generating a regular rhythm but ventricular rates are often faster and P waves tend to be further separated from the QRS complex (following the QRS either on the ST segment or in the T wave)
- In contrast to AVNRT, AVRT requires the presence of at least one accessory pathway, which may be “concealed” (i.e. normal baseline ECG) or “manifest” (i.e. evidence of accessory pathway on baseline ECG such as a delta wave in WPW)

Pathophysiology

- Anterograde conduction can occur via the AV node (with retrograde conduction up the accessory pathway, i.e. orthodromic AVRT) or via the accessory pathway (with retrograde conduction either through the AV node, or less commonly, via another accessory pathway, i.e. antidromic AVRT).
  - ◊ Orthodromic AVRT: More common (95%). Anterograde conduction though the AV node produces a narrow QRS complex unless there is aberrant conduction
  - ◊ Antidromic AVRT: Less common. Anterograde conduction down the accessory pathway produces a wide, maximally pre-excited QRS complex which may be mistaken for VT
- There are several, comment variants of AVRT that are worth noting:
  - ◊ Permanent junctional reentrant tachycardia (PJRT): This is a form of orthodromic AVRT in which a septal accessory pathway behaves like the AV node (the faster the stimulation, the slower the conduction). As suggested by the name, PJRT tends to be persistent and often results in a tachycardia-induced cardiomyopathy
  - ◊ Mahaim tachycardias: These represent a form of antidromic AVRTs in which antegrade conduction takes place via bypass tracts known as “Mahaim” fibers. These accessory pathways are typically atriofascicular and usually right-sided. The baseline ECG does not typically show pre-excitation (concealed), but as an antidromic AVRT, the tachycardia travels down the accessory pathway producing a wide QRS
  - ◊ Lown-Ganong-Levine Syndrome: The cause was previously thought to be an accessory pathway between the atrium and His bundle, but it is now believed to be related to an AV node that allows for unusually rapid conduction and may predispose to AVNRT with a short PR**.** Patients typically have a normal baseline ECG without evidence of pre-excitation (unlike WPW).

Treatment

- If QRS is narrow (orthodromic AVNRT): Tachycardia responds to AV nodal blockers as in AVNRT (adenosine, CCB, BB). Antidromic AVRT (with wide QRS) can be treated the same way if the diagnosis is certain but VT needs to be excluded. Note that nodal blockers and adenosine can be safely used to terminate orthodromic AVNRT in WPW (ECG demonstrates a regular, narrow complex tachycardia). These medications are dangerous in atrial fibrillation with pre-excitation because they will slow conduction through the AV node and facilitate anterograde conduction through the accessory pathway, which

can lead to VF. However, a regular rhythm effectively rules out atrial fibrillation.

- A wide, irregular QRS is suggestive of pre-excited AF. In these instances, alternative agents should be used to slow conduction through the accessory pathway. Ideal agents include procainamide or flecainide but amiodarone may also be used (see chapter on WCT).
- If the patient is unstable and/or the rhythm does not terminate with agents above, perform DCCV
- Definitive treatment requires ablation of the accessory pathway, which carries a success rate between 85–98% depending on the pathway's location

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26. Wide Complex Tachycardias (WCT)

Definition: QRS ≥ 120ms and rate > 100bpm

Overview
Assume it is VT until proven otherwise! VT is the most malignant of the WCTs and is also the most common. Therefore, upfront attention should be paid to distinguishing VT from other causes of WCT

The clinical presentation of WCT can be variable, from asymptomatic runs of NSVT to a patient who has coded. Given this, when you see WCT, assume this is VT→first feel for a pulse and obtain a blood pressure ASAP!

Nomenclature

- Bigeminy: A premature ventricular complex (PVC) follows every sinus beat.

- Trigeminy: Two sinus beats are followed by a PVC
- Pair/Couplet: Two successive PVCs
- Ventricular tachycardia (VT): Three or more consecutive PVCs with a rate > 100 bpm
- Non-sustained VT (NSVT): Three or more ventricular beats with a rate > 100 bpm that lasts *less than 30 seconds* and *terminates spontaneously*
- Sustained VT: Ventricular tachycardia that lasts more than 30 seconds or requires cardioversion
- Monomorphic VT: VT where all QRS complexes are nearly identical in amplitude, axis and duration
- Polymorphic VT: VT with QRS complexes that vary in amplitude, axis and duration from beat to beat

Differential Diagnosis of WCT

1) Ventricular Tachycardia
   Ectopic or reentrant ventricular impulse spreads electrical activity slowly through the ventricular myocytes and produces a wide QRS. It originates below or very rarely at the bundle of His. VT can be further classified as monomorphic or polymorphic. Monomorphic VT has a variety of etiologies (infarct/scar being a common one), while polymorphic in the setting of a normal QTc is often due to ischemia.

2) Supraventricular Tachycardia (SVT) with Aberrancy
   SVT (e.g. AT, AF) conducts an electrical impulse into the ventricles along the standard His-Purkinje system, but it is slowed along that path as a result of:
   a. Pre-existing or rate-related aberrant intraventricular conduction (e.g. bundle-branch block)
   b. Drugs (e.g. Class 1C anti-arrhythmics, digoxin), electrolyte abnormalities (e.g. hyperkalemia), or ischemia

3) Supraventricular Tachycardia with Pre-excitation
   SVT conducts an electrical impulse into the ventricles through an accessory conduction pathway (e.g., Wolff-Parkinson-White syndrome, antidromic AVRT), in which depolarization advances slowly through the ventricular myocytes rather than quickly

along the His-Purkinje system.

4) Pacemaker-Related Tachycardia
    a. Pacemaker-mediated: “Endless loop” tachycardia in which the aberrant circuit is generated by the pacemaker
        i. Electricity arising from the ventricular pacing lead conducts retrograde (typically, through the AV node) to the atria, producing atrial depolarization (seen as a retrograde P wave)
        ii. The atrial depolarization is sequentially recognized by the pacemaker, leading to atrial-sensed ventricular pacing
        iii. Another ventricular depolarization can conduct in retrograde fashion again through the AV node and produce a circuit
    b. Pacemaker-tracked tachycardia: SVT is tracked by the pacemaker
        i. SVT is sensed by the pacemaker, producing a wide complex beat. (This rhythm is less common now that devices have become sophisticated at mode switching to non-tracking modes such as VVI or DDI when the algorithm recognizes SVT or AF

*Note: Both pacemaker-tracked and pacemaker-mediated tachycardia can be terminated by the application of a magnet to the pacemaker, which changes the pacing mode to an asynchronous mode (VOO or DOO). This is not true for most ICDs, in which the magnet will temporarily disable ICD therapy, but will not alter the pacing mode.

Diagnostic Evaluation of WCT

First, assess for hemodynamic instability. Check pulses and vital signs, level of alertness, and for other s/sx of end-organ dysfunction (e.g. chest pain, SOB/hypoxemia, new crackles on lung exam, cool extremities). This assessment takes precedence over determining the precise etiology of the WCT. VT and SVT may present with stable or unstable VS.

<u>Clinical History</u>

- Ischemic or structural heart disease: Confers higher probability of VT
- Age: SVT more likely in young patients (<30yo) than in older patients, but VT is still the most common overall WCT
- Family history: Is there a family history of arrhythmia or sudden cardiac death?
- Ethnicity: Certain ethnic groups are prone to higher rates of ventricular arrhythmia (e.g. Brugada syndrome more common in males of South Asian descent)
- Medications: Is the patient receiving medications that could precipitate WCT:
    - QTc prolonging agents (which can precipitate polymorphic VT)
    - Medications that can produce aberrant conduction (e.g. class IC anti-arrhythmics)

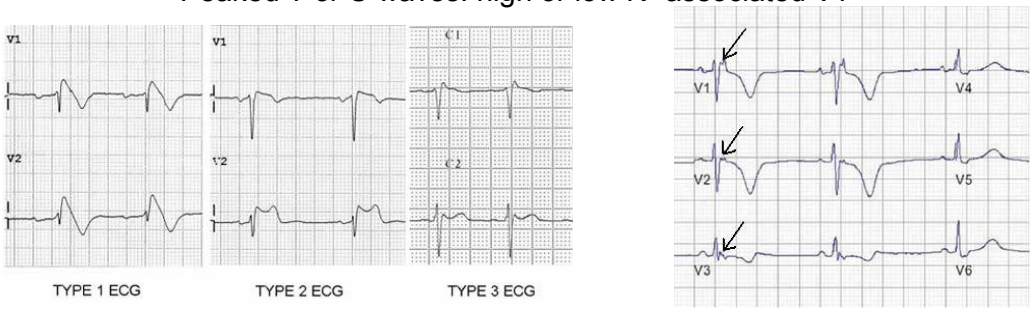
<u>Physical Examination</u>

- Clinical signs of A-V dyssynchrony (a hallmark of VT):
    - Cannon A-waves on CVP tracing or JVP: RA contracting against closed tricuspid valve
    - Blood pressure fluctuations on A-line tracing: beat-to-beat variation in LV filling and cardiac output

    - Variable intensity of heart sounds (cacophony, particularly of S1): inconsistent coordination and forcefulness of valve opening and closing
- Sternal scar (evidence of prior cardiac surgery), cardiac devices (ICD, PPM)
- Carotid, renal, and femoral bruits (PAD is CAD equivalent)
- Unequal pulses
- Murmurs and gallops (particularly S3)

Electrocardiogram and Rhythm Strip

- Baseline ECG:
    - Baseline bundle-branch block or wide QRS?
    - Pre-excitation (delta-wave, short PR), which could predispose to WPW or antidromic AVRT?
    - Predisposed to VT?
        - Q wave: Infarct/scar-related VT
        - Epsilon waves: ARVD associated with VT
        - Ischemic ST-T changes: Ischemia related VT
        - Brugada pattern in V1–3 (see below): Brugada syndrome associated polymorphic VT/VF
        - Prolonged QTc: Polymorphic VT/Torsades de pointes (TdP)
        - Peaked T or U waves: high or low K^+ associated VT



Brugada pattern tracing (left); Epsilon wave in ARVD (right)

Many different algorithms have been proposed to help distinguish VT from alternative etiologies of WCT.

Brugada Criteria: VT present if any of following criteria are met. SVT present if none met. Reported Sn 99%/Sp 96.5%.

- Concordance in precordial leads (no RS complex in V1–V6)
- RS interval is >100 msec
- AV dissociation present (e.g. fusion and/or capture beats)

Vereckei Criteria for aVR: Proven reliable in the literature. VT is implied if any of the following are met in aVR.

- Initial R wave
- Initial Q or R wave >40ms
- Presence of a notch on the descending limb of a predominantly negative QRS
- Ventricular activation ratio ≤ 1 (depolarization magnitude or vertical distance achieved over initial 40ms of QRS [v(i)] divided by vertical distance achieved over terminal 40ms of QRS [v(t)]: v(i)/v(t))

R Wave Peak Time (RWPT): Has been outperformed in the literature, but still a helpful adjunct.

- If RWPT >50ms, more likely to be VT

Yurchak Criteria: Unpublished, created at MGH by Dr. Yurchak. Reported Sn/Sp ≥ 90–95%.

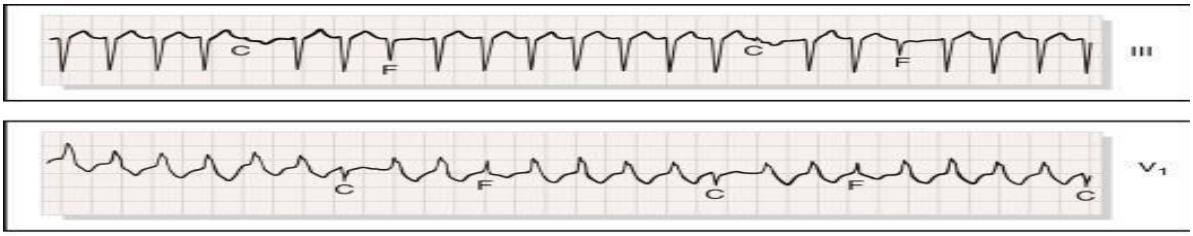
- If fusion beat, capture beat, AV dissociation, concordance or a NW axis present, then WCT is VT
- If none of the above are present, then proceed through following set of steps to calculate points for VT vs SVT. The rhythm with the "most points" wins

i. QRS > 160 msec	1 point for VT
ii. Left axis deviation	1 point for VT
iii. RBBB morphology plus:	
1. Triphasic V1	1 point for SVT
2. R, qR, RS, R < R' in V1	1 point for VT
3. R > S in V6	1 point SVT
4. R < S in V6	1 point for VT
iv. A LBBB morphology plus:	
1. R < 30 ms in V1	1 point for SVT
2. Wide/notched S	1 point VT
3. No Q in V6	1 point SVT
4. Q in V6	1 point for VT

<u>Additional Tips for Identifying Types of WCTs</u>

Examine the telemetry strip: Look for R-on-T at the start of the WCT, also look for AV dissociation (P waves marching through discordant to QRS, capture beats, fusion beats)

- Capture beat (labeled "C" in strip below): Atrial depolarization that is able to normally conduct a narrow QRS and transiently interrupts the spread of electricity from the VT focus
- Fusion beat (labeled "F" in strip below): Simultaneous conduction and blending on ECG of supraventricular beat and wide complex ventricular beat



- P waves can be accentuated with Lewis leads: Place the R arm electrode on the R second intercostal space adjacent to the sternum; move the L arm electrode to the R fourth intercostal space adjacent to the sternum. Read the Lewis lead as lead I on the ECG.

Look for AV association: A hallmark of SVT and PPM-associated tachycardia
(Note: Does not rule out VT with 1:1 V:A conduction)

- Antegrade association: SVT or PPM tracked tachycardia

- Retrograde association: Antidromic AVRT or PPM mediated tachycardia

Beat-to-beat variability in QRS morphology: Characteristic in polymorphic VT or SVT/AF with varying degrees of pre-excitation/fusion or rate-related aberrancy.

Pacer spikes: May indicate pacemaker-related etiology.

- Pacer-mediated: May see paced QRS followed by retrograde P wave
- Pacer-tracked: Most devices programmed only to track up to a certain atrial rate so you may see A-V association below a certain threshold (~110–130bmp). Above that threshold, the A-V association will cease and the paced (wide) ventricular rate will not exceed the pre-determined threshold

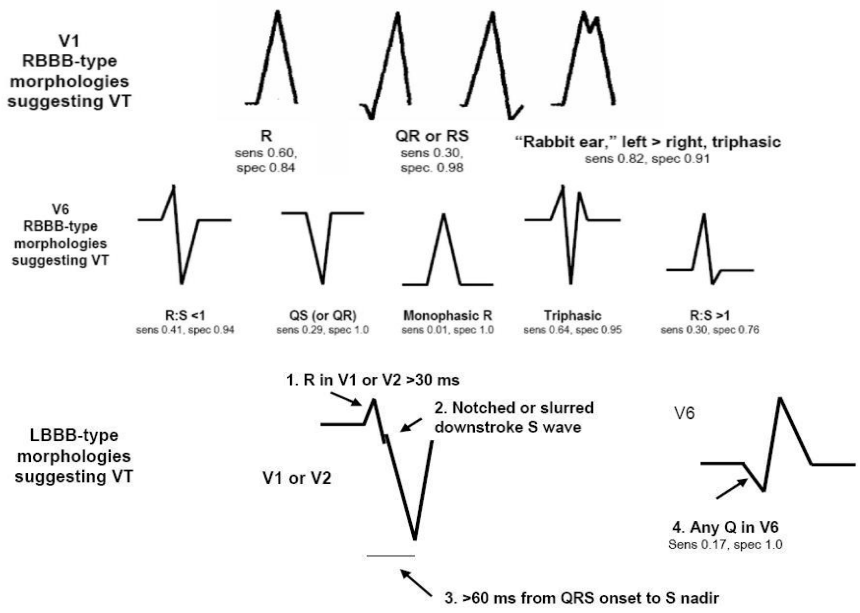
Compare baseline and WCT ECGs: WCT with similar axis and morphology to baseline QRS suggests SVT with aberrancy.

Measure QRS duration: In general, VT is more likely if:

- QRS is in a RBBB morphology and QRS is > 140msec OR
- QRS is in a LBBB morphology and QRS is > 160msec

Look at QRS morphology:

- A QRS > 160 msec has a 20:1 likelihood ratio of being VT. VT can be narrow (<140 msec) if it arises near the His-Purkinje system
- If LBBB or RBBB pattern, look for morphologies suggestive of VT:



Above V1 or V2 criteria, sens 1.0, spec 0.89

- Note: If there is VT with a RBBB pattern + inferiorly directed axis in a patient with a structurally normal heart, consider LVOT VT. Interestingly, this rhythm can respond to drugs that reduce cAMP, such as adenosine, verapamil or beta-blockers

- Note: If there is VT with a LBBB pattern + inferiorly directed axis in a patient with a structurally normal heart, consider **RVOT VT**. This rhythm also responds to drugs that reduce cAMP

Clinical Management of WCT

As with all arrhythmias, management is first dependent on level of stabitliy. As above, WCT should be considered VT until proven otherwise. At least 80% of WCT in patients with ischemic or structural heart disease is VT.

Initial Management According to Stability

- Pulseless: Immediately start the pulseless VT ACLS algorithm and prepare for unsynchronized DCCV

- Hemodynamically unstable or highly symptomatic:
  - Prepare for synchronized DCCV (fentanyl/versed for sedation)
  - Put pads on the patient
  - CALL FOR HELP:
    Fellow resident(s) and your attending
    Ward Cardiology fellow and/or EP Fellow on Call
    RICU if anticipate potential need for intubation
    Cardiac anesthesia for conscious sedation (though often no time)
  - Start amiodarone (150 mg x 1 Q 3–5 min, then drip @ 1 mg/min), and/or lidocaine (100 mg x 1, then drip @ 1–4 mg/min). Amiodarone typically is an appropriate anti-arrhythmic to start unless there is QT prolongation and concern or TdP
  - Worry about etiology AFTER YOU'VE STABILIZED PATIENT
  - If regular, monomorphic, and there is some suspicion for SVT, you can consider using adenosine as both a diagnostic and therapeutic intervention
  - If pacemaker-mediated or tracked WCT→ apply magnet

- Hemodynamically stable:
  - Put pads on patient
  - You have *some* time to determine etiology of WCT
  - If you suspect VT→ start amiodarone and/or lidocaine (consider empiric initiation while determining rhythm)
  - Most patients do not tolerate persistent VT (particularly if critically ill), so treat WCT (which is likely VT) as though it has high potential for precipitating hemodynamic instability. Thus, be ready to cardiovert, and even consider cardioverting stable VT that persists for many minutes. This requires the same algorithm as above, including putting pads on the patient and involving your fellow residents, attending, ward cardiology fellow, EP fellow, RICU and/or cardiac anesthesia.

Further Management According to Etiology

Monomorphic VT:

- Anti-arrhythmic drugs (AAD): Useful as acute medical therapy while trying to reverse the cause for VT. However, AADs have been ineffective in reducing mortality for patients

with life-threatening ventricular arrhythmias or in the prevention of SCD and may actually increase mortality when used as single chronic therapy to prevent VF/VT
    - Amiodarone: Administer as 150 mg bolus over 3–5 min, *followed by infusion at 1mg*/min for 6hrs and then 0.5 mg/min for 18 hours. If needed, amiodarone can be re-bolused at 150 mg multiple times
        - Default AAD of choice: Amio is effective for both ventricular and supraventricular arrhythmias (Na+ and K+ channel blocker; slows AV nodal conduction as well). Superior effectiveness compared to lidocaine
        - Remember: AV nodal blockade effects dominate until patient has received 6–7 grams of Amio. A full "Amio load" for VT is 10 grams (given over a period of days)
        - AVOID IN TDP: nodal-blocking activity slows HR and K^+ channel blocking effect prolongs the QTc, which can promote TdP
    - Procainamide: Administer as infusion at 20–50 mg/min until arrhythmia is controlled (stop if hypotension or if QRS complex widens by 50% of its original width, or total of 17 mg/kg is given). Maintenance infusion usually 1–6 mg/min
    - Lidocaine: Administer as 1–1.5 mg/kg bolus over 2–3 minutes (often 100mg), *followed by* 1–4 mg/min infusion (often start at 1)
        - Amiodarone and procainamide are generally preferred and have been proven to be superior for recurrent, stable VT
        - Lidocaine or procainamide preferred if WPW is possible as both drugs reduce accessory pathway conduction
- Electrolyte repletion:
    - Repletion of Mg^{2+}
    - Correction of K^+
- Electricity: Asynchronous DCCV (for pulseless VT) vs synchronized DCCV (for VT w/ pulse). Other options if patient has a Pacemaker include:
    - Over-drive pacing (anti-tachycardia pacing) at a faster rate than the VT may be useful in some cases (call Ward fellow and/or EP for help w/ ATP).
    - If PPM mediated/driven: a magnet will terminate pacemaker mediated/driven tachycardia by changing pacing to an asynchronous mode. The magnet rate is almost never fast enough to pace-terminate VT or SVT, however
    - If VT is refractory to the above measures, then you must consider further rescue measures such as urgent catheter ablation
      *Incessant VT = Hemodynamically stable VT >1hr
      *VT Storm = Multiple bouts of unstable VT within 24hr
- Reduction of autonomic tone:
    - Sedation with intubation (if needed for airway protection)
- Treatment of underlying ischemia:
    - Revascularization/cath lab
    - IABP to improve coronary perfusion
    - Reduce cardiac afterload
- Treatment of hypoxemia:
    - Put patient on oxygen
    - NRB +/– intubation if poor oxygenation
- Catheter-based ablation therapy: Radiofrequency (RF) ablation is often performed for refractory VT or VT storm. Acute procedural success (no inducible VT) rates are approximately 70%

Polymorphic VT:

- PMVT with normal QT (on ECG from earlier in day) is ischemia until proven otherwise
    - Treatment of Ischemia: Activate cath lab (revascularization, IABP), give ASA, UFH, IV BB
    - AAD: IV Amiodarone
    - Electrolytes: Maintain K > 4, Mg > 2
- Torsades/PMVT w/ prolonged QT (on ECG from earlier in day)
    - Electrolytes: Repletion of Mg^{2+} with 1–2 g IV bolus, with a total dose of 2–4 g over 10–15 min, can successfully terminate TdP within 5 minutes in up to 75% of patients, and within 15 minutes in virtually all patients. Replete K^{+} as well!
    - Chronotropes: Goal HR 80-100bpm will shorten the QTc and can abort the PMVT. Start IV infusion of isoproterenol (2–6 mcg bolus *followed by* 2–20 mg/min OR dopamine at a starting rate of at least 300 mcg/min
    - AAD: Lidocaine. AVOID NODAL AGENTS AND AMIODARONE
    - Electricity: Asynchronous DCCV (for sustained PMVT) or over-drive pacing at rates in the range of 80–100 bpm (to suppress pause-dependent initiation of PMVT). Call ward fellow to discuss temp wire

SVT with Aberrancy:

- AAD: Treat as you would any other SVT; consider adenosine, BB, CCB, amiodarone, correct toxicities/drug effect/electrolyte abnormalities
- Electricity: Synchronized DCCV for extremely symptomatic or unstable patients

SVT with Pre-Excitation:

- Adenosine: There is a common misconception that adenosine can't be used for SVT associated with WPW. Adenosine can and should be used (and is very effective) for terminating regular SVT associated with WPW (typically AVRT). Adenosine should not be used, however, for pre-excited AF (which will present as an irregular, wide complex tachycardia)
- AADs
    - 1st line: Procainamide (1 gm over 50 min IV)
    - 2nd line: Ibutilide (0.01 mg/kg over 10 minutes, max dose 1 mg, can repeat once after 20 mins)
    - 3rd line: Amiodarone (150 mg IV x 1, can repeat many times→then 1mg/min gtt)
- Electricity: DCCV for extremely symptomatic or unstable patients

Pacemaker-Tracked WCT:

- Treat SVT as you would any other SVT. Mode switch PPM to a non-tracking mode either by EP interrogation or with magnet.

Pacemaker-Mediated WCT:

- Magnet is 1st line therapy. Magnet will also stop the arrhythmia by mode switching to VOO or DOO to stop sensing the atria. Note that a magnet does will not change the pacing mode for an ICD; it will disable defibrillator therapies, thus a magnet will not terminate a pacemaker-mediated tachycardia in an ICD patient
- 2nd line: Adenosine, verapamil or beta-blockers can abort retrograde conduction and stop the circuit
- IMPORTANT: Call EP because patient will require pacemaker reprogramming to prevent further episodes of PMT

Maintenance Therapy

Devices:

- ICDs are recommended for secondary prophylaxis of VT/VF unless a reversible trigger is identified and treated
- The AVID trial demonstrated a 10% absolute mortality benefit with this strategy when compared to AAD alone (see ICD Section for more information)
- Specific guidelines are available for IHD, NICM, and other specific cardiomyopathies

Medical management:

- Beta-blockers reduce sympathetic tone, have some direct antiarrhythmic effect, and may reduce mortality in patients with previous VT/VF
- AADs are often continued unless a reversible VT/VF trigger (e.g. ischemia) is identified and treated, although there is no established mortality benefit with this strategy
- Patients with HFrEF should be treated with a BB, mineralocorticoid antagonist, ACEi/ARB/neprolysin inhibitor to reduce SCD and all-cause mortality

Procedures:

- Patients with VT/VF and ischemic heart disease should be revascularized as appropriate
- VT ablation:
    - The VANISH trial compared VT ablation to escalating maintenance anti-arrhythmic drugs in patients with ischemic cardiomyopathy with recurrent VT
        - Open-label RCT, 259 patients, median follow-up 23.4 months
        - 10% absolute reduction in composite death, VT storm, appropriate ICD shocks
        - No difference in mortality
    - A large multicenter registry recently reported 70% VT-free survival after VT ablation at 1 year in patients with refractory VT secondary to either ischemic or non-ischemic cardiomyopathies. Success rates are even higher in patients with idiopathic (typically outflow tract) VT without structural heart disease

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27. Atrial Fibrillation

Overview

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age (0.4% to almost 20%). It is characterized by uncoordinated atrial activation leading to deterioration of atrial mechanical function as well as risk of thromboembolism.

Nomenclature

AF Episode: Documented on ECG and has duration of at least 30 sec. If < 30 seconds, AF present continuously throughout the ECG monitoring tracing.

Paroxysmal AF (pAF): Recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.

Persistent AF: Continuous AF that is sustained beyond 7 days. Episodes in which a decision to cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.

Long-standing persistent AF: Duration > 12 months; efforts to terminate, either chemically or electrically, are typically unsuccessful although catheter ablation may restore sinus rhythm in some patients.

Permanent AF: Persistent AF where further attempts at rhythm control are indefinitely deferred

Pathophysiology

The mechanism of AF is highly debated, with theories that are not mutually exclusive and may coexist in the same patient. In general, AF results from an abnormal atrial response to reentry and/or rapid focal ectopic firing. In the case of reentry, fibrillitoary activity may be generated from a single localized reentry circuit or result from multiple functional reentry circuits that vary in time and space. Alternatively, there may be an ectopic focus that generates regularly firing, rapid discharges.

The natural history of AF may involve progression from paroxysmal to persistent to long-standing forms. At the tissue level, this can result from atrial remodeling caused by the arrhythmia itself and/or progression of underlying heart disease. AF-related electric remodeling results from altered expression and function of cardiac ion channels, which favor the development of functional reentry substrates. With AF termination, these changes are reversible, a process known as reverse remodeling. If left untreated, however, the remodeling becomes irreversible and contributes to persistent AF.

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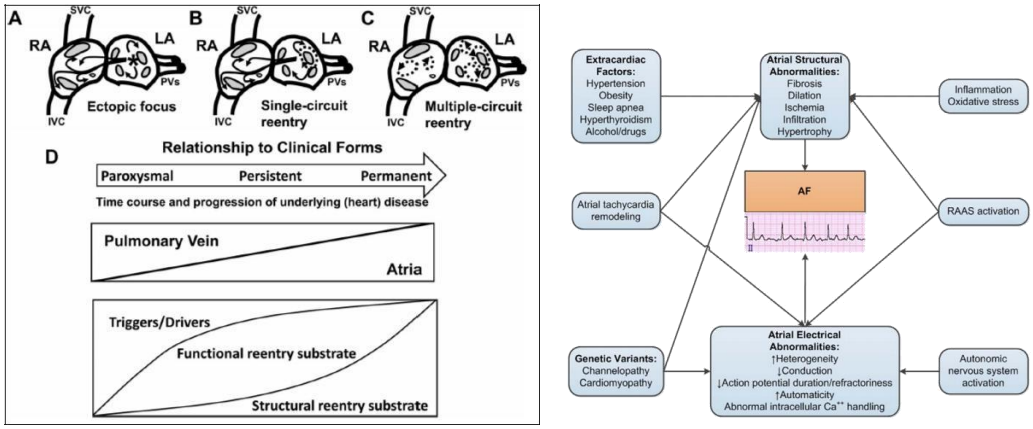
Figure 1: Pathophysiology and Mechanisms of AF[1]

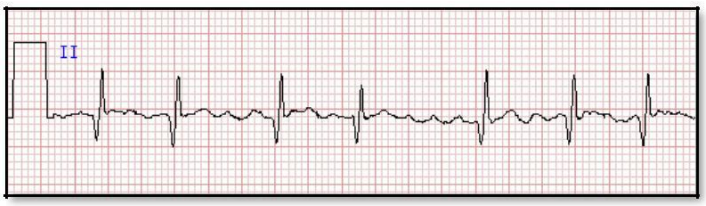


Clinical Presentation

Patients can be asymptomatic, but many describe palpitations, fatigue, dyspnea, lightheadedness and diaphoresis. In the CCU, patients usually present with chest pain, pulmonary edema and syncope (which are less common in the outpatient setting). Syncope can occur when patients with sinus node dysfunction spontaneously convert back to sinus rhythm with an accompanying pause. It can also be caused by rapid ventricular response (RVR) in patients with HCM, severe diastolic dysfunction, aortic stenosis, or accessory pathways. When sustained, AF can manifest as tachycardia-mediated cardiomyopathy. Thromboembolic CVA is the initial manifestation in 10–40% of patients.

Diagnostic Evaluation

ECG: Identify rhythm by noting “absolutely” irregular (i.e. irregularly irregular) RR intervals (in the absence of complete AV block), no distinct P waves, and an atrial cycle length (when visible) that is variable and <200ms. As below, fibrillatory (F) waves may be distinct. Also look for other markers of heart disease (i.e. LVH, ischemia).



TTE: Should be performed in patients who present with new-onset AF in order to evaluate for a structural etiology.

Additional lab testing: Thyroid function testing should routinely be performed, as hyperthyroidism predisposes to AF. Also consider renal and liver function tests, as well as cardiac biomarkers (including troponin and NT-proBNP) based on clinical presentation.

Clinical Management

Rate versus Rhythm Control

Several studies have attempted to clarify the best strategy for management of AF. Ultimately, the clinical status of the patient and their comorbidities often dictate treatment. If AF is self-limited, or has a potentially reversible cause, restoration of normal sinus rhythm should be pursued. Pharmacological or direct current cardioversion (DCCV) has a higher success rate when AF has been present for less than 24 hours. Remember the adage, “AF begets AF” (through irreversible electrical remodeling).

Studies that have examined rate control (plus anticoagulation) versus medical rhythm control have not detected differences in mortality or stroke rates. However, these studies enrolled predominantly older patients (average age 70), most of whom had persistent AF in the setting of structural heart disease and were able to tolerate AF from a symptomatic standpoint; younger patients and those with severe symptoms from AF were underrepresented. In addition, follow-up was limited to just a few years. Thus, the results of these trials do not necessarily apply to younger patients without heart disease or those whose dependency on SR is likely to change appreciably over time.

Unstable Atrial Fibrillation

The presentation of unstable AF includes patients with hypotension, hypoxemia, decompensated heart failure, pre-excitation, worsening ischemia, angina or decreased responsiveness. DCCV is often necessary in these patients, ideally preceded by sedation (usually fentanyl/midazolam or propofol depending on patient stability and coordinated by cardiac anesthesia, CCU or ER team). Alternatively, amiodarone may be used in conjunction with neo (given reflex bradycardia) in patients who are hypotensive. In addition, amiodarone may help to maintain SR after DCCV.

Acute Rate Control

This is usually achieved through AV nodal blockers (see Table 2). While in the CCU/SDU, be aware of the negative inotropic effects of drugs such as BB or CCB, which can worsen the clinical condition of these patients. Amiodarone can be an effective rate control agent for unstable patients with AF with somewhat less potential for hypotension than BB or CCB. In the case of atrial fibrillation in sepsis, a recent large retrospective analysis showed that IV BBs were associated with reduced hospital mortality when compared with CCBs, digoxin, and amiodarone.[8]

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Table 1: Summary of Trials Examining Rate vs Rhythm Control in AF

Trial	Characteristics	Results
Pharmacological Intervention in Atrial Fibrillation[2] (PIAF) *Lancet*, 2000	-Randomized trial (N=252) -Primary endpoint: Symptom improvement -Rate control with diltiazem (N=125) vs rhythm control with DCCV+amiodarone (N=127) -F/u interval: 1 year	-No difference in primary endpoint -Rhythm control strategy demonstrated improved exercise tolerance, but hospital admissions were more frequent in this group
Atrial Fibrillation Follow-up Investigation of Rhythm Management[3] (AFFIRM) *NEJM*, 2002	-Randomized multicenter trial (N=4060) -Primary endpoint: Overall mortality -Rate control with digoxin/BB/or CCB+warfarin vs rhythm control (many different agents used) -F/u interval: 3.5 years	-No difference in primary endpoint overall -Rate control strategy demonstrated mortality reduction for patients over the age of 65 (HR 0.76) and those who did not have a history of heart failure (HR 0.69) -Rhythm control group with more hospitaliztions and adverse drug effects
Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group[4] (RACE) *NEJM*, 2002	-Randomized trial (N=522) -Primary endpoint: Composite of CV death, admission for CHF, severe bleeding, need for PPM, or severe drug side effect -Rate control with digoxin/BB/or CCB (N=256) vs rhythm control with DCCV+anti-arthytmic (many agents used) (N=266) -F/u interval: 2.3 years	-Rate control non-inferior to rhythm control in terms of primary endpoint
Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation[5] (STAF) *JACC*, 2003	-Randomized multicenter trial (N=200) -Primary endpoint: Composite of death, need for CPR, CVA, and systemic embolism -Rate control (N=100) vs rhythm control (N=100) -F/u interval: 1.6 years	-No difference in terms of mortality, morbidity, and quality of life -However during follow up period, only 23% of rhythm control group remained in NSR, after up to 4 DCCVs
Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation[6] (HOT CAFE) *Chest*, 2004	-Randomized multicenter trial (N=205) -Primary endpoint: Composit of all-cause mortality, number of thromboembolic events, and major bleeding -Rate control (N=101) vs rhythm control with stepwise regimen of: disopyramide, propafenone, sotalol, and amiodarone (N=104) -F/u interval: 1.7 years	-No difference in primary endpoint -Rhythm control strategy demonstrated improved exercise tolerance, but hospital admissions were more frequent in this group (74% vs 12%)
Rhythm control versus rate control for atrial fibrillation and heart failure[7] (AF-CHF) *NEJM*, 2008	-Randomized multicenter trial (N=1376) in patients with both AF and CHF -Primary endpoint: Time to death from all cardiovascular causes -Rate control (N=694) vs rhythm control (N=682) -F/u interval: 3.1 years	-Rhythm control strategy does not reduce the rate of CV death when compared to rate control -Also no difference in all-cause mortality, stroke, and worsening HF

Table 2: IV and Oral Agents for HR control in AF

Drug	LOE	Loading Dose	Onset	Maintenance Dose	Major Side Effects
Esmolol*	I-C	500 mcg/kg IV over 1 min	5 min	60–200 mcg/kg/min IV	↓ BP/HR; HB; asthma, HF
Metoprolol*	I-C	2.5–5 mg IV over 2 min; up to 3 doses	5 min	NA	↓ BP/HR; HB; asthma, HF
Propranolol*	I-C	0.15 mg/kg IV	5 min	NA	↓ BP/HR; HB; asthma, HF
Diltiazem*	I-B	0.25 mg/kg IV over 2 min	2-7min	5–15 mg/h IV	↓ BP; HB, HF
Verapamil*	I-B	0.075–0.15 mg/kg IV over 2 min	3-5min	NA	↓ BP; HB, HF
Amiodarone^	IIa/C	150mg IV over 10 min	Days	0.5–1 mg/min IV	↓BP; HB, pulmonary toxicity, skin discoloration, hypo-/hyperthyroidism, corneal deposition, optic neuropathy, warfarin interaction, sinus bradycardia
Digoxin*^	I-B	1.5 mg load: 0.25 mg IV q2 x 6 OR 0.75 mg IV + 0.375 Q6H	60+ min	0.125–0.375 mg daily IV/PO	Digitalis toxicity, HB, ↓ HR

LOE: Level of evidence. *Avoid in patients with known or suspected accessory pathway. ^Useful in patients with concomitant HF.

Rhythm Control

Before initiating antiarrhythmic drug (AAD) therapy, treatment of precipitating or reversible causes of AF should be pursued. The goal of AAD therapy include a reduction in the frequency and duration of episodes of AF as well as an emerging goal of reducing mortality and hospitalizations associated with this condition. See Figure 2 and Table 3.

Electrical Cardioversion
(See EP Procedures section for more information)

DCCV is the most effective method of restoration of SR particularly for those who have symptoms of AF that are unacceptable. It is successful at least 80% of the time. If the

first attempt fails, a repeated shock can be delivered following the administration of an AAD (amiodarone, flecainide, ibutilide/dofetilide, propafenone or sotalol). However, if DCCV continues to fail, particularly if only able to induce short periods of SR between relapses, repeated attempts are not recommended. DCCV is relatively contraindicated in those with digitalis toxicity or hypokalemia.

The procedure is performed in a fasting state and under adequate anesthesia (conscious sedation preferred). The shock should be synchronized with the QRS complex. AF usually requires higher energy (100–360 J) when compared to AFL (which often converts with ~50-100 J). Traditionally, patients with AF of 48 hour duration or longer should be anticoagulated for at least 3 weeks prior and 4 weeks after cardioversion (irrespective of the method). An alternative strategy is to perform TEE in search of LA thrombus. If no thrombus can be found, DCCV can be performed immediately after anticoagulation with UFH or another agent has been started. Patients are then transitioned to oral anticoagulation. In the ACUTE trial, outcomes with TEE guidance have been found to be similar to the traditional prolonged anticoagulation strategy.[9]

Regardless of whether TEE-guidance is used, anticoagulation for at least 4 weeks following cardioversion is recommended to allow for recovery of the atrial transport mechanism and cardiac output, and to allow sufficient time for detection of recurrent AF. During this period, the risk of thromboembolism is substantially higher.

Chemical Cardioversion

In general, chemical cardioversion is less effective than DCCV. The success is significantly higher for acute (< 7 days) compared with longer-duration AF. Moreover, drug-induced torsades de pointes and other serious arrhythmias may result when using AADs for cardioversion. If desired, flecainide, propafenone or ibutilide are the recommended agents.

Ibutilide, an intravenous IKr blocker that also enhances the late inward sodium current is ~50% effective at restoring SR. It is slightly more effective for AFL than for AF. When used, patients need to be monitored closely for QT prolongation and TdP for at least 2 hour after infusion. Amiodarone is also a reasonable option of particular benefit in those with renal failure. Oral amiodarone can be used to convert AF to SR. It can be loaded over the course of 3–4 weeks with a rate of conversion of ~27%.

A high dose of flecainide (200–300mg) or propafenone (450–600mg) can be used as a “pill-in the-pocket” strategy outside the hospital once treatment has proven safe in-hospital for selected patients without sinus or AV node dysfunction, BBB, QT-interval prolongation, Brugada syndrome or structural heart disease. The overall rate of conversion tends to be >85%. Before these agents are initiated, a BB or CCB should be given to prevent atrial flutter with 1:1 ventricular conduction.

Figure 2: Choice of Antiarrhythmic Drug (AAD) Based on Cardiovascular Comorbidities

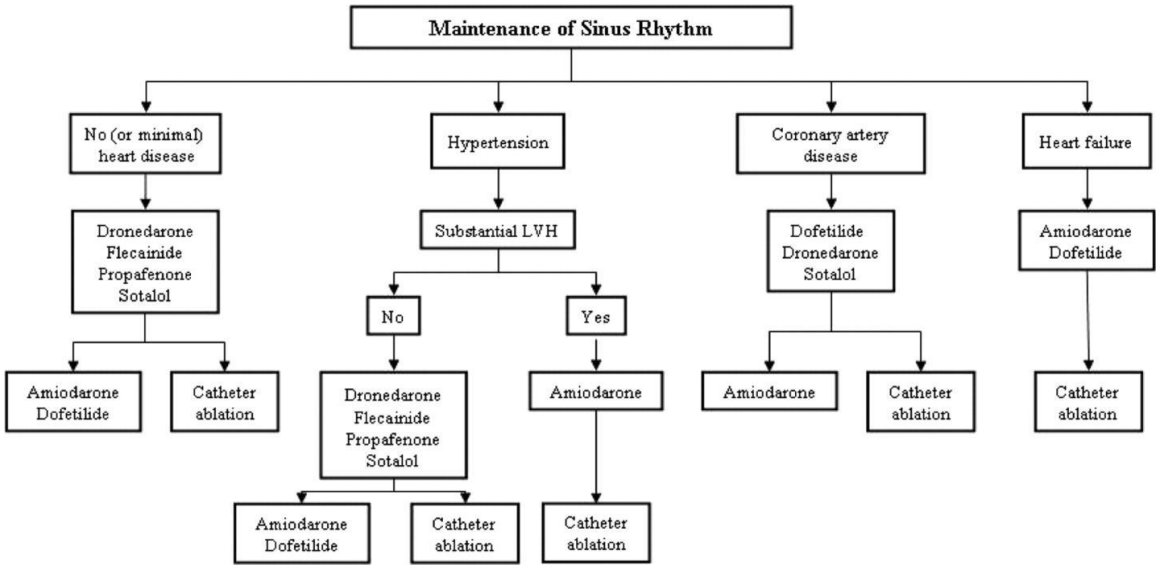

Table 3: Agents to maintain SR

Daily Dose(OR vs. control of maintaining SR after AF conversion, # of trials)	
Amiodarone 100–400 mg (6.8, 2 trials)	More effective than class I drugs, sotalol or placebo in the long-term maintenance of SR in paroxysmal or persistent AF refractory to other drugs. Drug of choice in patients with LVH, HF, CAD or prior MI since associated with low risk of proarrhythmia. Also effective for HR control (BB properties). Increases success rate of cardioversion and revents relapses by suppressing atrial ectopy, however high incidence of potentially severe extracardiac side effects limits its use and makes it second-line or last-resort agent in non-critically ill patients.
Flecainide 100–300 mg (4.3, 3 trials)	Effective in postponing the first recurrence of AF and overall time spent in AF. Limited to patients with no structural (LV dysfunction) or ischemic heart disease. Adverse effects include VT, HF and conversion to AFL with RVR.
Propafenone 450–900 mg (3.0, 4 trials)	Useful to prevent first recurrence of AF and post-DCCV. Avoid in those with ischemic heart disease or LV dysfunction as can be pro-arrhythmic.
Disopyramide 400–750 mg (2.9, 2 trials)	Prevents recurrent AF after DCCV. Considered first-line therapy in vagally induced AF; has negative inotropic and dromotropic effects that may cause HF or AV block; this negative inotropic effect may be desirable in HCM associated with dynamic outflow tract obstruction. Associated with TdP.
Sotalol 160–320 mg (2.5, 4 trials)	Not effective for chemical cardioversion but useful to prevent AF. Min effective dose is 160mg daily. Avoid in patients with asthma, HF, renal failure or prolonged QT. Requires inpatient initiation of therapy.
Dofetilide 500–1000 mcg	Useful for chemical cardioversion and maintenance of SR. Can be used in structural heart disease/CHF. Due to risk of proarrhythmia (QT prolongation), it must be started as inpatient, titrate to renal function.
Dronedarone 800 mg	Prolongs time to recurrence of AF. Decreases hospitalization rates. Not useful for chemical cardioversion or improving success of DCCV. Less efficacious than amiodarone but better tolerated. Associated with a significant reduction in the risk of stroke. Avoid in class IV or recently decompensated HF, particularly if depressed LV function (< 35%). Associated with increased mortality in patients with CHF or permanent AF.

Catheter Ablation

AATAC (2016): In patients with symptomatic (NYHA II-III) heart failure with reduced ejection fraction (HFrEF, LVEF ≤40%) and persistent atrial fibrillation (AF) chosen for a rhythm control strategy, AF ablation was associated with a 36% absolute increase in AF-free survival at 24 months. There was also a 26% absolute reduction in unplanned hospitalizations and a 10% absolute reduction in overall mortality with AF ablation.[10]

FIRE AND ICE (2016): In patients with symptomatic paroxysmal atrial fibrillation (pAF) resistant to antiarrhythmic drugs referred for pulmonary vein isolation (PVI), balloon cryoablation is noninferior to radiofrequency ablation in regards to a primary outcome of composite clinical failure (recurrent AF, prescription of antiarrhythmic drugs, or repeat ablation) more than 90 days after the index procedure.[11]

CASTLE-AF (2018): In patients with AF and symptomatic (NYHA II-IV) systolic heart failure (LVEF ≤ 35%), catheter ablation is associated with a 16.1% absolute reduction in death or hospitalization for heart failure when compared to medical therapy (rate or rhythm control). This difference was driven both by a 11.6% absolute reduction in death and a 15.2% absolute reduction in hospitalization for heart failure. Catheter ablation was also associated with greater improvement in LVEF and long-term maintenance of sinus rhythm.[12]

CABANA (2019): In patients with atrial fibrillation (AF) requiring treatment, catheter ablation was not associated with a significant reduction in death, disabling stroke, serious bleeding, or cardiac arrest when compared to medical therapy at 12 months. The results of this trial were incorporated in the AHA/ACC 2019 AF guidelines and as a result AF ablation in patients without systolic heart failure is likely to remain an elective procedure performed with the primary purpose of symptom relief in patients who have failed, are intolerant of, or decline anti-arrhythmic therapy.[13]

Anticoagulation: General Considerations

All patients with AF should be on anticoagulation except those at the lowest risk of thromboembolic stroke. Risk is greatly increased by personal history. The CHADS2VASc risk score is a useful tool for assessing ischemic stroke risk in patients with AF. Note that the AHA/ACC 2019 guidelines for atrial fibrillation recommend that NOACs – including dabigatran, rivaroxaban, apixaban and edoxaban – are now the preferred recommended drug class over warfarin to reduce stroke risk in appropriate AFib patients, unless patients have moderate-to-severe mitral stenosis or a mechanical heart valve.[14]

Risk factors	Score
CHF	1
HTN	1
Age 65-74	1
Age ≥75	2
DM	1
CVA/TIA	2
Vascular dz	1
Female	1

Anticoagulation: Specific Agents

Warfarin: Warfarin therapy should be targeted to an INR 2–3, as measured weekly during initiation of therapy and monthly thereafter. On average, warfarin provides an annual reduction of 68% in relative risk for stroke.

Dabigatran: Approved by the FDA as an alternative to warfarin for non-valvular AF, with superiority in the prevention of stroke compared to warfarin in the RE-LY trial.[15] Pro-drug, rapidly converted to active direct thrombin inhibitor. It is administered in fixed doses without laboratory monitoring of anticoagulation intensity. At a dose of 150 mg bid, it reduced the rate of stroke by 34% with no increase in major bleeding when compared to warfarin. For those with CrCl 15–30, a dose of 75 mg bid was also approved (dabigatran is not indicated for patients with CrCl < 15).

Rivaroxaban: A direct-thrombin inhibitor. In ROCKET-AF trial, it proved to be non-inferior to warfarin for the prevention of stroke and systemic embolism, with no difference in risk of major bleeding although ICH and fatal bleeding occurred less frequently with rivaroxaban.[16] It is administered at a dose of 20 mg daily, with dose reduction to 15 mg if renal impairment.

Apixaban: A direct-thrombin inhibitor, found to be superior to warfarin in preventing stroke or systemic embolism in the ARISTOTLE trial. It also caused less bleeding and lower mortality.[17] It is administered at a dose of 5 mg BID, or 2.5 mg BID if any two of the following: Age ≥ 80 years old, body weight ≤ 60 kg, serum Cr ≥ 1.5. In the AVERROES trial in patients with AF thought to be unsuitable candidates for anticoagulation with VKA, apixiban reduced the risk of stroke without increasing the risk of major bleeding compared to aspirin.[18]

Edoxaban: A direct-thrombin inhibitor, found to be equal in efficacy to warfarin in preventing stroke or systemic embolism in ENGAGE AF-TIMI 48. It caused less bleeding.[19] It is administered at a dose of 60 mg daily (or 30 mg daily for CrCl 15-50mL/min). Edoxaban is currently less commonly used used given more frequent clinical experience with rivaroxaban and apixaban as well as equivalence rather than superiority to warfarin.

Aspirin: A poor substitute for anticoagulation, though perhaps a plausible alternative in a very low-risk patient (i.e., CHA2DS2-Vasc = 1) or one at very high risk of bleeding. The relative risk reduction for stroke is variable, but perhaps around 20%.

Anticoagulation: Special Considerations for Patients Post-PCI

Up to 1 in 10 patients undergoing PCI have AF, and in general, the literature is in the early stages of understanding optimal anticoagulation in these cases. The WOEST trial found that in patients on oral anticoagulation undergoing PCI, use of clopidogrel + warfarin (double therapy) was associated with reduction in bleeding complications as well as lower combined secondary endpoints (death, MI, revascularization, stroke, stent thrombosis) when compared to the use of clopidogrel + warfarin + ASA (triple therapy).[20] Since the publication of WOEST, the ACC/AHA guidelines suggest that patients with nonvalvular AF undergoing PCI be maintained on oral anticoagulation and clopidogrel without aspirin.[14] There is increasing evidence supporting the use of DOACs in patients with AF (RE-LY, ARISTOTLE, ROCKET AF).[15-17] A more recent study, PIONEER AF-PCI, assessed the use of DOACs in patients with nonvalvular AF undergoing PCI with stent placement and found that low-dose rivaroxaban plus either single or dual antiplatelet therapy reduces the risk of bleeding when compared to warfarin + DAPT at 1 year post-procedure without having a significant effect on the rate of major adverse

cardiovascular events.[21] Note that the doses of rivaroxaban (15 mg daily or 2.5 mg BID) used in this trial are not FDA approved for AF or ACS and the results of this trial are preliminary with further trials now ongoing.

Percutaneous Left Atrial Appendage (LAA) Closure

Despite the efficacy of oral anticoagulation for preventing ischemic stroke, some patients may have contraindications to therapy, such as bleeding complications or increased risk of intra-cranial hemorrhage. TTE and autopsy studies have shown the left atrial appendage to be a common location of clot formation in non-valvular AF. LAA closure has emerged as a mechanical alternative to pharmacologic stroke prevention. There are multiple LAA occlusion devices, including the WATCHMAN, Amulet, WaveCrest, and LARIAT system devices (Amulet and WaveCrest are currently investigational in the U.S.).

The PROTECT-AF trial showed that percutaneous LAA closure with the WATCHMAN devise was non-inferior to warfarin for the prevention of the composite endpoint of ischemic stroke, hemorrhagic stroke, cardiovascular death, and systemic embolism.[22] The PREVAIL Trial subsequently found that LAA occlusion was non-inferior to warfarin for ischemic stroke prevention, although non-inferiority was not achieved for the overall efficacy endpoint (stroke, systemic embolism, and cardiovascular/unexplained death).[23]

Based on the results of these two trials, the WATCHMAN devise was approved by the US FDA in March 2015 for patients with nonvalvular AF for whom long-term anticoagulation is indicated but who have a contraindication. After placement of an LAA occlusion device, patients are treated with oral anticoagulation + ASA for 6 weeks, followed (if successful LAA closure is documented by TEE at 6 weeks post-implant) by clopidogrel + ASA for 6 months, followed by ASA for life. Patients with absolute contraindication to oral anticoagulants are given DAPT for 6 months.

Other Special Considerations in AF

Post-MI AF: The incidence of AF after AMI varies between 10–20% at 30 days. It is more common in older patients with higher Killip class (more severe AMI) and more severe LV dysfunction. As a general rule, it portends a worse outcome at 30 days when compared to sinus rhythm (29.3% vs. 19%). Similarly, stroke rates are higher in this population. As detailed above, management includes urgent DCCV if RVR produces intractable ischemia or instability. IV beta-blockers are useful for rate control and reduction of myocardial O2 demand and consumption.

AF and Pre-Excitation (WPW): Pharmacotherapy becomes challenging in the presence of an accessory pathway. As a general rule, IV beta-blockers, CCB, digitalis, and adenosine are contraindicated, as they can facilitate anterograde conduction through the accessory pathway and result in acceleration of the ventricular rate, hypotension or VF. When hemodynamically unstable, DCCV is the treatment of choice. For those who are hemodynamically stable, a class IA antiarrhythmic (typically procainamide) or amiodarone may be administered intravenously.

"Reversible" AF: Guidelines have proposed that AF can occur as an isolated event due to a reversible stressor (e.g., thyrotoxicosis, infection, MI, cardiac surgery). Nevertheless, in the Framingham cohort, 62% of patients with an isolated episode of AF due to a "reversible" cause had recurrent AF at 15 years.[24] Overall stroke risk and mortality were similar in groups with and without a reversible stressor, although heart failure risk was lower in those with a secondary

precipitant. Although future studies are needed, anticoagulation should not categorically be dismissed even in patients with a clear secondary precipitant of AF.

AF after Cardiac Surgery: This is a relatively common post-surgical compliation, with an incidence of 20-50%. A recent study found that there was no difference between rate and rhythm control in regards to total number of hospital days, rates of death, and serious adverse events such as thromboembolism or bleeding. At 60 days after AF onset, both patients receiving rate and those receiving rhythm control had similarly low rates of persistent AF.[25]

AF and Heart Failure: The 2016 Ablation versus Amiodarone for Treatment of persistent Atrial fibrillation in patients with congestive heart failure and an implanted device (AATAC) trial evaluated the efficacy of AF ablation versus amiodarone in patients with symptomatic HFrEF and persistent AF. At 2 years, ablation was associated with a 36% absolute increase in AF-free survival compared to amiodarone. Patients receiving AF ablation also experienced a 26% absolute reduction in unplanned hospitalizations and 10% absolute reduction in overall mortality. In summary, the AATAC trial suggests that among patients with HFrEF and AF, AF ablation is potentially superior to amiodarone as a method for achieving and maintaining sinus rhythm in terms of AF-free survival as well as in regards to cardiovascular outcomes and mortality.[26]

Prognosis

Whether AF is a primary disorder or a marker of underlying heart disease, its sole presence is associated with an increased long-term risk of stroke, HF, and all-cause mortality, especially in women. In general, mortality rates are doubled compared to patients in SR and directly linked to the severity of underlying heart disease.

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TOC

28. Temporary Pacing and Pacemaker Therapy

The purpose of this section is to review the specific indications for temporary pacing; permanent pacemakers (PPMs), cardiac resynchronization therapy (CRT), and implantable cardioverter-defibrillator (ICD) therapy.

Temporary Pacing

Temporary pacing is utilized in situations where either urgent electrical pacing is required (i.e. condition is likely to be permanent but placement of a PPM will take too long) or the condition is likely to be reversed and PPM is unlikely to be necessary (e.g. bradyarrhythmia secondary to medication effect).

Temporary pacing can be either transcutaneous (via pacer pads placed on the skin) or transvenous (which requires insertion of a temporary pacing wire, or "temp wire," typically via the internal jugular vein). Transcutaneous pacing can be performed on the floor and may be employed as a bridge to placement of a temp wire, which requires insertion by cardiology and then necessitates transfer to a cardiac unit.

Transcutaneous Pacing

Indications: Indications for transcutaneous pacing are provided in Table 1 below. Indications for pad placement (to allow for transcutaneous pacing instantly if needed) are also included and designated by an asterisk.

Table 1: Indications for Transcutaneous Pacing and Placement of Pacing Pads

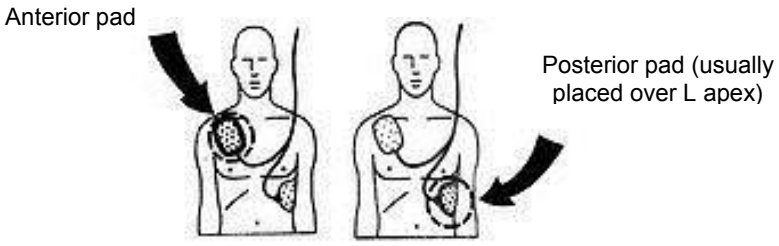
Class I
Sinus bradycardia (HR <50) with symptomatic hypotension (SBP < 80), refractory to drug therapy† 3ºAVB† Mobitz Type II 2ºAVB† Bilateral BBB (alternating BBB or RBBB + alternating LAFB/LPFB)* Newly acquired or age LBBB, LBBB and LAFB, RBBB and LPFB* RBBB or LBBB and 1ºAVB*
Class IIa
Stable bradycardia (SBP >90, no hemodynamic compromise or responsive to pharmacologic therapy)* Newly acquired or age-indeterminate 1ºAVB*
Class IIb
Uncomplicated acute MI without evidence of conduction system disease*
AVB = Atrioventricular Block, BBB = Bundle Branch Block, LBBB = Left Bundle Branch Block, RBBB = Right Bundle Branch Block, LAFB = Left Anterior Fasicicular Block, LPFB = Left Posterior Fasicular Block

† Indication for demand pacing
* Indication for pad placement only

Special considerations: In clinical scenarios when it is necessary to begin transcutaneous pacing on the floor, a rapid response should be called. The decision to begin pacing should be made with the Senior ON and nursing supervisors present. Note that transcutaneous pacing is usually painful and requires sedation and/or pain medication.

Instructions: A step-by-step guide on how to perform transcutaneous pacing is provided below.

1. Place pads: Note that all MGH defibrillators can provide transcutaneous pacing. Proper pad placement is shown in the figure below. Ensure that the pads are connected to the defibrillator and that the ECG leads are connected to the patient (white is right, smoke over fire = white lead on R shoulder, black lead on left shoulder, red lead on left leg) and the defibrillator.



2. Administer sedation: Involve anesthesia for all non-ACLS protocol transcutaneous pacing. They can assist with administration of medications that may cause respiratory compromise (such as IV midazolam/fentanyl). If pacing must be initiated immediately, IV morphine +/- IV ativan may be used safely.

3. Initiate Pacing: Turn the defibrillator dial to “pacer” and set the pacing rate and output, which is the electrical stimulus needed to produce capture; a higher output represents more energy and will generally be more painful. A reasonable initial rate and output are 100 bpm and 100 mA, but note that the upper limit is around 140 mA. In non-emergent situations where you do not need to ensure immediate capture, it is reasonable to start with a lower output around 40 mA and increase by 5-10 mA until capture is achieved.

4. Verify Capture: Because the pacing rate should be well above the patients native rate, all beats should be paced. Appropriate capture is confirmed if pacing spikes precede all QRS complexes (and fire are the set rate, e.g. 100 bpm). If this is not the case, increase the output by 5-10 mA up to 140 mA. Confirm that paced/captured beats are perfusing with either palpation or Doppler of femoral pulse.

5. Set Final Output: If capture is achieved immediately (e.g. with an initial output set to 100 mA), find the capture threshold by decreasing the output slowly until capture is lost. The minimum output needed to maintain output will then be 10% higher than the capture threshold. In healthy patients, theoretical thresholds should range from 40-80 mA (corresponding to an output range of 44-88 mA or, more practically, 45-90). In clinical practice, thresholds tend to be more variable, with a range between 20-140 mA.

Transvenous Pacing

Indications: Transvenous pacing is a more durable option than transcutaneous pacing and is employed as a temporary bridge to recovery or to PPM placement. Guideline-recommended indications for transvenous pacing are provided in Table 2 below. In addition, note the following common disease-specific indications:

- AVB after MI or cardiac surgery (post cardiac surgery, pacing may be performed via epicardial wires placed in the operating room)
- AVB due to Lyme disease or infective endocarditis (e.g. with valvular abscess)
- Intra/post-procedural support for AVNRT ablation, alcohol septal ablation, heart transplantation, or TAVR
- Overdrive pacing for polymorphic VT

Table 2: Indications for Transvenous Pacing

Class I
Asystole Symptomatic bradycardia Bilateral BBB (alternating BBB or RBBB with alternating LAFB/LPFB) New or age-indeterminate bifasicular block (RBBB with LAFB/LPFB or LBBB with 1ºAVB) Mobitz Type II (2ºAVB)
Class IIa
RBBB with 1ºAVB New or age-indeterminate LBBB Incessant VT for overdrive pacing Recurrent sinus pauses (> 3 sec) not responsive to atropine
Class IIb
Age-indeterminate bifasicular block New or age-indeterminate RBBB

Special considerations: In contrast to transcutaneous pacing (which can be performed urgently without input from cardiology), placement of a temp wire for transvenous pacing must be performed in the cath lab. The pacing lead is inserted into the right ventricle via the right internal jugular, left subclavian, or femoral veins (less reliable and increased risk for dislodgement). Temp wires may remain in place for up to 7-10 days but carry a risk of infection. For this reason, prophylactic antibiotics are indicated during and after implantation.

Additional complications include: Lead dislodgement, bleeding, RV perforation, tamponade, thrombophlebitis, PE or air embolism, pneumothorax, subdiaphragmatic stimulation, arrhythmias (ectopy/asystole), and/or permanent RBBB.

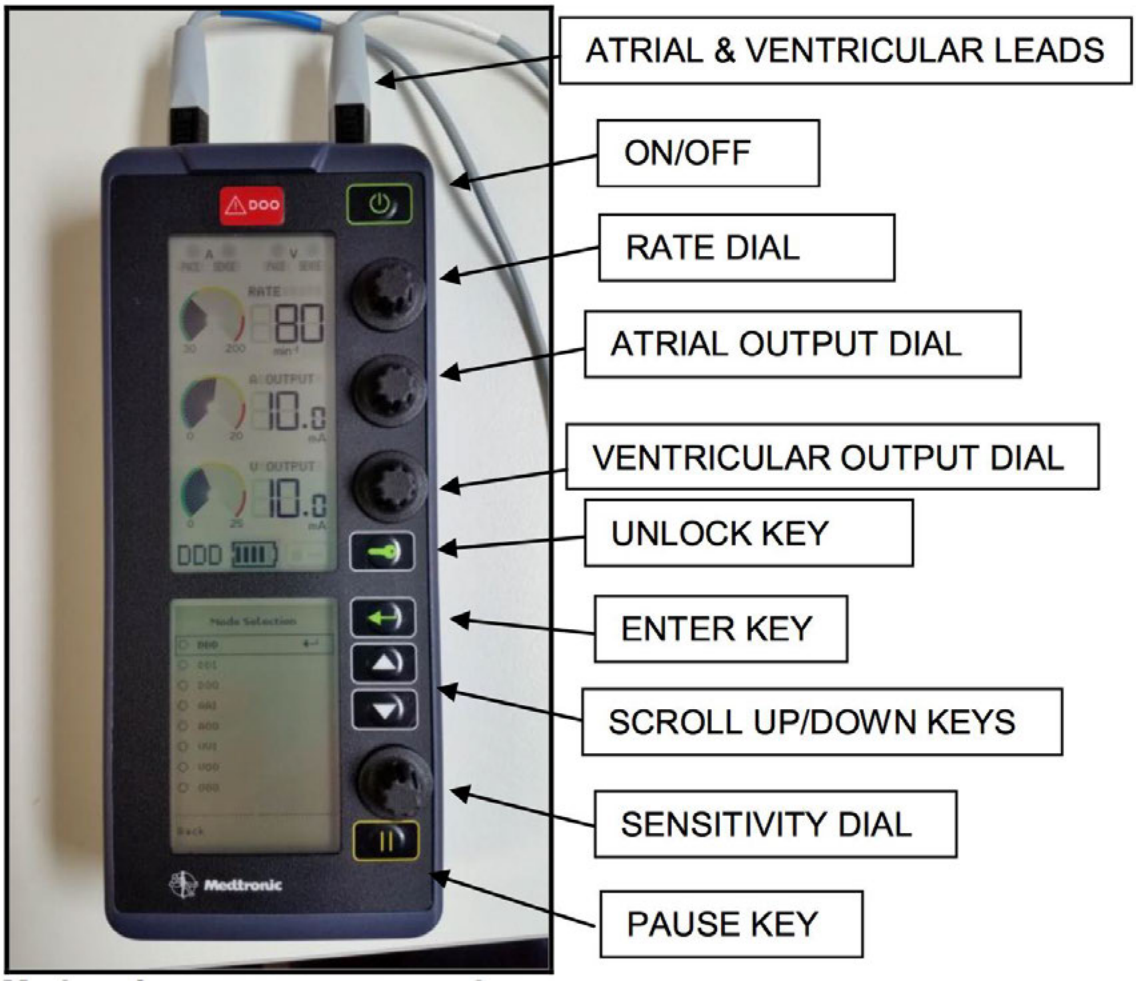
Instructions: While upfront placement is performed by the cardiology service, it is the responsibility of the resident team to ensure day-to-day maintenance/functioning. It may be the resident's responsibility to identify and troubleshoot basic issues that arise overnight. Routine maintenance requires daily threshold checks (described below) and CXRs to visually assess lead placement, particularly for perforation past the cardiac silhouette.

The control box has four set parameters (Figure 1):

- Heart Rate: This sets the backup/pacing rate (if rate set to 80, pacing will occur if intrinsic rate is < 80 but not if > or = to 80)
- Output: Electrical stimulus (mA) needed to produce capture (often set 5-10x higher) to ensure reliable capture. The output threshold must be assessed daily, as increased threshold may be an early sign of lead malfunction (e.g. migration, fracture). Note that the control box has separate dials for the atrial lead (if present) and ventricular lead (always present). Most medical patients will have only a single RV lead. In contrast,

post-cardiac surgery patients with epicardial wires will often have both atrial and right ventricular leads.

- Pacing Mode: Most set to VVI (both paces the ventricle and senses native ventricular activity, allowing for device inhibition, e.g. if the native rate is above the set rate)
- Sensitivity: Sets the device detection limit and represents the minimum energy generated by the heart that the device can detect. If the sensitivity is too low, the device will fail to detect intrinsic cardiac activity and may fire inappropriately. Alternatively, if the sensitivity is too high, the device may fail to fire



To test the output threshold:

1. Increase heart rate on device such that all beats are paced
2. Decrease output until pacing ceases and native rhythm is seen, this defines the output threshold of the temporary pacer
3. Increase output back up to its initial value (or 5-10x the threshold) and turn the rate back to its initial value
4. Do not touch sensitivity, unless troubleshooting
5. Document the threshold, output (in mA), and patient's native (underlying) rhythm

Note that for RV pacing, the ECG should show LBBB, with left superior axis-usually upright in I and aVL. Any change in pacing morphology is lead displacement until proven otherwise.

If there is concern for change in lead position, perform threshold testing again and get a STAT CXR

Troubleshooting common issues: The following issues may arise overnight and may first be detected on telemetry.

Failure to pace: Absence of pacing spikes and no paced QRS (which should have wide, LBBB morphology). Can result from:
1. Oversensing, i.e. pacer senses noise artifact (background activity) as a QRS complex and does not pace. Troubleshoot by decreasing sensitivity or by turning off sensing (asynchronous pacing, VOO)
2. Battery or connection problem. Troubleshoot by replacing battery or tightening connections

Failure to capture: Pacing spikes present but no paced QRS complex. Can result from:
1. Increased capture threshold due to fibrosis. Troubleshoot by increasing output
2. Lead migration (dangerous as epicardial lead migration can result in ventricular perforation!) Troubleshoot with unipolar ECG: connect V1 electrode to distal-most pacing electrode. Normal endocardial contact should result in negative QRS deflection with ST elevation. A positive or biphasic QRS is suggestive of lead migration
3. Physiologic effect: Such as ischemia, hypoxia, acidosis, alkalosis, hyperglycemia, hypercapnia, medication related. Attempt to reverse the underlying condition
4. Battery or connection problem. Troubleshoot by checking all connections

Failure to sense: The device does not detect intrinsic cardiac activity and fires inappropriately. Pacing spikes can be seen on top of or after native QRS (increases risk of R on T). Can result from:
1. Lead migration. Troubleshoot as above.
2. Sensitivity too low. Troubleshoot by increasing the sensitivity on the control box.
3. Ectopic beats. Consider/address reversible causes such as electrolytes
4. Pulse generator failure. Troubleshoot by replacing generator

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Permanent Pacing

Permanent pacing is indicated for symptomatic or dangerous forms of bradycardia that are not due to transient or reversible causes. Guideline-recommended indications for permanent pacing are provided in Table 3.

Table 3: Class I Indications for Implantable Pacemaker

Sinus Node Dysfunction
Symptomatic bradycardia or frequent, symptomatic sinus pauses Symptomatic chronotropic incompetence Symptomatic bradycardia resulting from drug therapy or medical conditions
AVB
○ 2°AVB causing symptomatic bradycardia ○ 2° or 3°AVB during exercise without evidence of myocardial ischemia ○ 3°AVB with HR≥40 if cardiomegaly or LV dysfunction present or if block below AV node ○ 3° or adv. 2°AVB causing symptomatic bradycardia or VT/VF ○ 3° or adv. 2°AVB and awake/asymptomatic in NSR w/ pause ≥3s, infranodal escape or escape HR<40 ○ 3° or adv. 2°AVB and awake/asymptomatic in AF w/ bradycardia and pause ≥5s ○ Persistent 3° or advanced 2°AVB occurring after AV node ablation or cardiac surgery
Chronic Bifasicular Block
Advanced 2° or 3°AVB Type 2° with alternating bundle branch block
AV Block after Acute MI
Persistent and symptomatic 2° or 3°AVB Persistent 2° infranodal AVB with alternating BBB or 3° infranodal AVB
Hypersensitive Carotid Sinus Syndrome/Neurocardiogenic Syncope
Recurrent syncope due to spontaneous carotid sinus stimulation with asystole ≥3 seconds

There are many different pacing modes, which are designated by a 1-5 letter code. These are outlined below. As an example, the 4-letter code DDDR implies that the device has both an atrial and ventricular lead and that:

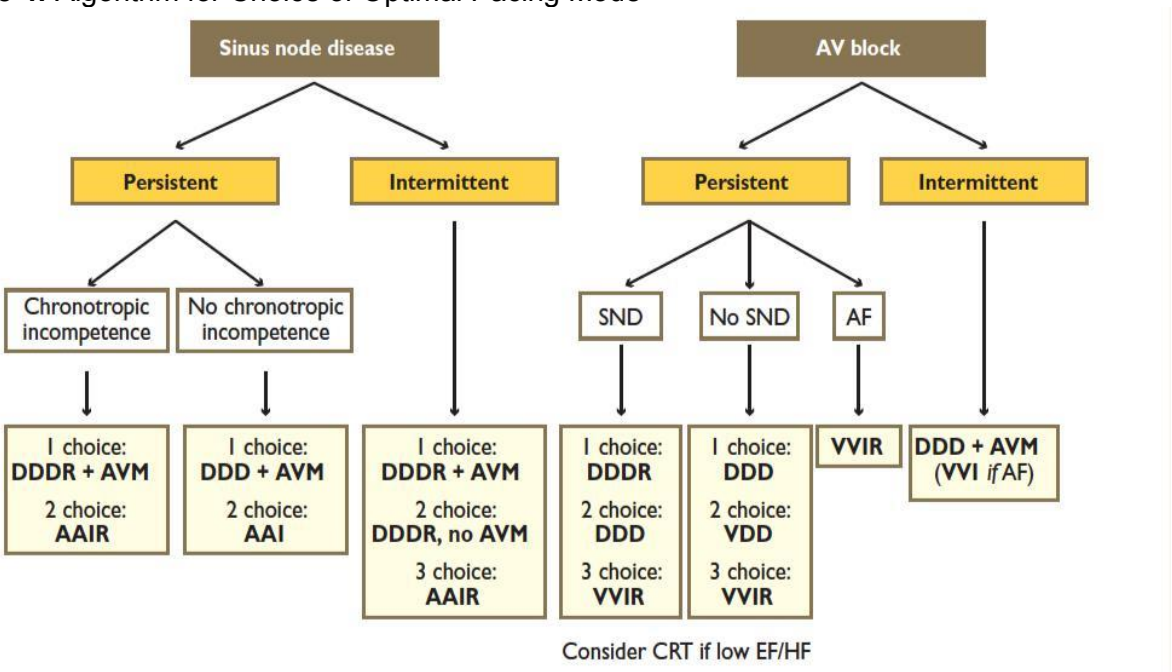
I: Both chambers (the atria and the ventricles) can be paced
II: Both chambers (the atria and the ventricles) can be sensed
III: In response to sensing, the device can either trigger activity or inhibit itself
IV: The device allows for rate modulation

O: None
A: Atrium
V: Ventricle
D: Dual (A+V for I-II and T+I for III)

Appropriate mode selection depends on the underlying condition/indication. The algorithm in Figure 4 provides a general framework. More information on common pacing modes is provided in text below.

Position I (Chamber Paced)	O – none, A – atrium, V – ventricle, D – dual (A+V)
Position II (Chamber Sensed)	O, A, V, D (A +V)
Position III (Response to Sensing)	O, T – triggered, I – inhibited, D – dual (T+I)
Position IV (Rate Modulation)	O, R – rate modulation (response to activity)
Position V (Multisite Pacing)	O, A, V, D- dual (A+V) *see chart below

Figure 4: Algorithm for Choice of Optimal Pacing Mode



AVM: AV delay management, SND: Sinus node dysfunction, AF: Atrial fibrillation, CRT: Cardiac resynchronization therapy.

AAI: Single atrial lead with atrial pacing and sensing. Device can inhibit itself if native atrial activity is sensed. Useful for patients with sinus node dysfunction, manifesting as sinus bradycardia or sinus pauses. Rate-responsiveness can be added for patients who cannot accelerate their heart rates (AAI-R). Patients must have intact AV conduction. A major disadvantage is that there is no protection from ventricular bradyarrhythmias in the setting of AV block. AV block develops in 0.6–5% of patients with sick-sinus syndrome per year. Pacemaker upgrade is often a higher-risk procedure than *de novo* implantation of a dual-chamber system. In patients with sinus node dysfunction, the presence of bundle-branch block at implantation is a relatively accurate predictor of subsequent AV block, and dual chamber pacemaker should be considered instead.

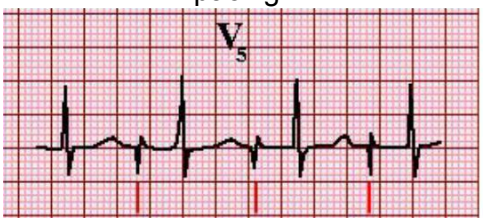
VVI: Single ventricular lead with ventricular pacing and sensing. Device can inhibit itself if native ventricular activity is sensed. Right ventricular VVI pacing is a pacing mode commonly used for the prevention of ventricular bradyarrhythmias or asystole. Virtually all devices currently in use are capable of VVI(R) pacing. As is the case with AAI pacing, the advantages of VVI pacing are that it requires only a single lead and that it can protect the patient from dangerous

bradyarrhythmias. However, unlike AAI pacing, VVI pacing is effective even in patients with impaired AV conduction or in patients at risk for future development of AV block. VVI(R) pacing in particular is indicated in patients with chronic atrial fibrillation with a slow ventricular response. The drawback to VVI pacing is that this mode cannot maintain AV synchrony and lack of AV synchrony can result in pacemaker syndrome as well as increased risk of atrial fibrillation (see complications below). This is why patients with intact sinus node function but requiring AV synchrony would be candidates for dual chamber (DDD) pacing, which preserves AV synchrony and maintains the heart rate response to activity.

DDD: Dual chamber in which both the atrium and the ventricle can be paced and sensed. DDD pacemakers provide physiologic pacing and assure maintenance of AV synchrony. Physiologic pacing reduces the risk of AF in sick sinus syndrome, resulting in a lower incidence of thromboembolic events, improves hemodynamics by preserving the atrial kick, and helps to avoid pacemaker syndrome. These pacing systems usually entail lead placement in the right atrial appendage and right ventricular apex. Patients with DDD pacing show one of four different rhythms: normal sinus rhythm, atrial pacing with intact AV conduction, AV sequential pacing, and atrial sensing and ventricular pacing (P-synchronous ventricular pacing). DDD is appropriate for patients with AV block with normal sinus node function, those with carotid sinus hypersensitivity, and those with combined sinus node and AV node dysfunction. DDD should be used cautiously with SVTs such as atrial fibrillation because rapid paced ventricular rates can occur. In most modern devices, though, a mode switch feature can automatically change the mode from DDD to DDI or VVI to prevent the pacer from tracking the rapid atrial rate in patients who have paroxysmal SVTs. DDD is the most commonly used mode. Note that most pacemaker manufacturers now have pacing modes available which can switch (for dual chamber devices) between AAI and DDD modes, to minimize ventricular pacing. At times this can result in single non-conducted P waves when in AAI mode which can reflect normal device function (with more prolonged AV block, the device will automatically switch to DDD).

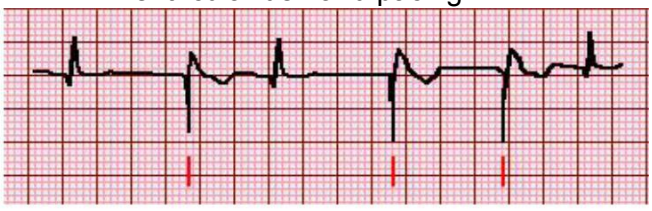
DDI: Dual chamber in which both the atrium and the ventricle can be paced and sensed, but when there is a sensed native atrial rate, the pacemaker will inhibit both atrial and ventricular output, thereby allowing native conduction to the ventricle. If AV block develops, ventricular pacing will occur at a programmed rate but will not be synchronized with the atrium.

A-pacing



Ventricular pacing with 100% capture (wide QRS with LBBB configuration)

Ventricular demand pacing



A-V sequential pacing (two spikes)

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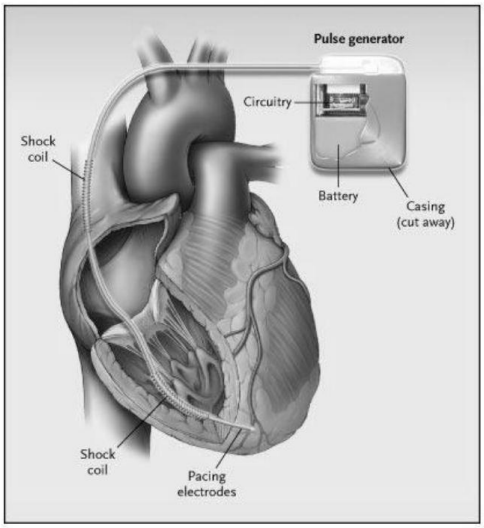
29. Implantable Cardioverter-Defibrillator (ICD) Therapy

ICDs are placed for prevention of sudden cardiac death and can be used with CRT for heart failure-related indications.



These devices have been shown to be 97% effective in terminating arrhythmias with defibrillation, cardioversion or antitachycardia pacing (ATP). Additionally, all ICDs can function as a pacemaker (though note that the reverse is not true). ICDs can be single-chamber (RV-lead) or dual chamber (RA/RV-lead) devices. They can be distinguished from dual chamber PPMs on CXR by presence of coils. The cost for primary implantations is around $25,000 and $18,000 for a device change.

Per AHA/ACC guidelines,[1-3] implantation of ICD should be considered in patients on optimal medical therapy who have an estimated survival of at least 1 year (with good functional status). They have Class I indications for both primary and secondary prevention, as well as Class II indications for conditions that increase the risk of sudden cardiac death (SCD).

Class I
Secondary Prevention:

- Survivors of cardiac arrest due to VF or sustained VT without reversible causes (AVID)

Primary Prevention:

- Ischemic cardiomyopathy and LVEF ≤ 30-40% at least 40 days post-MI (DINAMIT) or at least 3 months post-CABG (CABG-PATCH)
- LVEF ≤ 30% and NYHA Class I, II, or III (MADIT-II)
- LVEF ≤ 35% and NYHA Class II or III (SCD-HeFT)
- LVEF ≤ 40% and inducible VF or sustained VT at EP study (MUSTT)
- Non-ischemic cardiomyopathy with at least 3 months of documented
- CHF, LVEF ≤ 35%, and NYHA Class II or III (SCD-HeFT)*
- Syncope of unknown origin and VT/VF induced at EP study
- Spontaneous sustained VT (+/- hemodynamic instability) with structural heart disease
  (*DANISH Study: RCT of non-ischemic heart failure with EF ≤ 35%, showed no overall mortality benefit from ICD versus optimal medical therapy, however risk of SCD was reduced and a mortality benefit was observed in the subgroup that was <68 years old)

Class II
For numerous conditions that increase risk of SCD, with limited RCT data

- Hypertrophic cardiomyopathy: LV thickness >/= 30mm, family history of SCD, abnormal exercise BP
- Arrhythmogenic right ventricular cardiomyopathy (ARVC): extensive RV, LV involvement
- Long-QT syndrome: syncope and/or VT while on beta-blockers
- Brugada syndrome: syncope and/or VT
- Catecholiminergic polymorphic VT: syncope and/or sustained VT on beta-blockers

- Cardiac sarcoid, giant cell myocarditis, Chagas disease
- Unexplained syncope, significant LV dysfunction, and non-ischemic dilated cardiomyopathy
- Sustained VT with normal ventricular function
- Non-hospitalized patient awaiting heart transplant

Table 1: Landmark Trials of ICD for Primary SCD Death [4-8]

Trial	Entry Criteria	Relative RR (%)	Absolute RR (%)
MADIT	EF ≤ 35%, prior MI, NSVT, inducible VT not suppressed by antiarrhythmics	59	19
MUSTT	EF ≤ 40%, prior MI, NSVT, inducible VT	58	31
MADIT II	EF ≤ 30%, prior MI, NYHA I-III	28	6
SCD-HeFT	EF ≤ 35%, NYHA Class II or III (ischemic or non-ischemic)	23	7
DINAMIT	EF ≤ 35%, recent MI	---	---

Cardiac Resynchronization Therapy: Cardiac resynchronization therapy (CRT) devices have an RA, RV, and coronary sinus (epicardial pacing of LV) leads. This allows for optimization of A-V synchrony as well as V-V synchrony, which has been shown to improve stroke volume. For this reason, CRTs represent an important adjunctive therapy for patients with advanced heart failure, particularly with wide QRS (see figure 1). CRT devices may only provide BiV pacing (CRT-P) or may allow for BiV pacing plus defibrillation with ICD function (CRT-D). Data suggests that when indicated, placement of a CRT can: Improve NYHA functional class, improve 6 minute walk times, increases quality of life, decreases hospitalizations, and decreases all-cause mortality (specifically related to progression of HF).

Indications are based on numerous RCTS including but not limited to: MADIT-CRT (CRT benefit in NYHA I and II), RAFT (CRT benefit in NYHA II and III) and COMPANION and CARE-HF (CRT benefit in NYHA III and IV), BLOCK-HF (CRT benefit over RV pacing alone in AVB, EF <50%, and NYHA I, II or III) and ECHO-CRT (no CRT benefit/harm in NYHA class III/IV with QRS <130ms).[9-13]

Figure 1: Indications for CRT

Recommendations	Class	Level
1) LBBB with QRS duration >150 ms is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*)	I	A
2) LBBB with QRS duration 120-150 ms should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*)	I	B
3) Non-LBBB with QRS duration >150 ms should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*)	IIa	B
4) Non-LBBB with QRS duration 120-150 ms may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, and ambulatory IV despite adequate medical treatment. (*)	IIb	B
5) QRS duration <120 ms CRT in patients with chronic HF with QRS duration <120 ms is not recommended.	III	B

Wearable Cardiac Defibrillators: Wearable cardiac defibrillators (WCDs) are externally worn defibrillators (currently the only approved device is the LifeVest). These may be considered as interval therapy in patients awaiting ICD placement or more permanently in those at risk for SCD who are not candidates for ICD placement. The VEST Trail showed that among post-MI patients with EF ≤35%, WCDs did not reduce the primary endpoint of SCD and ventricular tachyarrythmias but did reduce the secondary endpoint of all-cause mortality up to 90 days.[14]

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30. Procedures in Electrophysiology and Electrophysiology Studies

The purpose of this section is to provide background/basic information on three commonly-employed EP procedures: synchronized cardioversion and defibrillation, diagnostic EP studies, and ablations.

Synchronized Cardioversion and Defibrillation

Cardioversion (DCCV) and defibrillation are non-invasive interventions that can terminate tachyarrhythmias by delivering an electrical shock to the heart. Cardioversion is performed by synchronizing the shock to a QRS complex (thus requires a rhythm in which the QRS complex is present), while defibrillation is unsynchronized and delivers a random shock during the cardiac cycle.

QRS synchronization is essential to prevent delivery of a shock during the vulnerable period of repolarization (risk of R on T which can trigger ventricular arrhythmias). Synchronized cardioversion is used for SVT, AF, and VT, while unsynchronized cardioversion is used for VF. Note that it is not possible for a defibrillator to synchronize to ventricular fibrillation, and an external defibrillator programmed with “synch on” will not deliver a shock for VF.

Indications and Contraindications

Emergent DCCV and defibrillation are generally indicated in cases of clinical instability. Planned DCCV may also be performed as an effective treatment for SVTs. Specific energy required by indications is provided in Table 1 below. Note that MGH defibrillators should all be biphasic; these more effectively cardiovert/defibrillate at lower energy levels. Some patients (especially larger patients) may be difficult to cardiovert/defibrillate even with 360J biphasic.

Table 1: Indications and Energy Dosing

CARDIOVERSION	**Monophasic (J)**	**Biphasic (J)**
Supraventricular Tachycardia[1]	50-100	<50-100
Atrial Flutter[2]	100	50-100
Atrial Fibrillation[2]	200	120-200
Ventricular tachycardia (stable)	200	100
DEFIBRILLATION	**Monophasic (J)**	**Biphasic (J)**
Ventricular tachycardia (pulseless/unstable)	360	150-200
Ventricular Fibrillation	360	150-200

[1]includes reentry arrhythmias AVRT and AVNRT (attempt adenosine first)
[2]includes:
AF/AFL of ≥48h (or unknown) duration and anticoagulated for 3–4 weeks (INR 2–3)
AF/AFL of <48h duration, for which anticoagulation is optional depending on risk
AF/AFL of unknown duration with CHF and absence of thrombus in LA on TEE acute onset
AF/AFL with hemodynamic compromise: MI, pulmonary edema, hypotension

In general, DCCV/defibrillation is contraindicated in the following cases:

1. Known atrial or ventricular thrombus without emergent indication (unless the thrombus is old, organized, and/or felt unlikely to embolize)
2. Unknown duration of AF/AFL in a non-anticoagulated patient in the absence of TEE (unless emergent)
3. Tachycardias associated with increased automaticity or triggered activity, as they typically recur within seconds after the shock, and the release of endogenous catecholamines consequent to the shock may further exacerbate the arrhythmia. These include MAT, junctional tachycardias, and AIVR.
4. Digitalis toxicity
5. Severe electrolyte imbalance

Additionally, the following considerations exist for these special populations:

1. Patients who are pregnant: Cardioversion/defibrillation can be performed without affecting the rhythm of the fetus. It is recommended that fetal heart rate be monitored during the procedure.
2. Patients who have pacemakers/ICDs: Cardioversion/defibrillation can be performed but the electrode should be at least 12 cm from the pulse generator and an anteroposterior electrode orientation is recommended. The pacemaker/ICD should be interrogated afterward to ensure proper functioning.

Mechanism and Procedure

The delivered shock depolarizes all or most excitable cardiac tissue and induces a refractory period that terminates reentrant activity. Cardioversion restores sinus rhythm in 70–95% of patients. Factors that decrease efficacy include high resistance in the vector of shock (increased electrode distance, increased tissue density, etc), increased arrhythmia duration, presence of structural heart disease, and involvement of multiple reentry circuits. Evidence is equivocal as to whether electrode orientation (anterolateral vs. anteroposterior) and electrode type (paddles vs. skin patches) have any effect on shock efficacy.

Step-by-step instructions for emergent cardioversion and defibrillation are provided below.

Cardioversion:

1. Turn the mode selector to DEFIB (red area). Select the desired energy using the up and down arrow keys in the front panel. See above for desired energy, or in general:
    a. Narrow, regular: 50 – 100 J (atrial flutter often converts with 50 J)
    b. Narrow, irregular: 120 – 200 J (atrial fibrillation typically requires 150 J)
    c. Wide, regular: 100 J
    d. Wide, irregular: 150 – 200 J (defibrillation dose)
2. Press the Sync On/Off button
    a. Confirm that a Sync marker appears on the monitor above each detected R wave to indicate where discharge will occur
    b. If necessary, use the LEAD and SIZE buttons to establish settings that yield the best display
3. Press the CHARGE button on the front panel
4. Ensure all are clear from the bed then press and hold the illuminated SHOCK button on the front panel. The defibrillator will discharge with the next detected R wave

5. If additional shocks are necessary, increase the energy level as needed

Defibrillation:

1. Turn the mode selector to DEFIB (red area)
    a. The unit displays DEFIB 120J SEL on the monitor
    b. The default energy selections for adult patients are Shock 1: 120J, Shock 2: 150J, Shock 3: 200J. You can use energy select (UP and DOWN arrow keys) to change settings
2. If the monitor shows a shockable rhythm, press the CHARGE button on the front panel. If patient is pulseless, continue CPR while charging
3. Ensure all are clear from the bed then press and hold the illuminated SHOCK button on the front panel
4. If patient is pulseless, resume CPR for 2 minutes before the next pulse and rhythm check

For non-emergent and routine procedures, patients should be fasting for at least 6–8 hours. Some may require periprocedural anticoagulation to prevent thromboembolism. Routine procedures are usually performed in the EP lab, CCU or ED, with assistance of cardiac anesthesia for conscious sedation. TEE is frequently paired with this procedure "TEE/Cardioversion" to look for the presence of a LA or LAA thrombus. The electrodes/paddles can be placed in anterolateral or antero-posterior orientation. Sedation is usually achieved with short-acting agents, such as midazolam 0.5–2mg over 2 minutes, infused every 2–3 minutes as needed. Pain is generally controlled with Fentanyl 50-100mcg IV push over 1-2 minutes. When anesthesia is involved, proprofol is typically used.

Complications

Immediately after shocking, ST and T wave changes may occur and typically resolve within about 5 minutes (avoid confusing with a new ischemic event). However, the following more serious complications may also occur:

- Arrhythmias/Conduction abnormalities: Self-limited and include sinus tachycardia, PAC, PVC, NSVT, VT, VF, and LBBB. Can cause hemodynamic instability requiring further intervention. Bradycardia can also occur after cardioversion, and transcutaneous pacing through the defibrillator might be required
- Thromboembolism: Occurs ~1% with anticoagulation and ~5% without anticoagulation
- Myocardial necrosis: Severity depends on strength and number of shocks delivered.
- Myocardial dysfunction/stunning: Global LV dysfunction can be present until 48 hours after shock. Interpret cardiac studies within this 48h window with caution
- Pulmonary edema: Rare complication seen in patients with AF and/or LV dysfunction
- Hypotension: Transient and can last several hours. Typically fluid-responsive but may require initiation of short-term pressors
- Cutaneous burns: Occurs ~20-25% of patients. Can use prophylactic steroid cream or topical NSAIDs at the site of electrodes

Electrophysiology Study (EPS)

An electrophysiology study is an elective, invasive, intracardiac catheter-based intervention that measures specific intervals within the cardiac cycle. The purpose is to better understand the etiology, clinical significance, and management of brady- and tachy-arrhythmias.

Indications and Contraindications

An EPS may be required in the following scenarios:

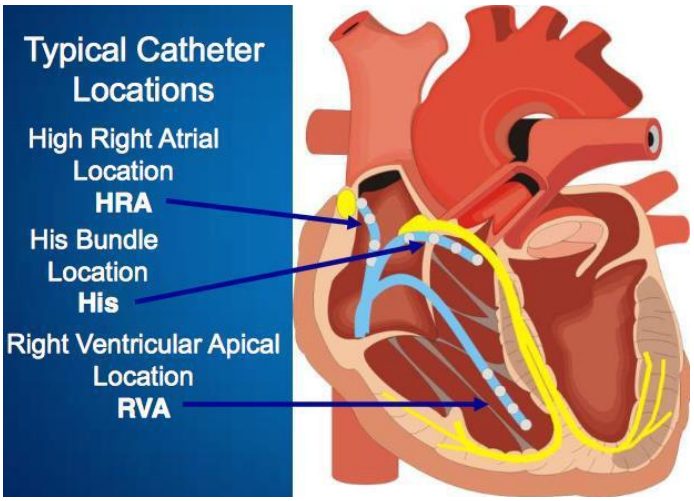
1. Bradyarrhythmias: To acquire corroborative data in symptomatic patients with episodic bradyarrhythmia or define level of AV conduction abnormality
2. Tachyarrhythmias: to define mechanism of NCT or WCT or reproduce a clinically defined tachycardia for mapping and ablation
3. ICD implantation and programming: To search for EPS-induced VT or VF in patients with structural heart disease, NSVT, or reduced LVEF to justify ICD implantation and define optimal ICD parameters
4. Syncope of unknown etiology: to assess SN function, AV conduction, and search for VT/VF in patients with syncope and organic heart disease
5. After cardiac surgery: to assess the effect of cardiac surgery on arrhythmia risk

In general, EP studies are contraindicated in the following cases: active ACS, bacteremia or septicemia, acute decompensated congestive heart failure (not caused by the arrhythmia), critical AS, severe HOCM, severe left main or 3-vessel disease, presence of a major bleeding diathesis, presence of an acute lower extremity venous thrombosis (if femoral vein cannulation is required).

Mechanism and Procedure

Patients are brought to the EP lab (1st Floor Gray/Bigelow 109, across from Coffee Central), given at least conscious sedation, and monitored either invasively or noninvasively, depending on the type of anesthesia used. Standard ECG leads and defibrillation pads are applied. Multiple sites of venous access (and at times, arterial access) are acquired for intracardiac catheter placement. Femoral access is most common. Catheters with electrode tips are placed in specific locations to allow for both pacing and recording. These sites include:

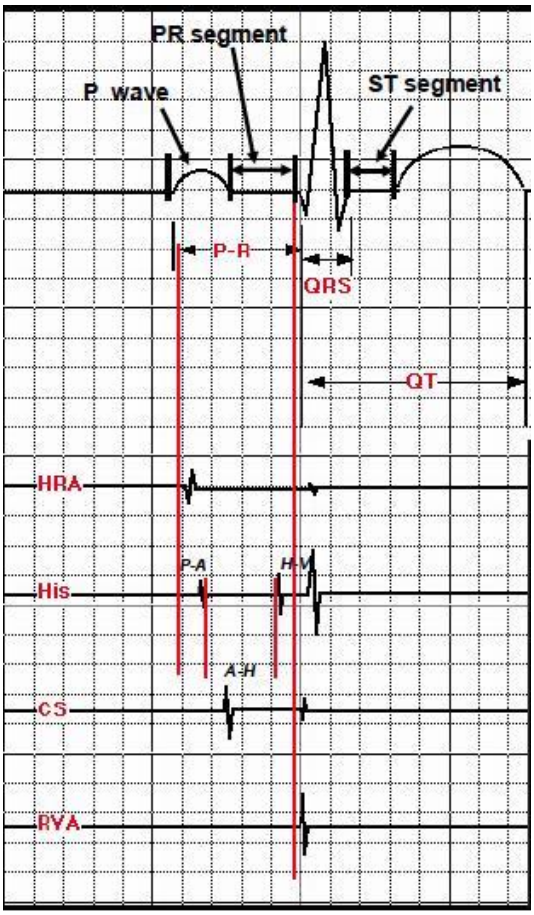
- High right atrium: Reflects SA node function, AV conduction, and direction of atrial activation
- Coronary sinus: Reflects LA activation. Obtained in patients with SVT or pre-excitation
- Tricuspid annulus (His): Tracings from low septal RA, His bundle, and high septal RV depolarization reflect His bundle activity
- RV apex: Reflects RV activity



- Left heart (via transseptal or retrograde aortic approach for mapping/ablation)

Real-time recordings are simultaneously taken from surface and intracardiac electrodes and displayed typically in order of cardiac activation. From these tracings, specific segment and interval lengths can be calculated.

Below is a sample of an intracardiac electrogram during EPS.



The PA interval is measured from the onset of the earliest registered P wave to the onset of the atrial deflection on the His bundle catheter recording, indicates SA to AV node conduction time.

The AH interval is measured from the earliest rapid deflection of the atrial recording seen on the His bundle ECG to the earliest onset of the His bundle deflection, indicates AV node conduction time.

The HV interval is measured from the earliest onset of the His bundle deflection to the earliest registered ventricular activation anywhere, indicates distal His to Purkinje tissue conduction time

Conduction times that fall outside the normal range for each of these intervals provide further insight into the etiology and mechanism of an arrhythmia.

Manipulation of the cardiac cycle with programmed stimulation and/or medications may be used to elicit arrhythmia. In many cases, diagnostic EPS is followed by mapping and ablation for treatment of an arrhythmia (next section). Commonly used medications for this purpose include:

Isoproterenol (0.5 to 5 mcg/kg/min)

- Mechanism: Potent, non-selective, synthetic beta-adrenergic agonist with very low affinity for alpha-adrenergic receptors.
- Uses: Shortens refractory period of AV node. Helpful for induction of nodal dependent SVT Enhances conduction, alters refractoriness and enhances automaticity related to

delayed after-depolarizations which is helpful for induction of VT (particularly useful in the evaluation of exercise-induced VT and RVOT VT). Induces repetitive rapid discharges from the pulmonary veins (at higher doses) that trigger initiation of atrial fibrillation, which is a useful feature when testing the efficacy of ablation sites during PVI.

- Contraindication: Critical coronary artery disease. It causes vasodilation and commonly results in hypotension despite an increased heart rate.

Procainamide (10 to 15 mg/kg)

- Mechanism: Class Ia anti-arrhythmic. Decreases myocardial excitability and conduction velocity.
- Uses: Evaluation of the His-Purkinje system during sinus rhythm and with atrial pacing. Normally prolongs H-V interval by 10-20%. Exaggerated responses may indicate the need for permanent pacing. Can unmask Brugada syndrome by blocking sodium channels (Brugada syndrome is caused by decreased sodium inflow current in myocardial tissue).

Adenosine (6 to 18 mg)

- Mechanism: Transiently slows or blocks AV nodal conduction, also dilates the coronary arteries (used in stress testing)
- Uses: To help define the mechanism of SVT by establishing AV node dependence or document the presence or absence of accessory pathway conduction before and after radiofrequency ablation. Must be given as a rapid IV bolus to be effective given its very short biologic half-life.

Complications

Related to percutaneous catheterization of veins and arteries	Pain/Infection/bleeding/hematoma at the access site
	Local thrombophlebitis
	Systemic thromboembolism (PE, DVT, etc)
	Vessel damage and dissection
	TIA/stroke
Related to intracardiac catheters and programmed cardiac stimulation	Cardiac chamber or coronary sinus perforation +/- hemopericardium/cardiac tamponade
	MI
	Arrhythmias (AF, VT, VF, RBBB/LBBB, etc)

EPS-Related Ablation

Following the diagnostic EPS, a subset of patients will undergo mapping and ablation for treatment of their arrhythmia. During mapping, intracardiac catheters stimulate and record action potentials within a region of interest to determine the temporal and spatial characteristics associated with the origin and spread of an arrhythmia. The created “map” is then used to guide and localize potential ablation sites. Mapping prior to ablation is not necessary for certain types of arrhythmias that have a defined anatomical course (i.e. typical atrial flutter). Focal tissue ablation is typically achieved with radiofrequency energy delivered through the tip of the catheter electrode to the endocardial surface.

Pulmonary Vein Isolation (PVI) can be accomplished with radiofrequency (RFA) or cryoablation. Comparison of the two techniques in patients with drug refractory, symptomatic paroxysmal AF revealed cryoablation to be non-inferior with similar rates of adverse events. Notably, cryoablation reduces procedural time, but increase fluoroscopy time as compared to RFA (FIRE and ICE, NEJM 2016).

Indications and Contraindications

Ablation may be indicated in the following scenarios:
1. Wolff-Parkinson-White, accessory pathway-mediated, and other variant pre-excitation states
2. Atrial fibrillation/flutter refractory to medications and/or with severe symptoms
3. Sinus, atrial or junctional tachycardia refractory to medications and/or with severe symptoms

4. Idiopathic ventricular premature depolarization arising in the right ventricular outflow tract associated with severe symptoms

5. Monomorphic VT (can consider cases of polymorphic VT)
6. VF (uncommon indication)
7. PVC-induced cardiomyopathy

Contraindications are generally the same as for EPS (see prior section).

Mechanism and Procedure

At MGH, PVI utilizing RFA and cryoablation are both performed. The procedure aims to electrically isolate the antral portion of the pulmonary veins, a region identified as containing >90% of the ectopic beats involved in the generation and maintenance of AF. PVI is indicated in patients with symptomatic AF who have either failed pharmacologic therapies for rhythm control or cannot tolerate medication side effects. Importantly, ablation does not negate the need for therapeutic anticoagulation. Advanced mapping can be performed with 3D imaging, intracardiac echo, CT and/or MRI.

It is not uncommon for atrial fibrillation and atrial flutter to occur in the same patient. As a result, Cavotricuspid Isthmus (a well-described electro-anatomical substrate for typical atrial flutter) ablation line can be performed during the same procedure.

All patients should be on anticoagulation peri-procedurally to reduce the risk of thromboembolic stroke/TIA. Patients who have AF>48hours should be on therapeutic (INR 2-3) anticoagulation with coumadin or DOAC for at least 3 weeks or have a TEE prior to PVI. Coumadin can be

continued without interruption or bridged to heparin. Anticoagulation should continued for at least two months after the procedure, although based on patient wishes, risk factors/stratification, and aggressive post-ablation monitoring some EP physicians will choose to discontinue anticoagulation. Specific guidelines are available for newer anticoagulants.

PVI efficacy is variable and dependent on the operator, patient's underlying cardiac anatomy/function, and AF characteristics. Efficacy at 1 year has been reported to be as high as 80-85% for paroxysmal AF but decreases to 50-60% for persistent AF.

There is recent evidence that in patients with systolic HF (LVEF ≤40%) and NYHA II-III symptoms with persistent AF who are chosen for a rhythm control strategy, PVI leads 36% absolute increase in AF-free survival at 24 months, 26% absolute reduction in unplanned hospitalizations, and a 10% absolute reduction in overall mortality with AF ablation as compared to amiodarone (AATAC, Circulation 2016). Whether this will lead to increased PVI utilization in HFrEF patients and AF remains to be seen.

Complications

The following are general complications related to ablation:
1. Complete heart block
2. Thromboembolism
3. Vascular access problems - bleeding, infection, hematoma, vascular injury
4. Cardiac trauma - myocardial perforation, tamponade, valvular damage
5. Coronary artery thrombosis/myocardial infarction
6. Cardiac arrhythmias
7. Pericarditis
8. Pulmonary vein stenosis
9. Phrenic nerve paralysis
10. Radiation skin burns
11. Possible late malignancy
12. Atrioesophageal fistula
13. Death from any of the above

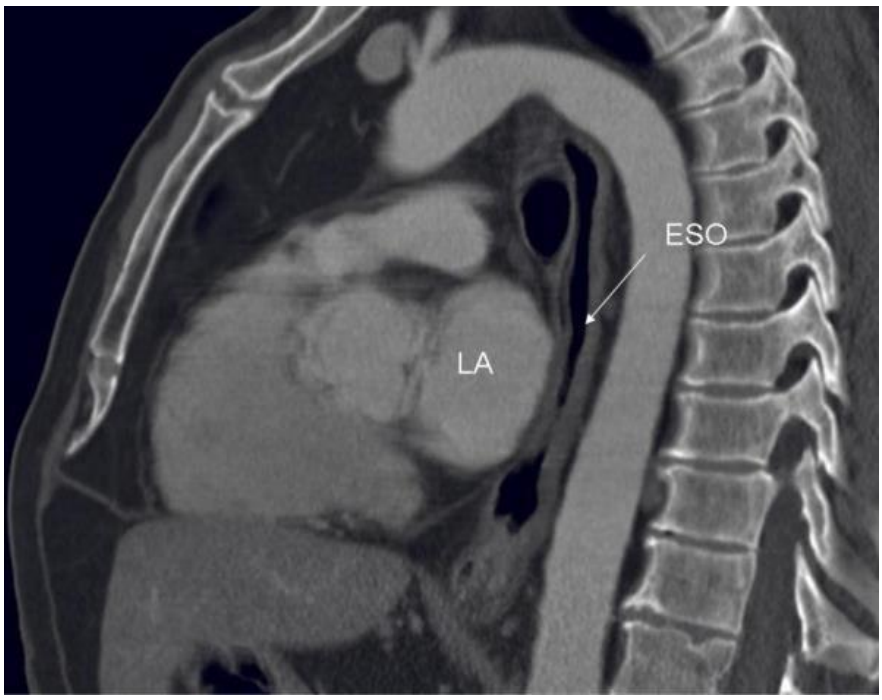
In addition, there are certain complications that are specific to PVI. Based on an analysis of 93,000+ PVI cases from 2000-2010, the overall complication rate was reported as 6.3%. There is evidence to support that this rate may decrease over time. In-hospital mortality rate was reported as high as 4.6 cases per thousand cases. The leading causes of death were cardiac tamponade, stroke, and atrioesophageal fistula. Pulmonary vein stenosis is a rare long-term complication.

Cardiac tamponade occurs in ~1% of cases and results from perforation of atrial or ventricular free wall from excessive energy use/overheating of tissue or traumatic catheter puncture. Delayed tamponade has been reported to occur as far out as 30 days post-PVI. Presentation, diagnosis and management of cardiac tamponade are the same as in any other setting.

Thromboembolism/Stroke occurs in 0.4-2% of cases and results from thromboembolic event from catheter manipulation and/or trauma to LA endothelium. For this reason, all patients should be on anticoagulation peri-procedurally. TEE should be considered to assess presence of thrombus. Otherwise, presentation, diagnosis and management of stroke/TIA are the same as in any other setting.

Atrioesophageal fistula (AEF) represents the most lethal form of thermal damage resulting from ablation to the posterior LA and nearby esophagus/mediastinum. It occurs in less than 0.2% of cases and presents 1-6 weeks s/p PVI. Patients usually report fever, chills, rigors, nausea, or develop sudden neurologic deterioration and endocarditis with hemodynamic instability. When suspected, CT and MR are the best diagnostic modalities, favoring the former since early surgical intervention is key for survival. In these cases, endoscopy should be avoided to prevent esophageal insufflation and air embolization. At MGH, patients are placed on a high-dose proton pump inhibitor for 6 weeks after AF ablation.

Sagittal view of the mediastinum demonstrating proximity of the Left Atrium (LA) to the esophagus (ESO)



Severe pulmonary vein stenosis occurs in ~1-3% of cases (likely lower in the current era) and results from thermal injury to the PV musculature, followed by a progressive vascular reaction whereby the damaged myocardium is replaced by collagen. Patients can be asymptomatic or present with dyspnea, cough, hemoptysis and recurrent pneumonia with mean onset 2-5 months post-PVI. The diagnosis is confirmed with CT, MRI, PV angiography or TEE. Treatment is usually required even in asymptomatic patients with severe PV stenosis to prevent the development of pulmonary hypertension and includes balloon dilatation, stenting of the pulmonary veins, and in rare cases surgery.

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QUICK REFERENCE GUIDE: ARRHYTHMIAS AND ELECTROPHYSIOLOGY

Narrow Complex Tachycardia (NCT)

- If unstable with NCT ⇒ DCCV with following energy
  - Regular → 50-100J
  - Irregular → 120-200J biphasic or 200J monophasic
- The following table characterizes the NCTs by mechanism and location

LOCATION	MECHANISM: ↑ AUTOMATICITY	MECHANISM: RE-ENTRY
SINUS NODE	Sinus Tachycardia • Secondary cause (HoTN, pain, fever, PE, CHF, acute MI, fistula, etc.) vs drug effect/toxicity/withdrawal • HR 100-150 in older pts; up to 200 in younger pts • Gradual onset • Treat underlying cause	Sino-Atrial Nodal Reentrant Tachycardia • Reentry within or around SA node • Paroxysmal, abrupt on/off • P wave morphology similar to baseline • Treat w/ vagal maneuvers, Valsalva; nodal blockade; ablation
ATRIUM	Atrial Tachycardia • Focal vs multifocal • Atrial rate 100-250, vent rate 90-120 (variable block) • Focal AT: Structural heart dz vs Dig toxicity; d/c Dig, rate control (BB vs CCB), ablation. • MAT: ≥3 P-wave morphologies, a/w chronic pulmonary disease; prefer CCB > BB if severe lung disease	Atrial Flutter • Macro-reentrant circuit • Atrial rate 250-300, vent rate 150 (if 2:1 conduction) • Slow and diagnose with vagal maneuvers ± adenosine • Similar mgmt. to atrial fib: rate/rhythm control, anticoagulation • Prefer BB, CCB, Dig to class 1A/1C meds → can enable 1:1 conduction • Typical flutter is amenable to ablation
AV NODE	Non-Reentrant Junctional Tachycardia • JET (junctional ectopic tach): infants > adults, particularly post-cardiac surgery for CHD; due to ectopic focus; high morbidity • NPJT (non-paroxysmal JT): adults > children; "accelerated junctional rhythm"; a/w digoxin toxicity and acute MI; difficult to distinguish from AVNRT w/o EP study; treat underlying cause	AVNRT • Reentry thru dual pathways in AV node • Abrupt on/off, rates 150-220 • Retrograde P, can be buried in QRS • Acute: vagal, adenosine • Mgmt: BB, CCB; ablation is definitive AVRT • Reentry thru acc. pathway + AV node • Narrow = orthodromic (antegrade thru AV node, retrograde thru acc. path); use nodal blockade • Wide/pre-excitation = antidromic; avoid nodal blockade (see WCT chapter) • Definitive tx: ablation

Wide Complex Tachycardia (WCT)

- Refers to rate > 100bpm and QRS ≥ 120ms
- The ddx for WCTs include
  - VT
  - SVT with aberrancy
  - SVT w/ pre-excitation, and
  - Pacemaker-related tachycardias
- The clinical presentation of WCT can be variable, from asymptomatic runs of NSVT to a patient who has coded. Becase most patients do not tolerate VT for long periods of time, when you see WCT, assume it is VT→first feel for a pulse and obtain a blood pressure ASAP!
- Many different ECG criteria have been developed to help distinguish VT from the differential above
  - Brugada Criteria: VT present if any of following criteria are met
    - Concordance in precordial leads (no RS complex in V1–V6)
    - RS interval is >100 msec
    - AV dissociation present (e.g. fusion and/or capture beats)
  - Vereckei Criteria: VT is implied if any of the following criteria are met in aVR
    - Initial R wave
    - Initial Q or R wave >40ms
    - Presence of a notch on the descending limb of a predominantly negative QRS
    - Ventricular activation ratio ≤ 1 (depolarization magnitude or vertical distance achieved over initial 40ms of QRS [v(i)] divided by vertical distance achieved over terminal 40ms of QRS [v(t)])
  - Yurchak Criteria: If fusion beat, capture beat, AV dissociation, concordance, or a NW axis present, then WCT is VT. If none of the above are present, then proceed through following set of steps to calculate points for VT vs SVT. The rhythm with the "most points" wins:

i. QRS > 160 msec	1 point for VT
ii. Left axis deviation	1 point for VT
iii. RBBB morphology plus:	
1. Triphasic V1	1 point for SVT
2. R, qR, RS, R < R' in V1	1 point for VT
3. R > S in V6	1 point SVT
4. R < S in V6	1 point for VT
iv. A LBBB morphology plus:	
1. R < 30 ms in V1	1 point for SVT
2. Wide/notched S	1 point VT
3. No Q in V6	1 point SVT
4. Q in V6	1 point for VT

- Approach the initial management of WCT according to patient stability (as below). See chapter for more details on mgmt according to etiology
  - Pulseless: Immediately start the pulseless VT ACLS algorithm and prepare for unsynchronized DCCV
  - Hemodynamically unstable or highly symptomatic: Worry about etiology AFTER YOU'VE STABILIZED PATIENT
    - Prepare for synchronized DCCV (fentanyl/versed for sedation), put pads on the patient, and call for help (e.g. cardiology, EP, RICU, etc.)

        - Start amiodarone (150 mg x 1 Q 3–5 min, then drip @ 1 mg/min), and/or lidocaine (100 mg x 1, then drip @ 1–4 mg/min). Amiodarone typically is an appropriate anti-arrhythmic to start unless there is QT prolongation and concern or TdP
        - If regular, monomorphic, and there is some suspicion for SVT, you can consider using adenosine as both a diagnostic and therapeutic intervention
        - If pacemaker-mediated or tracked WCT→ apply magnet

Atrial Fibrillation (AF)

- Atrial fibrillation is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age (0.4% to almost 20%)
- In general, AF results from an abnormal atrial response to reentry and/or rapid focal ectopic firing
- Patients can be asymptomatic, but many describe palpitations, fatigue, dyspnea, lightheadedness and diaphoresis
    - Thromboembolic CVA is the initial manifestation in 10–40% of patients
- TTE should be performed in all patients who present with new-onset AF in order to evaluate for a structural etiology. In addition, thyroid function testing should routinely be performed, as hyperthyroidism predisposes to AF. Also consider renal and liver function tests, as well as cardiac biomarkers (including troponin and NT-proBNP) based on clinical presentation
- Rate versus rhythm control: Studies that have examined rate control (plus anticoagulation) versus medical rhythm control have not detected differences in mortality or stroke rates
    - However, these studies enrolled predominantly older patients (average age 70), most of whom had persistent AF in the setting of structural heart disease and were able to tolerate AF from a symptomatic standpoint
- All patients with AF should be on anticoagulation except those at the lowest risk of thromboembolic stroke
    - The AHA/ACC 2019 guidelines for atrial fibrillation recommend that DOACs (including dabigatran, rivaroxaban, apixaban and edoxaban) are now the preferred drug class over warfarin to reduce stroke risk in appropriate AFib patients, unless patients have moderate-to-severe mitral stenosis or a mechanical heart valve

Temporary Pacing and Pacemaker Therapy

- Temporary pacing includes transcutaneous and transvenous pacing, both of which are indicated as urgent or emergent therapy in patients with hemodynamically significant bradyarrhythmia
- Transcutaneous pacing can be performed urgently without input from cardiology, but should involve the Senior ON and nursing supervisors
    - Short-acting sedation (e.g. with dilaudid/Ativan) is indicated in non-ACLS setting (consider early involvement of Anesthesia)
    - Pace by turning defibrillator to “Pacer” mode; a good rule of thumb is to set the HR and output at a starting rate 100 bpm and 100 mA, respectively
- Transvenous pacing is a more durable option than transcutaneous pacing, and is often employed as a temporary bridge to recovery or to PPM placement
    - In contrast to placement of a temp wire for transvenous pacing must be performed in the cath lab

    - The pacing lead is inserted into the right ventricle via the right internal jugular, left subclavian, or femoral veins (less reliable and increased risk for dislodgement)
    - Temp wires may remain in place for up to 7-10 days but carry a risk of infection
    - Daily maintenance includes CXR, threshold testing, and ECG (all to assess for lead migration)
- Permanent pacing is indicated for irreversible symptomatic bradycardia, chronotropic incompetence, or unstable conduction disorders
- There are many different pacing modes, which are designated by a 1-5 letter code. In the chart below, "position" refers to letter position
    - As an example, in the 4-letter code DDDR, the D in position I implies that both chambers (the atria and the ventricles) can be paced, the D in position II indicates that both chambers (the atria and the ventricles) can be sensed, the D in position III indicates that the device can respond to sensing by either triggering activity or inhibiting itself, and the R in position IV indicates that the device allows for rate modulation

Position I (Chamber Paced)	O – none, A – atrium, V – ventricle, D – dual (A+V)
Position II (Chamber Sensed)	O, A, V, D (A +V)
Position III (Response to Sensing)	O, T – triggered, I – inhibited, D – dual (T+I)
Position IV (Rate Modulation)	O, R – rate modulation (response to activity)
Position V (Multisite Pacing)	O, A, V, D- dual (A+V) *see chart below

Implantable Cardioverter-Defibrillator Therapy

- Per AHA/ACC guidelines, ICDs are indicated for both primary and second prevention in patients on optimal medical therapy who have an estimated survival of at least 1 year (with good functional status)
- Class I indications for secondary prevention include:
    - Survivors of cardiac arrest due to VF or sustained VT without reversible causes (AVID)
- Class I indications for primary prevention (with trial references) include:
    - Ischemic cardiomyopathy and LVEF ≤ 30-40% at least 40 days post-MI (DINAMIT) or at least 3 months post-CABG (CABG-PATCH)
    - LVEF ≤ 30% and NYHA Class I, II, or III (MADIT-II)
    - LVEF ≤ 35% and NYHA Class II or III (SCD-HeFT)
    - LVEF ≤ 40% and inducible VF or sustained VT at EP study (MUSTT)
    - Non-ischemic cardiomyopathy with at least 3 months of documented: CHF, LVEF ≤ 35%, and NYHA Class II or III (SCD-HeFT)
    - Syncope of unknown origin and VT/VF induced at EP study
    - Spontaneous sustained VT (+/- hemodynamic instability) with structural heart disease
- Cardiac resynchronization therapy (CRT) devices have an RA, RV, and coronary sinus (epicardial pacing of LV) leads, allowing for optimization of A-V and V-V synchrony, which has been shown to improve stroke volume
    - Class I indications: CRT implantation is recommended for patients with chronic heart failure (NYHA function class II, and ambulatory IV) with LVEF ≤ 35% and

LBBB w/ QRS duration > 150 ms and should be considered in these patients if QRS duration is 120-150 ms
    - CRT devices may only provide BiV pacing (CRT-P) or may allow for BiV pacing plus defibrillation with ICD function (CRT-D)
- Wearable cardiac defibrillators (WCDs) are externally worn defibrillators, generally considered as interval therapy in patients awaiting ICD
    - The VEST Trail showed that among post-MI patients with EF ≤35%, WCDs did not reduce SCD and ventricular tachyarrythmias but did reduce the secondary endpoint of all-cause mortality up to 90 days

Procedures in EP and EP Studies

- Cardioversion (DCCV) and defibrillation are non-invasive interventions that can terminate tachyarrhythmias by delivering an electrical shock to the heart
- Emergent DCCV and defibrillation are generally indicated in cases of clinical instability. Planned DCCV may also be performed as an effective treatment for SVTs
- The delivered shock depolarizes all or most excitable cardiac tissue and induces a refractory period that terminates reentrant activity
- Cardioversion is performed by synchronizing the shock to a QRS complex (thus requires a rhythm in which the QRS complex is present) and restores sinus rhythm in 70–95% of patients. The procedure is as follows:
    6. Turn the mode selector to DEFIB (red area). Select the desired energy using the up and down arrow keys in the front panel. In general:
        a. Narrow, regular: 50 – 100 J (atrial flutter often converts with 50 J)
        b. Narrow, irregular: 120 – 200 J (atrial fibrillation typically requires 150 J)
        c. Wide, regular: 100 J
        d. Wide, irregular: 150 – 200 J (defibrillation dose)
    7. Press the Sync On/Off button
        a. Confirm that a Sync marker appears on the monitor above each detected R wave to indicate where discharge will occur
        b. If necessary, use the LEAD and SIZE buttons to establish settings that yield the best display
    8. Press the CHARGE button on the front panel
    9. Ensure all are clear from the bed then press and hold the illuminated SHOCK button on the front panel. The defibrillator will discharge with the next detected R wave
    10. If additional shocks are necessary, increase the energy level as needed
- Defibrillation is unsynchronized and delivers a random shock during the cardiac cycle. The procedure is as follows:
    5. Turn the mode selector to DEFIB (red area)
        a. The unit displays DEFIB 120J SEL on the monitor
        b. The default energy selections for adult patients are Shock 1: 120J, Shock 2: 150J, Shock 3: 200J. You can use energy select (UP and DOWN arrow keys) to change settings
    6. If the monitor shows a shockable rhythm, press the CHARGE button on the front panel. If patient is pulseless, continue CPR while charging
    7. Ensure all are clear from the bed then press and hold the illuminated SHOCK button on the front panel
    8. If patient is pulseless, resume CPR for 2 minutes before the next pulse and rhythm check
- An electrophysiology study (EPS) is an elective, invasive, intracardiac catheter-based intervention that measures specific intervals within the cardiac cycle. The

purpose is to better understand the etiology, clinical significance, and management of brady-and tachy-arrhythmias
    - Following a diagnostic EPS, a subset of patients will undergo mapping and ablation for treatment of their arrhythmia
- A common procedure in EP is Pulmonary Vein Isolation (PVI), performed with either radiofrequency (RFA) or cryoablation, which involves electrical isolation of the antral portion of the pulmonary veins, a region identified as containing >90% of the ectopic beats involved in the generation and maintenance of atrial fibrillation
- PVI is indicated in patients with symptomatic atrial fibrillation who have either failed pharmacologic therapies for rhythm control or cannot tolerate medication side effects
- Importantly, ablation does not negate the need for therapeutic anticoagulation

VALVULAR HEART DISEASE

See Page 266 for Quick Reference Guide

31. Aortic Stenosis (AS)

Etiology and Epidemiology

Aortic Stenosis (AS) is the most common cardiac valve abnormality in the United States. Incidence is only 0.2% in patients aged 50-59 years, but increases to 9.8% at age 80-89, given that the majority of cases are mostly due to calcification of the aortic valve. Notably, in patients requiring aortic valve replacement (AVR) that are <70 years old, 60% have a bicuspid valve, and in patients >70 years old, 40% of have a bicuspid valve. The incidence of bicuspid valve varies between 0.5–2% worldwide and many will need replacement at some point. Rheumatic heart disease is responsible for the majority of cases in the developing world. Radiation-induced valve disease causing AS is increasingly recognized in patients who received mediastinal radiation therapy.

Clinical risk factors for calcific AS mirror risk factors for CAD. In patients with AS without other CV risk factors, over 50% of them will die of a CV cause. AS is more common in men, the elderly, persons with dyslipidemia, CKD (in part related to metastatic calcification), and atherosclerosis as the disease derives in part from an active inflammatory process. Aortic sclerosis, or calcification of the valve with no hemodynamic effects, is increasingly common with age, though over 5 years, only 10-15% of these patients will develop AS.

Pathophysiology and Clinical Course

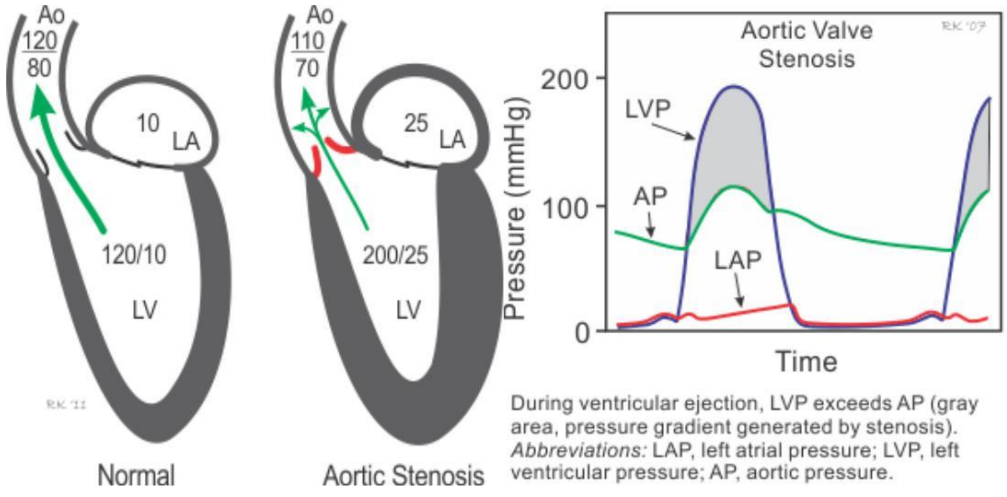


Figure 1. Aortic Stenosis. *CVPhysiology.com.*

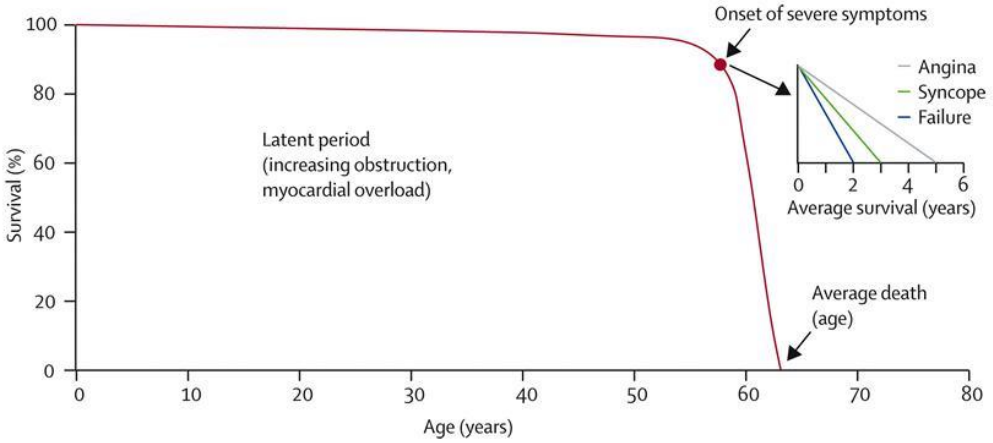


Figure 2. The natural history and rate of progression in aortic stenosis.[1]

Once symptoms develop, the average survival in patients with AS is significantly reduced: 5 years with angina, 3 years with syncope, and 1–2 years with heart failure. If the aortic valve is replaced, however, average survival returns to that of the general population.

- Angina: results from reduced coronary flow reserve and increased myocardial oxygen demand due to high afterload (does not necessarily require overt coronary artery disease). 35% of patients with AS present with angina.
- Syncope: exercise-induced decrease in total peripheral resistance is uncompensated because CO is restricted by stenotic valve. 15% present with syncope.
- Heart failure: systolic or diastolic dysfunction or both. 50% present with dyspnea.

Initial Clinical Evaluation

Physical exam findings: On physical exam, AS classically presents as a systolic ejection murmur at the R upper sternal border that radiates to the neck and occasionally a different quality of murmur which radiates to the apex (Gallavardin phenomenon). The murmur of AS decreases with maneuvers that decrease preload, such as standing and Valsalva. The severity of valvular disease may not correlate with the intensity of the murmur. Indicators of severe AS include a late-peaking murmur, delayed carotid upstroke (pulsus parvus et tardus), radiation to the left clavicle, and obliteration of the A2 component of S2. In general, TTE remains the diagnostic tool of choice for evaluation of AS. Cardiac catheterization may be indicated for hemodynamic assessment if clinical and echo data are inconclusive or to evaluate for CAD prior to aortic valve replacement.

Radiographic findings: The TTE exam in AS includes evaluation of valve anatomy and structure, valve gradients, and LV structure and function. Multiple views can show reduced leaflet excursion with a small aortic orifice. Short axis views “en-face” to the valve can demonstrate a bicuspid valve. Doppler echocardiography permits measurement of jet velocity and calculation of the LV-Aortic gradient, which are the standard parameters used for evaluation of stenosis severity.

The echocardiographic criteria for grading AS are shown in Table 1. The clinical progression of the disease is separated into stages A-D. Patients with bicuspid aortic valve or valvular sclerosis are termed Stage A, or “at risk.” Mild-to-moderate AS defines Stage B, or “progressive AS.”

Patients with Severe AS may be categorized as Stage C (asymptomatic) or Stage D (symptomatic). This becomes important with regard to indication for intervention (see below).

Table 1: 2014 ACC/AHA guidelines for grading of severity in aortic stenosis

	Valve area (cm^2)	Mean gradient (mmHg)	Jet velocity (m/s)
Mild	> 1.5	< 25	< 3.0
Moderate	1.0–1.5	25–40	3.0–4.0
Severe	< 1.0	> 40	> 4.0
Very Severe		> 60	> 5.0

Follow Up Evaluation and Surveillance

Guidelines are based upon the fact that only severe AS can cause symptoms. In general, there are minimal hemodynamic effects as the aortic valve area is reduced from normal (3–4 cm2) to 1.5–2 cm2. Additional reduction in valve area from half its normal size to one quarter (< 1 cm2) gradually leads to outflow obstruction, increased afterload and concentric LV hypertrophy, which is initially adaptive but becomes maladaptive with time. Following diagnosis, the aortic valve area generally decreases by 0.1 cm2 per year, though this rate can vary significantly from patient to patient and is often accelerated in the presence of CKD. Notably, valve area > 1 cm2 may be associated with symptoms if there is concomitant aortic insufficiency or atrial fibrillation, where there is loss of atrial kick.

Aortic stenosis results in a mechanical obstruction to flow and AVR is the only definitive treatment that has been shown to alleviate symptoms and reduce mortality. Patients with symptomatic severe AS require prompt AVR. Because of the risk of sudden death, AVR should be performed promptly after the onset of symptoms. Echo and stress testing may identify asymptomatic patients who are likely to benefit from AVR (though stress testing is contraindicated in patients with severe *symptomatic* AS). Balloon valvuloplasty may be a helpful bridge to AVR (LOR Class IIb, LOE C).

Patients with discordance between AV area and gradients (particularly those with a low AV area but less severe gradients than expected) are a particularly high-risk group (so termed “low-flow, low-gradient” AS); the low gradients may not be reassuring if they are due to poor myocardial function. Conversely, a normal valve may appear to have a low area if the ejection fraction and the flow across it are low (so termed “pseudo-severe” AS). In patients with low flow, low gradient AS, a dobutamine stress echo (DSE) or cardiac catheterization is a Class II indication in order to determine whether the severity of aortic stenosis is due to true valvular disease or other causes of low ejection fraction. Amongst patients with true low-flow, low-gradient AS, the mean AV gradient should increase to >40mmHg when the heart fuction is augmented with dobutamine. Alternatively, amongst patients with pseudo-severe AS, the increased cardiac output may “stent” open the valve, and increase calculated aortic valve area, while the mean AV gradient does not change or may even be reduced.

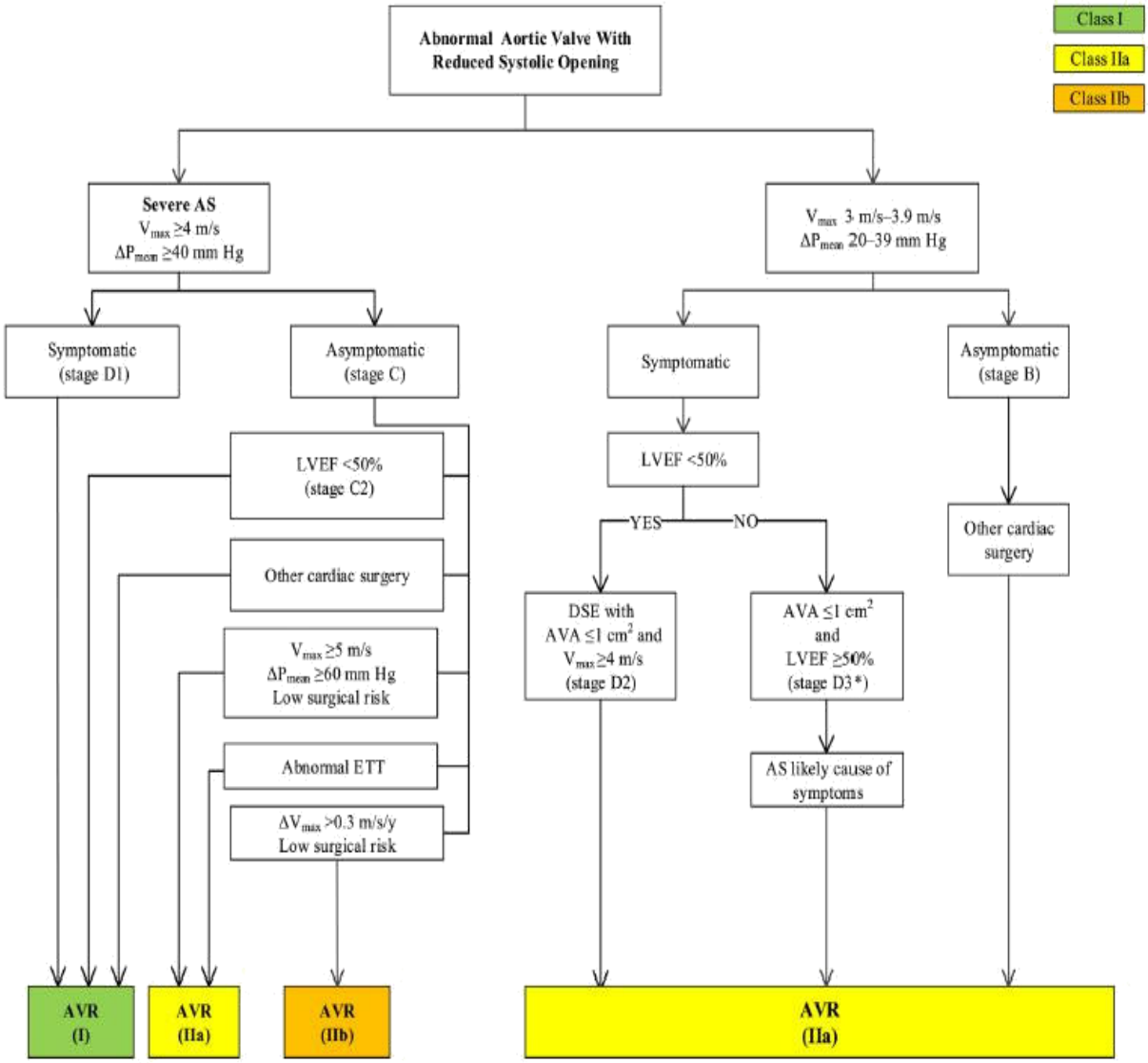
Medical Management

Volume status can be difficult to optimize in hospitalized patients with severe aortic stenosis. Adequate preload is necessary to ensure sufficient cardiac output in the face of a stenotic aortic valve. Nitrates and diuretics should be used with caution to avoid decreasing preload too quickly. Too high of an afterload can further potentiate high wall tension and diastolic dysfunction, resulting in flash pulmonary edema. Initial management of hypotension in patients with severe AS may require small fluid boluses (250cc) with careful monitoring of respiratory status. Patients with severe stenosis may easily “tip over” with volume overload and can rapidly experience pulmonary edema. See below for bullets on need-to-know for management of AS patients overnight.

As above, only AVR has been shown to improve symptoms and mortality in AS patients. Guidelines for longitudinal medical management involve treatment of hypertension in patients at risk of developing AS (stage A) or with asymptomatic AS (stages B and C). Statin therapy has not been shown to reduce progression of AS and therefore is not indicated.

Valvular Intervention

The risks of surgical AVR depend on patient age and comorbidities. Use of a multidisciplinary heart valve team is necessary in order to appropriately identify patients for AVR and whether this should be surgical or transcatheter AVR. Use of the Society of Thoracic Surgeons (STS) risk calculator is helpful in deciding between surgical vs. transcatheter approach. An STS score <4% qualifies as low risk. This risk calculator uses many variables including age, sex, race, symptoms, and comorbidities. Main risk factors that are not included in STS risk score are frailty, pulmonary hypertension, liver disease, and porcelain aorta. Presence of any of these could deem the patient high risk for surgery.



Percutaneous/transcatheter AV replacement (TAVR) is an alternative to surgical AVR (SAVR) for patients with symptomatic AS who are not operative candidates, or who are at intermediate or high risk for surgical AVR. Determining which patients should undergo SAVR vs. TAVR is a complicated decision and the data is accumulating that patients at less surgical risk may benefit from TAVR. 2017 AHA/ACC updated Valvular guidelines recommend TAVR for any patient at either prohibitive, high, or intermediate surgical risk and SAVR for patients at lo-risk. However, given recently published data regarding the efficacy and safety of TAVR vs SAVR in low-risk patients, these recommendations are expected to be revised soon.

- High-risk patients: In the PARTNER trial, patients who were not suitable candidates for surgery and underwent TAVR had reduced rates of death and hospitalization with a decrease in symptoms and improvement in valve hemodynamics at 2 years compared to medical therapy.[2] Another trial assessing patients from the PARTNER trial who were high risk but who were suitable for surgery (mean STS score 11%) showed that TAVR was associated with similar rates of mortality, reduction in symptoms, and improved valve hemodynamics compared to surgical AVR at 2 years. TAVR was also associated

with more frequent paravalvular regurgitation, increased late mortality, and more vascular complications and major bleeding.[3] A study showed improved mortality with the CoreValve in high risk surgical candidates compared to valve replacement surgery (14% vs 19%) and another non-randomized, prospective study using the CoreValve showed safety and decreased risk of a combination of mortality and stroke in patients with extreme surgical risk compared to historical outcomes in this patient population (26% vs 43%).[4,5]

- Intermediate and low-risk patients: A recent systematic review and meta-analysis of comparing TAVR with SAVR for patients with low and intermediate surgical risk found that TAVR was associated with reduced mortality and reduced risk of stroke, bleeding, atrial fibrillation, and acute kidney injury, but increased need for aortic valve reintervention, permanent pacemaker insertion, and symptoms of heart failure. This meta-analysis included results from four randomized clinical trials, the largest being the PARTNER 2A trial, which found that among patients with symptomatic severe AS who are intermediate-risk surgical candidates (expected peri-procedural mortality 4-8%), TAVR was non-inferior to SAVR for the primary outcome of all-cause mortality or disabling stroke at 2 years.[6] Hence, the option of TAVR is considered with intermediate risk patients. The PARTNER 3 trial studied the use of TAVR among patients who are low-risk. The primary outcome—all-cause mortality, stroke or rehospitalization (related to the procedure, valve, or heart failure) at 1 year—occurred in 8.5% of the TAVR group compared with 15.1% of the SAVR Group ($p < 0.001$ for non-inferiority, $p = 0.001$ for superiority). This landmark trial will extend the use of TAVR in treatment of aortic stenosis.

Transcatheter Aortic Valve Replacement Basics:

- There are 3 valve types that are currently FDA approved
  - Edwards Sapien – balloon expandable
  - Medtronic CoreValve – self expanding
  - Lotus Edge Valve- mechanically expandable (rarely used, recently approved)
- Steps of Procedure for Percutaneous Route (most commonly transfemoral)
  - Femoral artery access obtained using a 14F sheath or greater
  - Transvenous access obtained and RV pacing wire placed
  - Cross the aortic valve with a guide wire and balloon dilation performed
  - With prosthetic valve in place (with fluoro +TEE or TTE guidance), rapid ventricular pacing (>180bpm) is used to decrease stroke volume and allow valve to be deployed.
  - Should immediately see reduction in transvalvular gradient
- Periprocedural considerations
  - Access:
    - these are large bore sheaths and access sites and distal pulses (often with PVRs) require frequent monitoring.
    - In addition, these patients are heparinized during the procedure and then on DAPT so at high risk for bleeding. Vascular complications include retroperitoneal hemorrhage, femoral or iliac artery dissection, and development of femoral pseudoaneurysm. The major bleeding rates have decreased over the years with newer generation valves and better profile catheters (~4% in the TVT registry)
    - Hypotension, and suprainguinal or severe back pain after a TAVR should trigger rapid workup for possible retroperitoneal hemorrhage. Ask the

interventional attending or fellow specifically about management of the access site post procedure.

- Hemodynamics:
  - Patients will often be hypertensive given sudden reduction in obstruction that the heart is pumping against, and this can often be controlled with IV pushes of vasodilators (i.e. hydralazine) PRN, though occasionally will require drips
  - Occasionally patients will be hypotensive, which can be due to decreased preload. Left ventricular hypertrophy and diastolic heart disease means patients are usually volume responsive, so gentle fluid resuscitation should be attempted. Target a mean arterial pressure of 60-80.
- Rhythm:
  - High degree AV block is a known complication, occurs more often in patients who have baseline conduction abnormalities (particularly RBBB) and those who are receiving self-expanding valves. In those cases, temporary pacing wires are left in place. Patients can develop bundle brach blocks or AV block during or after the procedure.

Antithrombotic Management: Incidence of transcatheter heart valve (THV) thrombosis following TAVR is 7%, with larger valve size predisposing to higher rates of thrombosis.[7] The risk of stroke or TIA is greatest in the first 24 hours postoperatively and neurologic events peak in the first week.[8] Guidelines for anticoagulation after AVR (institutional preferences may vary, check with structural team, surgeon and/or fellow/attending):

- Surgical AVRs
  - Bioprosthetic AVR:
    - ASA 81 mg, 3-6 month of Coumadin for INR 2–3 after surgery. (Consider lifetime if Afib, EF<30–35%, prior clot, hypercoagulable)
    - Stop Coumadin 48–72 hours before procedure, restart 24hours afterwards
  - Mechanical AVR:
    - ASA 81 mg, INR 2–3 for life; if other risks factors (EF < 30%, AFib, prior clot, procoagulable disorder, Starr-Edwards Valve), INR goal 2.5–3.5.
    - IV heparin when INR < 2
  - If reversal of anticoagulation is urgent, FFP can be used (Class II), and is preferred over Vitamin K since it is thought to reduce the incidence of thrombotic complications (data is limited)
- Transcatheter AVRs
  - DAPT (ASA 81 mg and P2Y12 inhibitor) initially (6 months)), then ASA 81 mg thereafter. A retrospective analysis found a high incidence of subclinical leaflet thrombosis, which was improved with warfarin,[9] suggesting that DAPT may not be sufficient, but more data is needed.
  - If patient has a recent PCI, regimen is often Plavix and coumadin/ DOAC. If there is no recent PCI, then aspirin and coumadin/ DOAC are used for at least 6 months. Thereafter, single agent can be used based on the patient's age and other indications.

Cognitive Changes Post-TAVR: An emerging field of study focuses on assessing the cognitive impact of TAVR procedures. While TAVR can predispose patients to clinically significant stroke (~4%), and subsequent dementia, recent data have shown that TAVR is associated with global improvement in cognitive status at 1 year post-procedure, especially among those with cognitive impairment prior to TAVR.[10] However, TAVR may also contribute to a transient, early decline in

cognition manifesting as subcortical ischemic vascular dementia, as 25% of TAVR patients in the aforementioned study demonstrated early deterioration in at least one test assessing executive function, processing speed, or abstract reasoning. Additionally, approximately 75% of patients have evidence of new ischemic brain lesions on diffusion-weighted MRI post-TAVR,[11] although most of these are subclinical events. Predictors of TAVR patients at high risk for peri-procedural stroke include: female sex, chronic kidney disease, and new-onset atrial fibrillation. This has led to increased focus on implementing neuroprotective strategies, such as embolic protection devices during the procedure. Further larger-scale studies are needed to evaluate the cognitive trajectory of post-TAVR patients and identify which high-risk patients could most benefit from these neuroprotective interventions.

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32. Aortic Regurgitation (AR)

Acute and chronic AR have different etiologies, pathophysiological consequences, natural histories, and management strategies. In this chapter, we will review the pathophysiology and approach to managing each of these variations of AR in parallel.

Etiology and Epidemiology

Acute AR: Acute AR may result from abnormalities of the valve, such as infective endocarditis, or cusp prolapse, or acute abnormalities of the aorta, primarily aortic dissection. Acute AR may also occur among patients with mechanical or bioprosthesis if there is prosthetic leaflet dysfunction.

Chronic AR: The most common causes of chronic AR in the United States and other developed countries are bicuspid aortic valve, thoracic aneurysms and calcific valve disease. Rheumatic heart disease is the leading cause in many developing countries. AR also arises from primary diseases causing dilation of the ascending aorta or sinuses of Valsalva (e.g. genetic syndromes such as Marfan's Syndrome, systemic rheumatic disorders such as ankylosing spondylitis, and infectious aortitis).
Of note, the 2018 AHA/ACC Adult Congenital Cardiology guidelines provide a Class IIa recommendation to screen first-degree relatives of individuals with bicuspid aortic valve for valvular disease (present in 10% of relatives) and aortopathy (present in 32% of relatives).[1]

Pathophysiology and Clinical Course

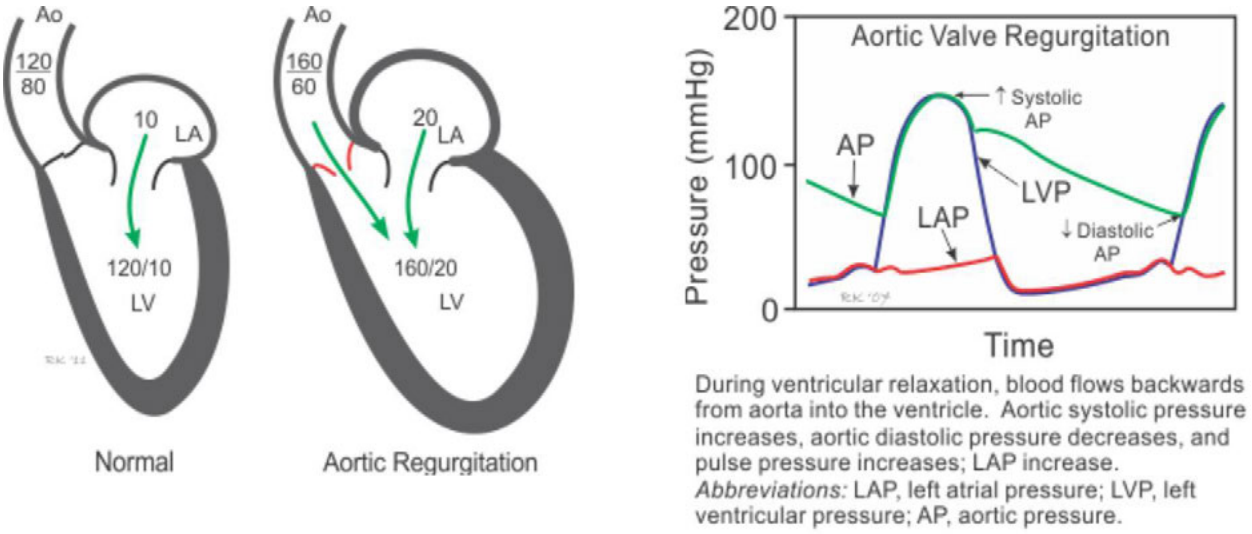

Figure 1. Aortic Regurgitation. *CVPhysiology.com.*

AR occurs when the aortic valve does not close (or coapt) completely and blood flows back into the LV from the aorta during diastole. As shown in **Figure 1**, this results in a rapid descent of aortic diastolic pressure (AP tracing). Backflow from Aorta to LV → Increase in LVEDV → increased LV preload → increased SV and SBP. Increased SBP and decreased DBP as described above result in characteristic wide pulse pressure.

Acute AR: In the uncompensated heart with acute AR, an increase in LVEDV (without acute LV enlargement) results in a large increase in left-sided pressures, which leads to congestive heart failure and pulmonary edema. Marked and rapid volume overload pushes the LV to the edge of its Frank-Starling curve. The LV cannot acutely increase total stroke volume, resulting in a decline in forward stroke volume and cardiac output.

Acute AR may be an **emergency**; if a patient is symptomatic from acute AR, surgical consultation should be pursued.

Chronic AR: Chronic AR typically leads to progressive LV and LA dilation. The added volume produces an increased wall tension and, over time, spherical remodeling and eccentric ventricular hypertrophy. Ventricular compliance increases to accommodate high volumes. The combination of ventricular hypertrophy and increased preload raises the stroke volume, and cardiac output is initially maintained. In this way, patients with moderate-severe AR may remain asymptomatic for years.

Over time, however, the LV continues to dilate and the hypertrophy is unable to keep pace, which eventually leads to a decline in both LV contractility and ejection fraction (EF). Interstitial fibrosis increases, compliance declines, and LVEDP rises, and symptoms of congestion ensue. Bradycardia is poorly tolerated because slow HRs increase diastolic filling (and regurgitant volume) time, which reduces effective forward stroke volume.

Initial Clinical Evaluation

Physical exam findings: The physical exam in AR may reveal the characteristic early decrescendo diastolic murmur at the LUSB or RUSB. This murmur typically **increases** with sitting forward, expiration, or handgrip (increase in afterload). The murmur is louder with more severe AR, except if AR is acute or in its late-stage when LV filling pressure rises and aortic pressure drops. The Austin Flint murmur, a diastolic rumble at the apex, may also be audible if the AR jet is directed posteriorly and interferes with mitral inflow. An S3 is common and can be heard in patients with AR and a preserved EF (due to LV dilation that is part of the normal pathophysiologic response to AR). Pulses may be bounding, and the pulse pressure is widened. These and dozens of other eponymous signs become increasingly prominent as the AR becomes more severe.

Radiographic evaluation: TTE is indicated in patients with signs or symptoms of AR for accurate diagnosis of the cause of regurgitation; assessment of regurgitant severity, LV size and LV systolic function; and for determining timing of valve intervention. See **Table 1** below for echocardiographic/clinical grading criteria.

AR is quantified by measuring the jet width in the LVOT and vena contracta (the narrowest width of the regurgitant jet before the LVOT) on Doppler as well as the regurgitant orifice size and regurgitant volume. With severe AR, Doppler shows steep deceleration in the jet velocity due to equalization of aortic and LV pressure, as well as prolonged diastolic flow reversal in the aorta (approaching holodiastolic duration in cases of severe AR).

Measurement of LV systolic and diastolic diameters, EF, and aortic width on TTE are also important as these are key parameters that influence decision for surgical intervention. Depressed ejection fraction and increased LVESV are associated with development of HF symptoms or death in asymptomatic patients. Cardiac MRI, which provides more accurate

measures of regurgitant volume/fraction, and LV volume and function, can be useful in circumstances where echocardiographic images are suboptimal.
Note: In cases of acute AR when aortic dissection is suspected, the sensitivity and specificity of TTE for dissection is only around 60 to 80%. In these instances, TEE or CTA should be employed, as the sensitivities and specificities for diagnosing aortic dissection exceed 95% for these modalities.

Table 1: 2014 ACC/AHA Guidelines for Staging Chronic AR[3]

	Progressive (stage B)	**Asymptomatic Severe (Stage C)**	**Symptomatic Severe (Stage D)**
Hemodynamics			
Jet width (% of LVOT)	Mild: <25% Moderate: 25-64%	Severe: ≥64%	Severe: ≥64%
Vena contracta (cm)	Mild: <0.3 cm Moderate: 0.3-0.6 cm	Severe: >0.6 cm	Severe: >0.6 cm
Regurgitant volume (ml/beat)	Mild: <30 ml Moderate: 30-59 ml	Severe: ≥60 ml	Severe: ≥60 ml
Regurgitant fraction (%)	Mild: <30% Moderate: 30-49%	Severe: ≥50%	Severe: ≥50%
Effective regurgitant orifice (cm^2)	Mild: <0.10 cm^2 Moderate: 0.10-0.29 cm^2	Severe: ≥0.3 cm^2	Severe: ≥0.3 cm^2
Diastolic aortic flow reversal	Sub-holosystolic	Holosystolic	Holosystolic
LV size/function	Normal LV volume or mild dilation. Normal LV systolic function	C1: LVEF ≥50%, mild-moderate LV dilation. C2: LVEF <50% or severe LV dilation (LVESD>50mm)	Moderate-to-severe LV dilation is present. Can occur with normal LVEF (≥50%), mild-moderate dysfunction (40-50%) or severe LV dysfunction (<40)

*****Note: **Stage A** refers to “at-risk” patients, such as patients with bicuspid aortic valve, diseases of the aortic sinus or ascending aorta, history of rheumatic fever, or infective endocarditis.

Follow up Evaluation and Surveillance

Repeat TTE should be performed to re-evaluate asymptomatic patients with AR, with recommended frequency determined by the severity of regurgitation (Severe: every 6-12 months, Moderate: every 1-2 years, Mild: every 3-5 years).

Medical Management

Acute or decompensated AR: The management of acute severe AR (most often resulting from infectious endocarditis or aortic dissection) consists of hemodynamic temporization and urgent surgical evaluation. Propensity-matched cohort studies among patients with infective endocarditis have demonstrated a 6% absolute risk reduction with early versus delayed surgery.[2]

Medical therapy:

- IV afterload reduction with agents like nitroprusside. Avoid vasoconstrictors which may increase diastolic regurgitant flow
- Inotropic support with dobutamine/milrinone as needed
- Chronotropic support with overdrive pacing or isoproterenol to reduce diastolic regurgitation time as needed. Use caution with beta blockade (often utilized in management of acute aortic dissection).
- Diuretics as needed to reduce LV filling pressures
- Consider PA line placement for guidance of above therapies
- Intra-aortic balloon pumps are **contraindicated** in severe AR: inflate during diastole → increase diastolic regurgitant flow dramatically

Chronic compensated AR: Medical therapy has a limited role in chronic AR. Guidelines recommend the use of ACE inhibitors/ARBs in patients with severe AR who have symptoms and/or LV dysfunction and are not candidates for surgical intervention. RCTs have not shown conclusively that these drugs alter the natural history of asymptomatic patients with chronic asymptomatic AR and normal LV systolic function, but cohort studies support their use in patients with systolic impairment.

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Valvular intervention

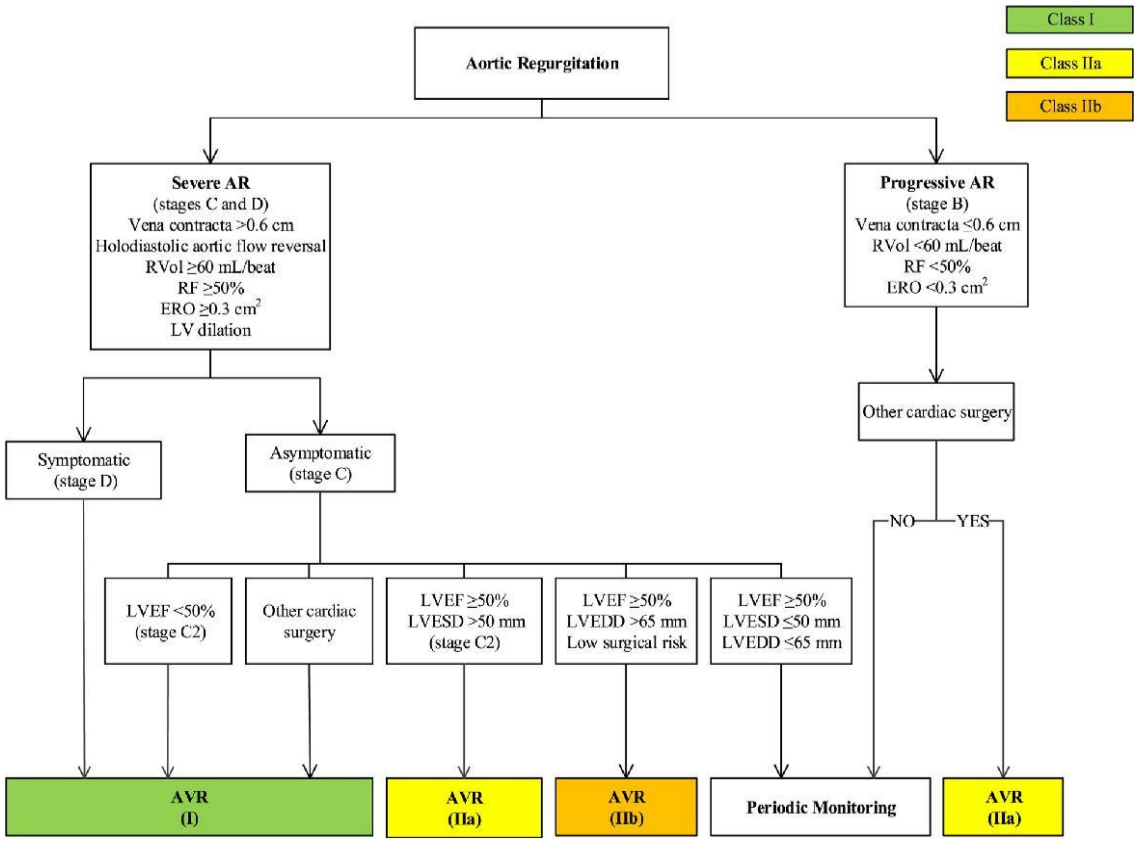

Figure 2. Timing of Valvular Intervention. *2014 ACC/AHA Guidelines 2014.*

Additional Notes:

- Once AR has been diagnosed, follow up evaluations should focus on the identification of symptoms. Symptomatic AR is an indication for surgical intervention, and intervening as early as possible—before LV systolic failure ensues or worsens—is paramount. Without AVR, these patients have a very high mortality rate (25% for NYHA class III/IV, 6% for NYHA Class II), and post-operative survival is significantly higher in patients who are still NYHA I/II at time of surgery compared with NYHA class III/IV (10 year survival of 80% vs 45%).[4]
- Even in symptomatic patients with severely depressed systolic function, surgery is recommended over medical therapy. The sooner AVR is performed after depressed EF is noted, the more systolic recovery occurs.

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33. Mitral Regurgitation (MR)

Etiology and Epidemiology

MR is first delineated into acute and chronic disease. Chronic MR is further delineated into two categories given significant divergence in their management: (1) primary (degenerative) and (2) secondary (functional).

Chronic primary MR is due to pathology of one or more of the components of the valve causing valvular incompetence. The most common cause of primary MR in the developed world is mitral valve prolapse (MVP). MVP in younger patients is often due to myxomatous degeneration, whereas in older patients it is due to fibroelastic degeneration of the valve. Additional etiologies of primary MR include endocarditis, rheumatic heart disease, and collagen vascular disease.

In chronic secondary MR, the valvular apparatus itself is typically normal but severe LV dysfunction is present leading to an abnormal, dilated ventricle which causes papillary muscle displacement. This leads to leaflet tethering with associated annular dilation, which prevents leaflet coaptation. The common causes of severe LV dysfunction leading to secondary MR include CAD, myocardial infarction, or idiopathic myocardial disease.

As the incidence of rheumatic heart disease has declined in the developed world, MVP and ischemic heart disease have become the most common etiologies of chronic MR.

Pathophysiology and Clinical Course

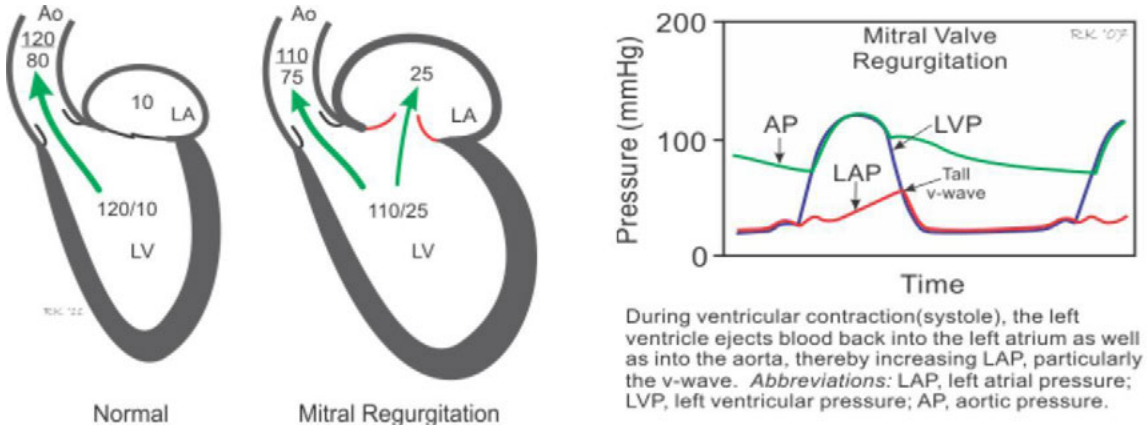

Figure 1. Mitral regurgitation. *CVphysiology.com.*

Acute Mitral Regurgitation: Acute MR can result from a flail leaflet secondary to rupture of the chordae**.** This can occur secondary to MVP, endocarditis, or rheumatic heart disease; as well as from papillary muscle dysfunction/rupture or ventricular dilation during acute coronary ischemia. In these situations, the LV does not have time to compensate for the sudden volume overload. This results in pulmonary edema, reduced stroke volume and cardiac output, and cardiogenic shock.

Chronic Primary Mitral Regurgitation: Chronic mitral regurgitation causes an increase in the LA volume and pressure (as the normal LA is not very compliant), leading to increased pressures in the pulmonary circulation as well as increased LVEDV, progressively enlarging the LV.

Enlargement of the LA can additionally lead to atrial fibrillation. As LV size increases, the mitral annulus and therefore the regurgitant orifice both enlarge, which worsens the degree of MR. LV mass subsequently increases in a pattern of volume overload (eccentric hypertrophy with compensatory dilation). Although this response initially maintains cardiac output, myocardial decompensation eventually results in symptoms of left-sided (and eventually right-sided) heart failure and an increased risk of sudden death.

In those who are symptomatic, exertional dyspnea, fatigue, and atrial fibrillation are the most common manifestations. Severe MR results in poor clinical outcomes (survival rates 33% at 8 years without MVR, mortality 5% per year). Most deaths are due to heart failure. There is a substantial rate of sudden death, highlighting the importance of ventricular arrhythmias.

Initial Clinical Evaluation

Physical exam findings: On auscultation, an apical holosystolic murmur that radiates to the axilla is most often heard, which can sometimes be decreased with maneuvers such as Valsalva that decrease venous return. Occasionally in acute MR, an early diastolic rumble or left-sided S4 can be heard. If severe, MR can result in a soft S1 and widely split S2 (due to pulmonary hypertension). A left-sided S3 suggests severe disease and does not necessarily mean CHF, as an S3 is heard when a large volume of blood stored in the LA during diastole rapidly fills the LV. The murmur of MR may be silent in the presence of a low systolic LA-LV pressure gradient (i.e. elevated LA pressure and relatively low systemic arterial pressures). Arterial pulse palpation reveals a sharp and high volume carotid upstroke in severe MR (whereas they are delayed in AS). Cardiac impulse is brisk and hyperdynamic, laterally displaced, and a prominent LV filling wave (S3) is frequently palpable.

Radiographic evaluation: EKG and CXR demonstrate a large LA, LV, or both. CXR may additionally demonstrate pulmonary edema, occasionally unilateral (often RUL due to a posteriorly directed regurgitant jet). The diagnosis is usually made with echocardiogram, though large V waves on right heart catheterization (visible on the wedge tracing, **Figure 1**) are also suggestive. Most important on echo is LV size and systolic function. EF in combination with end-systolic dimension provides a clinically useful measure of ventricular performance. TEE allows accurate assessment of the valve and should be performed before surgical intervention if the mechanism of MR and the feasibility of a repair are not delineated on the TTE; however, the degree of MR is sometimes reduced after sedation (which may vasodilate and thus reduce afterload).

ACC/AHA guidelines support the use of TTE for initial evaluation (EF, LV and LA sizes, and PA pressure) and then every 6–12 months for patients with asymptomatic severe MR for evaluation of EF.

The criteria for grading MR are shown in Table 1. The clinical progression of the disease is separated into stages A-D. Patients with Mild MR are **Stage A** or “at risk.” Moderate MR defines **Stage B** or “progressive MR.” Patients with Severe MR may be categorized as **Stage C** (asymptomatic) or **Stage D** (symptomatic). This staging becomes important with regard to indication for intervention (see below).

Table 1: 2014 ACC/AHA guidelines for grading severity in mitral regurgitation

	Mild	Moderate	Severe
Angiographic grade			
Color Doppler jet area	Small, central jet (<4 cm^2 or <20% LA area)	Signs of MR greater than mild present but no criteria for severe MR	Vena contracta width > 0.7 cm with large central MR jet (area > 40% of LA area) or with a wall-impinging jet of any size, swirling in LA
Doppler vena contracta width (cm)	< 0.3	0.3–0.69	≥ 0.70
Quantitative (cath or echo)			
Regurgitant volume (mL per beat)	< 30	30–59	≥ 60
Regurgitant fraction (%)	< 30	30–49	≥ 50
Regurgitant orifice area (cm^2)	< 0.20	0.20–0.39	≥ 0.40
Additional essential criteria			
LA/LV size			Enlarged

Medical Management

Acute MR: Management focuses primarily on afterload reduction and contractility augmentation as needed to support forward flow and maintain cardiac output. This may require the use of vasodilators such as sodium nitroprusside (SNP) for afterload reduction, inotropes such as dobutamine, and/or an intra-aortic balloon pump (IABP) for afterload reduction, pulmonary edema, and hypotension. These patients typically require urgent surgical repair and have a worse prognosis compared to those with chronic MR. It is worth noting that in patients with acute ischemic MR, early revascularization may arrest local maladaptive LV modeling, restore valve competence, and obviate the need for surgical repair.

Chronic primary MR: Among patients with severe symptomatic MR, mortality is as high as 8% per year, and the mainstay of therapy is surgery. Mitral valve repair is preferred over replacement if valve morphology is amenable, as valve repair is associated with superior post-operative survival and ventricular function. Involvement of the anterior leaflet (or both leaflets) may preclude repair and require replacement. Repair further eliminates the risks and pitfalls associated with prosthetic valves, including prosthesis degeneration. Around half of patients with bioprosthetic MVR will need another replacement within 15 years.

Medical therapy (i.e. goal-directed medical therapy for HF) for systolic dysfunction should be implemented for all patients with severe symptomatic MR and a depressed LVEF. For those who are symptomatic despite GDMT and have prohibitive surgical risk, transcatheter mitral valve repair with MitraClip can be considered

Chronic secondary MR: In contrast to primary MR, the utility of surgical intervention in chronic secondary MR is generally low due to the pathophysiology of this disease. Instead, the mainstay of therapy for patients with HFrEF is goal-directed medical therapy (ACE-I, ARBs, beta-blockers, aldosterone antagonists, cardiac resynchronization therapy, etc). Per the 2017

guidelines update on valvular heart disease, there are no Class I indications for MV surgery for chronic secondary MR, but Class II recommendations exist for patients with severe symptoms despite optimal medical therapy, as well as for patients undergoing CABG or AVR. Cardiac resynchronization therapy (CRT) can also be helpful in reducing the severity of functional MR if otherwise clinically indicated.[1]

Guidelines for anticoagulation after MVR (institutional preferences may vary, check with fellow/attending):

- Bioprosthetic MVR: 81 mg ASA, 3 month of Coumadin for INR 2–3 after surgery (lifetime if rheumatic MR or if EF<30–35, hypercoag, hx clot, AFib)
- Mechanical MVR: 81 mg ASA, INR 2.5–3.5 for life with IV heparin when INR <2.5

If reversal of anticoagulation is urgently needed, FFP can be used (Class II) and is preferred over Vitamin K since it is thought to reduce the incidence of thrombotic complications (though no good data).

Valvular Interventions

A percutaneous mitral valve repair system (MitraClip®) was approved by the FDA in 2013 for use in patients with symptomatic degenerative severe MR who are considered too high-risk for surgery. The device clips together the mitral valve leaflets at the site of the regurgitant jet, creating a double orifice. The EVEREST II trial included predominantly patients with primary chronic MR as well as a small subset of patients with secondary MR, demonstrated decreased efficacy in decreasing the MR severity of percutaneous vs. surgical repair but showed a superior safety profile and similar outcomes in symptoms and QoL.[2]

Most recently, the COAPT trial tested the efficacy and safety of the procedure in high-risk patients. Patients who had chronic obstructive pulmonary disease on continuous home oxygen therapy, severely dilated LV (LV end diastolic dimension > 70mm), hemodynamic instability, significant pulmonary hypertension (defined as estimated PASP > 70mmHg), or right ventricular systolic dysfunction were excluded. Transcutaneous mitral valve repair significantly reduced mortality and hospitalization for heart failure compared with maximal medical therapy at two years (29.1% vs 46.1% p<0.001 for mortality; 35.8 % vs 67.9% per patient-year, p< 0.001 for heart failure rehospitalization). Based on these surprising results, TMVR with MitraClip was approved in the U.S for treatment of secondary MR in severely symptomatic patients.[3]

Interestingly, MITRA-FR trial based in Europe (n~300 in ITT with only ~110 ultimately undergoing Mitra-Clip placement) which included “sicker” patients with worse LVEF and more dilated LV did not show a difference in primary outcome of death or unexpected heart failure hospitalizations.[4] The difference between these two trials highlight the importance of patient selection for optimal outcomes.

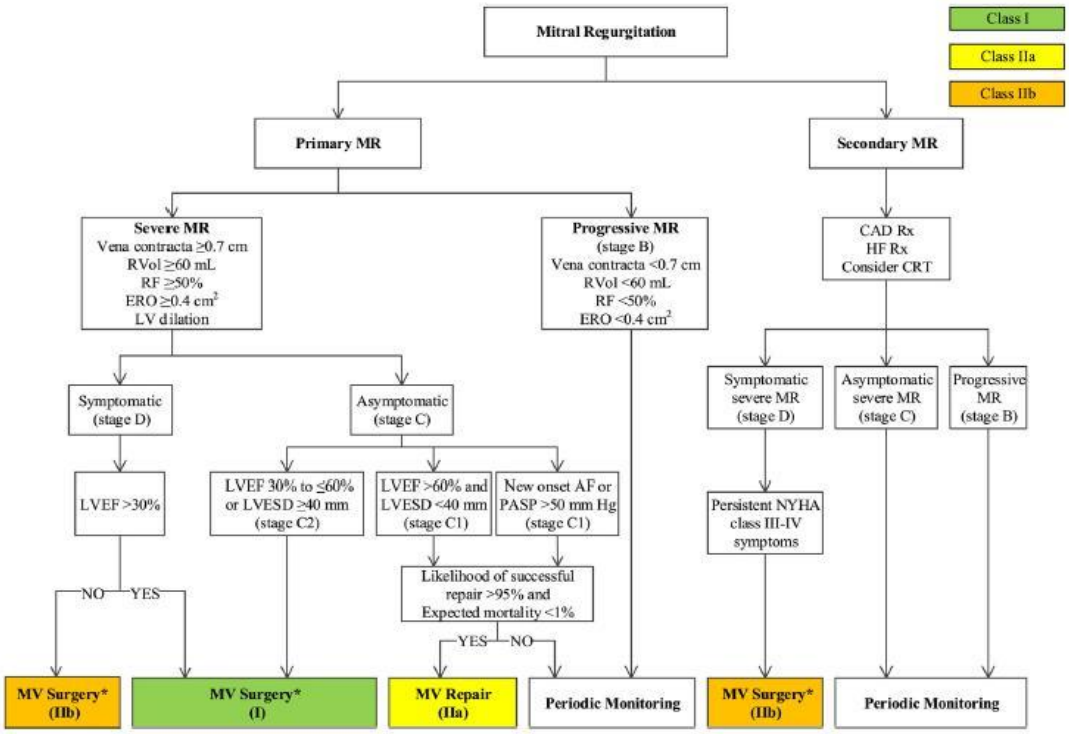

Figure 2. Indications for Intervention for Primary MR. *ACC/AHA 2014*[5]

References:

1. van Bommel RJ et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. Circulation. 2011;124(8):912-9.
2. Feldman T el a. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011;364(15): 1395-406
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4. Obadia JF et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379(24):2297-2306
5. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2014 Jun 10;63(22):2438

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34. Mitral Stenosis (MS)

Etiology and Epidemiology

The predominant cause of MS is rheumatic fever; at the time of mitral valve replacement, rheumatic changes are present in 99% of stenotic mitral valves. Rheumatic MS is a slowly progressive disease, resulting in thickening of the leaflet edges, fusion of the commissures, and chordal shortening and fusion. There is typically a prolonged latent phase between the initial rheumatic illness and the development of valve stenosis. This latent phase lasts decades in the developed world (mean interval between rheumatic fever and symptoms of ~16 years) but is considerably shorter in the developing world, likely due to recurrent carditis.

Senile calcific MS is found with increasing frequency in the elderly population in the Western world. Benign calcification of the mitral annulus extends into the leaflets, causing narrowing of the annulus and rigidity of the leaflets without commissural fusion. Radiation-induced valve disease causing calcific MS is another entity that is recognized in survivors of Hodgkin's lymphoma.

Other rare causes of mitral stenosis include congenital MS (e.g. parachute mitral valve, supramitral ring), often as part of the Shone's complex (multiple congenital left heart obstructions).

Pathophysiology and Clinical Course

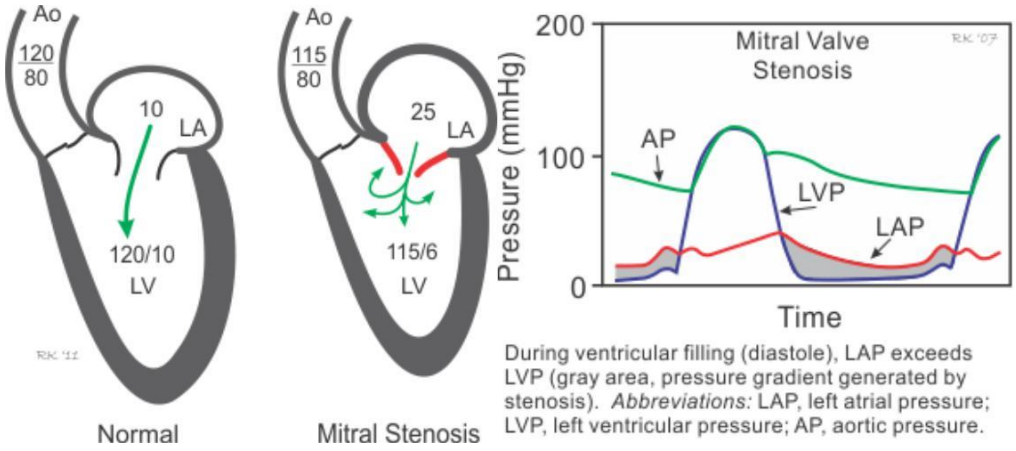

Figure 1. Mitral Stenosis. *CVPhysiology.com.*

MS causes obstruction of inflow from the LA to the LV. As a result, there is increased pressure within the LA with transmission of pressure to the pulmonary vasculature and secondarily to the right heart.LV pressure is unaffected.

While suspicion for MS may arise from clinical history (childhood rheumatic fever) or characteristic cardiac exam findings, most diagnoses are made echocardiographically in patients presenting with nonspecific complaints of exertional dyspnea, atrial fibrillation (often poorly tolerated due to loss of atrial kick and/or rapid heart rates), unexplained cardioembolism (not infrequent), or hemoptysis due to increased pulmonary vascular congestion and pulmonary hypertension. Very rarely, patients can also present with hoarseness due to LA enlargement and compression of the recurrent laryngeal nerve (Ortner's syndrome). If untreated, death from

MS is most commonly due to progressive pulmonary edema with resultant pulmonary hypertension and right heart failure (60% of cases). Mortality can also result from systemic thromboembolic events in the context of atrial fibrillation.

Initial Clinical Evaluation

Physical exam findings: As a result of elevated LA pressures, the stenotic mitral leaflets are still widely separated at the onset of ventricular contraction. Thus, the first heart sound (S1) is loud reflecting the increased leaflet excursion (and subsequently forceful closure). As the leaflets become more rigid and calcified, their motion is limited and S1 becomes soft.

An opening snap (OS) of the mitral valve is heard at the apex in diastole when the leaflets are still mobile. The OS following S2 may be mistaken for a split S2 unless the examiner recognizes that the OS is best appreciated at the apex, not the base.

The diastolic murmur is a low-pitched diastolic rumble that is most prominent at the apex. It is best heard in the left lateral decubitus position, with the patient lying on the left side in held expiration, and by using the bell of the stethoscope in a quiet environment.

Radiographic evaluation: Echocardiogram is indicated in patients with signs or symptoms of MS to establish the diagnosis, quantify hemodynamic severity (mean pressure gradient, mean valvular area, and pulmonary artery pressure), and demonstrate valve morphology to determine suitability for percutaneous mitral balloon commisurotomy (PMBC). See **Table 1** below for echocardiographic grading criteria.

Parasternal long-axis views can identify the characteristic diastolic doming of the mitral valve, whereas short-axis scanning will demonstrate commissural fusion and allow planimetry of the mitral orifice. 3D TTE may provide more accurate planimetry. Doppler hemodynamics are obtained from the apical 4-chamber view. Mitral valve morphology and favorability for PMBC can be assessed via the Wilkins/MGH score, which combines valve thickening, mobility, and calcification with subvalvular scarring in a 16-point scale (>8 less favorable).

TEE is an alternative approach to assess the severity of MS in patients with technically limited transthoracic windows and is necessary to exclude LAA thrombus prior to PMBC attempts.

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Table 1. 2014 ACC/AHA Guidelines for Staging Rheumatic MS

	Progressive (stage B)	Asymptomatic Severe (Stage C)	Symptomatic Severe (Stage D)
Valve Anatomy			
Visual appearance	commissural fusion and diastolic doming of the mitral valve leaflet	commissural fusion and diastolic doming of the mitral valve leaflet	commissural fusion and diastolic doming of the mitral valve leaflets
Mitral Valve Area (planimetered)	>1.5 cm^2	>1.5 cm^2 (≤1.0 cm^2 with very severe MS)	>1.5 cm^2 (≤1.0 cm^2 with very severe MS)
Hemodynamics			
Mitral Valve Area (measured by continuity equation)	>1.5 cm^2	>1.5 cm^2 (≤1.0 cm^2 with very severe MS)	>1.5 cm^2 (≤1.0 cm^2 with very severe MS)
Diastolic pressure half time	<150 msec	≥150 msec (≥220m msec with very severe MS)	≥150 msec (≥220m msec with very severe MS)
LA size	Mild-moderate enlargement	Severe enlargement	Severe enlargement
Pulmonary artery Systolic pressure	Normal pressure at rest	PASP >30 mmHg	PASP >30 mmHg

The transmitral mean pressure gradient should be obtained to further determine hemodynamic effect of MS and is usually >5-10mm Hg in severe MS; However, due to the variability of the gradient with HR and output, it is not included in criteria for severity

*Note: **Stage A** refers to "at-risk" patients with evidence of mild valve doming during diastole, but normal transmital flow velocity and no evidence of hemodynamic consequence.

Follow up and Surveillance

Repeat TTE should be performed to re-evaluate asymptomatic patients with MS; the recommended frequency is determined by the severity of stenosis (Very Severe: every year, Severe: every 1-2 years, Progressive MS: every 3-5 years). The mean rate of progressive valve narrowing is ~0.1cm^2 per year with appreciable variability.

Medical Management

Anticoagulation: Anticoagulation with VKAs for patients with MS and AF or prior embolism is absolutely necessary (regardless of CHADS score) and patients with MS have been excluded from AF trials examining the utility of anticoagulation. The efficacy of the direct oral

anticoagulant agents (NOACs) in preventing embolic events has not been studied in patients with MS.

Heart rate: The proportion of the cardiac cycle occupied by diastole decreases with increasing heart rate, increasing the mean flow rate across the stenotic mitral valve, with a rise in the mean mitral gradient. For this reason, beta blockade is often recommended in patients with MS in Afib and in sinus rhythm, with goal HR of ~60. Nevertheless, small RCTs on the impact of beta blockade on exercise capacity in MS have been disappointing. Beta blockade is used in pregnant pts with MS to blunt the physiologic tachycardia of pregnancy and prolong diastole, prevent pulmonary edema.

Diuretics: Diuretics are a mainstay of medical management to keep LA pressures down and manage pulmonary edema prior to intervention.

Valvular Intervention

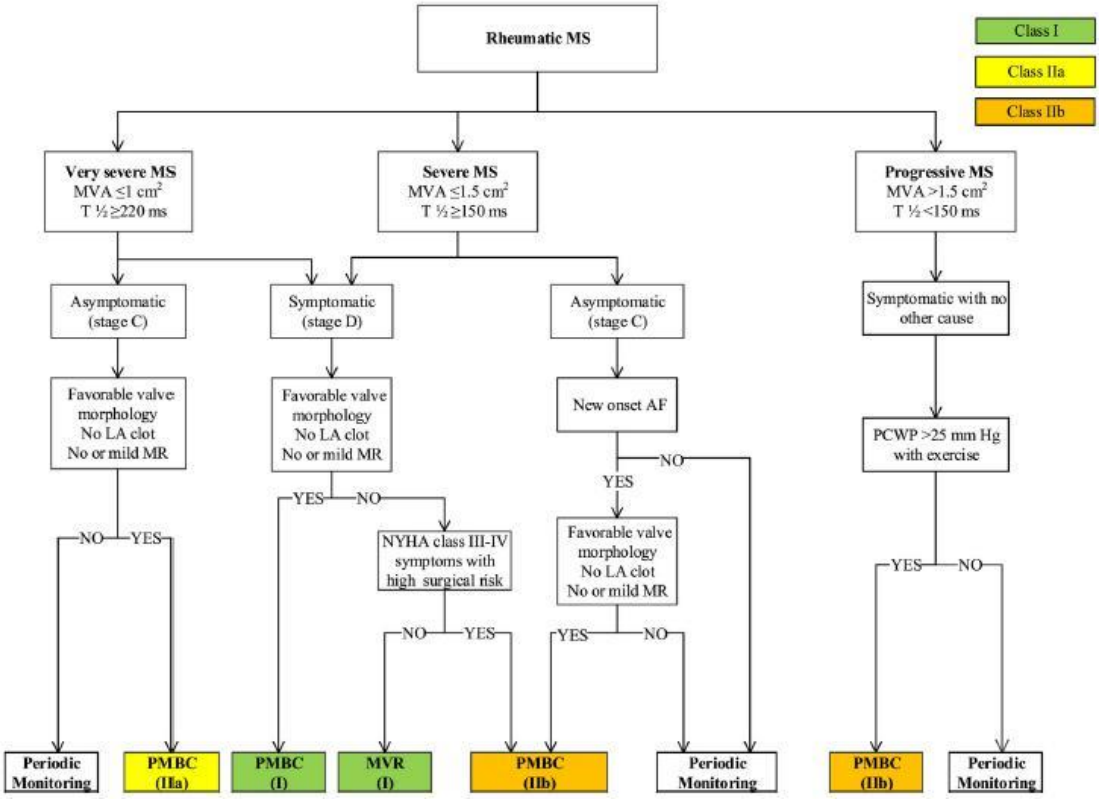

Figure 2. Indications for Intervention for Rheumatic MS. *ACC/AHA 2014*

QUICK REFERENCE GUIDE: VALVULAR HEART DISEASE

Aortic Stenosis

Etiologies and Clinical Course

- Common etiologies of AS include a bicuspid AV and rheumatic heart disease (developing world)
- Clinical RFs for AS mirror that for CAD
- Aortic sclerosis is calcification of the aortic valve without hemodynamic effects
    - Over 5 years, only 10-25% of patients with aortic sclerosis will develop AS

Clinical Evaluation and Surveillance

- Only severe aortic stenosis can cause symptoms (though valve area >1 cm^2 may cause symptoms if there is concomitant aortic insufficiency or atrial fibrillation, where there is loss of atrial kick)
- Historical evaluation should screen for symptoms of: Angina, syncope, and CHF
- On exam, indicators of severe AS include: Late-peaking murmur, delayed carotid upstroke, radiation to the left clavicle, obliteration of the A2 component of S2
- TTE is the diagnostic test of choice w/ severe AS defined as an AVA <1 cm^2, mean gradient >40 mmHg, and jet velocity >4 m/s
- Patients with discordance between AVA and gradients (particularly those with a low AVA but lower gradients than expected) are a particularly high-risk group, so termed “low-flow, low-gradient” AS
    - These patients should be further evaluated with a dobutamine stress echo (DSE) or cardiac catheterization (with measurement of transvalvular pressures)
- Following diagnosis, the aortic valve area generally decreases by 0.1 cm^2 per year
- AVR is the only definitive treatment shown to have a mortality benefit
- Because of the risk of sudden death, AVR should be performed promptly after the onset of symptoms

Overnight Management

- For hypovolemic patients with severe AS, use small fluid boluses (while closely monitoring oxygenation to avoid significant pulmonary edema)
- For euvolemic patients, avoid venodilation or significant preload reduction, as patients with severe AS are preload-dependent, and therefore at risk for sudden and significant drops in CO with decreased filling pressures
- For volume overloaded patients, diuretics are necessary
- In the setting of critical AS (severe parameters and manifestations of HF), it is generally advisable to avoid BB/CCBs (negative inotropes), as inotropy is necessary to overcome the high afterload of a stenotic valve; however, they can be used cautiously if needed for rate control
- IABP can be helpful in temporizing critical AS (as long as there is no concomitant AR), particularly if there is myocardial ischemia, by improving coronary blood flow during diastole, improving LV contractility, and decreasing afterload
- Inotropic agents (e.g., dobutamine) may be necessary to maintain contractility and cardiac output in severe decompensation

- Atrial fibrillation is not well tolerated in severe aortic stenosis since loss of the atrial "kick" reduces LV preload, and rapid heart rates do not allow for adequate LV filling. Rate control is essential, and if not possible, consider cardioversion

Longitudinal Management

- No medical therapy has been shown to improve symptoms or mortality in AS patients
- AVR can be performed surgically (SAVR) or by percutaneous/transcatheter approach (TAVR)
    - Classically, decisions regarding SAVR vs TAVR were based on surgical risk (evaluated by STS score), with low risk patients recommended for SAVR and intermediate and high-risk patients recommended for TAVR
    - However, recent studies suggest that TAVR may be preferable to SAVR in low-risk patients
- Surgical AVRs require some period of ASA 81 + AC (coumadin x3 mo s/p bioprosthetic AVR, lifelong s/p mechanical AVR) although practice is variable among surgeons
- Valves used in TAVR require up to 6 months of DAPT then lifelong ASA 81

Aortic Regurgitation

- Acute and chronic AR have different etiologies, pathophysiological consequences, natural histories, and management strategies

Acute AR	**Chronic AR**
Etiology	
• Common etiologies of acute AR include endocarditis or aortic dissection	• Common etiologies of chronic AR include bicuspid aortic valve and calcific valve disease
Clinical Evaluation and Surveillance	
• On exam, patients will have a widened pulse pressure and may have signs of acute HF and significant pulmonary edema • In cases where aortic dissection is thought to be the etiology of acute AR, initial evaluation should include either TEE or CTA, which have a Sn and Sp approaching 95% (versus TTE, where the Sn and Sp is only around 60-80%)	• On exam, patients demonstrate a characteristic early diastolic decrescendo murmur at LUSB/RUSB that increases with maneuvers that increase afterload (expiration, handgrip) • Pulses may be bounding and the pulse pressure is widened • An S3 is common and heard due to LV dilation (which is part of the physiologic response to AR) • TTE is typically the diagnostic tests of choice and used to assess width of regurgitant jet, regurgitant volume, and LV size/function
Overnight Management	**Longitudinal Management**
• Management of acute severe AR consists of hemodynamic temporization and urgent surgical evaluation	• In general, indications for surgical intervention include the development of symptoms or decrease in EF <50% • Medical therapy (ACE/ARBs, BB) has a limited role in chronic AR and can

• Nitroprusside can be used to reduce LV afterload • Chronotropic support (overdrive pacing, isoproterenol) can be used to reduce diastolic regurgitation time • Diuretics are used to reduce LV filling pressures • IABPs are contraindicated; vasoconstrictors and beta blockers (used in dissection) should be avoided	be used in patients with severe AR who are not surgical candidates • Serial TTE is performed at a recommended frequency that is determined by the severity of regurgitation (Severe: q6-12mo; mod: q1-2 yr; mild q3-5 yr)

Mitral Regurgitation

Etiologies and Clinical Course

- MR can be acute (flail leaflet secondary to chordae rupture from endocarditis or MI) or chronic
- Chronic MR is divided into primary MR (dysfunctional valve; MVP is most common cause) or secondary (ventricular dilatation leading to annular dilatation; ischemic heart disease is most common cause)
- Severe MR results in poor clinical outcomes (survival rates 33% at 8 years without MVR, mortality 5% per year), with most deaths due to heart failure

Clinical Evaluation and Surveillance

- History should focus on exertional dyspnea, fatigue, and palpitations (which are suggestive of atrial fibrillation)
- On exam, indicators of MR include an apical holosystolic murmur radiating to the axilla with more severe cases of chronic MR having a left-sided S3, soft S1, and widely split S2 from pulmonary hypertension
- TTE is the diagnostic test of choice to assess degree of regurgitation as well as LV volumes and function(TEE and cardiac MRI serve as ancillary tests)

Overnight Management for Acute MR

- For patients with acute MR, the primary goal of management is to reduce afterload and increase contractility to promote forward flow while awaiting more definitive surgical management
    - For afterload reduction, consider IV nitroprusside/nitroglycerin
    - For contractility, consider dobutamine
    - IABP can be helpful to both reduce preload and augment forward flow

Longitudinal Management for Chronic MR

- Primary MR
    - The management of severe, symptomatic primary MR is ideally surgical with mitral valve repair generally preferred over mitral valve replacement
    - For patients deemed not to be surgical candidates, medical management of HF and percutaneous intervention can be considered
- Secondary MR
    - The mainstay of therapy is guideline-directed medical therapy for HF, including CRT placement as appropriate
    - Surgery is only felt to be helpful in patients with persistent symptoms despite optimal medical therapy and for patients undergoing concurrent cardiac surgery

- In patients with persistent symptoms despite optimal medical therapy, percutaneous placement of MitraClip may reduce HF admissions and death

Mitral Stenosis

Etiologies and Clinical Course

- The predominant cause of MS is rheumatic fever, which results in thickening of the leaflet edges, fusion of the commissures, and chordal shortening and fusion
- Rheumatic MS is characterized by a prolonged latent phase between the initial rheumatic illness and the development of valve stenosis
- MS causes obstruction of inflow from the LA to the LV. As a result there is increased pressure within the LA, pulmonary vasculature, right heart, while the LV pressure is unaffected

Clinical Evaluation and Surveillance

- Physical exam may reveal a loud S1, opening snap of the S2, and low-pitched diastolic murmur that is most prominent at the ape
- TTE is the diagnostic modality of choice, and should be repeated at intervals determined by the severity of MS

Overnight and Long-term Management of MS:

- Anticoagulation with VKA is crucial (NOACs have not been studied)
- Beta blockers are helpful to prolong diastole and prevent pulmonary edema
- Diuretics are important to keep LA pressures down

CONGENITAL HEART DISEASE

See Page 292 for Quick Reference Guide

Adult Congenital Heart Disease Anatomic and Physiologic Classification System

The 2018 ACC/AHA Adult Congenital Heart Disease guidelines presented a new classification system for adult congenital heart disease. The adult congenital heart disease anatomic and physiological (ACHD AP) classification system uses both anatomic complexity and as well as physiologic status. Anatomic classification includes Class I (simple), Class II (moderate complexity), and Class III (great complexity). The physiological classification is divided into stages A-D and is overall similar to the AHA heart failure classification. The physiological classification system takes into account a patient's functional status as well as other factors including presence of valve disease, pulmonary hypertension, arrhythmias, aortic dilatation, end-organ function, and cyanosis.

Class I: Simple

Native disease
- Isolated small ASD
- Isolated small VSD
- Mild isolated pulmonic stenosis

Repaired conditions
- Previously ligated or occluded ductus arteriosus
- Repaired secundum ASD or sinus venosus defect without significant residual shunt or chamber enlargement
- Repaired VSD without significant residual shunt or chamber enlargement

Class II: Moderate Complexity

Repaired or unrepaired conditions
- Aorto-left ventricular fistula
- Anomalous pulmonary venous connection, partial or total
- Anomalous coronary artery arising from the pulmonary artery
- Anomalous aortic origin of a coronary artery from the opposite sinus
- AVSD (partial or complete, including primum ASD)
- Congenital aortic valve disease
- Congenital mitral valve disease
- Coarctation of the aorta
- Ebstein anomaly (disease spectrum includes mild, moderate, and severe variations)
- Infundibular right ventricular outflow obstruction
- Ostium primum ASD
- Moderate and large unrepaired secundum ASD
- Moderate and large persistently patent ductus arteriosus
- Pulmonary valve regurgitation (moderate or greater)
- Pulmonary valve stenosis (moderate or greater)
- Peripheral pulmonary stenosis
- Sinus of Valsalva fistula/aneurysm
- Sinus venosus defect
- Subvalvar aortic stenosis (excluding HCM; HCM not addressed in these guidelines)
- Supravalvar aortic stenosis
- Straddling atrioventricular valve
- Repaired tetralogy of Fallot
- VSD with associated abnormality and/or moderate or greater shunt

Class III: Great Complexity

- Cyanotic congenital heart defect (unrepaired or palliated, all forms)
- Double-outlet ventricle
- Fontan procedure
- Interrupted aortic arch
- Mitral atresia
- Single ventricle (including double inlet left ventricle, tricuspid atresia, hypoplastic left heart, any other anatomic abnormality with a functionally single ventricle)
- Pulmonary atresia (all forms)
- TGA (classic or d-TGA; CCTGA or l-TGA)
- Truncus arteriosus
- Other abnormalities of atrioventricular and ventriculoarterial connection (i.e., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

PHYSIOLOGIC Stage

Stage A

- NYHA FC I symptoms
- No hemodynamic or anatomic sequelae
- No arrhythmias
- Normal exercise capacity
- Normal renal/hepatic/pulmonary function

Stage B

- NYHA FC II symptoms
- Mild hemodynamic sequelae (mild aortic enlargement, mild ventricular enlargement, mild ventricular dysfunction)
- Mild valvular disease
- Trivial or small shunt (not hemodynamically significant)
- Arrhythmia not requiring treatment
- Abnormal objective cardiac limitation to exercise

Stage C

- NYHA FC III symptoms
- Significant (moderate or greater) valvular disease; moderate or greater ventricular dysfunction (systemic, pulmonic, or both)
- Moderate aortic enlargement
- Venous or arterial stenosis
- Mild or moderate hypoxemia/cyanosis
- Hemodynamically significant shunt
- Arrhythmias controlled with treatment
- Pulmonary hypertension (less than severe)
- End-organ dysfunction responsive to therapy

Stage D

- NYHA FC IV symptoms
- Severe aortic enlargement
- Arrhythmias refractory to treatment
- Severe hypoxemia (almost always associated with cyanosis)
- Severe pulmonary hypertension
- Eisenmenger syndrome
- Refractory end-organ dysfunction

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35. Patent Foramen Ovale (PFO)

Epidemiology/Presentation

Patent foramen ovale (PFO) occurs in 25-30% of the general population and the overwhelming majority of patients are asymptomatic with no clinical consequence. However PFOs are more common (40-50%) in patients presenting with cryptogenic stroke, especially in those who suffer strokes before age 55. There is also some controversy about their connection to severe migraine and vascular headaches. Other presenting symptoms include decompression sickness with paradoxical air embolism. Very rarely do PFOs result in right-to-left shunting and hypoxia, like platypnea-orthodeoxia syndrome (dyspnea and arterial desaturation in the upright position that improves in the supine position).

Anatomy/Pathophysiology

A PFO is defined as failure of the foramen ovale (part of the fetal circulation that allows blood to bypass the pulmonary vasculature) to close in the first few months of life, allowing a direct connection between the right and left atria. PFOs are generally smaller than atrial septal defects (ASDs), and as a result, are usually asymptomatic and often identified incidentally.

Evaluation/Diagnosis

Screening is indicated in the setting of a cerebral ischemic event of uncertain origin or other clinical manifestations of a PFO (i.e. platypnea-orthodeoxia).

Exam: Typically normal

Imaging: Echocardiogram with color flow Doppler or agitated saline contrast (a “bubble study”) is the diagnostic test of choice. TEE generally has higher sensitivity than TTE for the detection of PFO.

Management

Of note, PFO is not included in the 2018 ACHD guidelines.[1] Per AHA/ASA 2014 guidelines[2]:

Primary prevention of stroke in patients with a PFO is not indicated.

For *secondary prevention* in patients with ischemic stroke/TIA and found to have PFOs, mounting evidence suggests that percutaneous PFO closure is more effective for preventing recurrent ischemic stroke than antiplatelet therapy alone for highly selected patients (age ≤60 years) who have an embolic-appearing cryptogenic ischemic stroke and a PFO.* Thus recommends include:

- For patients aged ≤60 years with a cryptogenic embolic-appearing ischemic stroke who have a PFO and no other evident source of stroke despite a comprehensive evaluation, we suggest percutaneous PFO device closure in addition to antiplatelet therapy, rather than antiplatelet therapy alone.
- For patients with cryptogenic stroke and PFO who are >60 years of age, we suggest antiplatelet therapy rather than percutaneous PFO device closure or anticoagulation. This does not apply to selected patients with strong clinical evidence of paradoxical embolus

including patients with acute deep venous thrombosis, pulmonary embolism, or other venous thromboembolism, who are generally treated with anticoagulation.

*It is important to note, however, that a series of newer trials published in NEJM (Gore REDUCE, CLOSE, and the long-term follow up of the RESPECT trial) do suggest a statistically significant stroke risk reduction with PFO closure in appropriately selected patients. These trials were different from the original trials with respect to having longer duration of follow up (RESPECT long term follow up), including patients with “higher risk” PFOs (patients in the CLOSE trial were required to have a large interatrial shunt at rest or an atrial septum aneurysm, and patients in the Gore REDUCE trial were required to have a moderate-to-large interatrial shunt). Based on these studies, in patients who have had a stroke, are younger than 60 years of age (entry criteria), and have a PFO with characteristics that are highly likely to allow paradoxical embolism to occur, the effect of closure becomes persuasive.

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.
2. 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. 2014 Jun 10;63(22):2438

TOC

36. Atrial Septal Defect

Epidemiology/Presentation

In general, this congenital abnormality is quite common with an incidence of 1/1,500 live births and a 2:1 female to male predominance.

Anatomy/Pathophysiology

An atrial septal defect ([ASD], or any pretruscpid shunt lesion) initially results in a left-to-right atrial shunt due to increased compliance of the right heart. Right-sided volume overload will eventually lead to right atrial, right ventricular, and pulmonary artery enlargement. Patients are often asymptomatic for decades before developing atrial arrhythmias, and RV dilation/dysfunction. With large unrepaired ASDs, pulmonary hypertension may develop and very rarely become so severe that the left-to-right shunt can reverse, becoming right-to-left with systemic hypoxemia (Eisenmenger syndrome). With increased right-to-left shunting, there also becomes an increased risk of paradoxical embolization with subsequent stroke, such as with scuba diving or pregnancy/labor (increased risk of DVT, increased risk of right-to-left shunting with reduction in SVR and Valsalva).

There are several types of pretricuspid shunts (Figure 1), including primum ASDs, secundum ASDs, inferior or superior sinus venosus defects, and coronary sinus defects (of note: sinus venosus and coronary sinus defects are not technically defects of the atrial septum, but included here given similar physiology as they are all pretricuspid shunt lesions):

- Primum defect (10-15%): Also known as partial or complete AV canal defects. These are associated with mitral valve deformities such as cleft mitral valve
- Secundum defect (65%): These are the most common ASD. They vary in size and are usually isolated lesions but can be associated with other ASDs
- Sinus Venosus defect (10-15%): Often associated with partial anomalous pulmonary venous drainage
- Coronary sinus defect: This is very rare defect between the coronary sinus and left atrium and associated with other complex cardiac lesions

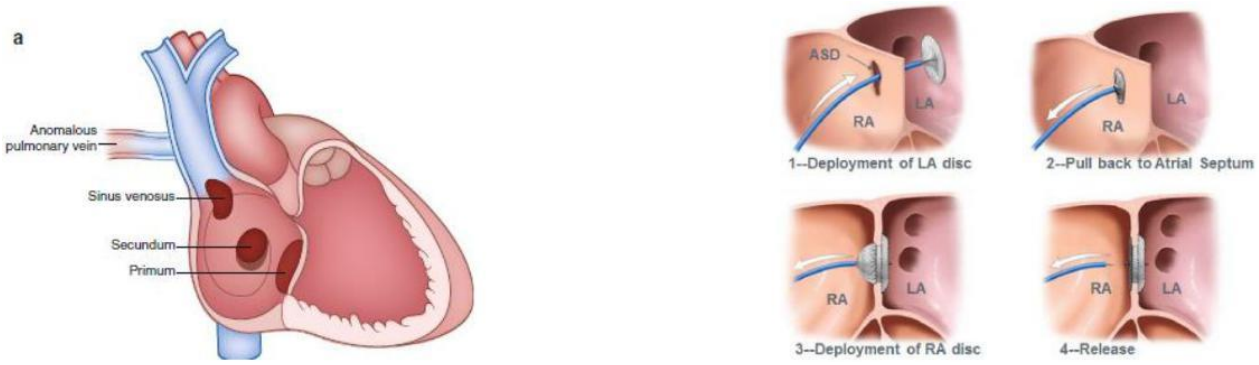

Figure 1. Left: Types of ASD **(***MGH Cardiology Board Review)*. Right: Percutaneous ASD repair (*St. Judes)*

Evaluation/Diagnosis

Exam: Large ASDs may result in a fixed and split S2 that does not vary with inspiration. A soft systolic crescendo-decrescendo systolic pulmonary flow murmur may be heard due to increased flow over the pulmonary valve. Precordial lift may be felt in cases or RV enlargement. Prominent P2 may be present at the apex if resting pulmonary hypertension has developed.

Imaging: TTE will generally make the diagnosis (though note that TTE may not easily identify sinus venosus defects). TEE, cardiac CT, or MRI may additionally be performed to help define the margins of the defect (an important consideration for device closure of secundum ASD) and to identify associated pulmonary venous anomalies. RHC with iNO may also be useful to assess for reversibility of pulmonary hypertension.

Management

Per AHA/ACC ACHD 2018 guidelines,[1] ASD repair (primum or secundum, either transcatheter or surgical) is indicated (Class I recommendation) if:

- The patient exhibits impaired functional capacity
- There is evidence of RA and/or RV enlargement
- AND there is net left-to-right shunting that is large enough to cause physiologic sequelae (Qp:Qs [the ratio between the flow through the pulmonary system and the flow through the system] $\geq$ 1.5, as long as systolic PA pressure < 1/2 systolic systemic pressure and PVR < 1/3 SVR)

ASD closure is NOT recommended (Class III: Harm) if:

- PA systolic pressure > 2/3 systemic pressure and PVR >2/3 SVR
- There is net right-to-left shunt

All sinus venosus, primum, and coronary sinus defects must be repaired surgically. For isolated secundum defects, percutaneous closure is the most common approach for repair, with extremely high success rates. In these patients, surgical repair is reserved for very large defects or patients with deficient septal rims.

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.

TOC

37. Ventricular Septal Defect

Epidemiology/Presentation

Ventricular septal defects (VSD)s are among the most common congenital heart entities in early childhood but only account for 10% of adult congenital heart disease, as most will close spontaneously.

Anatomy/Pathophysiology

A VSD allows shunting of blood from one ventricle to another. Small (restrictive) defects will result in high-velocity, low-volume left-to-right shunting that does not result in left-sided volume overload. However, larger defects may result in significant LV or biventricular volume (due to increased pulmonary venous return) and PA volume/pressure overload with severe pulmonary hypertension and the potential for right-to-left flow reversal. Congenital VSDs differ from post-infarct VSDs, which typically are muscular, larger, and impact RV function primarily.

There are several different types of VSDs, defined by location (Figure 1):

- Supracristal (5%): Result from deficiency of the septum inferior to the aortic and pulmonary valves. Aortic valve cusp can prolapse into the VSD, leading to progressive AR and occasionally sinus dilatation
- Perimembraneous (60-70%): Most common
- Muscular (10%): Can be small or large and single or, multiple. In adults, they are generally small
- Inlet (rare): Results from deficiency of the inlet septum located beneath both mitral and tricuspid valves. Does not result in mitral or tricuspid regurgitation unless associated with an AV canal defect and septum primum defect (often seen with Down's syndrome)

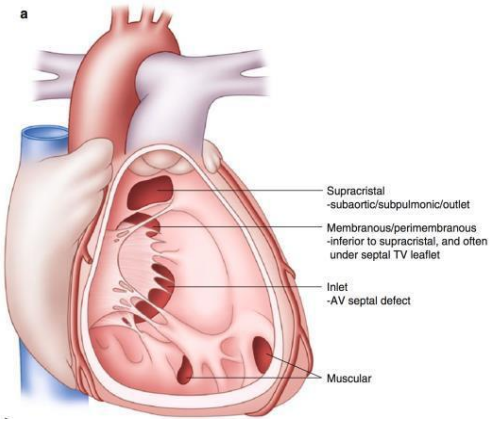

Figure 1. Types of VSD (*MGH Cardiology Board Review)*

Evaluation/Diagnosis

Exam: Small VSDs may be associated with a high-pitched pansystolic murmur. Larger VSDs tend to cause lower-frequency murmurs. These should augment with hand-grip (due to increased left ventricle afterload/left-sided pressures and therefore increased shunt fraction). Diastolic murmur may be heard with supracristal VSD causing aortic cusp prolapsed and aortic regurgitation. The presence of a diastolic murmur in a patient with known restrictive VSD must be further evaluated.

Imaging: TTE is sufficient to define the lesion and assess for biventricular size and function.

Management

Per AHA/ACC 2018 guidelines,[1] repair is indicated (Class I recommendations) if:

- There is evidence of LV volume overload and hemodynamically significant shunt (Qp:Qs ≥ 1.5:1) AND
- PA systolic pressure < 1/2 systemic systolic pressure and PVR < 1/3 SVR

Additionally, repair may be considered (Class II recommendations) if:

- There is worsening aortic regurgitation caused by VSD
- There is history of infective endocarditis caused by VSD (if not otherwise contraindicated)
- There is net left-to-right shunt (Qp:Qs ≥ 1.5:1) when PA systolic pressure >1/2 systemic systolic pressure and/or PVR > 1/3 SVR

Repair is contraindicated (Class III: Harm) when:

- PA systolic pressure > 2/3 systemic pressure, PVR > 2/3 SVR, and/or there is net R to L shunt

Transcatheter device occlusion can be used for select muscular defects. Surgical repair involves suture or patch closure of the defect.

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.

38. Coarctation of the Aorta

Epidemiology/Presentation

Coarctation of the Aorta (CoA) accounts for 4 to 6 percent of all congenital heart defects with a reported prevalence of approximately 4 per 10,000 live births. It occurs more commonly in males than in females (59 versus 41%). CoA can be accompanied by another congenital cardiac lesion. In infants and children, a considerable proportion of patients have associated complex congenital heart disease. In adults, bicuspid aortic valve is the most common associated defect (50-60% of CoA patients).

Anatomy/Pathophysiology

Aortic coarctation is characterized by discrete or diffuse narrowing of the aorta. The typical location is in the region of the ligamentum arteriosum, adjacent to the origin of the L subclavian artery (Figure 1).

The obstruction to blood flow leads to increased afterload on the LV, causing concentric left ventriclular hypertrophy. There is also differential hypertension, with higher blood pressure in vessels proximal to the obstruction and relative hypotension distally (patients may suffer from claudication).

Patients are at increased risk of aortic dissection, particularly with pregnancy. They are also at higher risk of circle of Willis aneurysm (as below, should be screened with a one-time MR/CTA).

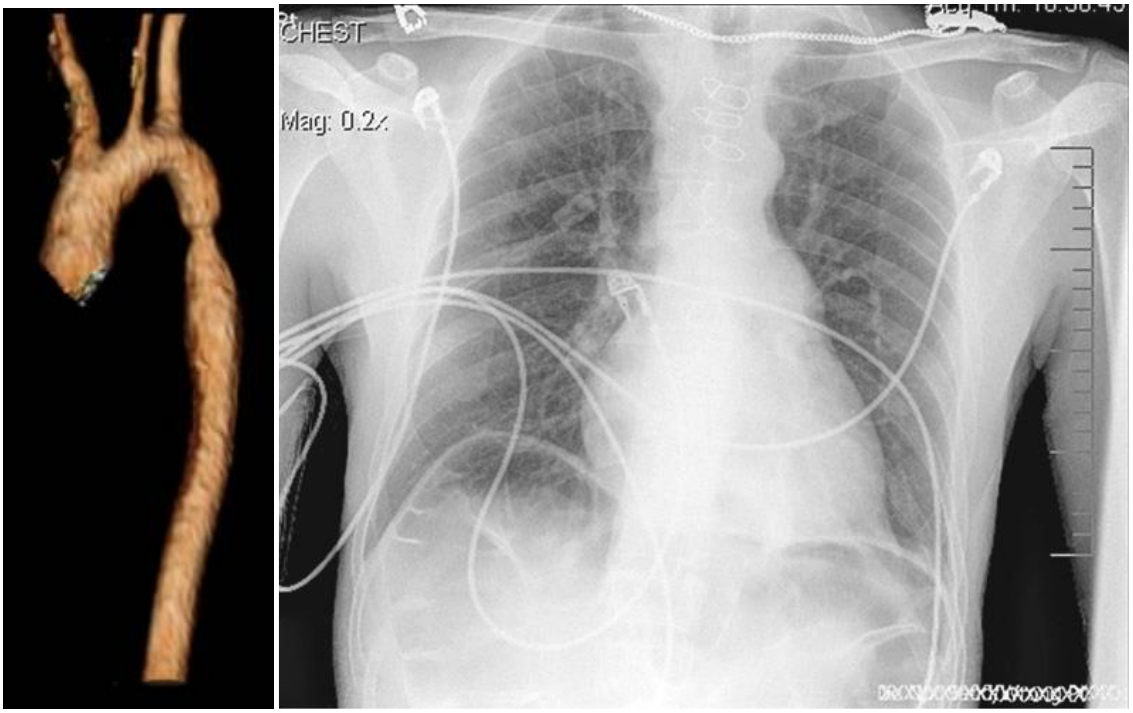

Figure 1. Left: Discrete coarctation anatomy by CT angiography, sagittal section (*Curr Cardiol Rep* 2015). Right: CXR demonstrating aortic indentation at the coarctation site ("3 sign") (*Cur Cardiol Rep* 2015)

Evaluation/Diagnosis

Exam: Differential hypertension can be measured by a gradient of 20mmHg between the arm and leg. Lower extremities may have diminished or late pulses (brachiofemoral delay). Systolic bruit may be heard along the scapular region.

Imaging: CXR may show aortic indentation at the coarctation site "3 sign," (Figure 1) and notching on the underside of the ribs from collateral vessels

TTE views from the suprasternal notch can demonstrate a narrowed aortic lumen. TTE also allows for measurement of the pressure gradient across the coarcation segment. However, additional imaging (including CT or MRA) is indicated to help guide interventional approach. These modalities are also preferred for screening for late complications (aneurysm, focal dissection, restenosis).

Management

Per AHA/ACC 2018 ACHD guidelines,[1] surgical repair is indicated in adults with native or recurrent CoA who have hypertension with a significant gradient >20mmHg.

Percutaneous stent implantation is the procedure of choice for adults with discrete coarctation that is clear of the subclavian artery. Surgical intervention may be needed for more complex or longer lesions, and approaches include resection with an extended end-to-end anastomosis or an interposition graft (more commonly used in adult patients).

As above, patients need to be followed with serial CT/MRAs (usually with an interval of 5 years) to assess for complications of CoA. Those who have had stent placement or surgical repair must also be screened for developed of recurrent CoA. Hypertension is a common late manifestation even among patients with well-repaired coarctation.

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.

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39. Tetralogy of Fallot

Epidemiology/Presentation

Tetralogy of Fallot (TOF) is the most common palliated complex congenital heart disease in adults. The initial diagnosis and management typically occurs by early childhood.

Anatomy/Pathophysiology

While the original pathologic description by Dr. Fallot included 4 seemingly separate abnormalities (pulmonic stenosis, VSD, dual overriding aorta, and right ventricular hypertrophy), the pathophysiology result from a single embryologic defect involving anterior deviation of the conal septum, which separates the aorta and the pulmonary artery (Figure 1). This leads to a diminutive pulmonary artery as well as a VSD. The aorta becomes anteriorly displaced and therefore overrides the ventricular septum. The RVOT gets crowded and infundibular pulmonic stenosis (PS) is typical, however, valvular and supravalvular PS can also be seen. RV hypertrophy results in response to PS and associated elevated RV afterload.

Most patients in the current era will have undergone surgical repair in early infancy. TOF repair (Figure 2) consists of patch closure of the VSD and a trans-annular or subannular incision with patch enlargement of the RV outflow tract. Residual defects following this repair include residual PS or patch-related VSDs. Pulmonary insufficiency commonly occurs, leading to RV dilation and dysfunction over time.

It is worth noting that some older adult patients may have undergone palliative shunting instead of TOF repair (Figure 3). These procedures were aimed solely to augment pulmonary artery blood flow in the setting of severe PS (the VSD was left uncorrected). Most commonly, the Blalock-Taussig shunt was used to direct blood through the subclavian artery into the right pulmonary artery. Other procedures, (Waterson and Potts shunts) were also performed, but because it was difficult to control the degree of pulmonary arterial blood flow through the shunt, these procedures often resulted in pulmonary hypertension and branch pulmonary artery stenosis, and were abandoned.

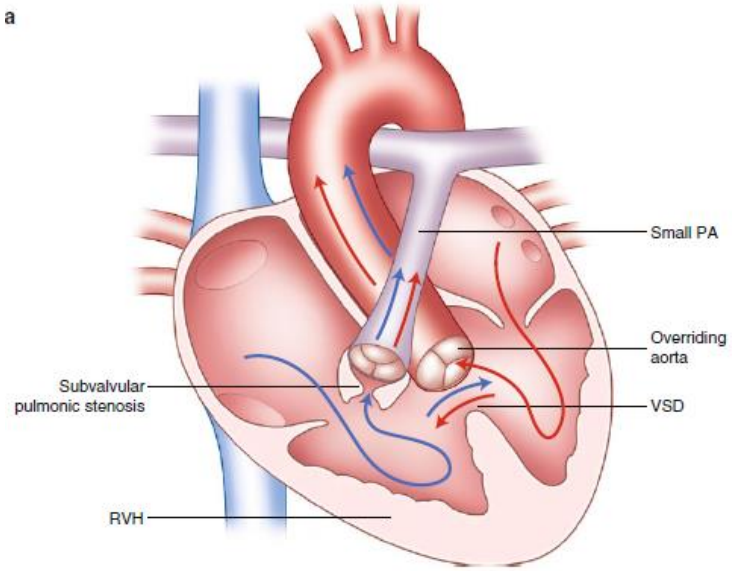

Figure 1. Native anatomy in TOF (*Adult Congenital Heart Disease in Clinic Practice* 2018)

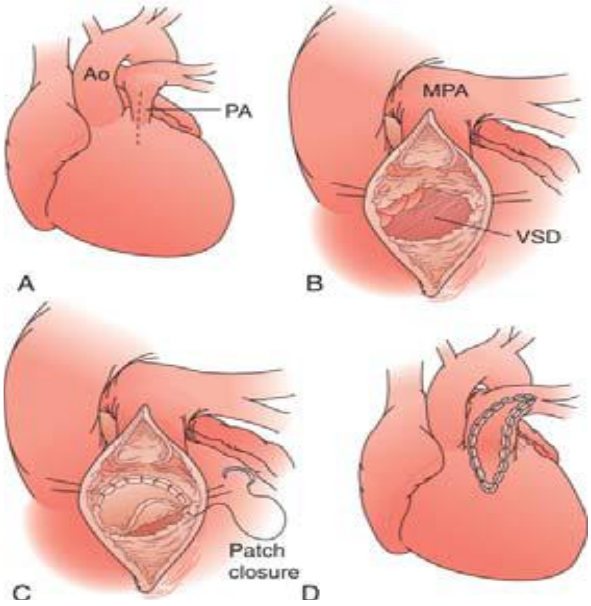

Figure 2. Surgical Tetralogy of Fallot Repair including VSD patch repair, infundibular resection and RVOT patch (*Adult Congenital Heart Disease in Clinic Practice* 2018)

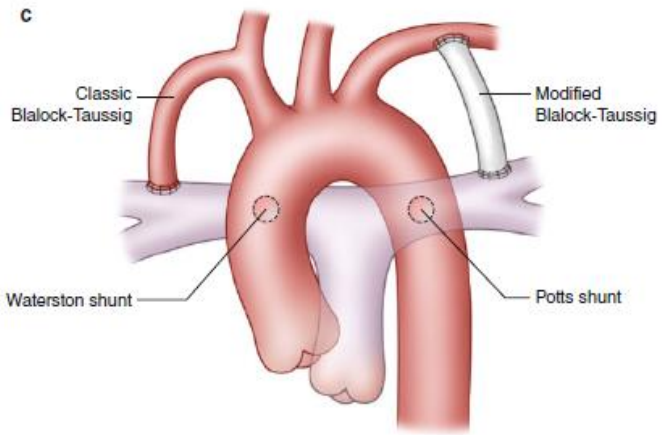

Figure 3. Palliative shunt (*Adult Congenital Heart Disease in Clinic Practice* 2018)

Evaluation/Diagnosis

Exam: Findings in adult patients are variable and will depend on prior management (e.g. repair versus palliative shunt).

Imaging: As above, a major complication of TOF repair includes pulmonary insufficiency. TTE is used to assess the degree of pulmonary regurgitation but is considered sub-optimal in assessing RV size and function over time. In patients with severe pulmonary insufficiency, cardiac MRI is the gold standard for following the RV and to assess for indications for pulmonary valve replacement (performed once RV volumes reach a certain size).

Management

Many long-term complications can be seen in adulthood late after childhood surgical repair. Adult management is additionally aimed at addressing these late complications including pulmonic insufficiency, recurrent pulmonary stenosis, complications of prior shunts and arrhythmia. Many patients require repeat pulmonary valve intervention during adulthood (either surgical or transcatheter). Because of abnormal anatomy and RV hemodynamics, adult TOF patients are at increased risk of sudden cardiac death (SCD). Risk factors include QRS prolongation (QRS >180msec) and evidence of abnormal RV anatomy or hemodynamics. These patients may require ICD for primary or secondary prevention as well as targeted anti-arrythmics and/or ablation.

40. D-Looped Transposition of The Great Arteries

Epidemiology/Presentation

The prevalence of transposition of the great arteries (TGA) in the United States is estimated to be 4.7 per 10,000 live births. The most common form of TGA is the dextro type (referred to as D-looped TGA [D-TGA]). The anatomical defect of D-TGA leads to cyanotic heart disease as the result of two parallel circulations. Thus, D-TGA typically is identified in infancy.

Anatomy/Pathophysiology

In *d looped*-TGA, the aorta arises from the RV anterior and to the right of the PA. This defect occurs due to a linear, rather than spiral development of the aorto-pulmonary septum. The D in D-TGA stands for dexter, or “right,” in Latin, referring to the normal looping orientation of the embryologic heart tube as it forms from the RV and LV (as opposed to *l looped*-TGA discussed in the next section). Infants with D-TGA have an aorta arising from the RV, returning de-oxygenated blood to the systemic circulation, while the PA arises from the LV and returns oxygenated blood to the pulmonary circulation. Short-term survival is dependent on mixing of these circuits via PFO, ASD, VSDs, and/or a patent ductus arteriosus.

The first surgical approach to garner widespread acceptance was the atrial switch or Mustard/Senning procedure. In this palliative procedure, systemic venous return is baffled across the atrial septum to the LV, which is left in continuity with the pulmonary artery. Pulmonary venous return is baffled to the RV, which pumps blood into the systemic circulation. The Senning procedure uses native tissue from the RA and atrial septum, while the Mustard procedure uses pericardial or artificial material. Residual complications include development of baffle obstruction or leak (increased risk with Mustard, as artificial material does not stretch with patient growth) as well as progressive systemic RV dilation/dysfunction after years of pumping against a systemic circulation.

In the 1980s, the arterial switch procedure became the intervention of choice, with the atrial switch procedure being performed only under circumstances where complex coronary anatomy made arterial switch unfeasible. In the arterial switch procedure, the PA and aorta are divided above the sinuses and transposed so that the aorta arises from the LV (through the native pulmonary root, now called the neo-aortic root), and the PA arises from the RV (through the native aortic root). The coronaries are taken off the aortic root (arising from the RV) and transposed to the pulmonary root (arising from the LV). Residual complications from this procedure include pulmonary branch stenosis (due to tension from anterior translocation of the main PA), aortic regurgitation of the neo-aortic valve, and coronary artery stenosis as a result of translocation (though this usually occurs early post-operatively). Longer-term complications of this procedure are still to be determined as this population ages.

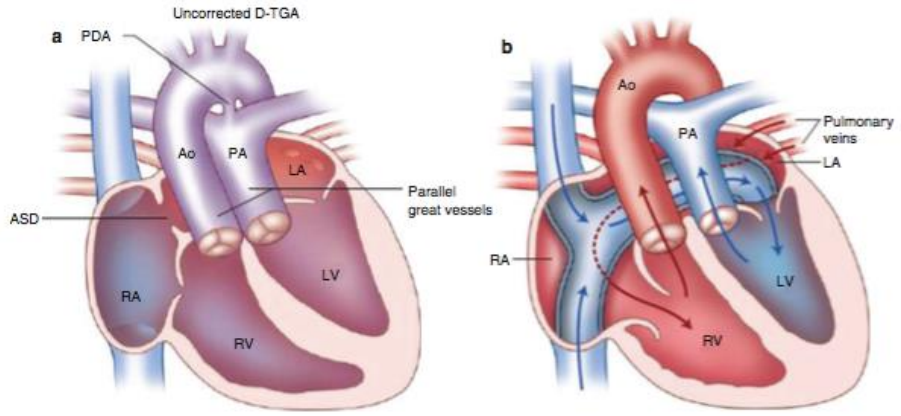

Figure 1. Left: Anatomy of unrepaired D-TGA. Right: Anatomy s/p atrial switch repair (*Adult Congenital Heart Disease in Clinic Practice* 2018)

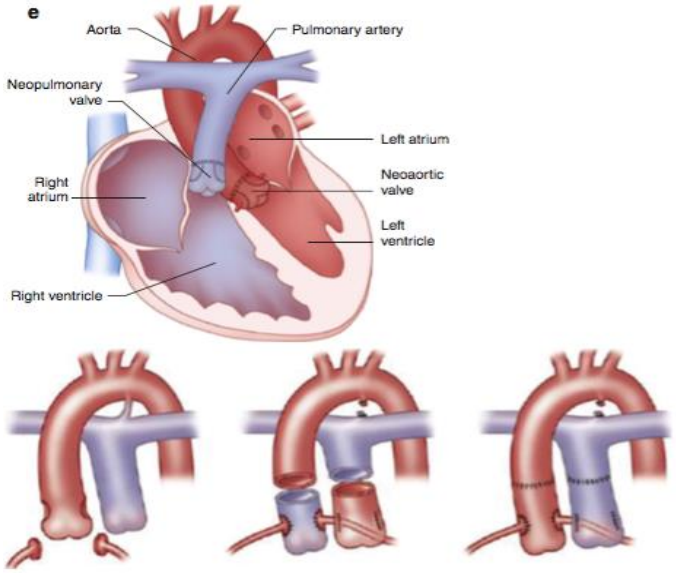

Figure 2. Anatomy of D-TGA after arterial switch (Jatene) operation (*Adult Congenital Heart Disease in Clinic Practice* 2018)

Evaluation/Diagnosis

Exam: Findings in adult patients are variable and will depend on prior management.

Imaging: Diagnostic studies will also largely depend on prior management. However, as below, cardiac MRI generally provides the best assessment of structural and functional complications.

Management

Management of the adult patient with *d*-TGA involves managing complications of prior intervention.

For patients who have undergone atrial switch, this includes management of arrhythmia, baffle obstruction/leak, and progressive RV dysfunction (systemic ventricle):

- Arrhythmia: AHA/ACC 2018 ACHD guidelines recommend ambulatory monitoring for bradycardia or sinus node dysfunction (especially true of pts treated with beta blockers/other rate-slowing medications).[1] Otherwise, standard targeted anti-arrhythmics and ablation procedures are the norm
- Baffle obstruction/leak: May present as edema of the face and upper extremities with superior baffle limb obstruction. If the inferior baffle limb is obstructed, cirrhosis and ascites may develop. These patients may also exhibit desaturation or paradoxical embolization if baffle leaks occur. Leaks/obstruction can be corrected percutaneously or surgically. Cardiac MRI provides the best assessment of structural and functional complications
- Progressive systemic RV dysfunction: In this patient population, ARBs have been studied with some marginally positive data for slowing RV remodeling. Additional afterload reduction may be used to reduce strain on the RV, but ultimately transplant may be indicated

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.

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41. L-Looped Transposition of The Great Arteries (L-TGA)

Epidemiology/Presentation

Because this is a “congenitally corrected” anomaly (as detailed below), patients may present in adulthood. Some adult patients will have undergone surgical correction in childhood, as a double switch procedure (concomitant atrial and arterial switch) may rarely be indicated.

Anatomy/Pathophysiology

In *L-looped*-TGA, the *L* stands for levo, or “left,” in Latin and refers to the abnormal leftward looping of the heart tube in development. This inverts the normal positioning of the ventricles, such that the morphologic RV is on the left and the morphologic LV is on the right. Concomitantly, there is linear, rather than spiral development of the aorto-pulmonary septum so that the great arteries, too, are in parallel and transposed. Systemic venous blood returns to the RA, crosses the mitral valve into the morphologic LV (the AV-valve morphology is determined by the ventricle it feeds into), and is ejected through the pulmonary valve into the pulmonary artery. Pulmonary venous blood enters the LA, crosses the tricuspid valve into RV, and is ejected across the aortic valve into the aorta. As a result of this concomitant atrioventricular and ventriculoarterial discordance, this disorder is known as “congenitally corrected”—the progression of flow through the pulmonary and systemic circuits still occurs in series.

However, associated congenital anomalies commonly occur in L-TGA. These are variable and include: VSD, pulmonary stenosis, apical displacement of systemic tricuspid valve, and displacement of the AV node with accessory AV node pathways (this often leads to complete heart block and/or re-entrant SVTs).

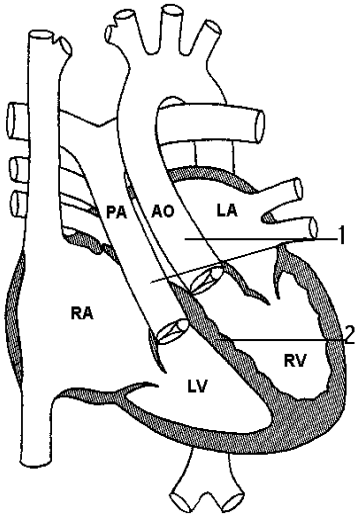

Figure 1. Unrepaired L-TGA anatomy (*Adult Congenital Heart Disease in Clinic Practice* 2018)

Evaluation/Diagnosis

Exam: Because of variability in associated anomalies, the exam of patients with *L*-TGA will also be highly variable. The aortic closureis often prominent as the aorta is anterior. However, the pathophysiology is generally dominated by the presence of a systemic RV with associated AV-

valve regurgitation. This leads to progressive hypertrophy and dilation, and patients will often present with sings/symptoms of 'left' heart failure (orthopnea, PND).

Imaging: TTE is generally the first most appropriate imaging study in patients presenting in adulthood. Advanced cross sectional imaging (MRI or CTA) is commonly required to assess baffle anatomy, patency, stenosis, and quantify RV volumes and function.

Management

Management of adult patients involves management of complications including arrhythmia and hemodynamic effects. As a result of AV nodal displacement, patients are at risk for CHB. Many will require pacemaker implantation (CHB occurs at a rate of 2% per year!). Ablation may also be necessary for accessory pathways contributing to AVRTs. With respect to hemodynamics, most patients suffer from severe systemic TR due to anterior leaflet dislocation, and TV repair can be considered in selected situations. However, in more severe cases, systemic RV failure may require transplantation.

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42. Single Ventricle Physiology (Fontan Palliation)

Epidemiology/Presentation

Single ventricle physiology (Fontan physiology) can result from many underlying congenital heart defects. The four most common are demonstrated in Figure 1 below and include: hypoplastic left heart syndrome, tricuspid atresia, double inlet LV, and AV canal defect.

What all of these anatomies have in common is that there is one functional ventricle that receives cardiac inflow, mixes oxygenated and deoxygenated blood, and distributes moderately oxygenated blood to both pulmonary and systemic circulations.

Anatomy/Pathophysiology

The primary issue of Fontan physiology in the adult patient is the lack of a sub pulmonary pump to drive blood into the pulmonary arteries (Figure 1). Therefore, cardiac output is limited by the ability of the downstream systemic ventricle to pull blood through the pulmonary bed, as well as the passive return from the systemic veins to the pulmonary artery through the Fontan circuit. This results in elevated CVP, which in the classical Fontan or Lateral tunnel can cause distention of the RA and increase risk for atrial arrhythmias or thromboembolism.

Due to elevated systemic venous pressures, venous collaterals may form from the systemic to the pulmonary veins, bypassing the pulmonary bed and resulting in systemic cyanosis. Congestive Fontan hepatopathy frequently complicates the course of these patients, often with progression to Fontan Associated Liver Disease (FALD) and HCC. Additionally, these patients often have a morphologic RV pumping systemically (as in the hypoplastic left heart syndrome) and develop progressive ventricular dysfunction.

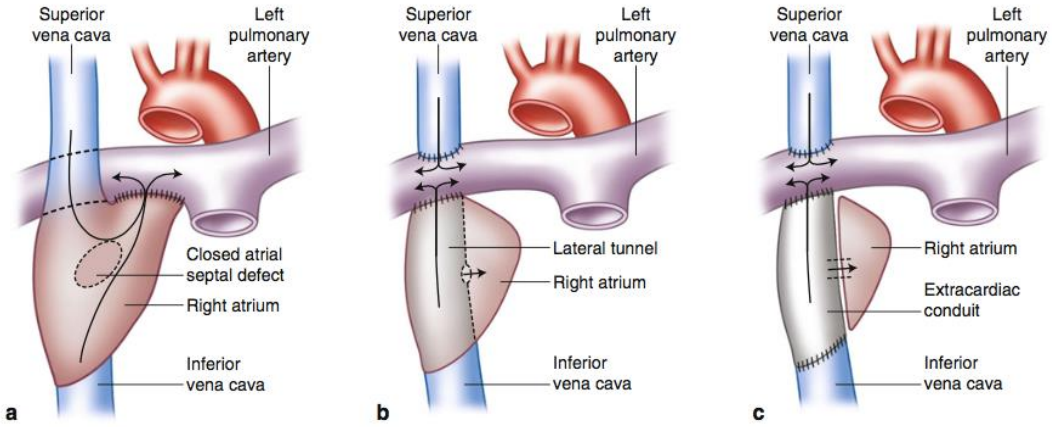

Figure 1. Fontan procedure (a. right atrial to pulmonary artery connection; b. Lateral tunnel Fontan, intracardiac; c. Extracardiac Fontan). (*MGH Cardiology Board Review*)

Management

These patients classically present in infancy, at which point initial urgent surgeries are performed to ensure that the basic physiologic pathway of bloodflow is preserved (i.e. receipt of cardiac inflow and subsequent distribution of blood to the pulmonary and systemic circulations). But of course, having moderately oxygenated blood perfusing the systemic circulation is not an ideal long-term solution.

In select cases, a fenestration between the Fontan and systemic circuit is created, which allows a small right-to-left shunt to persist. Benefits include increased cardiac output due to increased systemic preload (often limited by poor R-sided flow through pulmonary circuit) and decreased central venous pressures. However, fenestration is associated with increased risk of paradoxical thromboembolism. Hypoxemia/cyanosis may also occur in cases of excessive right greater than left shunting.

Specific management of adult patients with Fontan physiology is focused on specific, common complications:

- Arrhythmia: Atrial dysrhythmias are poorly tolerated. Targeted antiarrhythmics, ablation procedures, and ultimately conversion to extra-cardiac conduit may be indicated
- Cyanosis: RHC should be performed to look for systemic to pulmonary venous connections, which may be treated by transcatheter occlusion, however usually are only provide temporary palliation until new collaterals develop
- Thrombosis: Fontan physiology represents a low-flow state, and the degree of right-to-left shunting in these patients makes systemic thromboembolism a very high risk. Anticoagulation is indicated if there is history of atrial arrhythmia, fenestration, or EF <40% (even in patients without history of thromboembolism)
- Protein-losing enteropathy: Though the pathophysiology is poorly understood, this is a common complication occurring in 3-18% of patients. Furthermore, mortality is very high with only ~50% 5-year survival. Therapy is empiric and includes optimizing Fontan hemodynamics, considering fenestration, optimizing cardiac output, and reducing pulmonary vascular resistance
- Spontaneous fenestration closure: This occurs frequently and may be a silent event. However, in patients with poor cardiac output who were dependent on fenestration to augment ventricular preload, cardiac output may drop, systemic venous pressures may rise, and protein-losing enteropathy may ensue
- Heart failure: Symptoms may progress such that transplantation may be the only therapeutic option. Of note, early post procedure transplant outcomes within this population are poor relative to those with biventricular circulation, however if they survive, early post procedure window survival is on par with other age matched patients

43. Left-To-Right Shunting And Eisenmenger Physiology

Epidemiology/Presentation
There are several congenital abnormalities that cause blood to flow from the systemic to pulmonary circulation (Left-to-Right shunt). Rarely large, uncorrected shunts may progress to Eisenmenger physiology in which the development of pulmonary arterial disease and increased pulmonary vascular resistance (PVR) results in shunt reversal (Right-to-Left shunting) and cyanosis.

Adults presenting with the Eisenmenger syndrome typically have progressive dyspnea, chronic exercise intolerance, and symptoms of right heart failure. More rarely, they may present with arrhythmia, syncope, hemoptysis, or cyanosis (detailed below).

Anatomy/Pathophysiology
Systemic to pulmonary (left-to-right) shunt lesions result in volume overload, with resulting chamber enlargement (the chamber and degree of enlargement is dependent on shunt size and location). Pre-tricuspid valve shunts (ASD, anomalous pulmonary venous returns) typically result in RA/RV volume overload. Post-tricuspid valve shunts (VSD, PDA) result in LA/LV volume overload (LV systemic output decreased by shunt -> compensatory increase in intravascular volume until LVEDV is sufficient to produce normal CO -> LV volume overload).

In progression to Eisenmenger Syndrome, R-sided pressure overload results from both direct transmission of pressure from the higher-pressure LV as well as increased afterload due to pulmonary arterial remodeling. For example and in terms of direct transmission of pressure, a large unrestricted VSD will cause elevation in RV pressures, irrespective of pulmonary vascular remodeling. Similarly, a large PDA will cause significant elevations in pulmonary artery pressures. Over time, pulmonary over-circulation creates endothelial shear stress. This leads to local release of inflammatory mediators with subsequent structural changes, including medial hypertrophy of pulmonary arterioles (similar to PAH). Increased pulmonary vascular resistance results in elevated right-sided pressures as the RV aims to maintain cardiac output. If right-sided pressures approximate and then exceed left-sided pressures, the shunt direction can reverse, resulting in systemic desaturation.

The rate of progression of pulmonary hypertension is dependent on the type and size of the anatomic defect, as well as the magnitude of shunt flow. Patients with ventricular (i.e. VSD, AVSD) or arterial shunts (i.e. PDA, truncus arteriosus) are at higher risk of progressing rapidly to Einsenmenger syndrome compared to patients with pre-tricuspid shunt lesions. Occasionally smaller shunts can be associated with idiopathic PH, however not due to the shunt causing pulmonary vascular remodeling, and this is not Eisenmenger Syndrome.

Evaluation/Diagnosis
Exam: Examination may reveal signs of PH and RV failure (RV heave, loud P2, prominent venous a wave); chronic hypoxemia (cyanosis, clubbing); and/or TR/PR and murmur of the causative lesion (will become progressively more quiet as pulmonary and systemic pressures equalize).

Imaging: If the underlying etiology is unknown, initial diagnostic imaging should include TTE (as well as CT or cardiac MR in certain cases). In addition, alternative etiologies of PH should be evaluated.

In addition, cardiac catheterization should be performed at least once (ACC/AHA Class I recommendation). Pulmonary hypertension is defined as meanPAP > 25 mmHg with PVR >3 Woods units. Patients should undergo RHC with and without oxygen to determine whether the increased PVR is oxygen-responsive. Moreover, vasodilatory testing (typically inhaled NO) should be performed to assess for hemodynamic changes/to evaluate a dynamic component of the PH.

Management
Eisenmenger syndrome patients must be managed in conjunction with a specialist in Adult Congenital Heart Disease.

Per the 2018 ACC/AHA ACHD guidelines,[1] general care of patients with Eisenmenger syndrome includes avoidance of the following (Class I recommendations):

- Significant volume shifts (dehydration, or volume overload)
- Chronic exposure to high altitude
- Iron deficiency
- Strenuous activity (in particular, isometric exercise)
- Excessive heat (i.e. sauna, hot tub) due to risks associated with dehydration as well as worsening of right-to-left shunting through systemic vasodilation
- Unnecessary surgery or anesthesia
- Pregnancy

In addition, these patients require prompt workup and treatment for infection, as they may not have the cardiac reserve to support septic physiology. In addition, systemic vasodilation will worsen right-to left shunt flow.

For patients who have positive vasodilator testing on catheterization, the mainstay of medical therapy involves pulmonary arterial vasodilatation, which may improve pulmonary hemodynamics, functional class, and the 6-minute walk test, as well as prolong survival. However, these medications should be used cautiously and may be contraindicated in patients with pulmonary hypertension and severe left heart disease; when the compliance of the left heart is unable to accommodate increased pulmonary venous return asworsening pulmonary vascular congestion and hypoxia can occur.

All medication initiation/titration should be done in a closely monitored setting. With respect to specific agent selection, data exists for the following medication classes:

- Oral endothelin antagonists: Bosentan (pulmonary artery vasodilator); ambricentan; macitentan. Per AHA/ACC 2018 ACHD guidelines, bosentan is beneficial in symptomatic adults with Eisenmenger syndrome with ASD or VSD (Class I recommendations). It may also be used to treat symptomatic adults with Eisenmenger and one of the following: shunts other than ASD/VSD (ex: PDA), complex congenital heart lesions, or Down Syndrome (Class IIa recommendations)
- PDE inhibitors: Sildenafil and tadalafil. Per Per AHA/ACC 2018 ACHD guidelines, PDE-5 inhibitors can be used to treat symptomatic adults with Eisenmenger syndrome with ASD, VSD, or great artery shunt (Class IIa recommendations). In addition, the combination of bosentan with PDE-5 inhibitors may be considered if symptoms do not improve with either medication alone (Class IIa recommendations)
- Guanylate cyclase inhibitor: Riociguat
- Prostacyclin inhibitors: Selexipag is an oral prostacyclin inhibitor that has been approved for CHD-PH. Inhaled (treprostonil or iloprost) or subcutaneous (treprostolin) prostacyclin

inhibitors may also be used in patients with more severe disease. IV epoprostenol or treprostinil may be used in patients with WHO class IV symptoms (but is otherwise not first-line due to the risk of thrombus and paradoxical embolism with associated central lines)

- Note that in general, calcium channel blockers are contraindicated in patients with Eisenmenger syndrome due to risk of decreasing SVR more than PVR, thus worsening right-to-left shunting and hypoxemia

The only surgical option for patients who have progressed to Eisenmenger physiology is heart-lung transplant. Patients with Eisenmenger syndrome who are listed for transplant generally survive longer than patients with idiopathic pulmonary arterial hypertension while awaiting transplant (77% vs. 35% 3-year survival)

Additional management considerations relate to various complications. Common complications in these patients include:

Arrhythmia/SCD: Patients are at increased risk of both atrial and ventricular tachyarrhythmia. Arrhythmia may be very destabilizing and requires immediate attention. Endocardial pacing is not recommended in intravascular shunting due to risk of paradoxical emboli and infection

Hypoxemia: Due right-to-left shunting, although alternate causes of hypoxia should also be considered. Generally avoid intubation for temporary hypoxemia in the setting of anesthesia

Hemoptysis: Results secondary to pulmonary vascular hypertension; bronchial artery rupture can be severe

Thrombosis: Pulmonary arterial thrombi are often seen and are associated with worse disease. However, the use of oral anticoagulants is controversial given the risk of hemoptysis as above. In the absence of reliable data, oral anticoagulant therapy may be considered in patients with severe disease and no prior episodes of hemoptysis.

Paradoxical embolism: Filtering of all IVs is essential to prevent strokes. Avoidance of central lines and endocardial pacer leads is also encouraged to reduced risk of VTE and paradoxical embolism

Erythrocytosis/Hyperviscosity: Physiologic response to chronic hypoxemia to increase oxygen carrying capacity. Hyperviscocity may contribute to the increased risk of neurovascular events. Therapeutic phlebotomy should be performed only when neurologic symptoms are attributed to hyperviscocity and hemoglobin is > 20 g/dL or hematocrit is > 65%. Iron deficiency and dehydration must be excluded before phlebotomy considered. Iron deficiency worsens intravascular sludging and increases risk of stroke. CBC and iron stores should be checked at least yearly and repleted as necessary

Hyperuricemia: Increased uric acid levels are common in patients with cyanotic congenital heart disease and are due to increased production and decreased renal clearance. Serum uric acid increases in proportion to hemodynamic severity in adults with Eisenmenger syndrome and is associated with long-term mortality. Uric acid levels should be assessed annually, and treatment of hyperuricemia should be initiated in patients who develop gout.

References:

1. Stout KK et al. 2018 AHA/ACC Guideline for the management of adults with congenital heart disease. J am Coll Cardiol. 2019;73(12):1494-1563.

QUICK REFERENCE GUIDE: CONGENITAL HEART DISEASE

Patent Foramen Ovale

- Patent foramen ovale (PFO) occurs in 25-30% of the general population, and does not classically represent CHD
- PFOs are generally smaller than atrial septal defects (ASDs), and as a result, are usually asymptomatic and often identified incidentally
- PFOs are more common (40-50%) in patients presenting with cryptogenic stroke, especially in those who suffer strokes before age 55
- Screening (TTE with color flow Doppler or "bubble study"/agitated saline contrast) is indicated in the setting of a cerebral ischemic event of uncertain origin or other clinical manifestations of a PFO (i.e. platypnea-orthodeoxia)
- Primary prevention of stroke in patients with a PFO is not indicated
- For secondary prevention (i.e. for patients with ischemic stroke/TIA found to have a PFO), optimal management is an evolving field, but recent evidence supports the following:
    - For patients aged ≤60 years with a cryptogenic embolic-appearing ischemic stroke who have a PFO and no other evident source of stroke despite a comprehensive evaluation, we suggest percutaneous PFO device closure in addition to antiplatelet therapy, rather than antiplatelet therapy alone
    - For patients with cryptogenic stroke and PFO who are >60 years of age, we suggest antiplatelet therapy rather than percutaneous PFO device closure or anticoagulation

Atrial Septal Defect

- Quite common with an incidence of 1/1,500 live births and a 2:1 female to male predominance
- Initially results in a left-to-right atrial shunt due to increased compliance of the right heart
    - With large unrepaired ASDs, pulmonary hypertension may develop and, rarely, lead to flow reversal with systemic hypoxemia (i.e. Eisenmenger syndrome)
- There are several types of pretricuspid shunts (Figure 1), including primum ASDs, secundum ASDs, inferior or superior sinus venosus defects, and coronary sinus defects
- Per AHA/ACC ACHD 2018 guidelines, ASD repair (primum or secundum, either transcatheter or surgical) is indicated (Class I recommendation) if:
    - The patient exhibits impaired functional capacity
    - There is evidence of RA and/or RV enlargement AND
    - There is net left-to-right shunting that is large enough to cause physiologic sequelae (Qp:Qs [the ratio between the flow through the pulmonary system and the flow through the system] $\geq$ 1.5, as long as systolic PA pressure < 1/2 systolic systemic pressure and PVR < 1/3 SVR)

Ventricular Septal Defect

- Ventricular septal defects (VSDs) are among the most common congenital heart entities in early childhood but only account for 10% of adult congenital heart disease, as most will close spontaneously
- Congenital VSDs differ from post-infarct VSDs, which typically are muscular, larger, and predominantly impact RV function
- Per AHA/ACC 2018 guidelines, repair is indicated (Class I recommendation) if:

  - There is evidence of LV volume overload and hemodynamically significant shunt (Qp:Qs ≥ 1.5:1) AND
  - PA systolic pressure < 1/2 systemic systolic pressure and PVR < 1/3 SVR

Coarctation of the Aorta

- Coarctation of the aorta (CoA) accounts for 4 to 6 percent of all congenital heart defects (approximately 4 per 10,000 live births)
- Characterized by discrete or diffuse narrowing of the aorta, typically located in the region of the ligamentum arteriosum (adjacent to the origin of the L subclavian artery)
- Patients are at increased risk of aortic dissection; this risk appears to be significantly increased in pregnancy
- Per AHA/ACC 2018 ACHD guidelines, surgical repair is indicated in adults with native or recurrent CoA who have hypertension with a significant gradient >20mmHg

Tetralogy of Fallot

- Tetralogy of Fallot (TOF) is the most common palliated complex congenital heart disease in adults
- The original description included 4 seemingly separate abnormalities: pulmonic stenosis, VSD, dual overriding aorta, and right ventricular hypertrophy; all of which arise from a single embryologic defect involving anterior deviation of the conal septum (which separates the aorta and the pulmonary artery)
- Most patients in the current era will have undergone surgical repair in early infancy, consisting of patch closure of the VSD and a trans-annular or subannular incision with patch enlargement of the RV outflow tract
- Management of the adult patient is predominantly aimed at addressing late complications from childhood surgical repair, including pulmonic insufficiency, recurrent pulmonary stenosis, or complications from prior shunt procedures
  - Many patients will require repeat pulmonary valve intervention during adulthood (either surgical or transcatheter)
- Additionally, because of abnormal anatomy and RV hemodynamics, adult TOF patients are at increased risk of arrhythmia and sudden cardiac death (SCD)
  - Risk factors for SCD include QRS prolongation (QRS >180msec) and evidence of abnormal RV anatomy or hemodynamics
  - These patients may require ICD for primary or secondary prevention as well as targeted anti-arrhythmic therapy and/or ablation

D-Looped Transposition of The Great Arteries

- The prevalence of transposition of the great arteries (TGA) is estimated to be 4.7 per 10,000 live births with *d*-TGA more common than *l*-TGA
- In *d*-TGA, the aorta arises from the RV anterior and to the right of the PA. This leads to cyanotic heart disease as a result of two parallel circulations; thus, *d*-TGA typically is identified in infancy
- The first surgical approach to treatment was the atrial switch or Mustard/Senning procedure. Accordingly:
  - Systemic venous return is baffled across the atrial septum to the LV, which is left in continuity with the pulmonary artery
  - Pulmonary venous return is baffled to the RV, which pumps blood into the systemic circulation

    - Residual complications include development of baffle obstruction or leak, as well as progressive systemic RV dilation/dysfunction after years of pumping against a systemic circulation
- In the 1980s, the arterial switch procedure became the intervention of choice. Accordingly,
    - The PA and aorta are divided above the sinuses and transposed so that the aorta arises from the LV (through the native pulmonary root, now called the neo-aortic root), and the PA arises from the RV (through the native aortic root)
    - The coronaries are taken off the aortic root (arising from the RV) and transposed to the pulmonary root (arising from the LV)
    - Residual complications from this procedure include pulmonary branch stenosis (due to tension from anterior translocation of the main PA), aortic regurgitation of the neo-aortic valve, and coronary artery stenosis as a result of translocation (though this usually occurs early post-operatively)
- Management of the adult patient with *d*-TGA involves managing complications of prior intervention

L-Looped Transposition of The Great Arteries

- The prevalence of transposition of the great arteries (TGA) is estimated to be 4.7 per 10,000 live births with *l*-TGA less common than *d*-TGA
- In *L-looped*-TGA, the *L* stands for levo, referring to abnormal leftward looping of the heart tube in development. This inverts the normal positioning of the ventricles, such that the morphologic RV is on the left and the morphologic LV is on the right
    - Concomitantly, there is linear, rather than spiral development of the aorto-pulmonary septum so that the great arteries, too, are in parallel and transposed
    - Systemic venous blood returns to the RA, crosses the mitral valve into the morphologic LV (the AV-valve morphology is determined by the ventricle it feeds into), and is ejected through the pulmonary valve into the pulmonary artery
    - Pulmonary venous blood enters the LA, crosses the tricuspid valve into RV, and is ejected across the aortic valve into the aorta
- As a result of this concomitant atrioventricular and ventriculoarterial discordance, this disorder is known as “congenitally corrected,” and patients may present in adulthood
- Management of adult patients primarily relies on managing complications, including arrhythmia and hemodynamics
    - As a result of AV nodal displacement, CHB occurs at a rate of 2% per year! Ablation may also be necessary for accessory pathways contributing to AVRTs
    - Most patients suffer from severe systemic TR due to anterior leaflet dislocation, and TV repair can be considered in selected situations. In more severe cases, systemic RV failure may require cardiac transplantation

Single Ventricle (Fontan) Physiology

- Single ventricle physiology can result from many underlying congenital heart defects, but the four most common are: hypoplastic left heart syndrome, tricuspid atresia, double inlet LV, and AV canal defect
- In all of these anomalies, there is one functional ventricle that receives cardiac inflow, mixes oxygenated and deoxygenated blood, and distributes moderately oxygenated blood to both the pulmonary and systemic circulations
- In adult patients, the primary issue of Fontan physiology is lack of a sub-pulmonary pump to drive blood into the pulmonary arteries. This results in very elevated

- In some cases, a fenestration procedure is performed, allowing a small right-to-left shunt to persist between the Fontan and systemic circuit, which decreases central venous pressures and increases systemic preload (often limited by poor right-sided flow through pulmonary circuit) and augments cardiac output
- Management of adult patients with Fontan physiology is focused on specific, common complications (as below). In addition congestive Fontan hepatopathy frequently complicates the course for these patients, often with progression to Fontan Associated Liver Disease (FALD) and HCC
    - Arrhythmia: Atrial dysrhythmias are poorly tolerated. Targeted antiarrhythmics, ablation procedures, and ultimately conversion to extra-cardiac conduit may be indicated
    - Cyanosis: RHC should be performed to look for systemic to pulmonary venous connections, which may be treated by transcatheter occlusion, however usually are only provide temporary palliation until new collaterals develop
    - Thrombosis: Fontan physiology represents a low-flow state, and the degree of right-to-left shunting in these patients makes systemic thromboembolism a very high risk. Anticoagulation is indicated if there is history of atrial arrhythmia, fenestration, or EF <40% (even in patients without history of thromboembolism)
    - Protein-losing enteropathy: Though the pathophysiology is poorly understood, this is a common complication occurring in 3-18% of patients. Furthermore, mortality is very high with only ~50% 5-year survival. Therapy is empiric and includes optimizing Fontan hemodynamics, considering fenestration, optimizing cardiac output, and reducing pulmonary vascular resistance
    - Spontaneous fenestration closure: This occurs frequently and may be a silent event. However, in patients with poor cardiac output who were dependent on fenestration to augment ventricular preload, cardiac output may drop, systemic venous pressures may rise, and protein-losing enteropathy may ensue
    - Heart failure: Symptoms may progress such that transplantation may be the only therapeutic option. Of note, early post procedure transplant outcomes within this population are poor relative to those with biventricular circulation, however if they survive, early post procedure window survival is on par with other age matched patients

Left-to-Right Shunting/Eisenmenger Physiology

- There are several congenital abnormalities that result in left-to-right shunting (i.e. cause blood to flow from the systemic to the pulmonary circulation
- Rarely large, uncorrected shunts may progress to Eisenmenger physiology in which the development of pulmonary arterial disease and increased pulmonary vascular resistance (PVR) results in shunt reversal (right-to-left) and cyanosis
- Adults presenting with the Eisenmenger syndrome typically have progressive dyspnea, chronic exercise intolerance, and symptoms of right heart failure
    - More rarely, they may present with arrhythmia, syncope, hemoptysis, or cyanosis (detailed below)
- Workup of the adult patient includes RHC with pulmonary hypertension defined as meanPAP > 25 mmHg with PVR >3 Woods units

    - RHC should additionally be performed with and without supplemental oxygen to determine whether increased PVR is oxygen-responsive
    - Vasodilatory testing (typically with inhaled NO) should also be performed to assess hemodynamic responsiveness and guide medical mgmt
- For patients who have positive vasodilator testing, the mainstay of medical therapy involves pulmonary arterial vasodilatation. Medication classes include oral endothelin antagonists (e.g. bosentan), PDE inhibitors (e.g. sildenafil), guanylate cyclase inhibitors (e.g. riociguat), prostacyclin inhibitors (e.g. selexipag, iloprost, treprostolin, epoprostenol)
- The only surgical option for patients who have progressed to Eisenmenger physiology is heart-lung transplant
    - Though notably, patients with Eisenmenger syndrome who are listed for transplant generally survive longer than patients with idiopathic pulmonary arterial hypertension while awaiting transplant (77% vs. 35% 3-year survival)
- Additional management considerations relate to various complications. These include: Arrhythmia/SCD, hypoxemia, hemoptysis, thrombosis, paradoxical embolism, erythrocytosis/hyperviscosity, and hyperuricemia

INFECTIVE ENDOCARDITIS

See Page 308 for Quick Reference Guide

44. Infective Endocarditis

Infective endocarditis (IE) describes a remarkably heterogeneous collection of clinical syndromes that varies by patient demographic, microbiology, anatomy, clinical presentation, and management.

Epidemiology

Nationwide estimates place the incidence of IE at roughly 15 in 100,000.[1] However, because regulations for mandatory reporting of new cases are not uniform across the country, the exact incidence and frequency are not well known.

Globally, incidence and presentation further depend on the demographic profile of the region under study. In developing countries, IE tends to present in young adults with long-standing rheumatic heart disease. Etiologic organisms are those associated with a more subacute course, such as viridans group streptococci. In developed countries and tertiary care centers, IE presents more as an acute/fulminant illness, often due to *Staphylococcus* species with metastatic foci.

General risk factors for the development of IE include the following (but are highly dependent on the organism involved, as outlined in the "Microbiology" section below):

- Elderly age or male gender
- People who inject drugs (PWID)
- Presence of indwelling catheters/lines
- Valvular heart disease

Pathogenesis

Valvular damage and "non-bacterial thrombotic endocarditis" (NBTE): The current prevailing understanding of IE pathophysiology invokes valvular injury as a prerequisite for IE. In animal models, injected bacteria do not appear to readily adhere to un-injured valves. Mechanisms of valve injury include inflammation from systemic disease (e.g. rheumatic disease), turbulent blood flow, myxomatous degeneration, mechanical injury from instrumentation, and injection drug use. Endothelial damage results in fibrin-platelet deposition in a process called "non-bacterial thrombotic endocarditis".[2]

Valvular insufficiency is more strongly associated with IE than valvular stenosis.[3] A prevailing explanation is that shear stress on the endothelium from the regurgitant jet causes endothelial damage. Vegetations are then localized to the lower-pressure eddy zones on the upstream side of the regurgitant blood flow (Figure 1).[3]

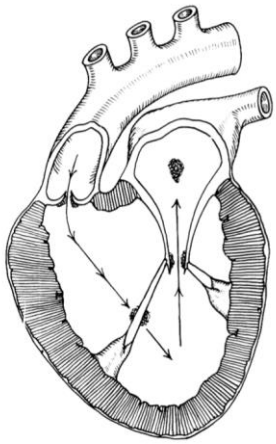

Figure 1. Proposed anatomic relationships between valvular insufficiency and hemodynamic susceptibility to shear stress, bacterial adherence, and vegetation growth.

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Bacteremia, microbial adhesion, and vegetation growth: Bacteremia, either transient or persistent, is an additional prerequisite for the development of IE. The minimum magnitude of bacteremia is not known. Low-grade bacteremia is common after dental procedures and everyday oral care, but is unlikely to cause IE.[4] The predominance of Gram-positive cocci among causative organisms in IE suggests important roles for species-specific surface adhesion proteins. Adhesion is followed by further platelet-fibrin aggregation, leading to growth of the vegetation (Figure 2).

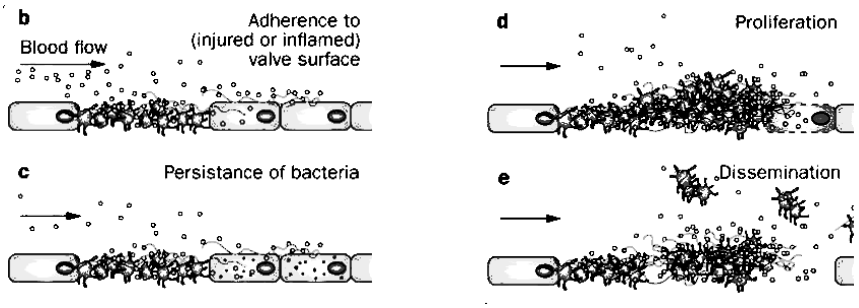

Figure 2. Pathophysiology of Infective Endocarditis

Microbiology

One of the major factors associated with the heterogeneity of presentation in IE patients is the etiologic organism involved. Table 1 below illustrates factors associated with various common causative organisms.

Table 1: Factors Associated with Various Common Causative Organisms in Infective Endocarditis

Organism	Native Valve				Prosthetic Valve	
	Community-acquired	Healthcare-associated		IVDU	Early IE	Late IE
		Noso-comial	Non-noso.			
S. aureus	21%	45%	42%	68%	34%	19%
Coag-negative staphylococci	6	12	15	3	28	20
Enterococcus spp.	10	14	16	5	10	13
Viridans group streptococci	26	10	6	10	1	11
S. gallolyticus (aka *S. bovis*)	10	3	3	1	1	7
HACEK organisms	3	0	0	0	0	2
Fungi	0	2	2	1	6	3
Other	13	7	10	7	6	15
Negative culture	11	7	6	5	14	10

Additional characteristic of IE based on causative organism are outline below:

Staphylococcus species: *S. aureus* often presents with acute onset, prominent systemic involvement and is associated with a high morbidity and mortality. Often vegetations may enlarge quickly and valvular regurgitation may progress during a hospital course. Embolic complications are more common. In contrast, IE caused by coagulase-negative *staphylococcus* (most commonly *S. epidermidis*) tends to have a more subacute presentation. An exception to this is *S. lugudensis*, which is generally more virulent.

Streptococci: Viridans group are the most prevelant of the streptococci. Typical IE presentation is subacute, with weeks to months of low-grade systemic symptoms. In contrast, IE caused by beta-hemolytic streptococci tend to be more virulent with an acute presentation. These infections are associations with IVDU and the elderly and are frequently uniquely sensitive to penicillin. *S. gallolyticus* (formerly *S. bovis*) is typically translocated from a GI source and should prompt consideration of GI malignancy in at-risk populations.

Enterococci: These infections are most often due to *E. faecalis* associated with a GU source and seen in patients of advanced age. They are increasingly associated with central venous catheter use as well. Multi-drug resistant organisms, including VRE, and particularly resistant *E. faecium*, can cause IE that is difficult to cure.

HACEK: This encompasses a group of slow-growing oropharyngeal and upper-respiratory GNRs and consist of: *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Aggregatibacter aphrophilus*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, and *Kingella denitrificans*. Presentation is typically indolent, leading to delayed detection and large vegetation growth with high risk of embolization.

Fungi: Fungal endocarditis is rare and more commonly seen in association with healthcare settings, indwelling central venous catheters, and prosthetic valve IE. The bulk of these infections are due to *Candida* spp. Presentation is variable and embolic complications are frequent.

Aerobic GNR: This represents a rare but important cause of endocarditis because of an association with bacteremia and sepsis.

Culture negative: Culture-negative endocarditis is most likely to be seen in association with recent exposure to antibiotics. Some organisms take longer to culture and may be missed if cultures are not held (*Coxiella*, *Bartonella*, *Brucella*, *Tropheryma*, *Mycoplasma, Legionella*). Serological testing and PCR of a surgical sample may be helpful.

Evaluation and Diagnosis

Presentation of IE can include a number of symptoms, signs, and complications (Table 2). Diagnosis is generally made by a composite of clinical, radiographic, serologic, and microbiologic observations, initially compiled into the Duke Criteria. The original criteria have since been modified to account for the changing epidemiology of IE, as well as to incorporate TEE as a relatively newer diagnostic modality (Table 3). The sensitivity and specificity for both the original and modified Duke Criteria are both ~80%.

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Table 2: Presenting Symptoms, Signs and Complications of Infective Endocarditis

Symptoms (percent affected)

Fever	80-95%
Chills	40-70
Weakness	40-50
Malaise	20-40
Sweats	20-40
Anorexia	20-40
Headache	20-40
Dyspnea	20-40
Cough	20-30
Weight loss	20-30
Myalgia/arthralgia	10-30
Stroke	10-20
Confusion/delirium	10-20
Nausea/vomiting	10-20
Edema	5-15
Chest pain	5-15
Abdominal pain	5-15
Hemoptysis	5-10
Back pain	5-10

Signs & Complications (percent affected)

Fever	86-96%
New murmur	48
Worsening of old murmur	20
Hematuria	26
Vascular embolic event	17
Splenomegaly	11
Splinter hemorrhages	8
Osler nodes	3
Janeway lesions	5
Roth spots	2
Complication	
Stroke	17-20
Non-stroke emboli	23-33
Heart failure	14-33
Intracardiac abscess	14-20
New conduction defect	8

Adapted from *Braunwald's Heart Disease: Textbook of Cardiovascular Medicine, and JAMA* 2018

Echocardiography: Echocardiography is essential in the diagnosis of vegetation associated with IE. Most patients can be evaluated initially with TTE, but note that the absence of vegetation on TTE does not necessarily exclude endocarditis, as there can be flat vegetations, undetectable biofilms on devices, and difficult-to-discern lesions on the aortic root. The sensitivity of TTE is about 66% for native valve endocarditis and <50% for PVE.

The sensitivity of TEE for endocarditis is about 95%, and there are certain scenarios in which initial evaluation with TEE is reasonable. These include: presence of prosthetic valves or cardiac devices, known valvular abnormality, prior endocarditis, and/or other anticipated technical difficulties with TTE. In addition, a TEE should be considered in most patients with a positive TTE to evaluate for complications of endocarditis as the sensitivity of complications is <33% on TTE. TTE often underestimates the size of vegetations.

Additional Imaging Modalities: The use of cardiac CTA or cardiac PET-CT has not been incorporated into the endocarditis guidelines and should be consider adjuvant until more robust data is obtained. Nonetheless, these imaging modalities can be helpful is certain cases and are gaining popularity in clinical practice.

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Table 3: Modified Duke Criteria

Clinical Criteria

- 2 major criteria, or
- 1 major criterion and 3 minor criteria, or
- 5 minor criteria

Major Criteria

- Blood culture findings positive for IE
  - Typical microorganisms consistent with IE from two separate blood cultures:
    - Viridans streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), *Staphylococcus aureus*, HACEK group, or
    - Community-acquired enterococci, in the absence of a primary focus, or
  - Microorganisms consistent with IE from persistently positive blood culture findings, defined as:
    - ≥2 positive culture findings of blood samples drawn >12 hr apart, or
    - 3 or most of ≥4 separate culture findings of blood (with first and last sample drawn ≥1 hour apart)
  - Single positive blood culture for *Coxiella burnetii* or anti-phase I IgG titer ≥ 1:800

- Evidence of endocardial involvement
  - Echocardiographic findings positive for IE:
    - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
    - Abscess, or
    - New partial dehiscence of prosthetic valve, or
    - New valvular regurgitation; worsening or changing of preexisting murmur not sufficient

Minor Criteria

- Predisposition, predisposing heart condition, or intravenous drug use
- Fever—temperature > 38° C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted above (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

Modified and adapted Clin Infect Dis 2000.

Cardiac CTA: Cardiac CTA can be used after a diagnosis of endocarditis is made to evaluate for complications of endocarditis that may require more urgent intervention. In a small series, Cardiac CTA was shown to be more sensitive than TEE in detecting complications of IE such as aortic root abscess. Cardiac CTA can also be used to diagnose NVE and PVE, however test characteristic in large studies have not been established and TEE remains the test of choice.

Cardiac PET-CT: Cardiac PET-CT is another tool to diagnose prosthetic valve endocarditis and performed well in a 188 patient series with PVE with sensitivity (93%), specificity (90%), and

positive (89%) and negative predictive (94%). Cardiac PET does not perform well in native valve endocarditis with a sensitivity of only 22% in that study.

Management

Management of endocarditis often requires a multidisciplinary approach with cardiology, cardiac surgery, infectious disease, neurology, and addiction medicine among others. Up to 50% of patients will develop clinical complications that may warrant surgical intervention.

Antibiotics: Multiple guidelines exist to inform the choice of antibiotics. For empiric management for native valve endocarditis or prosthetic valve endocarditis >12 months post-operative, vancomycin and ceftriaxone 2g q24h is preferable. Gentamycin can be considered in select patients with PVE, however, is not routinely used upfront. When an organism has been identified, the choice of antimicrobial depends on resistance pattern and the presence or absence of prosthetic material (Table 4).

Table 4: Abridged Antibiotic Recommendations for Infective Endocarditis based on Causative Organism *(See 2015 AHA/IDSA endocarditis guidelines for full tables)*

Organism	Antibiotic	
	Native value	**Prosthetic valve**
MRSA	VAN 30 mg/kg/12h and adjust based on levels× 6 weeks	VAN 30 mg/kg/12h + RIF 900mg/24h x 6 weeks + GEN 3mg/kg/24h for the first 2 weeks Note: This is ID provider dependent and RIF+LEVO is an alternative to RIF+GENT (if MRSA is sensitive) Note: Rifampin should not be used until blood cultures are cleared Consideration can be given to oral suppression if managed medically
MSSA	NAF 12g/24h × 6 weeks —or— CFZ 6g/24h × 6 weeks	NAF 12g/24h + RIF 900mg/24h x 6+ weeks + GEN 3mg/kg/24h first 2 weeks
Viridans group streptococci & *S.gallolyticus (S. bovis)*		
Penicillin-sensitive	PEN 12-18M units/24h × 4 weeks —or— CTX 2g/24h × 4 weeks —or— CTX 2g/24h + GEN 3mg/kg/24h × 2 weeks NOTE: GEN regimen rarely used now in practice	PEN 24M units/24h × 6 weeks —or— CTX 2g/24h ± GEN 3mg/kg/24h × 6 weeks —or— VAN 30 mg/kg/12h × 6 weeks NOTE: PEN or CTX together with GEN has not demonstrated superior cure rates compared with monotherapy with PEN or CTX for patients with highly susceptible strain; GEN therapy should not be administered to patients with creatinine clearance <30 mL/min.
Penicillin-resistant	PEN 24M units/24h × 4 weeks —or— CTX 2g/24h + GEN 3mg/kg/24h × 4 weeks —or— VAN 30 mg/kg/12h × 4 weeks	PEN 24M units/24h × 6 weeks —or— CTX 2g/24h + GEN 3mg/kg/24h × 6 weeks —or— VAN 30 mg/kg/12h × 4 weeks

Enterococcus	
Sensitive	AMP 12g/24h × 4-6 weeks —or— PEN 18-30M units/24h + GEN 3mg/kg/24h × 4-6 weeks —or— AMP 12g/24h + CTX 2g/12h × 4-6 weeks NOTE: This is the preferred regimen —or— VAN 30 mg/kg/12h + GEN 3mg/kg/24h × 6 weeks NOTE: Use only if patients cannot tolerate AMP
Gentamicin-resistant	AMP 12g/24h + CTX 2g/12h × 4-6 weeks NOTE: This is the preferred regimen —or— AMP 12g/24h × 4-6 weeks —or— PEN 24M units/24h + STR 15mg/kg/24h × 4-6 weeks —or— VAN 30 mg/kg/12h + STR 15mg/kg/24h × 6 weeks
Penicillin-resistant	SAM 12g/24h + GEN 3mg/kg/24h × 6 weeks —or— VAN 30 mg/kg/12h + GEN 3mg/kg/24h × 6 weeks NOTE: VRE should be treated with daptomycin or linezolid
HACEK	CTX 2g/24h × 4 weeks —or— SAM 12g/24h × 4 weeks —or— CIP 1g/24h PO or 0.8g/24h IV × 4 weeks NOTE: For PVE, duration is 6 weeks

Adapted from Braunwald's Heart Disease and 2015 AHA/IDSA Guidelines: AMP = Ampicillin; CTX = Ceftriaxone; CFZ = Cefazolin; CIP = Ciprofloxacin; GEN = Gentamicin; NAF = Nafcillin; PEN = Penicillin G; RIF = Rifampin; SAM = Ampicillin-sulbactam; STR = Streptomycin; VAN = Vancomycin.

Oral Antibiotics: In general, all patients with IE require intravenous antibiotics. However, there is some data to suggest oral antibiotics be non-inferior in select cases of endocarditis. The regimens used vary by organism and all patients received 2 oral agents. Until more data is available IVs should still be used except in rare cases with consultation with the multidisciplinary team.

Surgery: Many patients who present with IE will develop a complication that requires surgical intervention. The major guidelines that currently inform surgical management of IE are those of the AHA/ACC and ESC. Notably, this is an area that lacks robust clinical evidence. Thus clinical context is important, and decisions should be made with a multidisciplinary team of specialists including cardiologists, cardiothoracic surgeons, infectious disease consultants, and when relevant, neurologists and neurosurgeons. Of note, patients who inject drugs may still be considered for surgery, especially as therapies for substance use disorder evolve.

Generally accepted indications for surgery in left-sided, native-valve endocarditis include signs of ongoing infection despite appropriate antimicrobials (e.g. the presence of intracardiac abscess), hemodynamic instability, mobile vegetations with size > 10 mm in length, and evidence of recurrent embolic phenomena. Vegetation characteristics associated with a high risk of embolization include vegetation length >13 mm, location on the mitral (more so than aortic) valve, and *S. aureus* or fungus as the etiological organism.

Regarding surgical timing, the AHA/ACC and ESC generally support early surgical intervention. For the AHA/ACC, this is defined as taking place during the initial hospitalization and before completion of a full course of antibiotics. The ESC also includes a recommendation for emergency surgery (defined as within 24 hours) in patients where IE is complicated by hemodynamic compromise, such as in refractory pulmonary edema or cardiogenic shock.

Table 5: Guideline-Directed Indications for Early Surgery

AHA/ACC	**LOE**	**ESC**	**LOE**
IE with valve dysfunction resulting in symptoms of HF	IB	Surgery within 24 hours for severe acute regurgitation (aortic or mitral), obstruction or fistula causing refractory pulmonary edema or cardiogenic shock	IB
Left-sided IE caused by S. aureus, fungal, or other highly resistant organisms	IB	Surgery within a few days for severe regurgitation (aortic or mitral) or obstruction causing symptoms of heart failure or echocardiographic signs of poor hemodynamic tolerates	IB
IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	IB	Surgery within a few days for locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	IB

Evidence of persistent infection as manifested by persistent bacteremia or fevers lasting longer than 5 to 7 days after onset of appropriate antimicrobial therapy	IB	Surgery within a few days (or 1-2 weeks after antibiotics) in infection caused by fungi or multiresistant organisms	IC
In patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy	IIaB	Surgery within a few days in cases of persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIaB
Mobile vegetations greater than 10 mm in length (with or without clinical evidence of embolic phenomenon)	IIbB	Surgery within a few days with persistent vegetations >10 mm after one or more embolic episodes despite appropriate antibiotic therapy	IB

In this area, the only prospective randomized controlled trial to date was published in 2012. The EASE trial (Early Surgery versus Conventional Treatment in Infective Endocarditis) included 76 patients with left-sided native-valve endocarditis with severe valve disease and large vegetations at high risk for embolism.[5] Patients were randomized to early surgery (defined as within 48 hours) or to conventional treatment (defined according to the 2005 AHA/ACC guidelines: medical management with surgery only if symptoms persisted despite antibiotic therapy or in the case of a complication requiring urgent surgery). Inclusion criteria required a definitive diagnosis of IE, severe mitral or aortic valve disease, and a vegetation with a diameter greater than 10 mm. Notably however, patients with a strong indication for surgical management were excluded, including those patients with a need for urgent surgery, patients with moderate-to-severe heart failure, cases complicated by annular or aortic abscess, and those with fungal endocarditis. In this intention-to-treat analysis, greater than two-thirds of patients randomized to conventional treatment ultimately underwent surgery, either on initial hospitalization or in follow-up. Study results demonstrated that early surgery reduced the composite primary endpoint of in-hospital death and embolic events within 6 weeks after randomization.

Note that with respect to right-sided endocarditis, there are fewer consensuses regarding surgical timing, and in general, the urgency is less since embolic phenomenon are generally limited to the pulmonary vasculature (in absence of intracardiac shunt). Indications for right-sided valve repair or replacement include right heart failure secondary to severe tricuspid regurgitation with poor response to medical therapy, sustained infection caused by difficult-to-treat organisms (i.e. fungi, multidrug resistant bacteria) or lack of response to appropriate antimicrobial therapy, and tricuspid valve vegetations that are ≥20 mm in diameter and recurrent pulmonary embolism despite antimicrobial therapy. There may also be benefit to valve replacement in severe tricuspid regurgitation to reduce long-term complications.

Source of infection: A search for the source of infection should be undertaken based on organism identified to reduce the risk of recurrent endocarditis. This often includes a dental evaluation (for example in viridans strep) and consideration of a work-up for a GI source (for example enterococcus and *S. gallolyticus*). In patients who inject drugs, help from our addiction team is often a key piece of management.

Embolic sources/source control: Search for metastatic focus is often needed as based on patient symptoms and hemodynamics. For example, a patient who is hypotensive may need a CT A/P to look for an undrained intraabdominal abscess.

Neuroimaging: In general, imaging should be obtained on all patients with focal neurological findings to assess for mycotic aneurysms. In addition, strong consideration should be given to neuroimaging for patients undergoing cardiac surgery for endocarditis, as mycotic aneurysms can be intervened on prior to cardiac surgery to reduce the risk of bleed. CTA is more sensitive than MRI for distal mycotic aneurysms and the optimal sequence of imaging has not been determined. Prospective data is lacking.

Prophylaxis

Maintenance of oral health and hygiene is an important measure for preventing IE. Additionally, antibiotic prophylaxis is indicated for certain populations prior to high-risk procedures. These are outlined below. Prophylaxis can be achieved with one-time doses of the following, with amoxicillin as the preferred agent.

Route	Antibiotic	Dose
Oral	Amoxicillin	2 g
	Cephalexin	2 g
	Clindamycin	600 mg
	Azithromycin	500 mg
IV	Ampicillin	2 g
	Cefazolin	1 g
	Ceftriaxone	1 g
	Clindamycin	600 mg

Populations with an indication for antibiotic prophylaxis:

1. Prosthetic cardiac valve or prosthetic material used for cardiac repair
2. Prior history of IE
3. Unrepaired or palliated cyanotic congenital heart disease, including surgically constructed shunts and conduits
4. Completely repaired congenital heart disease with prosthetic material during the first 6 months after the procedure
5. Repaired congenital heart disease with residual defects at the site or near to the site of a prosthetic patch or device that inhibits endothelialization
6. Cardiac transplant patients with acquired cardiac valvulopathy

Types of procures where prophylaxis should be considered:

1. Dental procedures that involve gingival tissue, periapical region of the teeth, perforation of gingival mucosa
2. Respiratory tract procedures with incision or biopsy, and
3. GI or GU procedures in patients with infections at these sites

Prophylaxis is not recommended for non-dental procedures (i.e. EGD, colonoscopy, orthopedic procedures) unless active infection present.

Antibiotic prophylaxis before vaginal delivery is highly controversial with little supportive data. While there is no recommendation in the European guidelines, the AHA/ACC and some expert opinion guidelines suggest that antibiotics could be considered before vaginal delivery for patients with:

1. Prosthetic cardiac valves or prosthetic material used for cardiac repair
2. Unrepaired or palliated cyanotic congenital heart disease, including surgically constructed shunts and conduits (though note that these patients are rarely able to become pregnant)

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QUICK REFERENCE GUIDE: INFECTIVE ENDOCARDITIS

Epidemiology

- The term Infective endocarditis (IE) describes a remarkably heterogeneous collection of clinical syndromes that varies by patient demographic, microbiology, anatomy, clinical presentation, and management

Microbiology

- One of the major factors associated with the heterogeneity of presentation in IE patients is the etiologic organism involved
    - The most common pathogen in community-acquired native-valve endocarditis (NVE) is the viridans group streptococci (26%), followed by staph aureus (21%)
    - Staph aureus accounts for the majority of cases of healthcare-associated NVE (45%), IVUD-associated NVE, and prosthetic-valve endocarditis (PVE) (19-34%)
    - IE cases caused by *S. aureus* tend to present acutely, and patients are usually quite ill. Embolic complications are more common
    - Viridans IE tends to present in a more subacute fashion, with weeks to months of low-grade systemic symptoms

Evaluation and Diagnosis

- Diagnosis of IE is generally made by a composite of clinical, radiographic, serologic, and microbiologic observations, initially compiled into the Duke Criteria. These have since been revised to form the modified Duke Criteria, in which diagnosis requires:
    - 2 major criteria, or
    - 1 major criterion and 3 minor criteria, or
    - 5 minor criteria
- Major Criteria include:
    1. Blood culture findings positive for IE:
        - Typical microorganisms consistent with IE from two separate blood cultures:
            - Viridans streptococci
            - *Streptococcus gallolyticus* (formerly *S. bovis*)
            - *Staphylococcus aureus*
            - HACEK group
            - Community-acquired enterococci, in the absence of a primary focus, or
        - Microorganisms consistent with IE from persistently positive blood culture findings, defined as:
            - ≥2 positive culture findings of blood samples drawn >12 hr apart, or
            - All of 3 or most of ≥4 separate cultures of blood (with first and last sample drawn ≥1 hour apart)
            - Single positive blood culture for *Coxiella burnetii* or anti-phase I IgG titer ≥ 1:800
    2. Evidence of endocardial involvement
        - Echocardiographic findings positive for IE:
            - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
            - Abscess, or
            - New partial dehiscence of prosthetic valve
        - New valvular regurgitation; worsening or changing of preexisting murmur not sufficient

- Minor Criteria include:
    - Predisposition, predisposing heart condition, or intravenous drug use
    - Fever, temperature > 38° C
    - Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
    - Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
    - Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted above (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE
- The sensitivity of TTE for diagnosis of IE is about 66% for NVE and <50% for PVE
- The sensitivity of TEE is about 95%, and there are certain scenarios in which initial evaluation with TEE is reasonable. These include:
    - Presence of prosthetic valves or cardiac devices
    - Known valvular abnormality
    - Prior endocarditis, and/or
    - Other anticipated technical difficulties with TTE
- Additionally, TEE should be considered in most patients with a positive TTE to evaluate for complications of endocarditis, as the sensitivity of complications is <33% on TTE and TTE often underestimates the size of vegetations
- Cardiac CTA and Cardiac PET-CT are emerging imaging modalities for diagnosis of IE

<u>Management</u>

- Medical therapy with antibiotics is the mainstay of treatment for IE, but up to 50% of patients will develop clinical complications that may warrant surgical intervention
- For empiric management for NVE or PVE >12 months post-operative, vancomycin and ceftriaxone 2g q24h is preferable
    - Gentamycin can be considered in select patients with PVE, however, is not routinely used upfront
- When an organism has been identified, the choice of antimicrobial depends on resistance pattern and the presence or absence of prosthetic material (See Table 4, page 314 for antibiotic recommendations based on causative organism)
- Generally accepted indications for surgery in left-sided NVE include:
    - Signs of ongoing infection despite appropriate antimicrobials (e.g. the presence of intracardiac abscess)
    - Hemodynamic instability
    - Mobile vegetations with size > 10 mm in length, and
    - Evidence of recurrent embolic phenomena
        - Vegetation characteristics associated with a high risk of embolization include vegetation length >13 mm, location on the mitral (more so than aortic) valve, and *S. aureus* or fungus as the etiological organism
- The AHA/ACC guidelines generally support early surgical intervention, defined as taking place during the initial hospitalization and before completion of a full course of antibiotics
- There are fewer consensus guidelines with respect to surgery/surgical timing in right-sided endocarditis, and in general, the urgency is less since embolic phenomena are generally limited to the pulmonary vasculature (in absence of intracardiac shunt)
- Indications for right-sided valve repair or replacement generally include:

- Right heart failure secondary to severe tricuspid regurgitation with poor response to medical therapy
- Sustained infection caused by difficult-to-treat organisms (i.e. fungi, multidrug resistant bacteria) or lack of response to appropriate antimicrobial therapy, and
- Tricuspid valve vegetations that are ≥20 mm in diameter with recurrent pulmonary embolic phenomena despite antimicrobial therapy

Prophylaxis

- Antibiotic prophylaxis for IE is indicated for certain populations prior to high-risk procedures
  - Populations with an indication for antibiotic prophylaxis:
    - Prosthetic cardiac valve or prosthetic material used for cardiac repair
    - Prior history of IE
    - Unrepaired or palliated cyanotic congenital heart disease, including surgically constructed shunts and conduits
    - Completely repaired congenital heart disease with prosthetic material during the first 6 months after the procedure
    - Repaired congenital heart disease with residual defects at the site or near to the site of a prosthetic patch or device that inhibits endothelialization
    - Cardiac transplant patients with acquired cardiac valvulopathy
  - Types of procures where prophylaxis should be considered:
    - Dental procedures that involve gingival tissue, periapical region of the teeth, perforation of gingival mucosa
    - Respiratory tract procedures with incision or biopsy, and GI or GU procedures in patients with infections at these sites

VASCULAR MEDICINE

See Page 339 for Quick Reference Guide

45. Venous Thromboembolism

DEEP VEIN THROMBOSIS

Clinical Considerations

Therapeutic anticoagulation (AC) is indicated in all patients with lower extremity proximal DVT (i.e. arising in the popliteal, femoral, or iliac veins) and in some cases of distal DVT, in the absence of contraindications. Proximal lower-extremity DVTs are associated with a greater risk of pulmonary embolism and mortality.

Therapeutic AC should also be considered in cases of upper extremity DVT, though note that the majority of these cases are secondary to indwelling catheters (see Catheter Associated Thrombosis section below).

Management

Medical therapy: Direct oral anticoagulants (DOACs) (apixaban, rivaroxaban, edoxaban and dabigatran) are considered first-line agents for VTE in the majority of patients. Warfarin is favored in patients with APLAS. Traditionally, LMWH is considered first-line in patients with active malignancy. Emerging data suggest that edoxaban[1] and rivaroxaban[2] may be effective in patients with cancer, although further studies are needed before DOACs can be routinely prescribed for treatment of cancer-associated thrombosis.

Agent	Mechanism	Indications	Dose
Unfractionated Heparin	Inactivates thrombin & factor Xa through AT-dependent mechanism	• Treatment of DVT/PE	**Treatment:** 80U/kg bolus + initiate gtt at 18U/kg/hr and titrate per protocol for goal PTT 70-100
Warfarin (Coumadin)	Vitamin K antagonist	• Treatment of DVT/PE	**Treatment**: Dose depends on INR measurements and varies for typical INR goal 2-3 *Requires bridging with parenteral agent if INR <2*
Apixaban (Eliquis)	Factor Xa inhibitor	• Treatment of DVT/PE • DVT prophylaxis after hip/knee replacement surgery	**Treatment**: 10 mg BID x 7 days, then 5 mg BID during the first 6 months, and 2.5 mg BID thereafter for most patients **Prophylaxis**: 2.5 mg BID

Rivaroxaban (Xarelto)	Factor Xa inhibitor	• Reduction in risk of recurrent DVT/PE after 6 months of therapeutic anticoagulation	**Treatment**: 15 mg BID x 21 days, then 20 mg QD for the first 6 months, and 10 mg QD thereafter for most patients **Prophylaxis**: 10 mg QD *Should not be used in patients with CrCl <30 mL/min*
Edoxaban (Savaysa)	Factor Xa inhibitor	• Treatment of DVT/PE after 5-10 days of therapy with UFH/LMWH	**Treatment**: 60 mg QD (30 mg QD if CrCl 15-50 mL/min) **Prophylaxis**: Not approved
Dabigatran (Pradaxa)	Direct thrombin inhibitor	• Treatment of DVT/PE after 5-10 days of therapy with UFH/LMWH • DVT/PE prophylaxis after hip replacement surgery • Reduction in risk of recurrent DVT/PE following initial therapy	**Treatment**: 150 mg BID (CrCl >30 mL/min) **Prophylaxis**: 110 mg once, then 220 mg QD *Should not be used in patients with CrCl <30 mL/min*
Enoxaparin (Lovenox)	Activates ATIII to inactivate Xa > IIa	• Prophylaxis and treatment of DVT/PE	**Treatment:** 1 mg/kg BID or 1.5 mg/Kg QD **Prophylaxis**: 40 mg QD (30 mg BID if high-risk) *Should be used with caution in patients with reduced CrCl. Titration by anti-Xa may be useful*
Fondaparinux	Activates ATIII to inactivate Xa only	• Prophylaxis and treatment of DVT/PE	**Treatment**: 5 mg QD (if <50 kg), 7.5 mg QD (if 50-100 kg), 10 mg QD (if >100 kg) **Prophylaxis**: 2.5 mg QD *Should not be used in patients with CrCl <30 mL/min*
Argatroban	Direct IIa inhibitor	• Treatment of DVT/PE in patients with a history of HIT	**Treatment**: 0.2-1 mcg/kg/min

The majority of patients presenting after a first episode of provoked VTE should receive a minimum of three months of therapeutic anticoagulation. In patients with low risk of bleeding and persistent risk factors for DVT, such as immobility or hormone replacement therapy, an extended course (i.e. six to twelve months) can be considered to reduce the risk of recurrent VTE. Finally, long-term anticoagulation should be considered in select populations, including patients with unprovoked DVT/PE, recurrent provoked DVT/PE, or active malignancy, provided that the bleeding risk associated with long-term anticoagulation is acceptable.[3] The HERDOO2 rule (Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 ug/L; obesity with BMI ≥30; or older age ≥65 years) states that women presenting after a first unprovoked VTE event who meet zero or one of the above criteria may safely discontinue anticoagulation after a short (5-12 month) treatment course.

Catheter-directed thrombolysis: Anticoagulation therapy is the standard of care for most patients with DVT. The only widely accepted indication for catheter-directed thrombolysis (CDT) for lower extremity DVT is massive proximal clot burden leading to compromised lower extremity perfusion and risk of limb ischemia (i.e. phlegmasia cerulea dolens). Candidates for CDT should have fresh clot (<21 days old, as organized clot is less likely to respond to lysis) and low bleeding risk. Urokinase and tPA are the most common agents used for CDT and are typically administered over a 24-hour period, after which therapeutic anticoagulation is resumed. CDT may be associated with a lower risk of post-thrombotic syndrome (PTS), and especially moderate-to-severe PTS, following an acute ileo-femoral DVT per the CaVenT study.[4] Follow up after 5 years resulted in a persistent and increased clinical benefit but did not lead to better quality of life.[5] The ATTRACT trial showed that the addition of pharmacomechanical CDT to anticoagulation did not result in lower risk of PTS but did result in higher risk of major bleeding.[6]

IVC filters: Inferior vena cava (IVC) filters are generally deployed in the infrarenal IVC under fluoroscopic guidance. IVC filters may be either permanent or retrievable, although the latter have become increasingly popular due to the long-term complications associated with indwelling IVC filters (including filter migration, IVC wall penetration, and thrombosis).

IVC filters are indicated for prevention of PE in patients with acute proximal DVT who have either failed therapeutic anticoagulation or have an absolute contraindication to anticoagulation. In some cases, IVC filter placement can be placed prophylactically in patients at high risk for VTE, although this remains a controversial topic. The seminal PREPIC trial, conducted in the late 1990s, found that IVC filter placement in patients with proximal DVT decreased the incidence of subsequent PE but at the expense of recurrent DVT in patients with an IVC filter in place.[7] In a follow-up trial, PREPIC II, which enrolled patients with both PE and DVT, placement of an IVC filter in addition to therapeutic anticoagulation did not confer incremental benefit (in terms of recurrent PE) compared to anticoagulation alone.[8] Unfortunately, the utility of these trials is limited by the fact that there are many patients encountered in everyday clinical practice who do not fall into their inclusion criteria.

Generally speaking, IVC filter retrieval should be considered once the contraindication to anticoagulation has resolved. Close outpatient follow-up is critical to ensure prompt removal once the IVC filter is no longer indicated.[9]

PULMONARY EMBOLISM

Clinical Considerations

Risk stratification of pulmonary embolism depends on the presence or absence of hemodynamic instability and right heart strain. RV strain can be assessed via multiple modalities including cardiac biomarkers (NT-proBNP, hsTnT), EKG (RBBB, anterior T wave inversions, S1Q3T3), CT-PE (RV/LV ratio >0.9), or TTE (RV dilation, hypokinesis, or McConnell's sign, in which there is diffuse RV wall hypokinesis with apical sparing). High-risk or massive PE is characterized by the presence of hemodynamic instability and carries significant acute mortality risk (>15%). Intermediate-risk or submassive PE is characterized by right heart strain without hemodynamic instability and is associated with 3-15% short-term mortality risk (and higher intermediate-term mortality). Finally, low-risk or non-massive PE carries a low risk of short-term mortality and is characterized by the absence of right heart strain or hemodynamic changes.

Importantly, the presence or absence of hemodynamic instability does not always correlate with the anatomic location of clot or the degree of clot burden. For example, most patients with saddle PE do not present with hemodynamic instability. Conversely, a subset of patients with more distal PEs (i.e. segmental or subsegmental) may present with hemodynamic changes, especially if they have pre-existing cardiopulmonary disease.

Management

Low-risk and intermediate-risk PE: Patients with low-risk PE without hemodynamic instability or end-organ dysfunction should be promptly initiated on therapeutic (oral) anticoagulation, provided there is no contraindications to anticoagulation and risk of bleeding is low.

Patients with intermediate-risk PE (i.e. evidence of right heart strain and hemodynamically stable) should be anticoagulated and monitored closely for clinical signs of deterioration. It is recommended that most patients without hypotension are not treated with thrombolytic therapy.[3] However, patients with PE include a broad spectrum of presentations. In patients with PE who have associated cardiopulmonary deterioration that has not progressed to hypotension, thrombolysis or catheter-based therapies can be considered on a case-by-case basis weighing the risks and benefits of the procedure. If persistent dyspnea can consider PERT consult.

High-risk PE: Patients presenting with high-risk PE with hemodynamic instability should be considered for thrombolysis to rapidly reduce clot burden. Administration of systemic thrombolytics (alteplase [t-PA] and tenecteplase) is associated with decreased all-cause mortality, at the expense of significantly increased risk of major bleeding and intracranial hemorrhage.[10] Catheter-directed thrombolysis is an attractive alternative to systemic thrombolysis which may mitigate some of the bleeding risk associated with the latter, but requires the ability for rapid implementation that does not exist in most centers and / or in most hours of the day. Notably, other invasive stabilizing measures (e.g. ECMO) should also be considered in this patient population with input from the PERT team and in the absence of RCT data.

Finally, patients who have failed thrombolysis or have an absolute contraindication to the procedure should be considered for surgical thromboembolectomy.

PERT: The Pulmonary Embolism Response Team (x47378) at MGH is a rapid response, multidisciplinary team that can be activated for prompt assessment and management of patients with massive or submassive PEs. PERT should be consulted for all patients with massive PEs and in select patients with submassive PEs.

CATHETER-ASSOCIATED THROMBOSIS

Clinical Considerations

The rate of central venous catheter (CVC)-associated thrombosis is as high as 14-18%, although the majority of cases present without symptoms. Duplex ultrasound is the imaging modality of choice for diagnosing catheter-related thrombosis. Current guidelines recommended that systemic anticoagulation be administered for at least three months, with LMWH preferred over warfarin and DOACs in patients with malignancy.

If central access is required, the CVC can remain in place so long as it is appropriately positioned and functioning correctly without evidence of infection. If the catheter remains after three months of therapeutic anticoagulation, LMWH prophylaxis is recommended until the line is removed.[3]

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TOC

46. Peripheral Artery Disease

Peripheral artery disease (PAD) is atherosclerotic disease leading to peripheral artery obstruction. PAD is prevalent worldwide, and it is estimated that 202 million people are affected.[1]

Table 1. Risk factors for peripheral artery disease

Risk Factors
Age ≥70 years
Male sex
African American race
Smoking history
Diabetes Mellitus
Atherosclerosis at other sites
Hypertension
Hypercholesterolemia
Elevated homocysteine

Acute critical limb ischemia is a sudden decrease in limb perfusion presenting within 2 weeks of an inciting event.

- Almost always due to arterial occlusion, rarely from severe venous occlusion.
- Etiologies of arterial occlusion include thrombosis at site of atherosclerotic plaque in native artery (most common cause), thromboembolism, thrombosis of stent/graft, thrombosis of aneurysm, arterial dissection, and iatrogenic from arterial access sites.

Chronic limb ischemia is ischemia of >2 weeks duration sufficient to threaten the limb. This typically corresponds to ABI <0.4.

- Usually due to multilevel arterial stenoses or occlusion but can occur at a single vessel (i.e. isolated tibial vessel disease in diabetics). Usually aortoiliac and femoropopliteal or femoropopliteal and tibial segments.[2]

Clinical Considerations

Patients with PAD may present with symptoms such as leg pain. However, many will be asymptomatic and only identified through screening. Classic claudication is only present in 10-35% of patients with PAD (Table 2) and is described as exertional buttock, hip, thigh, calf, or foot pain that begins after a certain distance, causes the patient to stop walking, and is relieved within 10 minutes of rest.

Table 2. Prevalence of presentations of peripheral artery disease[2]

Presentation	Percent of PAD pts ≥ 50 y.o.
Asymptomatic (screening)	20-50%
Atypical leg pain	40-50%
Classic claudication	10-35%
Threatened limb (ulceration, gangrene)	1-2%

Physical exam findings associated with PAD include: iliac/femoral/popliteal bruit, unequal pulses, and ulceration.

Symptoms of critical limb ischemia

- Acute limb ischemia presents more rapidly due to the absence of collaterals and patients are more likely to experience the 6 P's (pain, paresthesias, paralysis, poikilothermia/coolness, pallor, reduced pulses)
- Acute-on-chronic ischemia occurs in patients with a history of PAD or revascularization and presents as suddenly increasing known symptoms over a period of hours to days due to presence of collateral circulation.
- Chronic limb ischemia presents as ischemic rest pain, often foot pain is worse when patient is recumbent or with elevation

Physical exam findings of critical limb ischemia

- Based on the 6 P's as above (see Table 1)
- Palpate all pulses (and Doppler distal pulses if available) and perform neurologic exam for sensation and strength
- Beside ABI <0.4 indicates severe ischemia
- Chronic limb ischemia presents with non-healing ulceration or gangrene

Table 1. Clinical categories of acute critical limb ischemia[2]

Category	**Clinical features**	**Doppler pulses**	**Management and Prognosis**
Viable	No sensory loss or muscle weakness	Audible	No immediate threat of tissue loss Obtain vascular imaging
Marginally threatened	Minimal pain with no sensory loss and weakness	Arterial pulses inaudible Venous pulses audible	Need to be treated promptly, but salvageable Obtain vascular imaging
Immediately threatened	Sensory loss, rest pain, mild-to-moderate weakness	Arterial pulses inaudible Venous pulses audible	Need immediate revascularization (no time for imaging), but salvageable
Irreversibly ischemic	Tissue loss or nerve damage → Profound sensory loss and weakness Paralysis or rigor possible	Inaudible	Require amputation, revascularization may allow for healing or lower amputation

Diagnosis

The USPSTF has stated that there is insufficient evidence to recommend routine screening for PAD with ankle-brachial index.[3] However, many believe that detection of PAD has value in that it identifies patients at risk for atherosclerosis at other sites and also may result in interventions such as aspirin, statins, and exercise that may lower the risk of CVD.

The diagnosis of PAD can be suspected clinically based on history of symptoms, risk factors for PAD, and physical exam findings. Ankle-brachial index (ABI) should be used to confirm the diagnosis.

1. Risk factors + symptoms + physical exam findings
    a. Probability of PAD is increased in patients age >70, age 50-69 with history of diabetes or smoking, or age 40-49 with diabetes and one additional risk factor (table 1)
2. ABI
    a. < 0.9 indicates PAD, <0.4 indicates critical limb ischemia
    b. 90% sensitive and 98% specific for detecting ≥ 50% stenosis.[3]
    c. May be falsely elevated from calcifications and in patients with DM
3. Segmental pressure and pulse volume recordings
    a. Formal recordings using blood pressure cuffs and Doppler waveforms in the vascular lab
    b. Helpful for identifying the site and severity of disease
4. Exercise testing
    a. Exercise adds sensitivity to normal and abnormal tests and should be considered as a component of ABI or segmental pressures
5. Vascular imaging (e.g. duplex ultrasonography, computed tomography or magnetic resonance angiography)
    a. Useful for pre-intervention planning

<u>Management</u>

PAD is generally managed with exercise and risk factor modification. Medications such as cilostazol have been shown to be effective when used for symptom relief. Revascularization is an option for patients with significant or disabling symptoms unresponsive to other treatment options.

Medical therapy focused on symptom relief:

- Supervised Exercise Therapy: First-line treatment in patients with claudication. Improves walking time and distance. Supervised exercise is more effective and has a lower dropout rate.[4] It is comparable to stent revascularization in improving functional status and QOL and both better than medical therapy alone.[5]
    - 36 sessions over 12 weeks, each exercise-training session lasting 30-60 minutes
- Cilostazol: Use for lifestyle-limiting claudication, especially if exercise ineffective and revascularization not possible. Goal is to decrease pain and increase walking distance.
    - Dose is 100 mg twice daily. Given multiple side effects, gradual dose increase is recommended

Medical therapy focused on lowering risk of CVD progression:

- Risk factor modification:
    - Diabetes management
    - Hypertension management
    - Weight loss
- Smoking cessation: Alters progression and lowers CV risk
- Antiplatelet agents:
    - Aspirin 81 or clopidogrel 75 mg are the first line agents. The benefits of these agents in PAD are unclear as recommendations for PAD have been extrapolated from studies in CVD.

    - DAPT is not recommended unless there is another indication due to increased bleeding risk without benefit.[6]
- Statin: Moderate and high-intensity statins provide reduction in vascular events (Heart Production Study) and may also improve symptoms.
- Rivaroxaban: The COMPASS trial showed that rivaroxaban (2.5mg BID) plus aspirin (100mg QD) led to lower risk of major adverse cardiovascular events but increased risk of major bleeding.[7]

Revascularization is recommended for patients with limb-threatening ischemia such as ischemic rest pain or ulceration and patients with significant or disabling symptoms unresponsive to above.[8] Options include percutaneous intervention or open surgical intervention depending on the location and extent of disease. Most patients are offered endovascular intervention.

Management of acute critical limb ischemia:

1. Immediate anticoagulation with heparin gtt
2. Revascularization
    a. Factors that favor surgical revascularization: immediately threatened limb, large proximal lesion, long segment lesion, diffuse multilevel disease
    b. Factors that favor endovascular revascularization: comorbidities that increase surgical risk, multi-level disease undergoing staged approach (endovascular-first), no suitable vessel for bypass graft
3. If irreversible ischemia (non-salvageable), amputation is recommended

Management of chronic limb ischemia: A subset of patients (based on transcutaneous oxygen and ABI) can be treated with conservative management consisting of aggressive wound care, pain control, and medical management.

Options for revascularization include endovascular therapy (percutaneous transluminal angioplasty) or bypass surgery. There has been persistent, widespread clinical uncertainty about the best means by which to revascularize patients with chronic limb threatening ischemia. In high level centers, common practice is that most patients receive endovascular therapy first. The BEST-CLI trial is currently enrolling patients and is designed to compare best endovascular therapy with best open surgical treatment in patients eligible for both treatments.

Amputation may be considered in patients with sepsis, limb paralysis, uncorrectable flexion contracture, or significant necrosis of weight-bearing parts of the foot.

Referral to a wound clinic or involvement of a wound care provider (e.g. nurse) is recommended.

1. Debridement: Devitalized tissue, foreign material, infected exudate, and necrotic muscle or fascia can prevent proper cellular response and healing. Extreme caution and expertise are required to do this properly and safely in the context of imperfect arterial flow to a limb as debridement may result in exacerbation of ulceration and eventually in limb loss.
    a. Surgical Debridement: If removing large areas of necrotic tissue, evidence of infection, or chronic nonhealing wounds
2. Irrigation: No evidence for any additive, generally use sterile normal saline or sterile water, though no increased infection risk in using tap water.
3. Dressing: Moisture and occlusion found to improve rate of healing. Should monitor and re-assess dressing requirements. In general, hydrogels for debridement, low-adherent

and moisture-retentive for granulation, and low-adherent for epithelialization. Change daily or every other day.
4. Antibiotics: only if concern for infection (cellulitis, purulence, malodor, wet gangrene, osteomyelitis, systemic sx)
5. Glycemic control: No clinical evidence for short-term control but usually done regardless

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47. Digital Ischemia

Clinical Considerations

Digital ischemic generally presents as painful, discolored (often blue) digits in the upper or lower extremities.

Diagnosis

Etiologies are generally categorized by vessel size[1]

- Small vessel: Connective tissue diseases (SLE, Scleroderma), pressor-related, hypercoagulability, embolus, polycythemia, trauma, frost-bite, post-procedural
- Medium vessel: Buerger's disease, polyarteritis nodosa, scleroderma, hypercoagulability, embolus, trauma, post-procedural
- Large vessel: Takayasu's, Kawasaki's, dissection, thoracic outlet syndrome, atherosclerosis

Effective diagnosis of etiology requires a multimodal approach that is highly predicated on history. This includes identification of:

- Risk factors for cardioemboli such as prior MI/Afib/valvular heart disease
- Risk factors for atherosclerosis
- Toxin ingestion
- Prior rheumatologic diagnoses
- Medication history (i.e. pressors)
- Tobacco and marijuana use

Depending on the above, initial lab workup may include: CBC with diff, coags, lipid panel, urine tox screen, TSH, scleroderma testing (Scl-70, anti-centromere, anti-RNP pol III), vasculitis testing (ANA, anti-dsDNA, RNP, Smith, C3/4, ESR, CRP, RF, ANCA, cryoglobulins), antiphospholipid antibodies, blood cultures, blood viscosity, serum electrophoresis.

Imaging may also support a diagnosis with various modalities including: Doppler (can help to distinguish between vasculopathy and vasculitis), Angiogram, CTA or MRA. Consider echocardiogram.

Management

Appropriate management involves identification and treatment of the underlying condition, but the following is a list of agents may be employed for specific treatment of digital ischemia.[1]

1. Short acting CCB (nifedipine, amlodipine) titrated up to maximal dose
2. Pain control. One option is injection of lidocaine or bupivacaine at base of finger, with repetition as necessary
3. If progressing despite above, add heparin gtt x 24-72 hours and IV prostacyclin (Iloprost, Epoprostenol, Alprostodil) because if embolus/thrombus is suspected, early anticoagulation is important
4. Once stable, convert to long acting CCB +/- Topical nitrates[2] or PDE-inhibitors (sildenafil tadalafil, vardenafil, cilostazol).[3]
5. Evaluate for infection and add antibiotics as necessary
6. If not improving with above, call hand surgery/plastic surgery (consideration of angioplasty or sympathectomy)
7. If the cause is Buerger's disease, complete smoking cessation is critical

If patients do not respond to the initial therapy above, seek consultant recommendations overnight. Otherwise, early surgical consultation is advised for all cases for assessment of when to intervene.

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48. Renal Artery Stenosis

Clinical Considerations

Renal artery stenosis (RAS) is a potential cause of secondary hypertension. It is characterized by narrowing of one or both renal arteries leading to impaired blood flow to the target kidney and resulting in a spectrum of clinical syndromes that range from asymptomatic obstruction (incidental RAS) to renal vascular hypertension (RVH) and ischemic nephropathy.[1] Renal artery stenosis is defined by high-grade and documented impediment to flow.

RAS likely accounts for 1-5% of patients with hypertension; however, among patients with acute, severe, or refractory hypertension, prevalence estimates are higher.[2] Risk factors include age, hyperlipidemia, and hypertension. Prevalence is increased in elderly patients with comorbidities such as diabetes, PAD, CAD, or hypertension.[3]

1. Atherosclerotic RAS (ARAS) accounts for 90% of all RAS.[4] Patients with ARAS are likely to have atherosclerotic disease in other areas of the body as well including CAD and PAD. ARAS is considered a progressive disease that can lead to worsening stenosis and eventual occlusion over time.
2. Fibromuscular Dysplasia (FMD) is a non-inflammatory, non-atherosclerotic vascular disease that commonly affects the renal arteries.[5] According to the FMD registry, the majority of patients affected with FMD are female (90%) and the mean age at diagnosis was 52 years.[6] In this registry FMD was identified in the renal artery in 66% of patients.
3. Other non-atherosclerotic forms of RAS include aneurysms, congenital or traumatic AV fistulas, vasculitis, neurofibromatosis, trauma, embolization, post-radiation therapy, dissection, or extrinsic compression of the renal arteries due to tumors.[7]

Diagnosis

The following table provides a list of factors that highlight when it is appropriate/important to consider renal artery stenosis.

Table 1. Clinical Clues to the Diagnosis of Renal Artery Stenosis

Clinical Clues to the Diagnosis of Renal Artery Stenosis
General Clinical Features Suggestive of Secondary Hypertension
1. Severe or resistant* hypertension 2. Acute rise in BP over a previously stable value 3. Age < 30, especially in non-obese, non-black patient with no family history of HTN 4. Malignant or accelerate HTN 5. HTN associated with electrolyte disorders including HypoK and metabolic acidosis
Clinical Features Suggestive of Renal Artery Stenosis
1. Onset of severe (HTN (SBP ≥ 180 and/or DBP ≥ 120) after the age of 55 2. Unexplained rise in serum Cr > 50% within 1 week of ACEi or ARB initiation 3. Severe HTN in patient with unexplained atrophic kidney or asymmetry in renal sizes >2cm 4. Severe HTN in patients with recurrent episodes of flash pulmonary edema or refractory HF (*NB: flash pulmonary edema more common in patients with bilateral RAS)* 5. Systolic-diastolic abdominal bruit that lateralizes to one side (Sn 40% Sp 99%)

Adapted from 2011 ACC/AHA Practice Guidelines for the Management of Patients with PAD

**Resistant HTN defined as persistence of HTN despite concurrent use of adequate doses of 4 antihypertensive agents from different classes, including a diuretic with documented compliance.*

Screening

Testing for renovascular disease is indicated for patients who present with clinical findings consistent with secondary hypertension.

Intervention for RAS has become uncommon, especially after the publication of the CORAL trial.[8] At the least, an intervention is planned if a significant stenotic lesion is found (see section on revascularization) AND patients present with cardio-renal syndrome, flash pulmonary edema OR resistant hypertension or deteriorating renal function in very specific cases.

Based on the above criteria, testing for RAS should proceed for patients thought to have a high likelihood of benefitting from possible revascularization (see Table 3). Testing should not be performed in patients who respond well to medical therapy or who have a low likelihood of having significant disease based on clinical clues.

Table 2. Imaging Modalities Commonly Used to Diagnose RAS

Study	Sens (%)	Spec (%)	Interpretation	Comments
Duplex Doppler US	84-98*	62-99*	Peak systolic velocity >200 cm/sec and an elevated renal-aortic peak systolic velocity ratio in the face or normal aortic flow suggest stenosis >60%	Pros: No IV contrast; Inexpensive Cons: None. But technically challenging and requires local expertise. Accessory renal arteries may be missed
CTA	86-93	90-100	Allows for direct visualization of the renal arteries	Pros: Visualizes adjacent structures including accessory renal arteries; less time-consuming; less operator-dependent Cons: Radiation; iodine contrast; difficult to eval severity in presence of significant calcification
MRA	94 (non-enhanced) 97 (gad-enhanced)	85 (non-enhanced) 93 (gad-enhanced)	Allows for direct visualization of the renal arteries	Pros: gad as alternative to contrast in pts with mild renal insufficiency/CHF/dye allergy; visualizes adjacent vessels; can assess renal perfusion using gad clearance Cons: $$$; incompatible with some implanted medical devices; cannot evaluate in-stent restenosis; may overestimate moderate stenosis
Arteriography				Pros: GOLD STANDARD if performed in conjunction with pressure measurements Cons: invasive, iodine contrast, risk of complications Indications: (1) patient in whom RAS is suspected who cannot undergo definitive non-invasive testing (2) patient in whom prior non-invasive testing was inconclusive or (3) as part of planned intervention

Adapted from 2011 ACC/AHA Practice Guidelines for the Management of Patients with PAD
**For detecting stenosis >60%*

Management

Medical Therapy: Medical therapy remains the mainstay of treatment for RAS. Treatment focuses on lowering cardiovascular risk through smoking cessation, glucose control, cholesterol reduction, primary prevention with ASA, and blood pressure control. Choice of anti-HTN medication should follow published guidelines as if for non-RAS patients.

Importantly, ACEi and ARB are not contraindicated. Between one-third and one-half of patients with RAS will usually have a mild decline in GFR within a few days after the administration of an ACEi. An increase in GFR ≥ 30% occurs in less than 5-10% of cases and may be an indication for therapy cessation or consideration of angioplasty or surgery.

Revascularization: Options for revascularization include percutaneous angioplasty +/- stenting and surgical revascularization. The CORAL trial demonstrated that renal artery stenting when added to medical therapy did not confer a significant benefit with respect to the prevention of clinical events.[8] However, some patients do benefit from revascularization and is recommended for those who have a high likelihood of benefiting from the intervention.[9] That includes patients with hemodynamically significant atherosclerotic RAS and 1) recurrent CHF or sudden-onset "flash" pulmonary edema; 2) refractory ACS; 3) resistant HTN; 4) progressive CKD stage IV. Revascularization strategy may vary depending on etiology of RAS (i.e. atherosclerotic RAS vs FMD).

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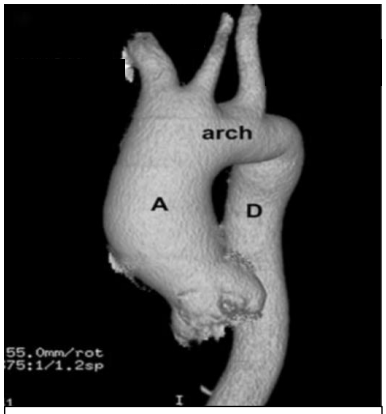
49. Thoracic Aortic Aneurysm

Clinical Considerations

A thoracic aortic aneurysm (TAA) is a full-thickness dilation of a segment of the thoracic aorta that is at least 50% larger than the expected diameter of that segment. The normal aortic diameter varies according to age, sex, and body size. Aneurysms are classified by their location (ascending aorta, aortic arch, descending thoracic aorta) and morphology (fusiform vs saccular). Incidence of TAA is increasing and is often diagnosed incidentally on imaging studies ordered for other indications.[1]



CT image of ascending thoracic aortic aneurysm. *Adapted from JACC 2010;55:e27.*

The natural history of TAA is characterized by slow expansion with progressive increase in risk of dissection as the aortic size increases. The mean growth for all thoracic aneurysms has been reported at 0.1 cm/year, but the rate of growth is higher for aneurysms of the descending aorta and aneurysms associated with genetic syndromes.[2] The risk of rupture or dissection increases abruptly as thoracic aneurysms approach 6 cm because at this size, distensibility of the aorta rapidly falls. The annual risk of rupture is 2% for TAAs <5 cm and 7% for TAAs >6.0 cm.[2]

TAA is most common in patients aged 50-70, and males are affected more frequently. Younger patients with TAA are more likely to have a genetic predisposition such as a connective tissue disorder. For many TAA there is likely a significant genetic component as an estimated 20% of patients with TAA have a family history of the disease.[3] Of patients with TAA, 20-25% are found to also have an abdominal aortic aneurysm.[4]

Etiology and Risk Factors

Thoracic aortic aneurysms can be sporadic or related to genetically mediated disorders. The majority of TAA are sporadic (degenerative) and are associated with risk factors for atherosclerosis (see Table 1). Hypertension is the most common risk factor, occurring in 60% of patients with TAA.[4] Conditions that affect the integrity of the aortic vessel wall including prior aortic dissection (especially type B dissection) and aortitis of infectious or inflammatory etiology are also associated with TAA. The most common inflammatory disorders leading to TAA formation are Takayasu arteritis and giant cell arteritis. In giant cell arteritis, TAA is often a late manifestation in patients who have previously been treated.

About 5% of TAAs are genetically mediated (syndromic or nonsyndromic). The most common genetic syndromes that cause TAA are listed in Table 1. Some patients have a strong family history of aneurysmal disease but do not meet criteria for known connective tissue syndromes and fall into the nonsyndromic TAA category. The most common of these is familial thoracic aortic aneurysm and dissection. Bicuspid aortic valve disease is another important nonsyndromic genetic cause of TAA.

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Table 1. Risk Factors for Thoracic Aortic Aneurysm

Sporadic	Genetically-mediated
Hypertension Smoking history Hypercholesterolemia Prior aortic dissection Aortitis (e.g. vasculitis, infection)	Marfan syndrome Ehlers-Danlos syndrome Loeys-Dietz syndrome Turner syndrome Familial thoracic aortic aneurysm and dissection Bicuspid aortic valve disease

Clinical Manifestations

TAA is typically a clinically silent disease unless a complication occurs (e.g. rupture, dissection). Patients who are symptomatic can present with symptoms due to compression of surrounding structures.[5] Symptoms vary depending on the location of the aneurysm.

- Ascending aorta/aortic arch
  - Heart failure due to aortic regurgitation
  - Myocardial ischemia or infarction due to compression of a coronary artery
  - Dysphagia due to esophageal compression
  - Hoarseness due to left recurrent laryngeal nerve compression
  - Hemidiaphragmatic paralysis due to phrenic nerve compression
  - Wheezing, cough, dyspnea due to compression of the tracheobronchial tree
  - SVC syndrome
- Descending aorta
  - Back pain from erosion into the adjacent spine

Diagnosis

Thoracic aortic aneurysm is commonly incidentally found on imaging studies such as chest x-ray or echocardiography. Further evaluation of the entire aorta using CT or MR angiography is recommended to determine the size and extent of the aneurysm. When aortic root or ascending aortic aneurysm is present, TTE should be performed to evaluate for the presence of a bicuspid aortic valve.

Patients with known connective tissue disease syndromes or first-degree relatives of patients with thoracic aortic aneurysm and/or dissection should undergo complete aortic imaging.[1] CTA or MRA can be used and choice depends on the clinical circumstance. MRA is useful for patients who require repeated thoracic aortic imaging due to the lack of ionizing radiation.

Management

For all patients with TAA who become symptomatic or who have complications related to the TAA, repair is recommended. For patients who are asymptomatic, repair is not recommended until the risk of rupture or other complications exceeds the risk associated with repair.

Indications for repair:[6]

- Symptomatic TAA
- Asymptomatic ascending TAA
  - End-diastolic aortic diameter >5.5 cm or aortic size index ≥2.75 cm/m^2
  - End-diastolic aortic diameter >4.5 cm if undergoing aortic valve surgery

- Asymptomatic descending TAA
  - Aortic diameter >5.5 cm
  - Aortic diameter ≥6 cm if high surgical risk
- Asymptomatic TAA with growth rate >0.5 cm/year
- Asymptomatic TAA associated with genetically mediated conditions
  - Thresholds for repair are lower depending on the specific genetic condition

Repair options include open surgery or endovascular repair. Choice of technique is a "moving target" in the era of developing endovascular technologies. Descending TAA may also be managed with open surgery, which often does not require full cardiopulmonary bypass, or endovascular repair. The choice depends among other factors on whether the TAA is sporadic or genetically mediated.

For asymptomatic TAA without an indication for repair, conservative management is recommended to prevent rupture or dissection.[5]

- Risk factor modification
  - Smoking cessation
  - Treatment of hypercholesterolemia per guideline recommendations with statin therapy
- Aggressive blood pressure control
  - Goal SBP 105-120 mm Hg
  - Beta blockers are preferred for their effect of decreasing aortic shear stress. If beta blockade is not tolerated, acceptable alternatives include ACE inhibitors or ARBs
- Avoidance of fluoroquinolones as they have been linked to an increased risk of aortic aneurysm or dissection.[7]

Surveillance

Asymptomatic patients with thoracic aortic aneurysm who do not meet indications for repair should undergo long-term monitoring. Imaging modalities used for surveillance include echocardiography, CT angiography, or MR angiography and choice depends on the location of the aneurysm. Ideally, serial studies should be performed using the same imaging technique.

Surveillance frequency depends on etiology, location, size and growth rate. It is typically recommended at 6 months following the initial diagnosis and then annually if there is no expansion or extension.

Table 2. Surveillance Recommendations for TAA[6]

Type of Aneurysm	Size	Surveillance timing
Aortic root or ascending aorta		
Sporadic	3.5-4.4 cm 4.5-5.4 cm	Annual Every 6 months
Genetically mediated	3.5-4.4 cm 4.5-5.0 cm	Annual Every 6 months
Descending aorta	4.0-5.0 cm 5.0-6.0 cm	Annual Every 6 months

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50. Abdominal Aortic Aneurysm

Clinical Considerations

An abdominal aortic aneurysm (AAA) is a full-thickness dilation of a segment of the abdominal aorta exceeding the normal vessel diameter by 50%, typically ≥3 cm. They can be classified by location (suprarenal, pararenal, or infrarenal) and morphology (fusiform vs saccular). In screening studies, the prevalence of AAA has been reported to be 1.4% in patients older than 50 years of age.[1,2]

The natural history is marked by progressive dilation over time, with large aneurysms expanding at faster rates compared to small aneurysms. Risk of rupture increases with aneurysm size with <1% annual rupture risk for AAA <4 cm in diameter and >10% annual rupture risk for AAA >6 cm in diameter.[3] Rupture is often lethal with mortality cited as 85-90%.[4] The rates of rupture appear to be declining, probably due to declining rates of smoking as well as increase in identification and early intervention through screening initiatives.

Etiology and Risk Factors

The risk factors for development of AAA are listed in Table 3. The modifiable risk factor that is most strongly associated with development of AAA is tobacco use. More than 90% of all patients with AAA have smoked cigarettes at some point in their lifetime.[3] The epidemiologic association of smoking with AAA is second only to lung cancer.

The risk factors for expansion and rupture of AAA are similar to those leading to development of AAA. One difference is that female sex appears to be a risk factor for rupture. Women make up one-fifth the number of AAAs compared to men but constitute approximately one-third of all AAA ruptures.[5] Initial large aneurysm diameter, rapid expansion, current smoking, and history of cardiac or renal transplant also increase the likelihood of AAA rupture.

Table 3. Risk Factors for Abdominal Aortic Aneurysm[2]

Risk Factors	Negative Risk Factors
Older age Smoking history First-degree relative with AAA History of other large vessel aneurysms Atherosclerosis Hypercholesterolemia Obesity Hypertension	African American race Asian race Hispanic ethnicity Diabetes Female sex

Clinical Manifestations

Patients with AAA are generally asymptomatic unless complications such as rupture occur. Patients may experience a sensation of pulsation near the umbilicus, constant abdominal pain, or back pain. Distal embolization of mural thrombus to the lower extremities (so called “trash foot”) is another type of clinical manifestation.

The classic presentation of ruptured AAA of severe acute pain, pulsatile abdominal mass, and hypotension is present in 50% of cases. Patients with rupture into the retroperitoneum may have more subtle symptoms that can mimic other diseases such as ureteral colic, myocardial infarction, diverticulitis, or ischemic bowel and is often misdiagnosed.[6]

Physical exam has a moderate sensitivity for detecting AAA (Table 4). As the aorta elongates and enlarges with age, location of a pulsatile mass can be variable. A focused exam with palpation of the upper abdominal quadrants is recommended.[3]

Diagnosis

Imaging modalities used to evaluate AAA include transabdominal ultrasound, CT imaging, and MR imaging. Transabdominal ultrasound is preferred for screening and surveillance due to high sensitivity and specificity coupled with a favorable safety profile and low cost. CT or MR imaging is preferred for pre-interventional planning.

For patients with abdominal or back pain and suspicion for AAA, ultrasound imaging is recommended. If AAA is detected, the patient should undergo CT aortography to exclude rupture and to facilitate preoperative planning. Patients presenting acutely should be imaged directly with CTA.

Abdominal aortic aneurysms are often detected incidentally on imaging studies done for unrelated conditions or through screening initiatives. Screening for AAA, followed by surgery, decreases mortality by about 50%, as has been shown by multiple randomized clinical trials.[2,7]

- The U.S. Preventive Services Task Force (USPSTF) recommends a one-time screening by abdominal ultrasound for men aged 65 to 75 years who have ever smoked (i.e. 100 or more lifetime cigarettes).
- Society guidelines also recommend ultrasound screening for AAA in first-degree relatives of patients with AAA who are >65 years of age.[3]

Table 4. Sensitivity and specificity of AAA screening modalities

Imaging Modality	Sensitivity	Specificity
Abdominal ultrasound	94-100%	98-100%
CT scan	90%	91%
Physical exam (pulsatile mass in epigastrium)	39-68%	75%

Management

For all symptomatic patients with AAA, repair is recommended to prevent rupture. For asymptomatic patients, elective repair is generally recommended when the risk of rupture exceeds the risk of repair.

Indications for Repair:[3]

- Symptomatic AAA regardless of diameter
- Asymptomatic AAA
    - Diameter ≥5.5 cm
    - Saccular abdominal aneurysms may be repaired at smaller diameters.
    - Rapid growth rate

- Distal embolization of aneurysm material (mural thrombus)

Repair options include open surgical repair or endovascular repair (EVAR). Three major randomized trials have compared open repair with EVAR (EVAR 1, DREAM, OVER trials), and they all had similar findings of initial survival benefit with EVAR but similar long-term mortality at 8-10 years. Patients who undergo EVAR require long-term surveillance with CT for development of endoleaks.

Smaller aneurysms <4.0 cm in diameter are at low risk of rupture and should be monitored. Management recommendations for intermediate sized aneurysms (4.0-5.4 cm) are based on two randomized trials of over 1000 patients each, which compared early elective open surgery to surveillance every 6 months over a period of 5-8 years. There was no significant mortality difference between the two strategies.[8,9]

Medical management is focused on preventing further enlargement.

- Smoking cessation is the most important intervention and is the only proven effective intervention at reducing rate of AAA enlargement.
- Risk factor modification with appropriate medical management of hypertension and hyperlipidemia is recommended.
- There is no clear evidence that pharmacotherapy (statins, beta blockers, ACE inhibitors) reduce AAA growth.

Surveillance

Surveillance imaging should be done using transabdominal ultrasound and is recommended until aneurysm diameter exceeds 5.5 cm, at which point repair is recommended to eliminate the risk of rupture. Surveillance timing varies depending on aneurysm size (table 5).

Table 5. Surveillance Recommendations for AAA[3]

Aneurysm size	Surveillance timing
3.0-3.9 cm	Every 2-3 years
4.0-4.9 cm	Every 12 months
5.0-5.4 cm	Every 6 months

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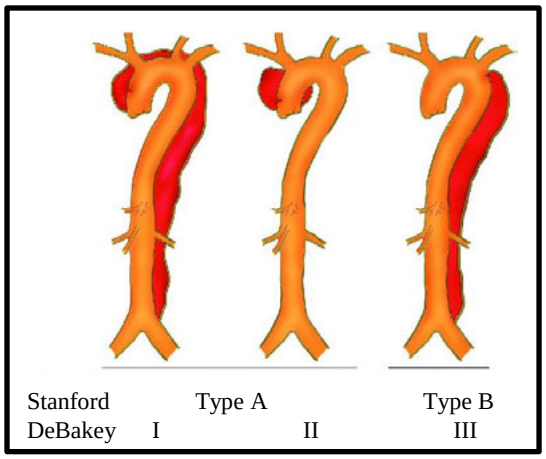
51. Aortic Dissection

Clinical Considerations

The Stanford system is the most widely used for classification as it helps guide management decisions. A Type A dissection involves the ascending +/- descending aorta, and a Type B dissection involves only the descending aorta.

Alternatively, the DeBakey system is based on site of origin. Type I dissections originate in the ascending aorta and involve at least the aortic arch. Type II dissections originate in and are confined to the ascending aorta. Type III dissections originate in the descending aorta.

Duration: acute (<2 weeks) vs chronic (>2 weeks)



Aortic dissection classifications. *Adapted from Ital J Vasc End Surg 2015;22:141.*

Etiology and Risk Factors

A tear in the aortic intima exposes the medial layer to the systemic pressure of intraluminal blood → pressure of pulsatile blood dissects the arterial wall into two layers longitudinally producing a false lumen that can propagate distally, or less commonly, in a retrograde direction.

Entities similar to aortic dissection include aortic intramural hematoma, intimal tear without hematoma, and penetrating atherosclerotic ulcer.

Complications of aortic dissection are mainly from propagation and include: aortic valve regurgitation, cardiac tamponade, obstruction of coronary artery ostia, coronary artery dissection, and end-organ failure due to abdominal aortic branch vessel obstruction.

Risk factors include:

- Hypertension – 72% of all patients.[1] More common in type B dissections compared to type A dissections (70 vs 36%).[2] Abrupt, transient increase in BP is associated with acute aortic dissection, especially with cocaine use or heavy weight lifting.
- Collagen disorders (see Table 1) –more common in younger patients, often associated with family history of aortic dissection
- Aortic surgery or instrumentation – can occur as a complication of CABG, coronary catheterization (particularly with femoral access), IABP, TAVR
- Preexisting aortic aneurysm
- Congenital heart defects – Bicuspid aortic valve, aortic coarctation (especially in Turner syndrome)
- Pregnancy and delivery

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Table 1. Genetic collagen disorders associated with aortic dissection

Genetic Syndrome	Genetic Defect	Clinical features	Risk of dissection
Marfan Syndrome	FBN1	Arachnodactyly, scoliosis, pectus deformity, ectopia lentis, MVP	30% by age 32, 60% by age 50.
Ehlers-Danlos Syndrome, vascular form	COL3A1	Translucent skin, easy bruising, bowel or uterine rupture	~70% lifetime prevalence, mean survival 48 yrs.
Loeys-Dietz Syndrome	TGFBR1	Hypertelorism, bifid uvula, cleft palate, vascular aneurysms (esp intracranial), premature skull fusion, cervical spine deformity, pectus deformity, MVP	Mean age first dissection 27, mean survival 26-37 yrs. Higher risk of dissection at smaller diameters.

Diagnosis

History: Most patients (90%) report abrupt onset of severe, sharp/stabbing or tearing chest pain radiating to the back, maximal at onset, +/- diaphoresis. Uncommonly, patients can be pain-free, which is more likely in older patients with an ascending dissection.

Exam: Pulse deficit, SBP variation >20 mm Hg between arms (in only ~20% of type A dissections), systolic ejection click of bicuspid AV (if present), diastolic murmur along the right sternal border (AI), syncope, Horner syndrome, hoarseness, findings associated with complications (see below). Evaluate for evidence of complications:

- Acute AI – new diastolic decrescendo murmur, wide pulse pressure, HoTN, CHF
- Tamponade – HoTN, narrow pulse pressure, elevated JVP, muffled heart sounds
- Hemothorax
- Malperfusion syndrome: end organ ischemia secondary to branch-vessel involvement, complicates 25-30% of aortic dissection.[3]
    - Acute MI – RCA most often affected,[4] infrequently associated with complete heart block
    - Acute stroke – focal neurologic deficits
    - Spinal cord ischemia – acute paraplegia
    - Mesenteric ischemia (poor prognosis) – abdominal pain, bloody diarrhea
    - AKI – often ATN
    - Limb ischemia – lower extremity pulse deficit, pain, pallor, paresthesias, poikilothermia, paresis

EKG: 31% normal, 42% nonspecific ST-T changes, 15% ischemia, 5% acute MI

D-dimer: Levels <500ng/mL has negative LR 0.07 and NPV 95% in first 24 hrs. D-dimer degrades over time, limiting utility >24h after symptom onset, and does not apply to intramural hematoma or penetrating ulcer. Routine use is controversial.[5]

Imaging: CT angiography is the most common initial test given its widespread availability and speed in diagnosis. If the patient is hemodynamically unstable, TEE is the first test of choice as it can be done at the bedside and can yield a diagnosis within minutes.

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Table 2. Imaging Modalities commonly used to diagnose aortic dissection[6]

Study	Sens (%)	Spec (%)	Comment
CXR	68-90	n/a	Mediastinal widening (64%), displaced intimal calcification (9%), pleural effusion (16%), abnormal aortic contour (76%), normal (12%)
TTE	30-80	83-96	Pros: Useful for assessing complications of dissection: AI, tamponade, LV and valvular function Cons: Not a good test to rule out dissection as only proximal aorta is visualized
Chest CTA	97-100	83-100	Order as chest CTA so that it is gated, which is more precise in identifying origin of tears. Also get CT neck, abdomen, and pelvis sometimes with leg runoffs to capture full extent of dissection Pros: widely available, rapidly preformed and can evaluate more than aortic pathology Cons: requires IV contrast, cannot evaluate coronaries or aortic valve reliably, site of tear often not defined
MRA	98-100	87-100	Pros: Test of choice for following chronic dissection (no radiation exposure), wide field of view, no contrast needed, evaluates pericardial effusion and can discern antegrade vs retrograde dissection Cons: Long image acquisition time, many patients have contraindications (claustrophobia, pacer wires, etc)
TEE	97-100	98-100	When suspicion is high and chest CT with contrast contraindicated, TEE can be most rapid assessment if readily available. Evaluates LV, AV morphology/function, proximal coronaries, and pericardial effusion

Note which critical vessels are perfused from the true (native aorta) vs false lumen (dissection flap). Distention of the false lumen with blood can constrict the true lumen leading to ischemia in organs still perfused by the native aorta.

Management

Acute management consists of the following:

- Access: All patients with an aortic dissection should have an arterial line placed in the arm with the highest auscultatory blood pressure. BP in both arms should be checked and documented frequently.
- Hemodynamically unstable patients should be intubated and have central venous access placed. Hypotensive patients should be resuscitated after ruling out tamponade and CHF and taken emergently to the OR.
- Control pain with morphine to reduce sympathetic drive
- Goal HR <60: HR control with IV BB (e.g. labetalol, esmolol) works to reduce the rate of rise in the force of LV contraction. Reduce HR first to blunt reflex increase in HR with

vasodilators and minimize shear stress. In patients with contraindications to BB, nondihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) can be utilized as an alternative (see Table 3).
    - A caveat to this approach is that reducing HR in the setting of acute *severe* AI will increase the diastole/systole ratio and may precipitate cardiogenic shock. Calcium channel blockers should also be used with caution in patients with pre-existing LV dysfunction.
- Goal SBP 100-120 mm Hg: If SBP remains elevated after appropriate HR control with IV BB and the patient has good mentation and renal function, IV nitroprusside or nicardipine should be used (see Table 3).
    - Vasodilator therapy should not be initiated prior to rate control, so as to avoid associated reflex sympathetic overdrive (tachycardia and inotropy).
    - Avoid use of hydralazine as this can increase hydraulic shear and may propagate the dissection.
- Urgent surgical consultation should be obtained for all patients
    - Stanford Type A: emergent surgical repair
    - Stanford Type B: managed medically unless life-threatening complications develop

Type A Dissection: Typically treated surgically with sternotomy, aortic root replacement with graft +/- valve repair/replacement since they are at high risk for complications. If untreated, mortality is 1-2% per hour for the first 48 hours in acute proximal dissections. With surgical therapy, mortality is 10-20% and with medical therapy only, mortality is >50%.[7]

Type B Dissection: Type B dissections are usually treated medically with BP and HR control. Surgical intervention is reserved for patients who develop complications related to the dissection. Thoracic endovascular aortic repair is an emerging treatment modality for type B dissections and has been shown to be associated with improved survival and delayed disease progression.

Many patients (64% of type B dissections) have refractory HTN (i.e. need for ≥ 4 anti-hypertensive medications). Hence, escalating doses and number of anti-hypertensives is to be expected in the first several days following type B dissection. Consider renal artery dissection if there is persistent HTN that lasts beyond several days. With surgical therapy, mortality is 31% compared to 11% with medical therapy.

Table 4. Agents used in the acute management of aortic dissection

Agent	Initial Dose	Comment
Labetalol	20-80 mg IV bolus 0.5-2 mg/min gtt	Can be used as a single agent Preferred PO agent
Propranolol	1-10 mg IV load 3 mg/h gtt	May be a more potent beta-blocker than esmolol
Esmolol	250-500 mcg/kg IV bolus 25-200 mcg/kg/min gtt (max 300 mcg/kg)	Preferable in acute setting due to short half-life Better tolerated in pts with asthma or CHF
Diltiazem	20 mg bolus 5-15 mg/h gtt	Useful when BB contraindicated Avoid if reduced LVEF (can precipitate cardiogenic shock)
Nitroprusside	0.25-0.5 mcg/kg/min gtt	Must be used in combination with BB If used alone, vasodilation→↑sympathetic nervous system→↑ventricular contraction→↑aortic wall shear stress Add if additional lowering of SBP needed
Nicardipine	2.5-15 mg/hr gtt	

After initial hospitalization, patients generally do well whether treated medically or surgically with 10-year survival rate ~60%.

Long-term therapy consists of control of hypertension and reduction of cardiac contractility with the use of beta-blockers plus other antihypertensive agents including ACE inhibitors or calcium channel blockers. Control of HTN (goal BP<120/80) can decrease the incidence of late complications and should be used indefinitely.

Thoracic MRA (preferred) or CTA imaging should be obtained prior to discharge as a “baseline scan.” Discuss with the surgical attending what his/her preference is for this scan as the same modality will likely be used for serial imaging over time. Serial imaging will be obtained at 3, 6, and 12 months and annually thereafter. This is to monitor for conditions that would require surgical intervention such as extension or recurrence of the dissection, aneurysm formation, or leakage at surgical anastomotic sites.

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QUICK REFERENCE GUIDE: VASCULAR MEDICINE

Venous Thromboembolism

- For the purposes of this document, the term venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT), pulmonary embolism (PE), and catheter-associated thrombosis

Deep Vein Thrombosis (DVT)

- Therapeutic anticoagulation is indicated in all patients with proximal lower-extremity DVT (arising in the popliteal, femoral, or iliac veins) and in some cases of distal DVT, in the absence of contraindications
- Therapeutic AC should also be considered in cases of upper extremity DVT, though note that the majority of these cases are secondary to indwelling catheters
- Direct oral anticoagulants (DOACs) including apixaban, rivaroxaban, edoxaban, and dabigatran are considered first-line agents for VTE in the majority of patients
    - Warfarin is favored in patients with APLAS
    - Traditionally, LMWH is considered first-line in patients with active malignancy, though emerging data suggest that edoxaban and rivaroxaban may be equally effective in this population
- Regarding duration of therapy:
    - The majority of patients with a first episode of provoked VTE should receive at least 3 months of therapeutic AC
    - Patients with low risk of bleeding and persistent risk factors (e.g. immobility or hormone replacement therapy) should be treated with an extended course (i.e. 6-12 months)
    - Long-term AC should be considered in select populations (provided that the bleeding risk is acceptable), including:
        - Patients with unprovoked DVT/PE
        - Recurrent provoked DVT/PE, or
        - Active malignancy
- The only widely accepted indication for catheter-directed thrombolysis (CDT) for lower extremity DVT is massive proximal clot burden leading to compromised lower extremity perfusion and risk of limb ischemia (i.e. phlegmasia cerulea dolens)
- IVC filters are indicated for prevention of PE in patients with acute proximal DVT who have either failed therapeutic anticoagulation or have an absolute contraindication to anticoagulation
    - Generally speaking, IVC filter retrieval should be considered once the contraindication to anticoagulation has resolved

Pulmonary Embolism (PE)

- Risk stratification of PE depends on the presence or absence of hemodynamic instability and right heart strain
    - RV strain can be assessed via multiple modalities including cardiac biomarkers (NT-proBNP, hsTnT), EKG (RBBB, anterior T wave inversions, S1Q3T3), CT-PE (RV/LV ratio >0.9), or TTE (RV dilation, hypokinesis, or McConnell's sign, in which there is diffuse RV wall hypokinesis with apical sparing)
- Based on the above, PE is generally classified as low-risk, intermediate-risk (e.g. submassive), and high-risk (e.g. massive)
- The MGH Pulmonary Embolism Response Team (PERT, x47378) is a multidisciplinary team that can be activated for prompt assessment and management of PE

    - The PERT team should be contacted for all cases of massive, as well as selective cases of submassive, PE
- Low-risk or non-massive PE carries a low risk of short-term mortality and is characterized by the absence of right heart strain or hemodynamic changes
    - Treatment involves prompt initiation of therapeutic (oral) anticoagulation, provided there is no contraindications to anticoagulation and risk of bleeding is low.
- Intermediate-risk or submassive PE is characterized by right heart strain without hemodynamic instability and is associated with 3-15% short-term mortality risk (and higher intermediate-term mortality)
    - Treatment involves prompt initiation of therapeutic AC
    - Additionally, these patients should be monitored closely for clinical signs of deterioration
    - Most patients without hypotension should not be treated with thrombolytic therapy
    - However, thrombolysis of catheter-based therapies may be considered in cases of cardiopulmonary deterioration that has not progressed to hypotension (e.g. persistent dyspnea)
- High-risk or massive PE is characterized by the presence of hemodynamic instability and carries significant acute mortality risk (>15%)
    - Treatment involves prompt consideration of thrombolysis to rapidly reduce clot burden
    - Administration of systemic thrombolytics (alteplase [t-PA] and tenecteplase) is associated with decreased all-cause mortality, but at the expense of significantly increased risk of major bleeding and intracranial hemorrhage
        - At MGH, this is typically employed in emergent situations only (e.g. during a Code Blue when PE is high on the differential)
    - Catheter-directed thrombolysis is an attractive alternative to systemic thrombolysis and requires involvement of the PERT Team (see above)
    - Other invasive stabilizing measures (e.g. ECMO) should also be considered in this patient population
    - Patients who have failed thrombolysis or have an absolute contraindication should be considered for surgical thromboembolectomy

<u>Catheter Associated Thrombosis</u>

- The rate of central venous catheter (CVC)-associated thrombosis is as high as 14-18%
- Current guidelines recommended that systemic anticoagulation be administered for at least 3 months, with LMWH preferred over warfarin and DOACs in patients with malignancy
- If ongoing, central access is required, the CVC can remain in place so long as it is appropriately positioned and functioning correctly without evidence of infection
    - If the catheter remains after three months of therapeutic anticoagulation, LMWH prophylaxis is recommended until the line is removed

Peripheral Artery Disease

- Peripheral artery disease (PAD) is atherosclerotic disease leading to peripheral artery obstruction
- The diagnosis of PAD can be suspected clinically based on history of symptoms, risk factors for PAD, and physical exam findings
- Diagnosis should be confirmed with ankle-brachial index (ABI)

    - ABI < 0.9 indicates PAD, <0.4 indicates critical limb ischemia
- Stable PAD is generally managed with exercise and risk-factor modification
    - Supervised exercise therapy is the first-line treatment with patients with PAD and claudication and has been shown to be comparable to stent revascularization in improving functional status and QOL
    - Risk-factor modification includes: Management of DM and HTN, weight loss, smoking cessation (shown to alter progression of disease)
- ASA 81 or clopidogrel 75 mg daily are often used as first-line agents in PAD, but the benefits are unclear, and recommendations have been extrapolated from studies in CVD
    - DAPT is not recommended unless there is another indication due to increased bleeding risk without clear benefit
- Moderate and high-intensity statins are indicated and provide reduction in vascular events and may also improve symptoms
- The COMPASS trial showed that rivaroxaban (2.5mg BID) plus aspirin (100mg QD) led to lower risk of major adverse cardiovascular events but increased risk of major bleeding
- Medications such as cilostazol are used for lifestyle-limiting claudication, especially if exercise ineffective and revascularization not possible
- Revascularization is an option for patients with significant or disabling symptoms unresponsive to other treatment options

Acute Critical Limb Ischemia

- This is defined as a sudden decrease in limb perfusion presenting within 2 weeks of an inciting event
    - Almost always due to arterial occlusion, rarely from severe venous occlusion
    - Etiologies of arterial occlusion include thrombosis at site of atherosclerotic plaque in native artery (most common cause), thromboembolism, thrombosis of stent/graft, thrombosis of aneurysm, arterial dissection, and iatrogenic from arterial access sites
- Management involves immediate anticoagulation with a heparin gtt and revascularization (either endovascular or surgical)
    - Factors that favor endovascular revascularization: Comorbidities that increase surgical risk, multi-level disease undergoing staged approach (endovascular-first), no suitable vessel for bypass graft
    - Factors that favor surgical revascularization: Immediately threatened limb, large proximal lesion, long segment lesion, diffuse multilevel disease
- If irreversible ischemia (non-salvageable), amputation is recommended

Chronic Critical Limb Ischemia

- This typically corresponds to ABI <0.4 and is defined as ischemia of >2 weeks duration sufficient to threaten the limb
    - Usually due to multilevel arterial stenoses or occlusion but can occur at a single vessel (i.e. isolated tibial vessel disease in diabetics)
    - Typically aortoiliac and femoropopliteal or femoropopliteal and tibial segments
- A subset of patients (based on transcutaneous oxygen and ABI) can be treated with conservative measures consisting of aggressive wound care, pain control, and medical management
- Many will required revascularization with either endovascular therapy (percutaneous transluminal angioplasty) or bypass surgery

    - There has been persistent clinical uncertainty about which approach is superior
    - In common practice, most patients receive endovascular therapy first
    - The BEST-CLI trial is currently enrolling patients and is designed to compare best endovascular therapy with best open surgical treatment in patients eligible for both
- Amputation may be indicated in patients with sepsis, limb paralysis, uncorrectable flexion contracture, or significant necrosis of weight-bearing parts of the foot

Digital Ischemia

- Generally presents as painful, discolored (often blue) digits in the upper or lower extremities
- Etiologies are generally categorized by vessel size
    - Small vessel: Connective tissue diseases (SLE, Scleroderma), pressor-related, hypercoagulability, embolus, polycythemia, trauma, frost-bite, post-procedural
    - Medium vessel: Buerger's disease, polyarteritis nodosa, scleroderma, hypercoagulability, embolus, trauma, post-procedural
    - Large vessel: Takayasu's, Kawasaki's, dissection, thoracic outlet syndrome, atherosclerosis
- Effective diagnosis is highly predicated on history. This includes identification of:
    - Risk factors for cardioemboli such as prior MI/Afib/valvular heart disease
    - Risk factors for atherosclerosis
    - Toxin ingestion
    - Prior rheumatologic diagnoses
    - Medication history (i.e. pressors)
    - Tobacco and marijuana use
- Depending on the above, initial lab workup may include: CBC with diff, coags, lipid panel, urine tox screen, TSH, scleroderma testing (Scl-70, anti-centromere, anti-RNP pol III), vasculitis testing (ANA, anti-dsDNA, RNP, Smith, C3/4, ESR, CRP, RF, ANCA, cryoglobulins), antiphospholipid antibodies, blood cultures, blood viscosity, serum electrophoresis
- Appropriate long-term management involves identification and treatment of the underlying condition
- Overnight management may include the following:
    - If embolus/thrombus is suspected, initiate treatment with heparin gtt
    - Evaluate for infection and add antibiotics as necessary
    - To promote vasodilation, consider topical nitrates or short acting CCB (e.g. nifedipine), titrated up to maximal dose
    - For pain control, consider injection of lidocaine or bupivacaine at base of digit, with repetition as necessary

Renal Artery Stenosis

- Renal artery stenosis (RAS) is characterized by narrowing of one or both renal arteries and accounts for an important cause of secondary HTN
    - Likely accounts for 1-5% of cases of HTN overall but likely more prevalent among patients with acute, severe, or refractory hypertension
- RAS leads to impaired blood flow to the target kidney, resulting in a spectrum of clinical syndromes that range from asymptomatic obstruction (incidental RAS) to renal vascular hypertension (RVH) and ischemic nephropathy
- Atherosclerotic RAS (ARAS) accounts for 90% of all RAS

    - ARAS is considered a progressive disease that can lead to worsening stenosis and eventual occlusion over time
- Fibromuscular Dysplasia (FMD), a non-inflammatory, non-atherosclerotic vascular disease, commonly affects the renal arteries (66% of patients)
    - The majority of FMD patients are female (90%) and the mean age at diagnosis was 52 years
- Other non-atherosclerotic forms of RAS include: Aneurysms, congenital or traumatic AV fistulas, vasculitis, neurofibromatosis, trauma, embolization, post-radiation therapy, dissection, or extrinsic compression of the renal arteries due to tumors
- Testing for RAS should only be pursued in patients thought to have a high likelihood of benefitting from revascularization (see below)
- Effective diagnostic/imaging modalities include: Duplex US of the renal arteries, CTA, MRA, and arteriography
- Generally-speaking, medical therapy remains the mainstay of treatment for RAS
    - Treatment focuses on lowering cardiovascular risk through smoking cessation, glucose control, cholesterol reduction, primary prevention with ASA, and blood pressure control
    - Choice of anti-HTN medication should follow published guidelines as if for non-RAS patients. Importantly, ACEi and ARB are not contraindicated
- Options for revascularization include percutaneous angioplasty +/- stenting and surgical revascularization, with strategy depended on etiology (i.e. ARAS vs FMD)
    - The CORAL trial demonstrated that renal artery stenting (when added to medical therapy) did not confer a significant benefit with respect to the prevention of clinical events
    - However, patients who may benefit from revascularization include those with hemodynamically significant atherosclerotic RAS and
        - Recurrent CHF or sudden-onset “flash” pulmonary edema
        - Refractory ACS
        - Resistant HTN, or
        - Progressive CKD stage IV

Thoracic Aortic Aneurysm

<u>Etiology and Risk Factors</u>

- A thoracic aortic aneurysm (TAA) is a full-thickness dilation of a segment of the thoracic aorta that is at least 50% larger than the expected diameter of that segment
- Aneurysms are classified by their location (ascending aorta, aortic arch, descending thoracic aorta) and morphology (fusiform vs saccular)
- The majority of TAAs are sporadic (degenerative) and are associated with risk factors for atherosclerosis
    - About 5% of TAAs are genetically mediated (syndromic or nonsyndromic)
- The natural history of TAA is characterized by slow expansion with progressive increase in risk of dissection as the aortic size increases
    - Mean growth for all thoracic aneurysms has been reported at 0.1 cm/year, but the rate of growth is higher for aneurysms of the descending aorta and those associated with genetic syndromes
    - The risk of rupture or dissection increases abruptly as thoracic aneurysms approach 6 cm
    - The annual risk of rupture is 2% for TAAs <5 cm and 7% for TAAs >6 cm

Diagnosis

- Commonly incidentally found on imaging studies performed for a different indication (e.g. CXR or TTE)
- In these instances, evaluation of the entire aorta using CT or MR angiography is recommended to determine the size and extent of the aneurysm
- When aortic root or ascending aortic aneurysm is present, TTE should be performed to evaluate for the presence of a bicuspid aortic valve
- Patients with known connective tissue disease syndromes or first-degree relatives of patients with thoracic aortic aneurysm and/or dissection should undergo screening with complete aortic imaging

Management

- Indications for repair include:
    - Symptomatic TAA (symptoms vary depending on the location of the aneurysm):
        - Ascending aorta/aortic arch: Heart failure due to aortic regurgitation; myocardial ischemia or infarction due to compression of a coronary artery; dysphagia due to esophageal compression; hoarseness due to left recurrent laryngeal nerve compression; hemidiaphragmatic paralysis due to phrenic nerve compression; wheezing, cough, dyspnea due to compression of the tracheobronchial tree, SVC syndrome
        - Descending aorta: Back pain from erosion into the adjacent spine
    - Asymptomatic ascending TAA
        - End-diastolic aortic diameter >5.5 cm or aortic size index ≥2.75 cm/m^2
        - End-diastolic aortic diameter >4.5 cm if undergoing aortic valve surgery
    - Asymptomatic descending TAA
        - Aortic diameter >5.5 cm
        - Aortic diameter ≥6 cm if high surgical risk
    - Asymptomatic TAA with growth rate >0.5 cm/year
    - Asymptomatic TAA associated with genetically-mediated conditions
        - Thresholds for repair depend on the specific genetic condition
- Repair options include open surgery or endovascular repair
- For asymptomatic patients without an indication for repair, conservative management is recommended to prevent rupture or dissection. This involves risk factor modification, blood pressure control, and surveillance
    - Risk factor modification: Smoking cessation, treatment of hypercholesterolemia per guideline recommendations with statin therapy
    - Blood pressure control with goal SBP 105-120 mm Hg
        - Beta-blockers are preferred for their effect of decreasing aortic shear stress
        - If BB is not tolerated, acceptable alternatives include ACEi or ARBs
    - Surveillance:
        - Imaging modalities include: TTE, MRA, CTA
        - Frequency depends on etiology, location, size, and growth rate (see Table 2, page 341) but is typically recommended at 6 months following the initial diagnosis and then annually if there is no expansion or extension

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Abdominal Aortic Aneurysm

Etiology and Risk Factors

- An abdominal aortic aneurysm (AAA) is a full-thickness dilation of a segment of the abdominal aorta exceeding the normal vessel diameter by 50%, typically ≥3 cm
- Aneurysms are classified by location (suprarenal, pararenal, or infrarenal) and morphology (fusiform vs saccular)
- The natural history is marked by progressive dilation over time
    - Risk of rupture increases with aneurysm size with <1% annual rupture risk for AAA <4 cm in diameter and >10% annual rupture risk for AAA >6 cm in diameter
    - Rupture is often lethal with mortality cited as 85-90%
- The modifiable risk factor that is most strongly associated with development of AAA is tobacco use
    - More than 90% of all patients with AAA have smoked cigarettes at some point in their lifetime

Diagnosis

- AAA are often detected incidentally on imaging studies performed for an alternative indication or through screening initiatives
    - The USPSTF recommends one-time screening by abdominal ultrasound for men aged 65 to 75 years who have ever smoked (i.e. 100 or more lifetime cigarettes)
- Patients with AAA are often asymptomatic (unless rupture has occurred) but may also present with sensation of pulsation near the umbilicus, constant abdominal pain, or back pain
    - Distal embolization of mural thrombus to the lower extremities (so called “trash foot”) is another type of clinical manifestation
- The classic triad of ruptured AAA (severe acute pain, pulsatile abdominal mass, and hypotension) is present in only 50% of cases, and patients with rupture into the retroperitoneum may have more subtle symptoms
    - These can mimic other diseases such as ureteral colic, myocardial infarction, diverticulitis, or ischemic bowel, and often go misdiagnosed
- In patients who present acutely, and in whom there is suspicion for ruptured AAA, CT aortography is the initial test of choice
- In patients who presents with abdominal or back pain and some suspicion for AAA, abdominal ultrasound is the initial test of choice
    - If AAA is detected, the patient should then undergo CT aortography to exclude rupture and to facilitate preoperative planning

Management

- Indications for repair include:
    - Symptomatic AAA regardless of diameter
    - Asymptomatic AAA
        - Diameter ≥5.5 cm
        - Saccular abdominal aneurysms may be repaired at smaller diameters
        - Rapid growth rate
        - Distal embolization of aneurysm material (mural thrombus)
- Repair options include open surgical repair or endovascular repair (EVAR)
    - Three major randomized trials have compared open repair with EVAR (EVAR 1, DREAM, OVER trials), all of which had similar findings of initial survival benefit with EVAR but similar long-term mortality at 8-10 years
    - Patients who undergo EVAR require long-term surveillance with CT for development of endoleaks

- Smaller aneurysms (<4.0 cm in diameter) are at low risk of rupture and should be monitored
- Medical management is focused on preventing further enlargement
    - Smoking cessation is the most important intervention and is the only proven effective intervention at reducing rate of AAA enlargement
    - Risk factor modification with appropriate medical management of hypertension and hyperlipidemia is recommended
    - There is no clear evidence that pharmacotherapy (statins, beta blockers, ACE inhibitors) reduce AAA growth
- Surveillance imaging should be performed using transabdominal ultrasound
    - Surveillance timing varies depending on aneurysm size (see Table 5, page 345)
    - Once aneurysm diameter exceeds 5.5 cm, repair is recommended to eliminate the risk of rupture

Aortic Dissection

Etiology and Risk Factors

- Aortic dissection occurs when a tear in the aortic intima exposes the medial layer to the systemic pressure of intraluminal blood
    - This pressure dissects the arterial wall into two layers, producing a false lumen that can propagate distally
- According to the Stanford classification system, Type A dissections involve the ascending +/- descending aorta, while Type B dissections involve only the descending aorta
- Risk factors for aortic dissection include HTN (most common), cocaine use, heavy lifting, and pregnancy
    - Genetic collagen disorders are predisposing factors for aortic dissection (more common in younger patients)
- Aortic dissection may also result as a complication of aortic surgery or instrumentation
    - This complication should be monitored for after CABG, coronary catheterization, IABP, and TAVR

Diagnosis

- Most patients with aortic dissection present with abrupt-onset severe, sharp chest pain that can radiate to the back
- Exam findings include a pulse deficit, SBP variation >20 mm Hg between arms, and findings associated with complications/distal propagation
    - These complications include: Acute AI, tamponade, and end-organ ischemia secondary to branch-vessel involvement
    - Patients should be closely monitored for acute MI; acute stroke; and ischemia of the spinal cord, bowel, kidneys, and limbs
- CT angiography is the most commonly performed imaging modality as it is widely available and is quick to determine if dissection is present or not
    - However, if the patient is hemodynamically unstable, TEE is the preferred diagnostic test given its high sensitivity and specificity

Management

- Type A dissections require emergent surgical evaluation for consideration of sternotomy and aortic root replacement with graft +/- valve repair/replacement
    - In untreated acute proximal dissection, mortality is 1-2% per hour for the first 48 hours

    - With surgical therapy, mortality is 10-20%
    - With medical therapy only, mortality is >50%
- In contrast, Type B dissections are typically managed medically, with surgical intervention reserved for patients who develop critical complications (e.g. end-organ ischemia secondary to branch-vessel involvement)
    - In these instances, emergent thoracic endovascular aortic repair has been shown to be associated with improved survival and delayed disease progression
- Acute medical management of Type B dissection involves pain control (especially important in reducing sympathetic drive) and anti-impulse therapy (strict HR and BP control)
    - Use IV beta blockers to aggressively reduce HR to goal <60 (reduces the rate of rise in the force of LV contraction)
    - Once HR goal achieved, use vasodilators (nitroprusside, nicardipine) to reduce SBP (goal SBP 100-120 mm Hg)
    - Do not use vasodilators alone without BB as this will increase sympathetic drive and increase aortic wall shear stress
- Longer-term management of Type B dissection involves ongoing therapy with anti-hypertensives (goal BP <120/80) to reduce incidence of late complications
    - Beta blockers or nondihydropyridine CCB and ACEi are preferred over hydralazine
- Obtain baseline imaging with MRA or CTA prior to discharge and repeat scans at 3, 6, and 12 months then annually thereafter to monitor for extension or recurrence of the dissection, aneurysm formation, or leakage at surgical anastomotic sites

PRIMARY PREVENTION

See Page 360 for Quick Reference Guide

52. Primary Prevention

Background

Ischemic heart disease is the leading cause of death worldwide. Prevalence is growing in developed nations due to aging populations, and incidence is increasing in developing nations with changing in lifestyle and health patterns. In addition, the economic and societal cost of ASCVD is growing; the total cost to the US economy in 2014-2015 was $318 billion. By 2035, this is expected to increase to $749 billion.

Prevention is key for reducing the burden for atherosclerotic cardiovascular disease globally and for the individual patient. ASCVD is readily amenable to prevention strategies due to:

1. High incidence
2. Multiple contributory behavioral and lifestyle factors
3. Long disease latency
4.

Sudden death is a most common presenting symptom of ASCVD; as such, preventive strategies are essential in treating silent incident disease.

Health-Related Behaviors

Diet: Longstanding data suggest that a “higher quality diet”, with an enriched in fruits, vegetables, nuts, whole grains and fish helps in prevention of many chronic diseases, including ASCVD. This general approach is recommended in the 2019 ACC/AHA primary prevention guidelines with a class I level of evidence B recommendation.[1] It is also recommended that saturated fats should be replaced with monounsaturated and polyunsaturated fats.
A number of studies exist regarding the role of diet in primary and secondary prevention of ASCVD. Studies have shown a role for the Mediterranean diet in both arenas of prevention. A traditional Mediterranean diet is characterized by a high intake of olive oil, fruit, tree nuts, vegetables, and cereals; a moderate intake of fatty fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and alcohol in moderation. Related to fat intake, it has a relatively higher proportion of polyunsaturated fats.

Exercise: Exercise has many health benefits; related to ASCVD, it has been shown to directly modify risk factors and improve mortality and morbidity. Recent studies have demonstrated reductions in concentration of atherogenic small LDL-C molecules with high volume, high intensity exercise. This has also been suggested to improve HDL “reverse transport” function. Physical activity also confers a CVD mortality benefit, with increasing risk reductions seen with increasing amounts of exercise in a dose-dependent way. The ACC/AHA 2019 primary prevention guidelines provide a Class I, level of evidence B recommendation that adults should engage in at least 150 minutes of moderate-intensity exercise (defined as brisk walking, biking, ballroom dancing, active yoga, recreational swimming) a week or 75 minutes of vigorous-intensity exercise per week (jogging/running, biking, tennis, swimming laps).[1]

Combined lifestyle modifications: Previous observational data suggest that cardiovascular disease can be prevented by several optimal health behaviors. These behaviors include eating

a healthy, varied diet; moderate alcohol intake (10-30g/day); smoking cessation; regular exercise and preventing abdominal obesity.

Hyperlipidemia

Blood lipoproteins are associated with cardiovascular disease risk in observational cohorts. Candidacy for preventive therapy is determined based on identifying individuals at high absolute risk for events due to atherosclerotic cardiovascular disease (ASCVD) over the next 10 years, and this should be assessed every 4-6 years from age 40-79. Those with high risk for ASCVD events include individuals with established ASCVD, diabetes mellitus, LDL cholesterol (LDL-C) > 190mg/dl, or high estimated risk (>20%/10y) using the 2013 ACC/AHA Pooled Cohort Equation. In asymptomatic individuals at intermediate risk (7.5-20%/10y), additional risk-enhancing factors, including family history of premature CAD, LDL-C ≥160mg/dL, CKD, metabolic syndrome, inflammatory diseases, ethnicity (south Asian), elevated triglycerides (≥175 mg/dL), hs-CRP ≥2 mg/L, apoB ≥130 mg/dL, Lp(a) ≥50 mg/dL, and ABI <0.9 can help adjudicate statin suitability. After incorporating these factors into shared-decision making, if questions about statin prescription persist, then coronary artery calcification (CAC) scoring may be pursued; if CAC score is 0, then withholding a statin may be suitable.

Additionally, genetics may identify individuals at very high risk. Specifically, 1 in 200-250 individuals has familial hypercholesterolemia (FH), characterized by pathogenic mutations in the *LDLR*, *APOB*, and *PCSK9* genes. These individuals are at ~10-20-fold increased risk of a premature myocardial infarction.

The classification of FH is complex and worth noting in the context of predicting risk of disease progression. Among monogenic causes of FH, there are both autosomal dominant and autosomal recessive forms. Autosomal dominant homozygous FH may present as homozygous FH or compound heterozygous FH, which involves either homozygous loss-of-function alleles in *LDLR* or one copy each of different loss-of-function alleles in the same gene. The prevalence of this form is approximately 1:300,000 to 1:400,000. These patients typically have LDL-C above 500 mg/dl and, for null *LDLR* mutations, levels can easily exceed 800 mg/dl. These patients often develop severe atherosclerosis and incur MIs before the age of 20. In contrast, the heterozygous FH syndrome is characterized by LDL-C levels in the 190-500 mg/dl range, though patients with LDL-C in this range may alternatively have homozygous mutations in *APOB* or *PCSK9*.

It is important to note that recent genetic sequencing efforts have shown that even among those individuals with LDL-C > 190 mg/dl, the main criteria for diagnosing severe hypercholesterolemia, only ~2% have known FH mutations. However, for any level of LDL-C, having a documented FH mutation increases risk for CAD substantially above that for the same LDL-C level without a FH mutation. Given the relatively high prevalence of severe hypercholesterolemia, and the fact that the disorder is under-diagnosed, it is important to be familiar with the diagnostic criteria. Below are several of the validated FH diagnostic criteria.

<u>Simon Broome Criteria</u>

Definite FH:

- Total Cholesterol >7.5 mmol/L (>290 mg/dL) or LDL-C >4.9 mmol/L (>190 mg/dL) and tendon xanthomas, or evidence of these signs in first- or second-degree relatives OR

- DNA-based evidence of a pathogenic *LDLR*, *APOB*, or *PCSK9* mutation

Possible FH:

- Total Cholesterol >7.5 mmol/L (>290 mg/dL) or LDL-C >4.9 mmol/L (>190 mg/dL) and one of the following:
  - Family history of myocardial infarction (younger than 50 years in second-degree relative or younger than 60 years in first-degree relative)
  - Family history of elevated total cholesterol (>7.5 mmol/L [>290 mg/dL) in adult first- or second-degree relative or >6.5 mmol/L [>260 mg/dL] in a child, brother or sister age <16 years)

Dutch Lipid Clinic Network (DLCN) Criteria

Criteria	**Points**
Family History	
First-degree relative with premature CAD (<55 years in men, <60 years in women)	1
First-degree relative with LDL-C >95th percentile by age, gender	1
First-degree relative with tendon xanthoma and/or corneal arcus	2
Children <18 years with LDL-C >95th percentile by age, gender	2
Personal Clinical History	
Premature CAD (<55 years in men, <60 years in women)	2
Premature cerebrovascular or peripheral vascular disease (<55 years in men, <60 years in women)	1
Physical Exam	
Tendon xanthoma	6
Corneal arcus in subject <45 years	4
LDL-C Level	
>325 mg/dL (>8.5 mmol/L)	8
251-325 mg/dL (6.5-8.4 mmol/L)	5
191-250 mg/dL (5.0-6.4 mmol/L)	3
155-190 mg/dL (4.0-4.9 mmol/L)	1
Genetic Testing	
Causative mutation in *LDLR*, *APOB*, or *PCSK9* genes	8

Definite FH: >8 points Probable FH: 6-8 points Possible FH: 3-5 points Unlikely FH: 0-2 points

MEDPED Criteria

Age (years)	**General Population (Total Cholesterol cutpoint, mg/dL)**	**First-degree relative with FH (Total Cholesterol cutpoint, mg/dL)**	**Second- degree relative with FH (Total Cholesterol cutpoint, mg/dL)**	**Third-degree relative with FH (Total Cholesterol cutpoint, mg/dL)**
<20	270	220	230	240
20-29	290	240	250	260
30-39	340	270	280	290
≥40	360	290	300	310

Definite FH diagnosed if total cholesterol level exceeds the cut point

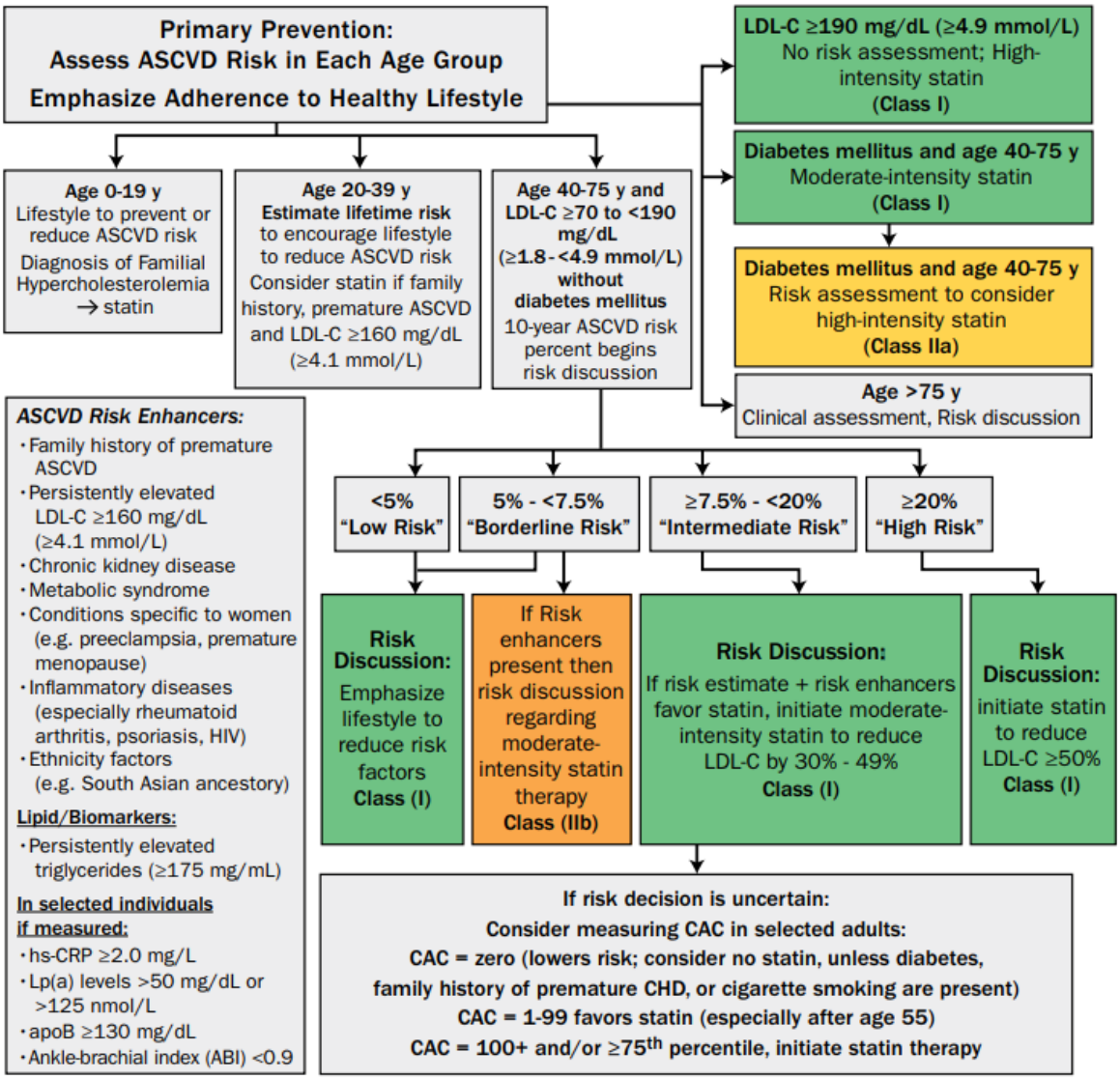
Pharmacotherapy for HLD

Statins: Statins are a mainstay of therapy for secondary prevention in atherosclerotic cardiovascular disease (ASCVD) with data supporting their use in reducing MACE events. Data show that the net absolute benefit of statins in primary prevention varies by CV risk. This, of course, must be weighed against statin harms. The 2018 AHA/ACC guidelines for the management of cholesterol for prevention of ASCVD focus on matching statin intensity and goal % LDL cholesterol reduction with degree of CV risk. The *higher* the risk, the greater the benefit from statin (lower number-needed-to-treat to prevent a first event), and the *higher* the recommended dose, given the weight of benefits over harms.

The key primary prevention recommendations of the guideline are outlined in the image on the next page from the ACC/AHA Task Force on Clinical Practice Guidelines: 2018 Guideline on the Management of Blood Cholesterol (https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf).

The clinician is to use the ASCVD risk calculator, to determine a given patient's risk for ASCVD in the next 10 years (http://tools.acc.org/ASCVD-Risk-Estimator/). In EPIC, you can pull in the ASCVD 10 year risk for a patient in their note based on their most recent assessments using the dot phrase ".ASCVD".

	High-intensity	Moderate-intensity	Low-intensity
LDL-C Lowering	>/= 50%	30% to 49%	< 30%
Statins	Atorvastatin 40-80mg Rosuvastatin 20-40mg	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40-80mg Fluvastatin XL 80mg Fluvastatin 40mg BID Pitavastatin 1-4mg	Simvastatin 10mg Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20-40mg


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin
Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history, premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70 to <190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
• Family history of premature ASCVD
• Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
• Chronic kidney disease
• Metabolic syndrome
• Conditions specific to women (e.g. preeclampsia, premature menopause)
• Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
• Ethnicity factors (e.g. South Asian ancestory)
Lipid/Biomarkers:
• Persistently elevated triglycerides (≥175 mg/mL)
In selected individuals if measured:
• hs-CRP ≥2.0 mg/L
• Lp(a) levels >50 mg/dL or >125 nmol/L
• apoB ≥130 mg/dL
• Ankle-brachial index (ABI) <0.9
<5% "Low Risk"
5% - <7.5% "Borderline Risk"
≥7.5% - <20% "Intermediate Risk"
≥20% "High Risk"
Risk Discussion:
Emphasize lifestyle to reduce risk factors
Class (I)
If Risk enhancers present then risk discussion regarding moderate-intensity statin therapy
Class (IIb)
Risk Discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
Class (I)
Risk Discussion:
initiate statin to reduce LDL-C ≥50%
Class (I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

As one of the most widely prescribed classes of drugs in the world, there is extensive literature, both scientific and lay press, about statin side effects. Furthermore, media coverage of statins has been shown to influence statin adherence. Expect that any patient in whom you initiate statin treatment will encounter this information. It is best for your therapeutic relationship and their long-term adherence if you discuss these side effects with them in advance. There are numerous approaches for this conversation. One suggestion is the "5 M's of statin side effects," a mnemonic for addressing side effects in the clinic.[2]

5	The Adverse Effect	Patient-Centered Summary
Metabolism	Risk of new-onset diabetes	The risk of new-onset diabetes is low with a slightly higher risk for the most potent statins. This risk is highest in those with diabetes risk factors. Those who progress to diabetes still derive strong benefit from statins.
Muscle	Risk of muscle symptoms ranging from asymptomatic CK elevations to rhabdomyolysis	Muscle complaints are common symptoms (~1 in 20) but are not always a class effect. If clearly related to statin use, change in statin dose or a different statin may prove useful. Severe muscle symptoms can occur, but these are very infrequent and drug–drug interactions are often the cause.
Medication interactions	Statins interact with numerous medications, most commonly macrolide antibiotics and azole antifungals. Certain medications are contraindicated with statins	Patients and physicians alike should be aware that with statins, like many other drugs, drug interactions can occur because some drugs elevate statin concentration. Some statins have more drug-drug interactions than others. Macrolide antibiotics such as clarithromycin and erythromycin can do this for specific statins, including simvastatin, lovastatin, and atorvastatin. Those on multidrug regimens such as transplant patients and those undergoing therapy for HIV need careful evaluation before statins are prescribed (pitavastatin a reasonable option in the latter).
Major organ effects such as liver or kidney	Statins cause a transaminitis	Baseline liver tests should be done, but routine follow-up is not needed if they are in the normal range. The FDA concluded that serious liver injury with statins is rare and unpredictable in individual patients. Routine monitoring of liver tests does not appear to be effective in detecting or preventing serious liver injury despite minor elevations of transaminases.
Kidney injury	Statins are associated with an increased risk of acute kidney injury in observational studies	Although there is an association in observational studies, acute kidney injury due to statins has not been validated in randomized trials.
Memory	Memory loss and confusion have been reported with statin use	Individually reported events have resolved within 3 weeks of stopping the statin. A significant risk of cognitive problems was not seen more commonly in those on statins compared to those on placebo in 2 large trials.

There is a tool for assessing muscle side effects at http://tools.acc.org/StatinIntolerance/

In general, if statin intolerance is encountered, switching to another statin or a lower dose of the same statin is recommended. Referral to a lipid specialist may be indicated, if an evidence-based treatment regimen cannot be identified. As above, statins have been shown to reduce both LDL-C levels and the risk of cardiovascular disease. However, due to the residual risk of recurrent cardiovascular events and safety concerns associated with high-dose statin therapies, additional lipid-modifying therapies have been sought.

Ezetimibe: Ezetimibe targets the Niemann-Pick C1-like 1 protein, which results in reduced absorption of cholesterol from the intestine. So far, the data for ezetimibe are for secondary prevention as add-on therapy to statins in patients with recent ACS. Details are discussed in the ACS chapter. Ezetimibe is reasonable to add to maximally tolerated statin in the setting of severe hypercholesterolemia if suitable LDL-C is not reached.

PCSK9 Inhibitors: In 2015, the FDA approved alirocumab and evolocumab for clinical use. These first-in-class medications are fully humanized monoclonal antibodies that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9), which, as mentioned above, promotes degradation of the LDL receptor. Details of the studies demonstrating their efficacy in LDL-C lowering and reduction in mortality and adverse cardiac events are summarized in the ACS chapter. For primary prevention, these medicines are reasonable in the setting of untreated LDL-C > 190 mg/dl and presence of familial hypercholesterolemia with persistent LDL-C > 100 mg/dl on statins and ezetimibe, or untreated LDL-C > 220 mg/dl with persistent LDL-C > 130 mg/dl on statins and ezetimibe per the 2018 ACC/AHA cholesterol guidelines.

> *Alirocumab*: FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional LDL-cholesterol lowering.
> Dosing: 75mg or 150mg SC Q2weeks
> Side effect: Most commonly injection site reactions, nasopharyngitis, and flu.
>
> *Evolocumab*: FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional LDL-cholesterol lowering. Also approved as an adjunct to diet and other LDL-lowering therapies for the treatment of patients with homozygous familial hypercholesterolemia who require additional LDL-cholesterol lowering.
> Dosing: 140mg SC Q2weeks, or 420mg SC Q4weeks (for homozygous FH currently)
> Side effect: Most commonly nasopharyngitis, upper respiratory infection, flu, back pain, and injection site reactions.

Of note, both drugs remain very expensive, with an annual cost recently reduced to ~$7,000. Referral to the following specialists may be considered if:

- Patients or physicians are uncertain about PCSK9 inhibitor suitability
- There here is concern for a primary lipid disorder, such as familial hypercholesterolemia, in either the primary or secondary prevention setting
- PCSK9 inhibitor prescription is denied by insurers, but there is still a desire for clinical reevaluation for PCSK9 inhibitors

Specialists: Dr. Pradeep Natarajan (Cardiology), Dr. Linda Hemphill (Cardiology), Dr. Mason Freeman (Endocrinology)

Omega-3 fatty acids: Recently the REDUCE-IT trial of >8,000 patients with elevated triglyceride levels, on statins and either established CAD or diabetes along with other risk factors showed that high dose purified EPA treatment (icosapent ethyl [Vascepa] 2g bid) reduced cardiovascular death, nonfatal MI/stroke, coronary revascularization or unstable angina after about 2 years of treatment. The FDA has approved the use of Vascepa for severe hypertriglyceridemia, and indication for CVD prevention will soon be reviewed by FDA.

Diabetes

Diabetes increases risk of CAD, leads to a greater extent of coronary ischemia, and increases the likelihood of MI and silent myocardial ischemia. Type 2 diabetes is a CAD risk equivalent. Risk factor reduction is effective for secondary prevention. The ACS chapter provides more details on the benefits SGLT2-inhibitors and GLP-1 analogue in the prevention of secondary cardiovascular events in patients with diabetes. Briefly, with regard to SGLT2-inhibitors, the EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 studies have provided the most relevant information. The EMPA-REG OUTCOME study showed that empagliflozin reduced cardiovascular death, MI, and stroke in a study of >7,000 type 2 diabetes patients.[4] Similarly, the CANVAS study showed that canagliflozin reduced cardiovascular events in type 2 diabetes patients in 2 trials of a total of >10,000 patients but did cause greater risk of toe or metatarsal amputation.[5] The DECLARE-TIMI 58 study showed in >17,000 patients with type 2 diabetes (including >10,000 without ASCVD) that dapagliflozin did not result in a higher or lower rate of major adverse cardiovascular events than placebo but did reduce rate of cardiovascular death or hospitalization for heart failure.[6] With regard to GLP-1 analogues, the LEADER study showed that liraglutide reduced first occurrence of death from cardiovascular causes, nonfatal MI and stroke in a study of >9,300 type 2 diabetes patients compared to placebo.[7] These studies and others have greatly increased the scope for targeting these pathways for cardiovascular risk reduction in type 2 diabetes patients. Per the 2019 ACC/AHA prevention guidelines, these agents may be reasonable in primary prevention for type 2 diabetes if several CVD risk factors are also present.

Hypertension

Clinical trials have demonstrated that treatment of hypertension reduces the risk of adverse cardiovascular disease outcomes; however, the target blood pressure has long been uncertain. Treatment conventions and guidelines have called for the treatment of systolic blood pressure (SBP) to <140 mmHg, but no large randomized trials have demonstrated the benefit of this target or whether more intensive therapy is more efficacious.

2010: Action to Control Cardiovascular Risk In Diabetes-Blood Pressure (ACCORD-BP)
- Cohort: Patients with diabetes,
- Intervention: Intensive SBP control to <120 mmHg
- Control: Convention SBP target <140mmHg
- Outcome: NO improvement in cardiovascular outcomes compared with the convention target of <140 mmHg.

2013: Secondary Prevention of Small Subcortical Strokes blood pressure arm (SPS3-BP)
- Cohort: Patients with recent lacunar stroke
- Intervention: Intensive SBP control <130mmHg
- Control: Conventional control 130-150mmHg
- Outcome: NO improvement in recurrent CVA

TOC

2015: Systolic Blood Pressure Intervention Trail (SPRINT)

Cohort: Patients >50 with “increased risk” of CVD but without diabetes or stroke history
Intervention: Intensive SBP control <120mmHg
Control: Standard control >140mmHg
Outcome: Early cessation of trial after interim analysis at 3 years demonstrated superiority of intervention (as below).

- Reduced rate of MACE (MI, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) 1.65% per year vs. 2.19% per year (HR 0.75; 95% CI 0.64 – 0.89; P<0.001)
- Reduced all-cause mortality (HR 0.73; 95% CI 0.60 – 0.90; P<0.003)

Though notably also increased rates of serious adverse events including hypotension, syncope, electrolyte abnormalities, AKI higher in treatment group

The impact of SPRINT on patient care has yet to be determined. Questions remain about the implications of widespread intensive blood pressure therapy and its potential for complications. The 2017 ACC/AHA guidelines for definition and management of hypertension differ somewhat from previous JNC8 guidelines. Notably, they recommend stratifying those with Stage 1 hypertension (SBP >130, SBP >80) based on their ASCVD risk score before deciding on therapeutic strategy.[8]

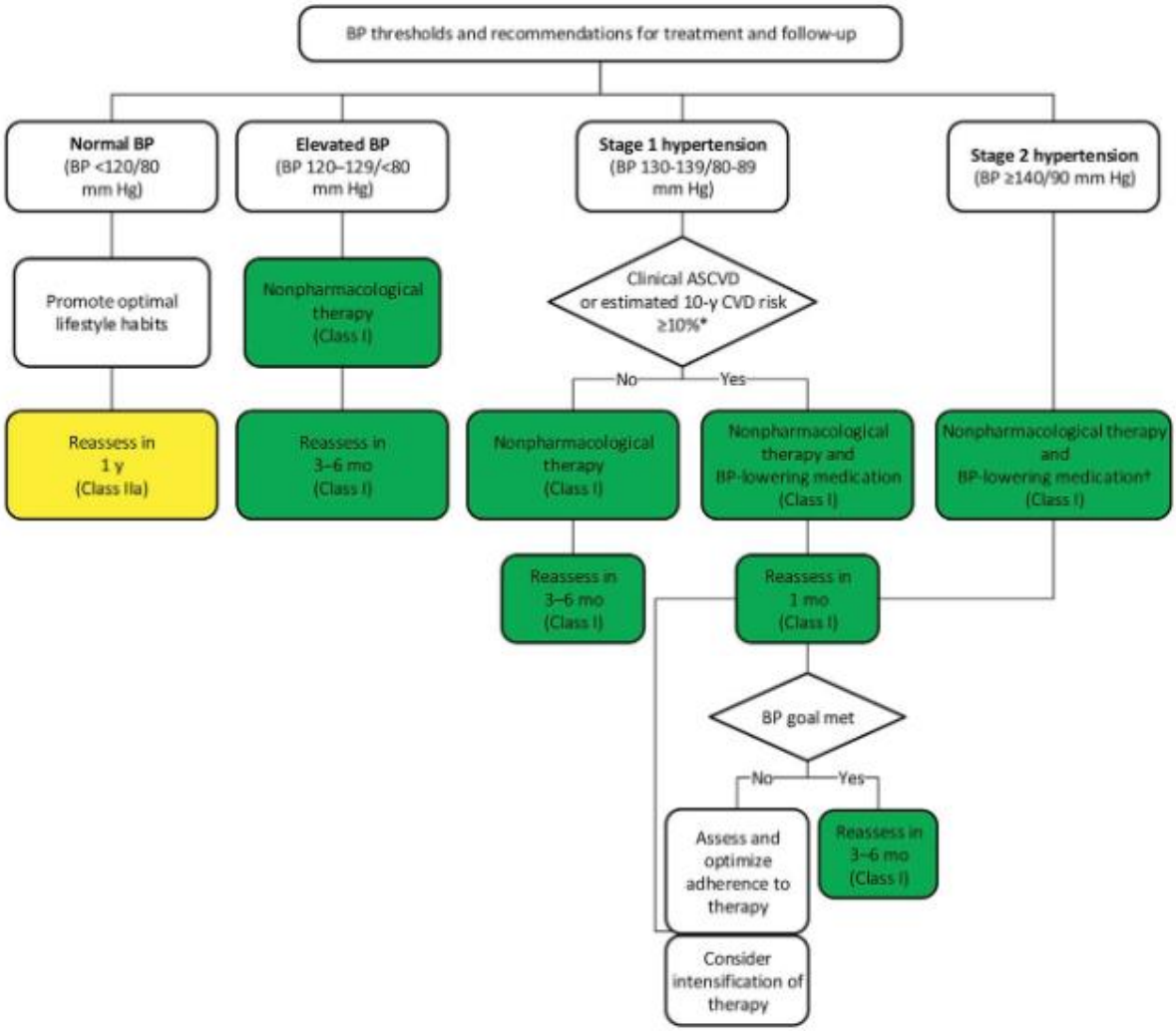


Figure 1. ACC/AHA 2017 algorithm for BP thresholds for treatment and recommended follow-up

The 2017 ACC/AHA guidelines do not make specific recommendations on what agent to choose as an initial therapy – recommendation is for any of thiazide diuretic, CCB, ACEI or ARB, with some comment that chlorthalidone may be preferred and more effective at preventing HF than ACEI or CCB.[8]

Aspirin

The benefit of aspirin for secondary prevention of atherothrombotic vascular complications is well-established and discussed elsewhere in this guide. However, the use of aspirin for primary prevention is more contentious with recent publication of three multicenter, double-blind RCTs: ARRIVE, ASCEND and ASPREE trials.

Trial name	Population	Primary endpoint	Outcome	Notes
ARRIVE	Healthy adults (M>55, F>60)	Composite time to first CVD event	- No benefit from aspirin in preventing incident CVD - Slightly increased minor GIB risk	Low rate of incident CVD overall
ASCEND	Diabetic adults, no known CVD	Serious vascular event (nonfatal MI, nonfatal stroke, transient ischemic attack, or death from any vascular cause)	- Slight reduction in serious vascular events - Increased rate of major GIB	- Trial authors concluded absolute benefit of ASA counterbalanced by bleeding risk - No difference in incidence of GIT cancers
ASPREE	Healthy adults >70	Disability free survival	- No difference in primary outcome - Slightly increased risk all-cause mortality - Increased risk cancer related death	

Anecdotally, many are changing practice on the basis of the above trial results, by discontinuing aspirin for primary prevention and discontinuing it in older adults. The latest guideline recommendations are reported in the table below.

It should also be noted that where aspirin is appropriate or being considered in an aspirin-allergic patient, clopidogrel should be used in its place.

Organization	Last update	Population	Recommendation Summary	Level of Evidence
ACC/AHA primary prevention guideline	2019	Age 40 to 70 who are at higher ASCVD risk but not at increased bleeding risk	Consider aspirin	A
ACC/AHA primary prevention guideline	2019	Age >70	Avoid aspirin	B

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5. Neal B, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657
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QUICK REFERENCE GUIDE: PRIMARY PREVENTION

The ABCDEs of Primary Prevention

A- Aspirin: May be considered for the primary prevention of CVD for patients aged 50-70 years if they have high ASCVD risk and low bleeding risk. Aspirin should be avoided for primary prevention in those over the age of 70 years

B- Blood pressure: Management should focus on lifestyle measures. For patients with stage 1 hypertension (BP 130-139/80-89) and an estimated 10-y CVD risk ≥10%, consider initiating an antihypertensive. For patients with stage 2 hypertension (BP ≥140/90) initiate BP-lowering medication

C- Cholesterol and Cigarette use: Initiate statin therapy in patients with high ASCVD risk, including established CVD, DM, LDL cholesterol (LDL-C) > 190mg/dl, or high estimated risk (>20%/10y) using the 2013 ACC/AHA Pooled Cohort Equation. In asymptomatic individuals at intermediate risk (7.5-20%/10y), initiate moderate intensity statin if other risk modifiers present. In adults who use tobacco, a combination of behavioral interventions plus pharmacotherapy is recommended to maximize quit rates

D- Diet and Diabetes: A diet enriched in fruits, vegetables, nuts, whole grains, and fish is recommended to prevent CVD. For patients with type 2 DM, a tailored nutrition plan is recommended. It is reasonable to initiate metformin as first-line therapy anti-glycemic agent in patients with DM. For adults with additional ASCVD risk factors who require glucose-lowering therapy despite lifestyle changes and metformin, it is reasonable to initiate SGLTi or GLP-1R agonist to improve glycemic control and reduce CVD risk

E- Exercise: It is recommended that adults engage in at least 150 minutes of moderate-intensity exercise (defined as brisk walking, biking, ballroom dancing, active yoga, recreational swimming) a week or 75 minutes of vigorous-intensity exercise per week (jogging/running)

COMMON TOXIDROMES

See Page 370 for Quick Reference Guide

53. Common Toxidromes

For any patient presenting with a known or suspected toxic ingestion or exposure early consultation with the national Poison Control Center (1-800-222-1222) is advised.

Identifying a toxidrome may provide useful information to help identify and treat the underlying condition. It is important to remember however, that toxidromes often have overlapping features or lack a classic sign or symptom of that toxidrome.

There are three broad categories of toxidromes: (1) electrocardiographic (2) physical and (3) laboratory toxidromes which will be discussed below.

Electrocardiographic Toxidromes

QT Prolongation

Prolongation of QT on ECG to ≥ 500 msec reflects impaired myocardial repolarization and is associated with increased risk of torsades de pointes (TdP). Bazett's formula: $QTc = \frac{QT}{\sqrt{RR\ inteval\ (secs)}}$ can be used to correct the QT interval for differing heart rates.

Numerous cardiac and non-cardiac drugs can prolong the QT interval including:

- Antiarrhythmics (procainamide, quinidine, amiodarone, sotalol, disopyramide, dofetilide)
- Calcium channel blockers
- Antihistamines
- Antibiotics including macrolides and fluoroquinolones azoles
- Psychotropic medications (haloperidol, methadone, citalopram, venlafaxine)

An updated list of QTc prolonging medications can be found at the following website: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf

Risk of acquired (i.e. drug induced) QT prolongation is increased in the setting of HF, hypokalemia, hypomagnesemia, and bradycardia; female patients are also at higher risk of drug-induced torsades.[2]

Mechanism:

- Myocardial repolarization is driven primarily by outward K^+ channels and blockage of these channels leads to a prolonged repolarization and QT interval prolongation.
- This may result in activation of inward depolarization currents (early afterdepolarizations (EAD)) that can then lead to re-entry tachycardia and subsequent ventricular tachycardia. Most often this is torsades de pointes (TdP) with variation in axis and/or morphology of QRS noted on electrocardiogram.
- Bradycardia with drug-induced QT prolongation is more likely to degrade into torsades de pointes than the same QT interval with tachycardia.[1]

Treatment:

- Discontinue offending agents and assess medication interactions
- Correct contributing metabolic derangements such as hypokalemia, hypomagnesemia, and hypocalcemia
- If TdP and hemodynamically unstable, defibrillation is indicated. If patient becomes pulseless, follow standard ACLS algorithm
- First line is IV magnesium, 2g IV bolus if patient is hemodynamically stable
    - Can repeat bolus or place patients on continuous infusion of IV magnesium at a rate of 3-20 mg/min
- Temporary transvenous overdrive pacing is reserved for patients with torsades de pointes who do not respond to IV magnesium. Pacing at a rate of ~100 beats per minute will decrease the development of early afterdepolarizations, reducing triggers for TdP
- Isoproterenol (starting at 2 mcg/min, titrated to achieve a HR of 100) can also be used as a temporizing measure before pacing to increase HR and decrease QT interval.
- Consider repletion of K to levels of 4.5-5 mmol/L, although of uncertain benefit[5]
- If TdP due to quinidine, plasma alkalization with sodium bicarbonate is useful
- Anti-arrhythmic therapy for TdP is limited, but amiodarone should be avoided due to QT prolonging effects but lidocaine (1.5mg/kg load) may have efficacy

QRS Prolongation

QRS interval prolongation can be caused by agents that block cardiac voltage gated Na^+ channels. Drugs known to cause sodium channel blockade include class IA and IC antiarrhythmics, cocaine, TCAs, and calcium channel blockers (diltiazem and verapamil). Patients poisoned with sodium channel blocking drugs may have varied presentations based on the other effects these medications may have (i.e. calcium and potassium efflux channel effects).

Mechanism[1]

- Drug blocks cardiac voltage gated Na^+ channels leading to delayed Na^+ entry into myocytes.
- Resulting in a slowed depolarization and widening of the QRS complex.
- This can progress to bundle branch block morphology, sine wave QRS patterns, and asystole.

Treatment:

- Therapy with hypertonic saline or sodium bicarbonate can be considered for poisoned patients that have a prolonged QRS interval.
- Hemodynamically unstable patients should be empirically treated with 1 - 2 mEq/kg of sodium bicarbonate, as it can improve inotropy and help prevent arrhythmias. A shortening of the QRS with this therapy may also confirm the presence of a Na^+ channel blocking agent.[1]

Bradycardia: Calcium Channel Blocker Overdose

Calcium channel blocker (CCB) overdose can present with hypotension, bradycardia, or decreased myocardial contractility. ECG can have sinus bradycardia, varying degrees of AV block, or escape rhythms. Widening of the QRS can be also seen.

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Mechanism:

- CCBs are classified as dihydropyridines or non-dihydropyridines, based on their physiological effects. However, at higher levels of toxicity, selectivity can be lost.
- Dihydropyridines (amlodipine/nicardipine/nifedipine) preferentially block L-type calcium channels in the vasculature leading to vasodilation. Toxicity presents with arterial vasodilation and reflex tachycardia.
- Non-dihydropyridines (diltiazem/verapamil) preferentially block L-type calcium channels in the myocardium leading to decreased inotropy and chronotropy. Toxicity will present with bradycardia, decreased cardiac inotropy, and peripheral vasodilation.
- Blockade of pancreatic calcium channels required for insulin secretion can lead to hyperglycemia.
    - This unique characteristic of CCB overdose may help differentiate from beta-blocker poisoning.

Treatment:

- For all patients, gastrointestinal decontamination should be considered
    - Orogastric lavage in patients who present within 1-2h of ingestion; due to vagal stimulation, hypotension and bradycardia may be exacerbated.
    - Activated charcoal is most useful within 1h of ingestion; should not be used in patients with altered mental status unless intubated.
    - Whole bowel irrigation can be done in cases where ingestion of an extended- or sustained-release formulation has been confirmed or is highly suspected.
- For the asymptomatic patient, observation for 8 hours (if ingestion is confirmed to be immediate-release CCB) to 24 hours (if ingestion was extended- or sustained-release) is warranted. Patients may deteriorate quickly even if stable-appearing initially.
- For the symptomatic patient:
    - Isotonic IVF: continued administration as long as the patient demonstrates evidence of fluid responsiveness.
    - Calcium IV to increase blood pressure and contractility:
        - 10% calcium gluconate 30-60mL (3-6g) via central or peripheral access q10-20min or infusion at 0.2-0.4 ml/kg/hr.
        - 10% calcium chloride 10-20mL via central access q10-20min or infusion at 0.2-0.4 ml/kg/h.
        - Monitor ionized calcium and ECGs for changes of hypercalcemia: shortened QT, ST elevation.
    - High dose insulin to increase contractility:
        - 1 U/kg of regular insulin bolus, then continuous 1 U/kg/hr infusion. Can titrate up to 10 U/kg/hr if unresponsive to first line therapies.
        - Monitor serum potassium and use dextrose infusions to maintain euglycemia.
    - Vasopressors/chronotropes guided by type of shock:
        - Norepinephrine or Epinephrine with addition of vasopressin (use of vasopressin alone is not recommended) for vasoplegic shock or if myocardial function has not yet been assessed
        - Dobutamine/Epinephrine for treatment of cardiogenic shock.
        - Dopamine is not recommended.
    - Atropine for symptomatic bradycardia/conduction disturbance
        - 0.5-1mg every 3-5 minutes.
    - Glucagon to increase HR

        - Dosing has not been established in human clinical trials. Consider initial 5mg IV bolus q10min x 3; if there is a response, consider infusion.
- For patients who fail above 1st line therapy
    - Consider IV lipid-emulsion and increasing insulin to max dose as above.
    - Consider pacing or temporary pacemaker placement for unstable bradycardia or high-grade AV block.
    - VA-ECMO has shown survival benefit for refractory shock due to CCBs.[2]

Bradycardia: Beta-Blocker Overdose

Mechanism:
Beta-blockers decrease conduction velocity across the atrioventricular (AV) node, resulting in PR prolongation; they also slow automaticity within the sinoatrial (SA) node, causing bradycardia.

Treatment:
- Isotonic IVF: for hypotension.
- Atropine*:* for bradycardia.
    - 0.5 to 1 mg every 3-5 minutes up to a total of 0.03 to 0.04 mg/kg.
- Glucagon IV
    - Given as a bolus of 5mg IV over 1 minute, if no increase in pulse or BP after 10-15 minutes, repeat bolus. If there is an increase pulse or BP after either administration, start infusion at 2-5mg/hour, titrated to maintain a MAP of 60mmHg.

Lithium ECG changes

Nonspecific T wave inversions or flattening, prolonged QTc and bradycardia. In patients with lithium toxicity, hydration maximizes renal clearance and is essential; hemodialysis should be considered.

Physical Exam Toxidromes

Anticholinergic Toxidrome

Toxicity can be seen in anticholinergic drugs or those with anticholinergic side effects such as diphenhydramine, scopolamine (which can be cut into heroin), doxylamine and TCAs (amitriptyline).

Classically presents as: dry as a bone (anhidrosis), blind as a bat (nonreactive mydriasis), red as a beet (cutaneous vasodilation), hot as a hare (hyperthermia), mad as a hatter (a spectrum of delirium to seizure), and full as a flask (urinary retention).

Tachycardia, although not reflective above, is the most reliable and often the first sign of anticholinergic toxicity. Reduced bowel sounds can be seen as well.

ECG should be obtained as certain drugs with anticholinergic side effects may have primary cardiac toxicity reflected in QRS prolongation (>100msec) or arrhythmias (i.e. TCAs).

Mechanism:

- Anticholinergic agents inhibit binding of acetylcholine to muscarinic receptors in the parasympathetic nervous system. Muscarinic receptors are found on the eye, heart, respiratory tract, GI tract, skin and bladder.
-

Treatment:

- Generally supportive including managing ABCs, foley for urinary retention, benzodiazepines for seizures, and cooling for hyperthermia.
- Consider gastric decontamination with activated charcoal (50g dose) if mental status is intact and ingestion was likely.
- Sodium bicarbonate should be used in the treatment of prolonged QRS intervals or for arrhythmias related to anticholinergic poisoning. This is commonly dosed as 2-3 vials of 50mL syringes (8.4% HCO3); if there is no response, an additional dose may be repeated after 5 minutes with telemetry running throughout to assess for QRS response.
- *Physostigmine* (a reversible acetylcholinesterase inhibitor) use is controversial, but it can be used to reverse central and peripheral antimuscarinic effects. It can be effective with symptoms of agitation, delirium, and/or hallucinations. Consultation with the Poison Control Center is recommended prior to use and side effects can include excessive cholinergic effects of bradycardia, bronchospasm, and bronchorrhea.
    - The recommended dose is 0.5-2 mg (0.02mg/kg IV) given over 5 minutes and can repeat every 10-30 minutes until response occurs.

Cholinergic Toxidrome

Can be remembered with mnemonics DUMBBELS (defecation, urination, miosis, bronchorrhea, bronchoconstriction, emesis, lacrimation, and salivation).

Associated with profound respiratory effects include watery nasal discharge, nasal hyperemia, marked salivation, bronchorrhea, and bronchoconstriction. Patients can present with cough, wheezing, and prolonged expiratory phase.

Profuse diaphoresis and gastrointestinal hyperactivity can be seen with vomiting, cramping, tenesmus, and uncontrolled defecation/involuntary urination.

Seizures are frequently seen due to the effect of excess ACh on the CNS.

Stimulation of nicotinic receptors at the motor end plate can lead to fasciculations, tremors, and even flaccid paralysis.

Mechanism:

- Cholinergic agents act by activating muscarinic acetylcholine (ACh) receptors but different agents can have variable presentations due to their effects on other receptors.
- Organophosphates and carbamates cause cholinergic toxicity by inhibiting acetylcholinesterase (AChE) decreasing the inactivation of acetylcholine and increasing muscarinic and nicotinic receptor stimulation.
- Nicotinic poisoning acts by direct stimulation of nicotinic receptors.

Treatment:

- Airway protection as many patients will develop rapid respiratory compromise.

    - Avoid succinylcholine during intubation as it is metabolized by the AChE inhibited by organophosphates
- Atropine: works as muscarinic receptor antagonist.
    - 2-5mg IV and repeated with doubling dose every 3-5 minutes until pulmonary cholinergic toxicity is alleviated (i.e. clearing of respiratory secretions and cessation of bronchoconstriction).
    - Tachycardia should not be considered a contraindication to atropine administration in these patients. Atropine also has no effect on the nicotinic receptors, so muscle weakness, fasciculations, tremors, and paralysis are not indications for further atropine dosing.
- Pralidoxime chloride: acts by reactivating AChE and can alleviate both nicotinic and muscarinic effects. It should NOT be administered without concurrent atropine.
    - Dose of 30mg/kg administered slowly over 30 minutes followed by an infusion of of 8mg/kg per hour.
    - Side effects include hypertension, headache, blurred vision, epigastric discomfort, nausea, and vomiting. Rapid administration can result in laryngospasm, muscle rigidity, and transient impairment of respiration.
- Benzodiazepines for seizures due to cholinergic poisoning and prophylactic diazepam (i.e. 10mg once) can be used in the setting of organophosphate poisoning to decrease risk of seizure and neurocognitive dysfunction.

Opioid Toxidrome

The classic toxidrome consists of CNS depression, miosis, respiratory depression and decreased gastrointestinal motility with decreased or absent bowel sounds.

Non-classical signs can be seen with specific opioids:
- Normal pupils with meperidine
- Seizures with tramadol, propoxyphene, and meperidine
- QRS widening and ventricular tachycardia with loperamide and propoxyphene
- QT prolongation with methadone
- Movement disorders including chest wall rigidity with fentanyl
- Serotonin syndromes are possible due to the serotonergic properties of meperidine, fentanyl, and tramadol
- Adulterants can also alter presentation of opioid toxidrome

<u>Mechanism:</u>
- Opioids exert their clinical effects by binding to the major opioid receptors: mu (μ), kappa (κ), and delta (δ). Mu receptors are primarily responsible for the sensation of euphoria. Each type of opioid has different affinity profiles with each receptor, and therefore, each has different clinical effects.
-

<u>Treatment:</u>
- IV naloxone:
    - 0.04-0.05mg if spontaneous ventilation is present
    - 0.2-1mg in apneic patients and 2mg in the setting of cardiac arrest.
    - Uptitrate dose and re-administer every 2-3 minute intervals until the patient has restoration of respiratory function, ability to protect the airway, and an improved level of consciousness or until maximum dose of 10mg.

- Naloxone can precipitate severe withdrawal symptoms in opiate dependent patients.
- Alternative routes of administration include IM, IO, intranasal, and inhalation but have different doses and are more difficult to titrate.

Sympathomimetic Toxidrome

Common agents responsible for this toxidrome include cocaine (short acting; 30 minutes), methamphetamines (longer acting; 20 hours), PCP (duration < 8 hours), and theophylline. Non-toxicologic agents capable of producing this syndrome include thyrotoxicosis, pheochromocytoma, ICH or CVA, and temporal lobe epilepsy.

Physical exam will often reveal agitation, hypertension, tachycardia, hyperpyrexia/hyperthermia, diaphoresis and minimally reactive mydriasis. Severe cases may lead to cardiac arrhythmias and coma.[1]

Mechanism:

- Activation of the sympathetic nervous system occurs through direct stimulation of receptors or through increased norepinephrine by increasing its release or decreasing its breakdown

Treatment:

- Treatment is primarily supportive. Managing the airway and controlling agitation are the mainstays of treatment for sympathomimetic overdose or poisonings
- Agitation can be treated with benzodiazepines
- Standard cooling measures for hyperthermia and treating agitation can reduce core body temperature
- Chest pain and hypertension can be treated with benzodiazepines, nitroglycerin, and nitroprusside (for refractory hypertension)
  - For cocaine associated chest pain, benzodiazepines with NTG is superior in relieving chest pain than with NTG alone[12]
  - In the absence of matched alpha blockade, beta blockade can result in coronary artery and peripheral vasospasm. Notably, the alpha:beta antagonism ratio of labetalol is only 1:7
  - If needed, phentolamine provides selective alpha antagonism.
    - 5 to 10 mg IV every 5-15 minutes PRN

Hyperthermic Toxidromes

There are several toxin-mediated causes of hyperthermia. These include sympathomimetic hyperthermia, uncoupling syndrome, serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, and anticholinergic poisoning. It is important to recognize the underlying mechanism as it drives management.

Mechanism and Treatment:

- Sympathomimetic hyperthermia is caused by excess release of serotonin and dopamine resulting in thermal deregulation.
  - Treatment is supportive with active cooling and benzodiazepines for agitation.
- Uncoupling syndrome (most commonly seen with salicylate poisoning) results from the disruption of the oxidative phosphorylation pathway leading to heat generation.

    - Alkalinize urine with sodium bicarbonate, 1-2 mEq/kg (maximum 100 mEq) IV push over 3 to 5 minutes, followed by maintenance of 100-150 mEq sodium bicarbonate in 1 L of D5W, run at 250 mL/hour in adults, titrating rate to urine pH of 7.5-8.
    - Discussion with Renal about dialysis.
- Serotonin syndrome is a result of excess serotonin at the peripheral and central serotonergic receptors.
    - Discontinue offending agents and supportive care: i.e. active cooling.
    - Cyproheptadine, an H1-receptor antagonist with non-specific anti-serotonergic properties, but is only available orally.
        - 12mg dose should be administered followed by 2mg every 2 hours until clinical response is seen.
- Neuroleptic malignant syndrome is characterized by fever, dysautonomia, rigidity and mental status change; it is likely caused by central dopamine receptor blockade. Can be seen with high potency antipsychotics and non-psychiatric medications such as metoclopramide and promethazine. It is also associated with abrupt withdrawal from dopamine agonist therapy in those treated for parkinsonism.
    - Discontinue offending agents and supportive care: i.e. active cooling.
    - Benzodiazepines either lorazepam, 1-2mg IM or IV every 4-6 hours, or diazepam 10mg IV every 8 hours.
    - Dantrolene, a direct-acting skeletal muscle relaxant (1-2.5mg/kg IV, repeated to a maximum dose of 10mg/kg/day).
        - Avoid with LFT abnormalities.
    - Bromocriptine, a dopamine agonist, can also be used.
        - 2.5mg every 6-8 hours.
    - Amantadine can also be used for its dopaminergic and anticholinergic effects.
        - Initial dose of 100mg orally, can be titrated to maximum dose of 200mg every 12 hours.
- Malignant hyperthermia can result when genetically susceptible individuals are exposed to depolarizing neuromuscular blocking agents such as succinylcholine and volatile general anesthetics.
    - Same as NMS treatment above.
- Anticholinergic poisoning can result in hyperthermia secondary to impairment of the normal physiologic cooling mechanisms such as sweating.
    - Treatment is supportive with active cooling and benzos for agitation.

Laboratory Toxidromes

Osmolar Gap

The serum osmolar gap may be useful in evaluating for suspected toxic ingestion. It can be especially helpful when patients have an unexplained anion gap metabolic acidosis and a toxic ingestion is suspected. Toxic ingestions that can cause an elevated serum osmolar gap include: ethylene glycol, methanol, ethanol, isopropyl alcohol, and mannitol.

$$Osmolar\ Gap = Measure\ Serum\ Osmoles - Calculated\ Serum\ Osmoles$$

$$Calculated\ Osmolality = 2Na + \frac{Glucose}{18} + \frac{BUN}{2.8} + \frac{Ethanol}{3.7}$$

TOC

A gap exists when measured osmolality is 10 mosm/kg greater than calculated osmolalilty.

This gap must be interpreted with caution as small errors in sodium, urea nitrogen, glucose, and osmolality can result in large variations in the osmolar gap. Additionally, a normal osmolar gap may be falsely reassuring.

For suspicion of toxic alcohol ingestion, empiric treatment with:

- Sodium Bicarbonate
  - 1-2 mEq/kg (maximum 100 mEq) IV push over 3 to 5 minutes, followed by maintenance of 100-150 mEq sodium bicarbonate in 1 L of D5W at a rate of 150-250 ml/hr.
- Fomepizole to inhibit alcohol dehydrogenase.
  - 15mg/kg IV followed by 10 mg/kg every 12 hours.
- Hemodialysis should be considered[1].

Anion Gap

$$\boldsymbol{Anion\ Gap} = Na^{+} - [Cl^{-} + HCO_3^{-}]$$

An increase of the anion gap reflects an increase in "unmeasured anions". The anion gap increases due to decreases of the concentration of bicarbonate relative to levels of sodium and chloride because of overproduction of acid (in ketoacidosis, lactic acidosis, and drug and alcohol intoxications), under-excretion of acid (renal disease), cell lysis, or other circumstances like the use of penicillin-derived antibiotics. Two mnemonics below represent the majority of causes of increased anions.

MUDPILES	**GOLDMARRK**
Methanol	**G**lycols: ethylene and propylene
Uremia	5-**O**xoproline
Diabetic/alcoholic/ starvation ketoacidosis	**L-**lactate
Paraldehyde	**D**-lactate
Iron, inhalants (carbon monoxide, cyanide), toluene, isoniazid, ibuprofen	**M**ethanol
Lactic acidosis	**A**spirin
Ethylene glycol, ethanol ketoacidosis	**R**enal failure
Salicylates, starvation ketoacidosis, sympathomimetics	**R**habdomyolysis
	Ketoacidosis

- Lactic acidosis accounts for around half of cases of high anion gap, but roughly half of patients with lactate levels between 3-5 mmol/L have a normal anion gap[3]
- Low or negative anion gaps can be observed with lithium, bromide, or iodide toxicity, monoclonal IgG gammopathy, or high levels of calcium or magnesium

References:

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2. Masson R et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012 Nov;83(11):1413-7
3. Berend K et al. Physiological approach to assessment of acid-base disturbances. N Engl J Med. 2014;371(15):1434-45

QUICK REFERENCE GUIDE: COMMON TOXIDROMES

Overview of Common Toxidromes

- For any patient presenting with a known or suspected toxic ingestion or exposure early consultation with the national Poison Control Center (1-800-222-1222) is advised
- There are three broad categories of toxidromes based on mode of identification, including:
    - Electrocardiographic
    - Physical exam, and
    - Laboratory

Electrocardiographic Toxidromes

- QTc prolongation: An updated list of QTc prolonging medications can be found at the following website: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf
- QRS prolongation: Caused by agents that block cardiac voltage gated Na^+ channels
    - Drugs known to cause sodium channel blockade include class IA and IC antiarrhythmics, cocaine, TCAs, and calcium channel blockers (diltiazem and verapamil)
- Bradycardia: Secondary to CCB overdose and BB overdose. For the symptomatic patient, management includes
    - Isotonic IVF
    - Calcium IV to increase blood pressure and contractility: 10% calcium gluconate 30-60mL (3-6g) via central or peripheral access q10-20min or infusion at 0.2-0.4 ml/kg/hr
    - High dose insulin to increase contractility
    - Vasopressors/chronotropes guided by type of shock
    - Atropine for symptomatic bradycardia/conduction disturbance: 0.5-1mg every 3-5 minutes
    - Glucagon to increase heart rate: Consider a bolus of 5mg IV over 1 minute; if no increase in pulse or BP after 10-15 minutes, repeat bolus. If there is an increase pulse or BP after either administration, start infusion at 2-5mg/hour, titrated to maintain a MAP of 60mmHg
- Lithium: Toxicity results in nonspecific T wave inversions or flattening, prolonged QTc and bradycardia
    - In patients with lithium toxicity, hydration maximizes renal clearance and is essential; hemodialysis should be considered

Physical Exam Toxidromes

- Anticholinergic:
    - Can be seen in anticholinergic drugs or those with anticholinergic side effects such as diphenhydramine, scopolamine (which can be cut into heroin), doxylamine and TCAs (amitriptyline)
    - Classically presents as: dry as a bone (anhidrosis), blind as a bat (nonreactive mydriasis), red as a beet (cutaneous vasodilation), hot as a hare (hyperthermia), mad as a hatter (a spectrum of delirium to seizure), and full as a flask (urinary retention)
    - Treatment is generally supportive, including managing ABCs, foley for urinary retention, benzodiazepines for seizures, and cooling for hyperthermia.

- Cholinergic:
  - Can be remembered with mnemonics DUMBBELS (defecation, urination, miosis, bronchorrhea, bronchoconstriction, emesis, lacrimation, and salivation)
  - The most important management consideration is airway protection, as many patients will develop rapid respiratory compromise. Avoid succinylcholine during intubation as it is metabolized by the AChE inhibited by organophosphates
  - Additional medical management:
    - Atropine: Works as muscarinic receptor antagonist. Administer as 2-5mg IV push, repeated with doubling dose every 3-5 minutes until pulmonary cholinergic toxicity is alleviated (i.e. clearing of respiratory secretions and cessation of bronchoconstriction)
    - Pralidoxime chloride: Acts by reactivating AChE and can alleviate both nicotinic and muscarinic effects; should NOT be administered without concurrent atropine. Administer as 30mg/kg administered slowly over 30 minutes followed by an infusion of of 8mg/kg per hour
    - Benzodiazepines: Prophylactic diazepam (i.e. 10mg once) can be used in the setting of organophosphate poisoning to decrease risk of seizure and neurocognitive dysfunction
- Opiate:
  - The classic toxidrome consists of CNS depression, miosis, respiratory depression and decreased gastrointestinal motility with decreased or absent bowel sounds
  - Treat with IV naloxone
    - If spontaneous ventilation is present: 0.04-0.05 mg
    - If patient apneic but with a pulse: 0.2-1 mg
    - If cardiac arrest: 2 mg
- Sympathomimetic:
  - Common agents responsible for this toxidrome include cocaine (short acting; 30 minutes), methamphetamines (longer acting; 20 hours), PCP (duration < 8 hours), and theophylline
  - Non-toxicologic agents capable of producing this syndrome include thyrotoxicosis, pheochromocytoma, ICH or CVA, and temporal lobe epilepsy
  - Treatment, which is primarily supportive, requires management of airway and controlling agitation (can be treated with benzodiazepines)
- Hyperthermic:
  - Toxin-mediated causes of hyperthermia include sympathomimetic hyperthermia, uncoupling syndrome, serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, and anticholinergic poisoning
  - Underlying mechanisms drives management (see section for individual mgmt)

Laboratory Toxidromes

- Osmolar gap:
  - May be particularly useful when patients have an unexplained anion gap metabolic acidosis and toxic ingestion is suspected
    - Toxic ingestions resulting in a high osmolar gap include: Ethylene glycol, methanol, ethanol, isopropyl alcohol, and mannitol
  - Calculation requires measurement of: Serum osms, BMP (Na, BUN, glucose), and ethanol
  - Gap is present when measured osmolality is 10 mosm/kg greater than the calculated osmolalilty

- Anion gap:
  - High anion gap reflects an increase in “unmeasured anions”
  - Results when there are decreased concentrations of bicarbonate relative to levels of sodium and chloride
  - This can occur as a result of: overproduction of acid (in ketoacidosis, lactic acidosis, and drug and alcohol intoxications), under-excretion of acid (renal disease), cell lysis, or with use of certain medications (e.g. penicillin-derived antibiotics)
  - Lactic acidosis accounts for about half of cases of AGMA, but roughly half of patients with lactate levels between 3-5 mmol/L have a normal anion gap
  - A low or negative anion gap can be observed with: Lithium, bromide, or iodide toxicity, monoclonal IgG gammopathy, or high levels of calcium or magnesium