

POCKET
NOTEBOOK

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POCKET

CARDIOLOGY

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 **Wolters Kluwer**

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Preface

With *Pocket Cardiology*, we now offer those taking care of patients with complex cardiovascular disease a focused and concise reference to aid them in their daily clinical care. *Pocket Cardiology* has been designed to either supplant the Cardiology section in *Pocket Medicine* or serve as a stand-alone handbook. *Pocket Cardiology* provides greatly expanded coverage of the latest treatment options for the major common cardiovascular diseases as well as new sections on advanced heart failure, vascular, and electrophysiology topics.

We have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Cardiology* went to press. We welcome any suggestions for further improvement. Although the recommendations herein are as evidence based as possible, sound clinical judgement must be applied to every scenario.

This book would not have been possible without the help of Melinda Cuerda, who shepherded the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be.

It is a privilege to take care of patients, especially when working with the house officers, fellows, and attendings at Brigham and Women's Hospital and the Massachusetts General Hospital. The rapid advances in cardiovascular medicine are truly amazing. We hope the information contained within *Pocket Cardiology* proves useful in your quest to deliver the best possible care to your patients.

Marc S. Sabatine, MD, MPH

Coronary Disease

ELECTROCARDIOGRAPHY

Approach (*a systematic approach is vital*)

- **Rate** (? tachy or brady)
- **Rhythm** (? P waves, ? relationship between P and QRS, ? regular)
- **Intervals** (PR, QRS, QT) and **axis** (? LAD or RAD)
- **Chamber abnormality** (? LAA and/or RAA, ? LVH and/or RVH)
- **QRST changes** (? Q waves, poor R-wave progression V₁-V₆, ST ↑/↓ or T-wave Δs)

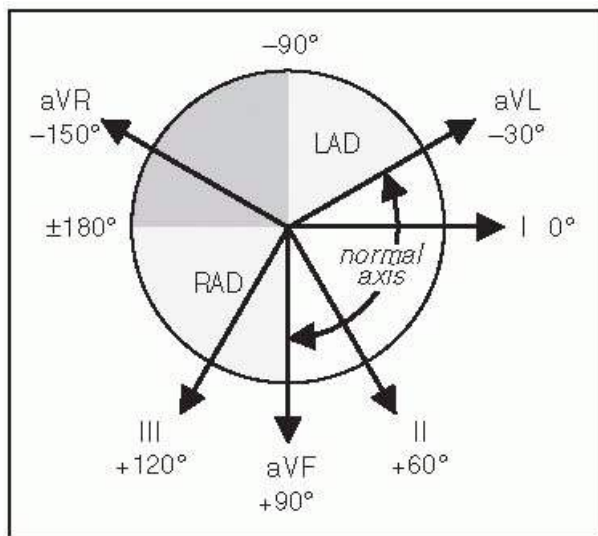


Figure 1-1 QRS axis

Left axis deviation (LAD)

- **Definition:** axis beyond -30° ($S > R$ in lead II)
- **Etiologies:** LVH, LBBB, inferior MI, WPW
- **Left anterior fascicular block (LAFB):** LAD (-45 to -90°) and qR in aVL and QRS < 120 msec and no other cause of LAD (eg, IMI)

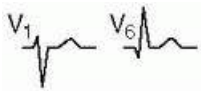
Right axis deviation (RAD)

- **Definition:** axis beyond $+90^\circ$ ($S > R$ in lead I)
- **Etiologies:** RVH, PE, COPD (usually not $> +110^\circ$), septal defects, lateral MI, WPW
- **Left posterior fascicular block (LPFB):** RAD (90 - 180°) and rS in I & aVL and qR in III & aVF and QRS < 120 msec and no other cause of RAD

Bundle Branch Blocks (*Circ* 2009;119:e235)

Initial depol. is left-to-right across septum (r in V₁ & q in V₆; nb, absent in

Normal



LBBB) followed by **LV** & **RV** free wall, with **LV** dominating (nb, **RV** depol. later and visible in **RBBB**).

RBBB



1. QRS ≥ 120 msec (110-119 = incomplete) 2. rSR' in R precordial leads (V_1, V_2) 3. Wide S wave in I and V_6 4. \pm ST \downarrow or TWI in R precordial leads

LBBB



1. QRS ≥ 120 msec (110-119 = incomplete) 2. Broad, slurred, monophasic R in I, aVL, V_5 - V_6 (\pm RS in V_5 - V_6 if cardiomegaly) 3. Absence of Q in I, V_5 and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. \pm PRWP, LAD, Qw's in inferior leads

Bifascicular block: **RBBB** + **LAFB/LPFB**. Trifascicular block: bifascicular block + 1° **AVB** (nb, misnomer as 1° **AVB** involves **AV** node but no fascicle per se).

Prolonged QT interval (*NEJM* 2008;358:169; www.torsades.org)

- QT measured from beginning of QRS complex to end of T wave (measure longest QT)
- QT varies w/ HR \rightarrow corrected w/ Bazett formula: $QT_c = QT/\sqrt{RR}$ (RR in sec, can be estimated by 60/HR), overcorrects at high HR and undercorrects at low HR (nl $QT_c < 440$ msec $\text{\textcircled{M}}$ and < 460 msec $\text{\textcircled{F}}$)
- Fridericia's formula preferred at very high or low HR: $QT_c = QT/\sqrt[3]{RR}$
- QT prolongation a/w \uparrow risk TdP (espec > 500 msec); perform baseline/serial ECGs if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:

Antiarrhythmics: class Ia (procainamide, disopyramide), class III (amio, sotalol, dofet)

Psych drugs: antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? **SSRI**, **TCA**

Antimicrobials: macrolides, quinolones, azoles, pentamidine, atovaquone, atazanavir

Other: antiemetics (droperidol, 5-HT₃ antagonists), alfuzosin, methadone, ranolazine

Electrolyte disturbances: hypoCa (nb, hyperCa a/w \uparrow QT), \pm hypoK, ? hypoMg

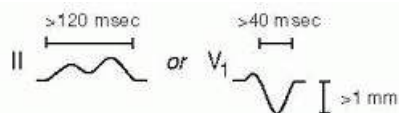
Autonomic dysfxn: **ICH** (deep TWI), stroke, carotid endarterectomy, neck dissection

Congenital (long QT syndrome): K, Na, & Ca channelopathies (*Circ* 2013;127:126)

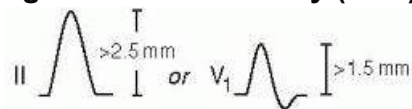
Misc: **CAD**, **CMP**, bradycardia, high-grade **AVB**, hypothyroidism, hypothermia, **BBB**

ECG P-wave Criteria

Left Atrial Abnormality (LAA)



Right Atrial Abnormality (RAA)



Left ventricular hypertrophy (LVH) (*Circ* 2009;119:e251)

- Etiologies: HTN, AS/AI, HCMP, coarctation of aorta
- Criteria (all w/ Se <50%, Sp >85%; accuracy affected by age, sex, race, BMI)

Romhilt-Estes point-score system (4 points = probable; 5 points = diagnostic):

| Criteria | Points |
|---|--------|
| Voltage (any of the following): R or S in limb leads ≥ 20 mm; S in V ₁ or V ₂ ≥ 30 mm; R in V ₅ or V ₆ ≥ 30 mm | 3 |
| ST-T displacement opposite to QRS deflection (either): | |
| ◦ Pt not on digoxin | 3 |
| ◦ Pt on digoxin | 1 |
| Left atrial enlargement | 3 |
| Left axis deviation | 2 |
| QRS duration ≥ 90 msec | 1 |
| Delayed intrinsicoid deflection (QRS onset to R peak) in V ₅ or V ₆ >50 msec | 1 |

Sokolow-Lyon: S in V₁ + R in V₅ or V₆ ≥ 35 mm or R in aVL ≥ 11 mm

Cornell: R in aVL + S in V₃ >28 mm in men or >20 mm in women If LAD/LAFB, S in III + max (R+S) in precordium ≥ 30 mm

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251)

- Etiologies: cor pulmonale, congenital (tetralogy, TGA, PS, ASD, VSD), MS, TR
- Criteria (all tend to be insensitive, but highly specific, except in COPD) R > S in V₁ or R in V₁ ≥ 7 mm, S in V₅ or V₆ ≥ 7 mm, drop in R/S ratio across precordium RAD $\geq +110^\circ$ (LVH + RAD or prominent S in V₅ or V₆ → biventricular hypertrophy)

Ddx of dominant R wave in V₁ or V₂

- Ventricular enlargement: RVH (RAD, RAA, deep S waves in I, V₅, V₆); HCMP
- Myocardial injury: posterior MI (anterior Rw = posterior Qw; often with IMI)
- Abnormal depolarization: RBBB (QRS > 120 msec, rSR'); WPW (↓ PR, δ wave, ↑ QRS)

- Other: dextroversion; Duchenne muscular dystrophy; lead misplacement; **nl** variant

Poor R wave progression (PRWP) (*Am Heart J* 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V_1 - V_3); R wave in $V_3 \leq 3$ mm
- Possible etiologies (nonspecific):
 - old anteroseptal **MI** (usually w/ R wave $V_3 \leq 1.5$ mm, \pm persistent **ST** \uparrow or **TWI** V_2 & V_3) cardiomyopathy
 - LVH** (delayed RWP with prominent left precordial voltage), **RVH**, **COPD** (which may also have **RAA**, **RAD**, limb lead QRS amplitude ≤ 5 , $S_I S_{II} S_{III}$ w/ R/S ratio < 1 in those leads)
 - LBBB**; **WPW**; clockwise rotation of the heart; lead misplacement; **PTX**

Pathologic Q waves

- Definition: ≥ 30 msec (≥ 20 msec V_2 - V_3) or $> 25\%$ height of R wave in that QRS complex
- Small (septal) q waves in **I**, **aVL**, V_5 & V_6 are **nl**, as can be isolated **Qw** in **III**, **aVR**, V_1
- "Pseudoinfarct" pattern may be seen in **LBBB**, infiltrative dis., **HCM**, **COPD**, **PTX**, **WPW**
- In **WPW**, **Qw** pattern may help localize site of accessory pathway (Bundle of Kent)

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e262)

- **Acute MI** (upward convexity \pm **TWI**) or prior **MI** with persistent **STE**
- **Coronary spasm** (Prinzmetal's angina; transient **STE** in a coronary distribution)
- **Pericarditis** (diffuse, upward concavity **STE**; a/w **PR** \downarrow ; **Tw** usually upright)
- **HCM**, **Takotsubo CMP**, **ventricular aneurysm**, cardiac contusion
- **Pulmonary embolism** (occ. **STE** V_1 - V_3 ; classically a/w **TWI** V_1 - V_4 , **RAD**, **RBBB**, $S_1 Q_3 T_3$)
- **Repolarization abnormalities**

LBBB (\uparrow QRS duration, **STE** discordant from QRS complex) **dx of MI in setting of LBBB**: Sgarbossa criteria (*NEJM* 1996;334:481) ≥ 1 mm **STE** concordant w/ QRS (**Se** 73%, **Sp** 92%) **STD** ≥ 1 mm V_1 - V_3 (**Se** 25%, **Sp** 96%) **STE** ≥ 5 mm discordant w/ QRS (**Se** 31%, **Sp** 92%)

LVH (\uparrow QRS amplitude)

Brugada syndrome (rSR', downsloping **STE** V_1 - V_2 ; Na channelopathy a/w **SCD**)

Hyperkalemia (see below)

Hypothermia: Osborn waves



⊕ deflection at J point, typically in R-precordial leads proportional to degree of hypothermia

- **aVR**: **STE** > 1 mm a/w \uparrow mortality in **STEMI**; **STE** **aVR** $> V_1$ a/w left main disease
- **Early repolarization**: most often seen in V_2 - V_5 in young adults (*JACC* 2015;66:470)

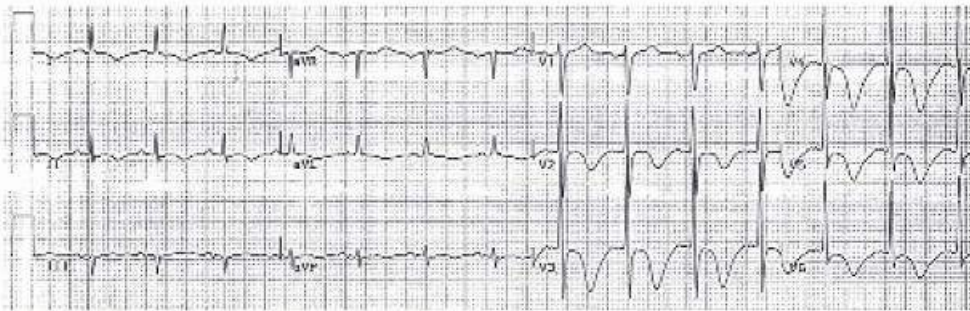
1-4 mm elev of peak of notch or start of slurred downstroke of R wave (ie, J point); \pm up concavity of **ST** & large **Tw** (∴ ratio of **STE**/T wave $< 25\%$; may disappear w/ exercise)

ST depression (STD)

- Myocardial ischemia (± Tw abnl) or acute true posterior MI (V₁-V₃)
- Digitalis effect (downsloping ST ± Tw abnl, does not correlate w/ dig levels)
- Hypokalemia (± U wave)
- Repolarization abnl in a/w LBBB or LVH (usually in leads V₅, V₆, I, aVL)

T wave inversion (TWI; generally ≥1 mm; deep if ≥5 mm) (Circ 2009;119:e241)

- Ischemia or infarct; Wellens' sign (deep, symmetric precordial TWI) → proximal LCA lesion



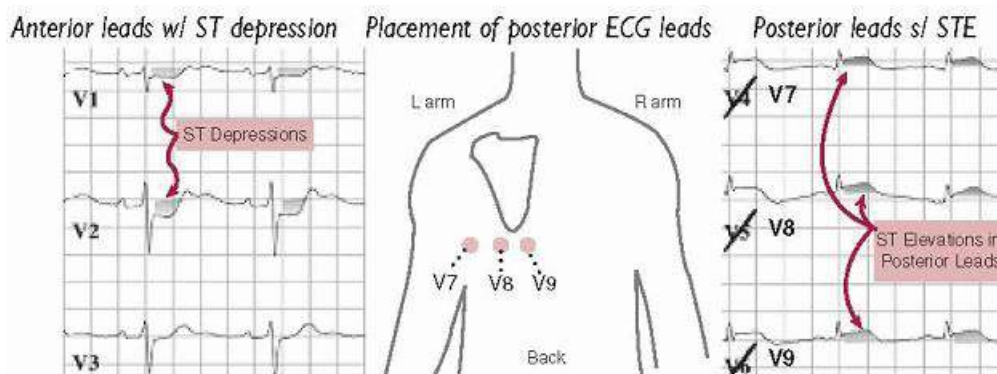
(Wellens' sign, from Cuculich

PS and Kates AM. *The Washington Manual Cardiology Subspecialty Consult*, 3rd ed. Philadelphia: Wolters Kluwer Health, 2014:286.)

- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWI V₁-V₄)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"), BBB
- Posttachycardia or postpacing
- Electrolyte, digoxin, PaO₂, PaCO₂, pH or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually w/ ↑ QT)
- Normal variant in children (V₁-V₄) and leads in which QRS complex predominantly ⊖

True posterior MI (posterior STE appearing as anterior STD)

- STD ± ↑ R wave in leads V₁-V₄ may correspond to acute posterior "ST-elevation" MI
- ✓ Posterior ECG leads; manage as a STEMI with rapid reperfusion



(Modified from Martindale JL, Brown DFM. *Rapid Interpretation of ECGs in Emergency Medicine*. Philadelphia:

Low voltage

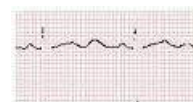
- QRS amplitude (R + S) <5 mm in all limb leads & <10 mm in all precordial leads
- Etiologies: COPD (precordial leads only), pericardial effusion, myxedema, obesity, pleural effusion, restrictive or infiltrative CMP, diffuse CAD

Electrolyte Abnormalities

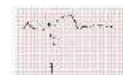
→ Tented Tw, ↓ QT Small Pw, ↑ PR, AVB Wide QRS → sinusoidal pattern STE
K (typically V₁-V₂)



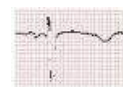
→ Flattened Tw U waves (⊕ deflection after T) ST depression Ectopy; ↑ QT &
K TdP



↑ ↓ QT, flattened Tw & Pw J point elevation
Ca



↓ ↑ QT; Tw Δs
Ca



(ECGs modified from Wagner GS, Strauss DG. *Marriott's Practical Electrocardiography*, 12th ed. Philadelphia: Lippincott Williams & Wilkins, 2014)

CHEST PAIN

Disorder Typical Characteristics & Diagnostic Studies

Cardiac Causes

ACS (15-25% of chest pain in ED) Substernal pressure radiating to neck, jaw, arm. ± Dyspnea, diaphoresis, NV; a/w exertion; ↓ w/ NTG or rest; however, not reliable indicator (*Annals EM* 2005;45:581). ± ECG Δs: STE, STD, TWI, Qw. ± ↑ Troponin.

Pericarditis & myo-pericarditis Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myocarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.

Aortic dissection Abrupt-onset severe tearing, knifelike pain (absence \ominus LR 0.3), ant or post midscapular. HTN or HoTN. \pm Asymmetric (> 20 mmHg) BP or pulse deficit (\oplus LR 5.7), focal neuro deficit (\oplus LR >6), AI, widened mediastinum on CXR (absence \ominus LR 0.3); false lumen on imaging. (*JAMA* 2002;287:2262)

Pulmonary Causes

Pneumonia Pleuritic; dyspnea, fever, cough, sputum. \uparrow RR, crackles. CXR infiltrate.

Pleuritis Sharp, pleuritic pain. \pm Pleuritic friction rub.

PTX Sudden onset, sharp pleuritic pain. Hyperresonance, \uparrow BS. PTX on CXR.

PE Sudden onset pleuritic pain. \uparrow RR & HR, \downarrow S_aO₂, ECG Δ s (sinus tach, RAD, RBBB, S_IQ_{III}T_{III}, TWI V₁-V₄, occ STE V₁-V₃). \oplus CTA or V/Q.

Pulm HTN Exertional pressure, DOE. \downarrow S_aO₂, loud P₂, RV heave, right S₃ and/or S₄.

GI Causes

Esophageal reflux Substernal burning, acid taste in mouth, water brash. \uparrow by meals, recumbency; \uparrow by antacids. EGD, manometry, pH monitoring.

Esoph spasm Intense substernal pain. \uparrow by swallowing, \downarrow by NTG/CCB. Manometry.

Mallory-Weiss Esophageal tear precipitated by vomiting. EGD.

Boerhaave syndrome Esoph. rupture typically precipitated by vomiting. Severe pain, \uparrow w/ swallowing. Palpable SC emphysema; mediastinal air on chest CT.

PUD Epigastric pain, relieved by antacids. \pm GIB. EGD, \pm *H. pylori* test.

Biliary dis. RUQ pain, N/V. \uparrow by fatty foods. RUQ U/S; \uparrow LFTs.

Pancreatitis Epigastric/back discomfort. \uparrow amylase & lipase; abd CT.

Musculoskeletal and Miscellaneous Causes

Costochond Localized sharp pain. \uparrow w/ movement. Reproduced by palpation.

Zoster Intense unilateral pain. Pain may precede dermatomal rash.

Anxiety "Tightness," dyspnea, palpitations, other somatic symptoms

Initial approach

- **Focused history:** quality & severity of pain; location & radiation; provoking & palliating factors; intensity at onset; duration, frequency & pattern; setting in which it occurred; associated **sx**; cardiac **hx** and risk factors

| Pain Feature | Classic for ACS | Atypical for ACS |
|----------------------|--|--|
| Quality | Pressure (⊕ LR 1.3), tightness, "Levine" sign (clenched fist over chest), squeezing, fullness, heavy weight, more than prior angina or ≈ prior MI (⊕ LR 1.8) | Sharp (⊕ LR 0.3) |
| Region/radiation | Substernal, radiating to L or R arm or shoulder (⊕ LR 2.3-4.7), jaw, teeth, neck | Small area, points w/ 1 finger, radiation to back |
| Provocation | Exertion (⊕ LR 2.4; but may be absent) | Pleuritic, positional or w/ palp (⊕ LR ≤0.3), eating |
| Associated sx | Diaphoresis (⊕ LR 2.0), N/V (⊕ LR 1.9), dyspnea | |

(JAMA 2005;294:2623)

- **Targeted exam:** VS (including BP in both arms), cardiac gallops, murmurs or rubs; signs of vascular disease (carotid or femoral bruits, ↓ pulses), signs of heart failure; lung & abdominal exam; chest wall exam for reproducibility of pain
- **12-lead ECG:** obtain w/in 10 min; c/w priors & obtain serial ECGs. In addition, consider:
 - posterior leads* (V₇-V₉; remove V₄-V₆ and place in post axillary, mid-clav & L paraspinal position) useful to ✓ for posterior STEMI if hx c/w ACS but std ECG unrevealing, espec if ST ↓ V₁-V₄ (ant ischemia vs post STEMI) or R/S V₁-V₂ > 1
 - R-sided leads* (place V₃-V₆ in mirror image position on R side of chest) in inferior STEMI to detect RV involvement

P.1-5

- **CXR;** other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing
- **Biomarkers** (see below): Tn preferred biomarker, ✓ at baseline & 3-6 h after sx onset

Biomarkers

- **Troponin:** level >99th %ile w/ rise & fall in approp. setting is dx of MI; >95% Se, 90% Sp Detectable 1-6 h after injury, peaks 24 h, may remain elevated for 7-14 d in STEMI Tn may be ↑ in CKD in absence of ACS, ∴ add CK-MB/serial Tn for confirmation Sensitive Tn assays: 98% Se, 90% Sp, 75% PPV, 99% NPV w/in 3 h of admit to ED, 82% Se & 95% NPV at time of admission to ED (JAMA 2011;306:2684)

High-sensitivity Tn assays quantify Tn in majority of healthy individ.; prog value in asx general pop., stable CAD & DM (NEJM 2009;361:2538 & 2015;373:610; JAMA 2010;304:2503)

- **CK-MB:** less Se & Sp than Tn for dx of MI

Sources include skeletal muscle, tongue, diaphragm, intestine, uterus, prostate

CK-MB relative index (ratio of CK-MB to CK) >2.5-3 suggests cardiac vs skel. muscle

CK-MB begins to rise 4-6 h post MI (may take 12 h) and returns to baseline w/in 36-48 h

May aid in gauging timing of MI (⊕ Tn & ⊖ CK-MB suggests MI several days ago)

May help dx reinfarction if Tn already elevated; however, Tn should ↑ as well

- Myoglobin & heart-type fatty acid binding protein are smaller molecules that may appear in circulation as early as 30 min after MI, but lack of specificity limits utility
- **D-dimer:** low level useful to r/o PE (qv) and aortic dissection (qv)
- B-type natriuretic peptide (BNP): elevations not specific for ACS but suggest ↑ ventricular wall stress seen not only in decompensated HF, but also ACS & PE

Interpretation of elevated cardiac biomarkers (troponin or CK-MB)

- Does it reflect true myocardial injury? Almost always the case for Tn; CK-MB less specific.
- If myocardial injury, what is the pathobiology? Ddx includes:

MI (injury due to ischemia): rise and/or fall in cardiac biomarker (preferably Tn)

>99th %ile w/ ≥1 of the following:

1) sx of ischemia

2) new Qw

3) new STΔ or LBBB

4) intracoronary thrombus

5) imaging evidence of new loss of myocardium or regional wall motion abnl non-ischemic injury (eg, myocarditis/toxic CMP, cardiac contusion) multifactorial (eg, PE, sepsis, severe HF, renal failure, Takotsubo, infiltrative disease)

- If MI, what type? (Circ 2012;126:2020)

| Type | Descriptor | Features |
|------|---------------|---|
| 1 | Spontaneous | Pathologic process in wall of coronary artery (eg, plaque rupture) resulting in intraluminal thrombus |
| 2 | Supply-demand | Mismatch due to, eg, ↑↑ or ↓↓ HR or BP, profound anemia or |

| | | |
|----|--|---|
| | mismatch not due to Δ in CAD | hypoxemia, coronary vasospasm, HCM, severe AS |
| 3 | Sudden cardiac death | |
| 4a | Related to PCI | Tn >5x 99 th %ile or >20% rise if already elevated + \geq 1 MI clinical/imaging criteria above |
| 4b | Stent thrombosis | |
| 5 | Related to CABG | Tn > 10x 99 th %ile + new Qw or LBBB , angio confirmation, or new wall motion abnl |

- Classification important as antithrombotic **Rx** relevant for type 1 but not type 2 **MI**, whereas anti-ischemic **Rx** (\uparrow O_2 supply & \downarrow demand) particularly important for type 2

Early noninvasive imaging (also see noninvasive evaluation of CAD)

- If low prob of **ACS** (eg, \ominus **ECG** & **Tn**) & stable \rightarrow noninvasive fxnal or imaging test
- Treadmill electrocardiography: can be performed after 6-8 h of evaluation
- Radionuclide imaging in Pts who cannot exercise or have uninterpretable **ECG**
- Can perform acute rest perfusion imaging if ongoing or recent (w/in 2 h) pain (\ominus scan **r/o** ischemia; \oplus scan could represent ischemia or infarct, need pain-free rest images)
- Echo (**w/** or **w/o** stress) to assess for regional wall motion **abnl**; interpretation difficult in those **w/ h/o** prior **MI**
- Coronary **CT** angio (**CCTA**): **NPV** 98% for signif **CAD**, but **PPV** 35% for **ACS**; helpful to **r/o** **CAD** if low-intermed prob of **ACS**. **CCTA** vs noninvasive fxnal test for ischemia \rightarrow \downarrow time to **dx** & **LOS**, but \uparrow probability of cath/**PCI**, contrast exposure & \uparrow radiation (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880)
- “Triple **r/o**” **CT** angiogram for **CAD**, **PE**, **AoD**

P.1-6

NONINVASIVE EVALUATION OF CAD

Stress testing (*Circ* 2007;115:1464; *JACC* 2012;60:1828)

- **Indications:** **dx** **CAD**, evaluate Δ in clinical status in **Pt w/** known **CAD**, risk stratify **s/p** **ACS**, evaluate exercise tolerance, localize ischemia (imaging required)
- **Contraindications** (*Circ* 2002;106:1883; & 2012;126:2465)

Absolute: **AMI** w/in 48 h, high-risk **UA**, acute **PE**, severe **sx** **AS**, uncontrolled **HF**, uncontrolled arrhythmias, myopericarditis, acute aortic dissection

Relative: left main **CAD**, mod valvular stenosis, severe **HTN**, **HCMP** high-degree **AVB**, severe electrolyte **abnl**

Exercise tolerance test

- Generally preferred if patient can exercise to a meaningful level; **Se** \sim 65%, **Sp** \sim 80%
- Typically via treadmill

| Protocol | Description |
|----------------|---|
| Standard Bruce | ↑ speed & incline q3min until 85% max predicted HR or sxs |
| Modified Bruce | Adds two stages at start that require less work than standard Bruce stage 1; consider in sedentary/deconditioned Pt |
| Submaximal | Stop earlier (eg, 70% max predicted HR or 5 METs or any anginal sx); consider if recent MI |

- Stationary cycle or arm ergometry (lower max workload) if Pt cannot walk
- Hold anti-ischemic meds (eg, nitrates, βB, CCB, ranolazine) if trying to dx obstructive CAD, but continue meds when assessing if Pt ischemic on current med regimen

Pharmacologic stress test (nb, requires imaging as ECG not interpretable)

- Use if unable to exercise, low exercise tolerance, or recent MI. Se & Sp ≈ exercise.
- Preferred if LBBB or V-paced, as higher prob of false ⊕ exercise imaging (typically reversible or fixed anteroseptal defect).
- **Coronary vasodilator:** diffuse coronary arteriolar vasodilation → relative “coronary steal” from vessels w/ fixed epicardial disease. Reveals CAD, but *not* if Pt ischemic w/ exercise. Options include:
 - Adenosine or dipyridamole (↑ adenosine reuptake). Side effects: flushing, bradycardia & AVB, dyspnea & bronchospasm.
 - Selective A2A receptor agonist (eg, regadenoson): less flushing, dyspnea, bronchospasm
 - Longer half-life of dipyridamole & regadenoson allow to be combined w/ exercise
 - Avoid caffeine (adenosine receptor antagonist) w/in 12 h of test. Conversely, can use aminophylline to reverse effects of these agents.
 - Contraindic: HoTN, sick sinus, high-degree AVB, bronchospasm (selective agents safer)
- **Chronotropes/inotropes** (more physiologic): dobutamine (may precip tachyarrhythmia)

Imaging for stress test (see Photo Inserts)

- Use if uninterpretable ECG (V-paced, LBBB, resting ST ↑ >1 mm, digoxin, LVH, WPW), after indeterminate ECG test, or if pharmacologic test
- Use when need to localize ischemia (often used if prior coronary revasc)
- Ideally use exercise as stress modality rather than pharmacologic
- **Radionuclide myocardial perfusion imaging** w/ images obtained at rest & w/ stress
 - SPECT** (eg, ^{99m}Tc-sestamibi): Se ~85%, Sp ~80%
 - PET** (rubidium-82): Se ~90%, Sp ~85%

ECG-gated imaging allows assessment of LV fxn (including regional systolic wall thickening or lack thereof as a sign of ischemia/infarction)

- **Echo** (exercise or dobuta): **Se** ~85%, **Sp** ~85%; no radiation; operator dependent
- Cardiac **MRI** (w/ pharmacologic stress) another option with excellent **Se** & **Sp**

Test results

- **HR** (must achieve $\geq 85\%$ of max pred **HR** $[220 - \text{age}]$ for *exer.* test to be **dx**), **BP** response, peak **double product** ($\text{HR} \times \text{BP}$; $\text{nl} > 20\text{k}$), **HR** recovery ($\text{HR}_{\text{peak}} - \text{HR}_{1 \text{ min later}}$; $\text{nl} > 12$)
- **Max exercise capacity** achieved (METS or **min**)
- Occurrence of **symptoms** (at what level of exertion and similarity to presenting **sx**)
- **ECG Δ s**: *downsloping* or *horizontal* **ST** \downarrow ($\geq 1 \text{ mm}$) 80 ms after QRS predictive of **CAD** upsloping **ST** \downarrow w/ rapid return to baseline usually due to \uparrow **HR** & atrial repol artifact lead V_5 most sensitive; Δ s isolated to inferior leads may be artifact location of **ST** \downarrow does *not* localize ischemic territory
STE: highly predictive of **CAD** & localizes; in aVR suggests **LM CAD**; nonspecific if in leads w/ prior **Qw**
- **Duke treadmill score** = exercise **min** - (5 \times max **ST** dev) - (4 \times angina index) [angina index = 0 none, 1 nonlimiting **sxs**, 2 limiting **sxs**]

P.1-7

| Category | CAD | 1-y mort | 5-y survival |
|--------------------------|-------------------------|------------|--------------|
| Low risk (≥ 5) | 60% w/o signif stenosis | <1% | 97% |
| Moderate risk (-10 to 4) | 31% w/ 3VD or LM | 2-3% | 90% |
| High risk (≤ -11) | 74% w/ 3VD or LM | $\geq 5\%$ | 65% |

- **Imaging**: radionuclide defects or echocardiographic regional wall motion abnormalities reversible defect = ischemia; fixed defect = infarct; transient isch dilation = severe **CAD** false \oplus : breast \rightarrow ant "defect" and diaphragm \rightarrow inf "defect" false \ominus may be seen if balanced (eg, 3VD) ischemia (global \downarrow perfusion w/o regional Δ s)

High-risk test results

- **ECG**: **ST** \downarrow $\geq 2 \text{ mm}$ or $\geq 1 \text{ mm}$ in stage 1 or in ≥ 5 leads or $\geq 5 \text{ min}$ in recovery; **STE**; **VT**
- Physiologic: \downarrow or fail to \uparrow **BP**, < 4 METS, angina during exercise, Duke score ≤ -11 ; \downarrow **EF**
- Radionuclide: $\geq 1 \text{ lg}$ or $\geq 2 \text{ mod.}$ reversible defects, transient **LV** cavity dilation, \uparrow lung uptake
- High-risk test has **PPV** $\sim 50\%$ for **LM** or 3VD, \therefore consider coronary angio

Myocardial viability (*Circ* 2008;117:103; *Eur Heart J* 2011;31:2984 & 2011;32:810)

- Viable myocardium = dysfxn at rest, but not scarred and has potential for recovery
- Goal: identify hibernating or stunned myocardium that could regain fxn after revasc

| Viability Test | Sens | Spec | Mechanism |
|--|------|------|---|
| MRI | ~85% | ~75% | Assesses cellular integrity |
| PET | ~90% | ~65% | Assesses cell metabolism |
| Dobut stress echo | ~80% | ~80% | Assesses contractile reserve |
| Myocard contrast echo | ~85% | ~50% | Assesses cellular integrity |
| Thallium: rest-redistrib or stress-reinjection | ~85% | ~55% | Assesses cellular integrity (K ⁺ analogue taken up by Na/K-ATPase) |
| Technetium-MIBI | ~85% | ~65% | Assesses cellular integrity (requires intact mitochondria) |

- However, in Pts w/ ↓ EF, presence of viability did not identify differential clinical benefit from CABG vs med Rx (*NEJM* 2011;364:1617)

Coronary CT angio (CCTA; *NEJM* 2008;359:2324; *Circ* 2010;121:2509)

- High NPV to r/o CAD, but low PPV
- In Pts presenting with CP, presence of plaque sensitive (100%) but not specific (54%) for ACS, ∴ NPV 100%, PPV 17% (*JACC* 2009;53:1642). CCTA vs noninvasive fxnal test for ischemia → ↓ time to dx & LOS, but ↑ probability of cath/PCI, contrast exposure & ↑ radiation (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880).
- In sx outPt, CCTA vs fxnal testing led to more radiation, coronary angiography & revascularization, but no difference in clinical outcomes (PROMISE *NEJM* 2015;372:1291)
- CCTA images may be limited if: HR >60-70 bpm, irregular rhythm, calcium deposition or stents (may create artifact), inability to breath hold 5 sec, vessel diameter < 1.5 mm. Image quality best at slower & regular HR (? give βB if possible, goal HR 55-60).
- Useful for assessing patency of bypass grafts

MRI angiography (*Lancet* 2012;379:453)

- Unlike CCTA, does not require iodinated contrast, HR control or radiation exposure. Can also assess LV fxn, enhancement (early = microvasc obstruction; late = MI). Limitations: cost, operator-dependent, long duration, ↓ spatial resolution.
- In head-to-head comparisons, CMRI and CCTA appear to have grossly comparable sensitivity and specificity (*JACC* 2005;46:92; *Annals* 2006;145:207)

Coronary artery calcium score (*NEJM* 2012;366:294; *JAMA* 2012;308:788)

- Quantifies extent of calcium; thus *estimates* plaque burden (but *not* % coronary stenosis)
- Compared w/ CCTA, CAC score assessment requires lower radiation exposure (1-2 mSv)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD

| CAC Score | Suggested plaque burden |
|-----------|-------------------------|
| 0 | No disease |
| 1-99 | Mild disease |
| 100-399 | Moderate disease |
| >400 | Severe disease |

- ? value as screening test to r/o CAD in *sx* Pt (CACS <100 → 3% probability of signif CAD; but interpretation affected by age, gender)
- May provide incremental value to clinical scores for risk stratification (*JAMA* 2004;291:210). ACC/AHA guidelines note CAC assessment is reasonable in *asx* Pts w/ intermed risk (10-20% 10-y Framingham risk; ? value if 6-10% 10-y risk) (*Circ* 2010;122:e584).

P.1-8

STABLE ISCHEMIC HEART DISEASE

Epidemiology is U.S. (*Circ* 2015;131:e29)

- Prevalence: 20-39 y: <1%; 40-59 y: 5-6%; 60-79 y: 21% in ♂ & 11% in ♀; ≥80 y: 35% in ♂ & 19% in ♀; lifetime risk after age 40: 50% in men & 32% in women
- Ischemic heart disease (IHD) remains leading cause of death in both men & women

Workup (*Circ* 2012;126:e354)

- Initiate workup if suspected new dx of IHD or Δ in clinical status
- H&P, ECG (looking for ischemic or prior infarct Δs such as Qw, PRWP, ST or Tw abnl)

| Pretest Likelihood of CAD (%) (<i>NEJM</i> 1979;300:1350; <i>Annals</i> 1993;118:81) | | | | | | |
|---|----------------------------|--------|--------------------------------|--------|-----------------------------------|---------|
| Age | Nonanginal (≤1 <i>sx</i>) | | Atypical angina (2 <i>sx</i>) | | Typical angina (all 3 <i>sx</i>) | |
| | Men | Women | Men | Women | Men | Women |
| 35 | 3 ↔ 35 | 1 ↔ 19 | 8 ↔ 59 | 2 ↔ 39 | 30 ↔ 88 | 10 ↔ 78 |

| | | | | | | |
|----|---------|--------|---------|---------|---------|---------|
| 45 | 9 ↔ 47 | 2 ↔ 22 | 21 ↔ 70 | 5 ↔ 43 | 51 ↔ 92 | 20 ↔ 79 |
| 55 | 23 ↔ 59 | 4 ↔ 21 | 45 ↔ 79 | 10 ↔ 47 | 80 ↔ 95 | 38 ↔ 82 |
| 65 | 49 ↔ 69 | 9 ↔ 29 | 71 ↔ 86 | 20 ↔ 51 | 93 ↔ 97 | 56 ↔ 84 |

Classic angina **sx**: substernal chest pain, provoked by exertion, relieved by rest or **NTG**. W/in each cell, 1st # is % for **Pt** w/o risk factors; 2nd is for **Pt w/ DM**, smoking, & hyperchol.

- **Noninvasive testing** (qv) if intermediate risk (ie, >10-20% & <80-90%). If **Pt** has low prob, then ↑ risk false ⊕; if very high prob, ⊖ test does not adeq **r/o CAD**, ∴ consider cor angio.
- **Coronary angio** if: high-risk noninv results (qv); very high pretest prob; refract angina; uncertain **dx** after noninvasive testing (& compelling need to determine **dx**), occupational need for definitive **dx** (eg, pilot) or inability to undergo noninvasive testing; survivor of **SCD** or life-threatening vent. arrhythmia; unexplained heart failure or ↓ **EF**; suspected spasm or nonatherosclerotic cause of ischemia (eg, anomalous coronary)

Optimal medical therapy (OMT) (*Circ* 2012;126:e354 & 2014;130:1749; HTN 2015;65:1372)

- **ASA** 75-162 βg/d; **βB** for 3 y post **MI** or if ↓ **EF**; **statin** (typically high intensity; see “Lipids”)
- **ACEI** (or **ARB**) if **HTN**, **DM**, **CKD** or ↓ **EF**
- Risk factor targets: **BP** <140/90 (consider <130/80 if prior **MI**), **Hb_{A1c}** 7-9% (<7% if long life expect.), **BMI** 18.5-24.9 kg/m²
- Smoking cessation; influenza vaccine
- Diet: ↑ veg, fruits, whole grains; ↓ sweets, sugar-sweetened bevs & red meat; sat fat 5-6% total cals, *trans* fat <1% total cals, chol <200 mg/d; Na ≤2400 mg/d (ideally ≤1500 mg/d)
- Exercise: ~40 min moderate-to-vigorous physical activity 3-4x/wk

Medical therapies for symptomatic relief (*Circ* 2012;126:e354)

- **Beta blockers** 1st-line therapy
- **CCB** (verap/dilt or long-acting dihydro) or **long-acting nitrates**: add-on or if **βB** intolerant
- **Ranolazine** (↓ late inward Na⁺ current to ↓ myocardial demand): add-on or if **βB** intolerant

Coronary revascularization (*Circ* 2011;124:e574)

- If unacceptable angina despite max tolerated med **Rx** or if potential to improve survival
- **OMT** should be initial focus if stable & w/o critical anatomy & w/ normal **EF**
- Older studies showed survival benefit w/ revasc (**CABG**) vs med **Rx** (pre-statin era) if: **LM** (≥50% stenosis), **3VD** (≥70% stenoses) espec if ↑ **EF**, **2VD w/** critical prox **LAD**, ? 1-2 **VD w/** large area of viable, ischemic myocardium

Recent Studies of Revascularization in Modern Era of OMT

| Compare | Trial | Pts | Result |
|---|------------------------|---------------------------|--|
| PCI vs OMT | COURAGE ^a | 1-3VD, EF >30% | PCI does <i>not</i> ↓ D/MI; faster <i>sx</i> resolution |
| | FAME-II ^b | ≥1VD w/ FFR (qv) ≤0.8 | PCI ↑ peri-PCI MI, but then 44% ↓ death/spont MI; ? greater benefit if FFR <0.65 |
| CABG vs OMT | STITCH ^c | EF ≤35% (majority w/ 3VD) | CABG 20% ↓ CV death, no Δ in all-cause mortality |
| CABG vs PCI | SYNTAX ^d | 3VD or LM | CABG ↓ D/MI & revasc but ± ↑ stroke High SYNTAX/SYNTAX II score ^g ID's those who benefit most from CABG |
| | PRECOMBAT ^e | LM | PCI ? noninferior but ↑ repeat revasc |
| | FREEDOM ^f | DM w/ ≥2VD | CABG ↓ D/MI, but ↑ stroke |
| ^a NEJM 2007;356:1503; | | | |
| ^b NEJM 2014;371:1208; | | | |
| ^c NEJM 2011;364:1607; | | | |
| ^d Lancet 2013;381:629 & 639; | | | |
| ^e NEJM 2011;364:1718; | | | |
| ^f NEJM 2012;367:2375; | | | |
| ^g www.syntaxscore.com | | | |

- LM or 3VD: CABG, espec if ↑ EF or DM; consider PCI if SYNTAX score ≤22 & high surg risk
- 2VD w/ prox LAD, ↓ EF, or extensive ischemia: CABG (espec if DM) or ? PCI
- ? 1VD (low FFR) w/ prox LAD + either ↓ EF or extensive ischemia: PCI or CABG (w/ LIMA)
- Exp't device to narrow coronary sinus ↓ angina (NEJM 2015;372:517)

Measurements

- Lipoproteins = lipids (cholesterol esters & triglycerides) + phospholipids + proteins include: chylomicrons, **VLDL**, **IDL**, **LDL**, **HDL**, Lp(a)
- Measure after 12-h fast; **LDL** is typically calculated w/ Friedewald equation:
$$\text{LDL-C} = \text{TC} - \text{HDL-C} - (\text{TG}/5)$$
 [last term assumes **TG:VLDL** ratio = 5:1]; underestim. if **TG** >400 or **LDL-C** <70 mg/dL (*JAMA* 2013;310:2061); ∴ directly measure **LDL-C**
Non-HDL-C (**TC** - **HDL-C**) and apoB are alternative nonfasting measures of risk
Lipid levels stable up to 24 h after **ACS** and other acute illnesses, then ↓ and may take 6 wk to return to **nl**
- Metabolic syndrome (≥3 of following): waist ≥40" (♂) or ≥35" (♀); **TG** ≤150; **HDL** <40 mg/dL (♂) or <50 mg/dL (♀); **BP** ≤130/85 mmHg; fasting **glc** ≤100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = **LDL** particle bound to apo(a) via apoB; genetic variants a/w **MI** (*NEJM* 2009;361:2518)

Primary dyslipidemias

- Familial hypercholesterolemia (**FH**, 1:500): defective **LDL** receptor; ↑↑ chol, **nl TG**; ↑ **CAD**
- Familial defective apoB100 (1:1000): similar to **FH**
- Familial combined hyperlipidemia (1:200): polygenic; ↑ chol, ↑ **TG**, ↓ **HDL**; ↑ **CAD**
- Familial dysbetalipoproteinemia (1:10,000): ↑ chol & **TG**; xanthomas; ↑ **CAD**
- Familial hypertriglyceridemia (**FHTG**, 1:500): ↑ **TG**, ± ↑ chol, ↓ **HDL**, pancreatitis

Secondary Dyslipidemias

| Category | Disorders |
|-------------------------|--|
| Endocrinopathies | Type 2 diabetes (↑ TG , ↓ HDL); lipodystrophy (↑ TG) Hypothyroidism (↑ LDL , ↑ TG); hyperthyroidism (↓ LDL) Cushing's syndrome & exogenous steroids (↑ LDL , ↑ TG) |
| Renal diseases | Renal failure (↑ LDL , ↑ TG); nephrotic syndrome (↑ LDL , ↑ TG) |
| Hepatic diseases | Cholestasis, PBC (↑ LDL); liver failure (↓ LDL); acute hepatitis (↑ TG) |
| Lifestyle | Obesity, sat & trans fat (↑ TG , ↓ HDL , ↑ LDL); sedentary lifestyle (↓ HDL); alcohol (↑ TG , ↑ HDL); tobacco (↓ HDL); anorexia (↑ LDL); very low-fat diet, high-refined-carb diet (↑ TG); preg (↑ LDL , ↑ TG) |
| Medications | Thiazides (↑ LDL , ↑ TG); βB (except carvedilol, ↑ TG , ↓ HDL); protease inhib (↑ TG); estrogens (↑ TG , ↑ HDL); androgens (↓ HDL); cyclosporine, amiodarone (↑ LDL); bile acid sequestrants, protease inhib, retin. acid, sirolimus, raloxifene, tamoxifen (↑ TG) |

Physical exam findings

- Tendon xanthomas: seen on Achilles, elbows and hands; implies **LDL** >300 mg/dL
- Eruptive xanthomas: pimple-like lesions on extensor surfaces; implies **TG** >1000 mg/dL
- Xanthelasma: yellowish streaks on eyelids seen in various dyslipidemias
- Corneal arcus: common in older adults, imply hyperlipidemia in young Pts

| Drug Treatment | | | | |
|------------------|-----------------|-----------------|----------------|---|
| Drug | ↓ LDL | ↑ HDL | ↓ TG | Side effects/comments |
| Statins | 20-60% | 5-10% | 10-25% | Doubling of dose → 6% further ↓ LDL . ↑ ALT in 0.5-3% (dose-dependent); ✓ before starting and then after as clinically indicated Myalgias <10% (not always ↑ CK), myositis 0.5%, rhabdo <0.1%, risk dose-dependent ↑ risk of DM (may be related to LDL-R; <i>JAMA</i> 2015;313:1029); screen if risk factors |
| Ezetimibe | 15-20% | — | — | Well tolerated; typically w/ statin |
| Fibrates | 5-15% | 5-15% | 35-50% | Myopathy risk ↑ w/ statin (gemfibrozil > fenofibrate). Dyspepsia, gallstones, ↑ Cr . ✓ renal fxn at baseline, 3 mo, q6mo. |
| Niacin | 10-25% | ~30% | 40% | Flushing (less w/ sustained release; ASA preRx may ↓), hyperglycemia, ↑ UA . ✓ renal fxn, UA , glc ± HbA1c at baseline and q6mo or w/ uptitration. |
| Resins | 20% | 3-5% | ↑ | Bloating, binds other meds |
| Ω-3 FA | 5% ↑ | 3% | 25-50% | Dyspepsia, diarrhea, skin Δs, bleeding |
| PCSK9 inhibitors | 40-65% | 5-10% | 15-25% | mAb inj SC q2w or q4w (<i>Lancet</i> 2012;380:2007 & <i>JACC</i> 2015;65:2638) |
| CETP inhibitors | ~30% | 140% | 5-10% | <i>Investigational</i> (<i>NEJM</i> 2010;363:2406; <i>Lancet</i> 2015;386:452) |

Treatment of LDL-C (*Lancet* 2014;384:607)

- **Statins:** every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (**CV** death, **MI**, stroke, revasc) in individuals w/ & w/o **CAD** (*Lancet* 2010;376:1670); ∴ *mainstay of therapy as potent, safe and well-tolerated*

- Consistent CV benefit even in individuals starting w/ LDL-C \leq 60 mg/dL (*JACC* 2011;57:1666)
- No clear evidence to date to suggest any harm from achieving very low LDL-C levels
- Elevated hs-CRP *may* identify Pts who derive \uparrow benefit (*NEJM* 2001;344:1959 & 2008;359:2195)
- Similar clinical benefit also seen w/ some older nonstatin Rx (resins, fibrates, niacin) when sufficiently lowered LDL-C (*JACC* 2005;46:1855)
- **Ezetimibe**: \downarrow major vascular events incl MI & stroke when added to statin post-ACS, w/ magnitude of benefit consistent w/ LDL-statin relationship (IMPROVE-IT, *NEJM* 2015;372:2387)
- **PCSK9 inhibitors**: \sim 60% \downarrow LDL on top of statin, as monoRx, and in FH (*EHJ* 2014;35:2249); prelim data w/ encouraging \downarrow CV outcomes (*NEJM* 2015;372:1500), definitive trials ongoing

Treatment of HDL-C (*Lancet* 2014;384:618)

- Low levels of HDL-C associated with \uparrow risk of MI
- However, Mendelian randomization studies do not support causal role (*Lancet* 2011;380:572)
- **Niacin**: in Pts w/ well-controlled LDL-C (<80 mg/dL) on a statin, minimally \downarrow LDL, modestly \uparrow HDL, and did not \uparrow CV events (*NEJM* 2011;365:2255 & 2014;371:203)
- **CETP inhibitors**: one that \uparrow HDL-C by 25% did not lead to clinical benefit in Pts w/ well-controlled LDL-C on a statin (*NEJM* 2012;367:2089); CV outcomes trials of inhibitors that \uparrow HDL-C by 140% and \uparrow LDL-C by \sim 30% ongoing (*NEJM* 2010;363:2406; *JAMA* 2011;306:2099)

Treatment of hypertriglyceridemia (*Lancet* 2014;384:626)

- Reasonable to treat very high levels (>500- 1000 mg/dL) to \downarrow risk of pancreatitis
- High levels of TG associated with \uparrow risk of MI, but whether causal remains debated
- **Fibrates** (gemfibrozil & fenofibrate): mixed data in terms of \uparrow vascular events, ? greater benefit if high TG (*Circ* 1992;85:37; *NEJM* 1999;341:410; *Lancet* 2005;366:1849; *NEJM* 2010;362:1563)
- **Fish oil** (containing Ω -3 fatty acids EPA & DHA): recent meta-analyses suggest supplementation w/o meaningful effect on CV events (*JAMA* 2012;308:1024)
- APOC3 inhibitors under study and \uparrow TG by up to \sim 70% (*NEJM* 2015;373:438)

Treatment of Lp(a)

- Consider \downarrow to <50 mg/dL w/ niacin in intermed- to high-risk Pts (*EHJ* 2010;31:2844-53); however, benefit unclear espec if LDL-C well controlled (*JACC* 2014;63:520)

Guidelines (*Circ* 2014;129(Suppl 2):S1)

- Focus now on statin strategies, rather than achieving LDL-C goals
- Clinical atherosclerotic CV disease (ASCVD) includes h/o ACS, stable angina, arterial revasc, stroke, TIA, or PAD presumed to be of atherosclerotic origin
- 10-y CV Risk Score for CHD or stroke based on age, sex, race, SBP, TC, LDL, DM, tobacco, BP Rx; <http://my.americanheart.org/cvriskcalculator>
- Additional risk factors to consider include: LDL-C \geq 160 mg/dL, genetic hyperlipid., FHx premature ASCVD, hsCRP >2 mg/L, CAC score \geq 300 or \geq 75th %ile, ABI <0.9.

2013 ACC/AHA Guideline of Treatment of Blood Cholesterol

| Population | 10-y CV risk | Statin Recommendation |
|-------------------------------------|--------------|--|
| Clinical ASCVD (ie, 2° prevention) | n/a | High intensity. If age >75 y, eval risk-benefit for high vs moderate intensity |
| LDL-C ≥190 mg/dL | n/a | High intensity |
| DM (type 1 or 2); age 40-75 y | ≥7.5% | High intensity |
| | <7.5% | Moderate intensity |
| Age 40-75 y (and none of the above) | ≥7.5% | High or moderate intensity |
| | 5- <7.5% | Reasonable to offer moderate intensity |
| | <5% | Consider statin if additional risk factor |

- If statin intolerant or LDL-C remains elevated despite high-intensity statin (as well as reinforcement of med adherence, lifestyle changes and exclusion of 2° causes of dyslipidemia) nonstatin LDL-lowering therapies remain reasonable
- If Pt does not tolerate high-intensity statin, consider dose reduction before d/c statin

Statin Doses & LDL-C Reduction

| Intensity | ↓ LDL-C | Rosuva | Atorva | Simva | Prava | Lova | Fluva | Pitava |
|-----------|---------|--------|--------|-------|-------|------|-------|--------|
| High | ≥50% | 20-40 | 40-80 | (80) | | | | |
| Mod | 30-50% | 5-10 | 10-20 | 20-40 | 40-80 | 40 | 80 | 2-4 |
| Low | <30% | | | 10 | 10-20 | 20 | 20-40 | 1 |

Doses are in mg. Simva 80 mg has ↑ myopathy risk and should not be used unless dose already tolerated >12 mo.

ANGIOGRAPHY, PCI, & CABG

Precath checklist

- Document peripheral arterial exam (radial, femoral, DP, **PT** pulses; bruits); if plan for radial artery access, ✓ palmar arch intact (eg, **w/** pulse oximetry & plethysmography), although value remains unproven (*JACC* 2014;63:1833)
- Ensure **Pt** can lie flat for several hours
- ✓ **CBC**, PT-INR (ideally ≤ 1.5), & **Cr**; blood bank sample
- **NPO** >6 h; **IVF** if appropriate (\pm bicarb; acetylcysteine no longer rec; see “**CIAKI**”)

Vascular access

- Femoral artery commonly used; high puncture \uparrow risk of retroperitoneal bleed; low puncture \uparrow risk of peripheral arterial complic.; can access a synthetic graft if a few months old
- Radial artery: 33% \downarrow major bleeding, trend to 15% \downarrow in **MACE** & 28% \downarrow mortality, espec if >80% of cases at center done radially (*Lancet* 2015;385:2465)

Periprocedural pharmacotherapy for PCI

- **Aspirin**: 325 mg \times 1 (≥ 2 h prior to angio) \rightarrow 81 mg qd
- **P2Y₁₂ inhibitor** (choose one):
 - clopidogrel: 600 mg \times 1 \rightarrow 75 mg qd; preRx \downarrow **MACE** (*JAMA* 2005;294:1224 & 2012;308:2507) prasugrel or ticagrelor (only in **ACS**, qv)
 - cangrelor (IV, short-acting): \downarrow early ischemic events vs clopi given w/o preload (*NEJM* 2013;368:1303)
- **GP IIb/IIIa inhibitor**: consider adding abciximab, eptifibatide, or tirofiban; data showing \downarrow **MACE** largely before routine P2Y₁₂ inhibition and **w/ UFH** as anticoagulant. Remains reasonable espec if using clopidogrel and did not preRx.
- **Anticoagulant** (choose one; typically d/c'd at end of **PCI**):
 - UFH**: most common choice in U.S.
 - bivalirudin: \downarrow bleeding (espec vs **UFH** + GP IIb/IIIa inhib; *JAMA* 2015;313:1336), \pm \uparrow **MI**, \uparrow stent thrombosis in **STEMI** (not mitigated by longer infusion), \uparrow mortality in some but not all trials (*Lancet* 2014;384:599; *MATRIX NEJM* 2015); use if **Pt** has **HIT** enoxaparin (nb, cannot ✓ degree of anticoag)
- **Statin** (high-dose): PreRx \downarrow peri-PCI myonecrosis (*Circ* 2011;123:1622) & \downarrow risk of contrast-induced nephropathy (*JACC* 2014;63:71)

PCI options

- **Balloon angioplasty (POBA)**: effective, but c/b dissection & elastic recoil & neointimal hyperplasia \rightarrow restenosis; now reserved for small lesions & ? some **SVG** lesions
- **Bare metal stents (BMS)**: \downarrow elastic recoil \rightarrow 33-50% \downarrow restenosis & repeat revasc (to \sim 10% by 1 y) **c/w POBA**; requires P2Y₁₂ inhibitor ≥ 4 weeks (ideally up to 6 mo)
- **Drug-eluting stents (DES)**

antiproliferative drug released over several weeks → ↓ neointimal hyperplasia ~75% ↓ restenosis, ~50% ↓ repeat revasc (to <5% by 1 y), no Δ D/MI (*NEJM* 2013;368:254)

delayed re-endothelialization & potentially proinflammatory polymers may cause ↑ in risk of late stent thrombosis; requires P2Y₁₂ inhibitor ≥6 mo

next generation DES (eg, w/ everolimus) w/ lower risk of stent thrombosis vs BMS (*Lancet* 2012;379:1393)

Other peri-PCI interventions

- **Fractional flow reserve (FFR):** ratio of max flow (induced by IV or IC adenosine) distal vs proximal to a stenosis; if used to guide PCI (ie, revasc only if FFR <0.8) → ↓ # stents & ↓ D/MI/revasc (*NEJM* 2009;360:213)
- Thrombus aspiration: small study showed manual aspiration of thrombus pre-PCI in STEMI ↓ mortality, but larger studies show no benefit and ↑ stroke (*Lancet* 2008;371:1915; *NEJM* 2013;369:1587 & 2015;372:1389)

Post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr
- Vascular closure devices speed time to hemostasis and ↓ incidence of hematoma (*JAMA* 2014;312:1981)

- **Bleeding**

hematoma/overt bleeding: manual compression, reverse/stop anticoag

retroperitoneal bleed (if puncture above inguinal ligament)

may p/w ↓ Hct ± flank or back pain; ↑ HR & ↓ BP late

Dx w/ abd/pelvic CT (†)

Rx: reverse/stop anticoag (d/w interventionalist), IV fluids/PRBC/plts as required; if bleeding uncontrolled, consult performing interventionalist or surgery

P.1-12

- **Vascular damage** (~1% of dx angio, ~5% of PCI; *Circ* 2007;115:2666)

pseudoaneurysm: hematoma w/ continued communication to artery can present w/ triad of pain, expansile mass, systolic bruit; diagnose w/ U/S;

Rx (if pain or >2 cm): U/S-directed thrombin injection (>95% success, depends on anatomy); surgical repair if very large or if minimally invasive Rx fails

AV fistula: continuous bruit; Dx: U/S; Rx: surgical repair

limb ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: pulse volume recording (PVR), angio; Rx: percutaneous or surgical repair

- **Peri-PCI MI:** >5× ULN of Tn/CK-MB + either sx or ECG/angio/imaging Δs; Qw MI in <1%

- **Renal failure:** contrast-induced manifests w/in 24 h, peaks 3-5 d (see “CIAKI”)

- **Cholesterol emboli syndrome**

typically seen in middle-aged & elderly and w/ heavy burden of aortic atheroma multiple clinical manifestations (although may be delay between cath & s/s) including: intact distal pulses but livedo reticularis pattern and toe necrosis (“blue toe syndrome”) renal failure: late and progressive (thus unlike CIAKI), ± eos in urine mesenteric ischemia: abd pain, GIB, pancreatitis

CNS: TIA, stroke, amaurosis fugax, Hollenhorst plaques (bright retinal lesion)

Dx: can only be confirmed by biopsy; may see ↑ circulating eos, ↓ complement, ↑ CRP, ↑ ESR, ↑ plts, ↑ fibrinogen

Rx: supportive; no clear benefit for anti-inflam or anticoagulant Rx

- **Stent thrombosis** (acute clot formation in stent): rare event, but high mortality can occur anytime between mins to yrs after PCI typically p/w ACS (often STEMI)
typically due to either **mechanical problem** (stent underexpansion or unrecognized dissection, typically presents early) or **d/c of antiplt Rx** (espec if d/c both ASA & P2Y₁₂ inhib; JAMA 2005;293:2126)
- **In-stent restenosis** (neointimal hyperplasia): months after PCI, typically p/w gradual ↑ angina (10% p/w ACS). Due to combination of elastic recoil and neointimal hyperplasia; ↓ w/ DES vs BMS.

Duration of P2Y₁₂ inhibition

- In Pts w/ MI (qv), goal of antiplatelet therapy is ↑ CVD, MI, and stroke as well as rarer event of stent thrombosis. ∴ Long-term therapy beyond 12 mo is logical and has been shown to ↓ CV death, MI, and stroke (NEJM 2015;372:1791; JACC 2007;49:1982 & 2015;65:2211).
- In Pts w/ SIHD, concern for late (>30 d) stent thrombosis led to recs for 12-mo duration, but newer generation stents have lower risk of stent thrombosis
- Several small trials showed shorter duration of P2Y₁₂ inhibition (3-6 vs 12 mo) led to nonstatistically significant higher rates of MI and ST (but still infrequent) but less bleeding (JACC 2012;60:1340; JAMA 2013;310:2510; EHJ 2015;36:1252)
- Much larger DAPT trial showed that longer inhibition (30 vs 12 mo) led to 29% ↓ MACE and 71% ↓ ST (although rates and absolute risk reduction very low with newer generation stents), but ↑ bleeding and, in Pts w/ SIHD, marginally significant ↑ mortality (driven by non-CV mortality) (NEJM 2014;371:2155)

Need for premature discontinuation of antiplatelet therapy

- If possible, postpone major invasive procedures ≥1 mo after BMS or ≥3-6 mo after DES
- If not possible and high of risk bleeding during procedure, d/c prasugrel 7 d, clopidogrel 5 d, or ticagrelor 5 d (per prescribing information, but in major clinical trial, just ~3 d) prior to procedure. Continue ASA and resume P2Y₁₂ inhibitor w/ loading dose ASAP per surgery.
- If high-risk stent and bridging required, consider short-acting GP IIb/IIIa inhibitor (eptifi-batide or tirofiban) from 3 d until 4-6 h prior to surgery (Circ 2013;128:2785). Consider cangrelor (IV reversible P2Y₁₂ inhib) (JAMA 2012;307:265).



Advances in CABG technique

- **“Mini-CABG”** = minimally invasive. Thoracotomy or partial sternotomy rather than full sternotomy. Advantages include ↓ pain & ↓ LOS. May be on- or off-pump.
- **Off-pump** (“beating heart surgery”): avoids cardiopulmonary bypass but makes anastomotic suturing more challenging. In 1 study, ↑ CV death and ↓ graft patency at 12 mo c/w on-pump (NEJM 2009;361:1827); other studies w/ ≈ mortality w/ off- vs on-pump.
- **Robotic**: type of mini-CABG where endoscopic instruments inserted via small incisions to anastomose the

LIMA to the LAD on closed chest and beating heart

- **Hybrid procedures:** typically involves combo of LIMA-LAD mini-CABG with PCI of other vessels

ACUTE CORONARY SYNDROMES

| Spectrum of Acute Coronary Syndromes | | | |
|--------------------------------------|---|--------------------|---|
| Dx | UA | NSTEMI | STEMI |
| Coronary thrombosis | | Subtotal occlusion | Total occlusion |
| History | angina that is new-onset, crescendo or at rest; usually <30 min | | angina at rest |
| ECG | ± ST depression and/or TWI  | | ST elevations  |
| Troponin/CK-MB | ⊖ | ⊕ | ⊕⊕ |

Ddx (causes of myocardial ischemia/infarction other than atherosclerotic plaque rupture)

- **Nonatherosclerotic coronary artery disease**

Spasm: Prinzmetal's variant, cocaine-induced (6% of CP + cocaine use r/i for MI)

Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (catheter, surgery, trauma)

Embolism (*Circ* 2015;132:241): AF, thrombus/myxoma, endocard., prosth valve; thrombosis

Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA

Congenital: anomalous origin from aorta or PA (coronary compressed), myocardial bridge (intramural segment)

- **Ischemic imbalance not due to plaque rupture** ("type 2" MI): ↑ myocardial O₂ demand (eg, ↑ HR, anemia, AS) or ↑ supply (hypotension, severe anemia)
- **Direct myocardial injury:** myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

Clinical manifestations (*JAMA* 2005;294:2623)

- **Typical angina:** retrosternal pressure/pain/tightness ± radiation to neck, jaw or arms precip. by exertion, relieved by rest or NTG; in ACS, new-onset, crescendo or at rest; see "Chest Pain" for likelihood ratios for different sx
- **Associated symptoms:** dyspnea, diaphoresis, N/V, palpitations or lightheadedness
- Many MIs (~20% in older series) are initially unrecognized b/c silent or atypical sx

- Atypical sx (incl N/V & epig pain) may be more common with inferior ischemia
- Women may have ↑ freq of atypical sx vs men

Physical exam

- Signs of ischemia: S4, new MR murmur 2° pap. muscle dysfxn, paradoxical S₂, diaphoresis
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S₃, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP (aortic dissection or subclavian disease), carotid or femoral bruits, ↓ distal pulses

ECG

- ✓ w/in 10 min of presentation, q15-30min × 1 h if initial ECG non-dx, w/ any Δ in sx, and routinely at 6-12 h; compare w/ baseline
- Signs of ischemia (*JAMA* 1998;280:1256)
 - STE: generally ≥1 mm in ≥2 contiguous leads (see “STEMI” for details) new or presumed new (ie, not known to be old) LBBB w/ compelling H&P
 - STD ≥0.5 mm (⊕ LR 3-5), TWI ≥2 mm (⊕ LR 2-3), hyperacute Tw
- Qw or PRWP may suggest prior MI, ∴ higher pretest probability of CAD
- Dx of STEMI if old LBBB (Sgarbossa's criteria): ≥1 mm STE concordant w/ direction of QRS (Se 73%, Sp 92%), STD ≥1 mm V₁-V₃ (Se 25%, Sp 96%) or STE ≥5 mm discordant w/ QRS (Se 31%, Sp 92%)

| Localization of MI | | |
|--------------------|---|------------------------|
| Anatomic area | ECG leads w/ STE | Coronary artery |
| Septal | V ₁ -V ₂ | Proximal LAD |
| Anterior | V ₃ -V ₄ | LAD |
| Apical | V ₅ -V ₆ | Distal LAD, LCx or RCA |
| Lateral | I, aVL | LCx |
| Inferior | II, III, aVF | RCA (~85%), LCx (~15%) |
| RV | V ₁ -V ₂ & V ₄ R (most Se) | Proximal RCA |
| Posterior | ST depression V ₁ -V ₃ (= STE V ₇ -V ₉ posterior leads) | RCA or LCx |

If ECG non-dx and suspicion high, consider addt'l lateral (posterior) leads (V₇-V₉) to further assess distal LCx/RCA territory. Check right-sided precordial leads in patients with IMI to help detect RV involvement

(STE in V₄R most Se). STE in III > STE in II and lack of STE in I or aVL suggest RCA rather than LCx culprit in IMI.

Cardiac biomarkers

- Troponin (Tn) preferred over CK-MB
- ✓ Tn at baseline & 3-6 h after sx onset; may also ✓ beyond 6 h if high index of suspicion based on clinical presentation or ECGs or if sx Δ
- Rise to >99th %ile in approp. clinical setting dx of MI (see "Chest Pain")
- In Pts w/ ACS & ↓ CrCl, ↓ Tn still portends poor prognosis (NEJM 2002;346:2047)

Other potential dx tests

- If low prob, stress test, CT angio or rest perfusion imaging to r/o CAD (see "Chest Pain")
- TTE (new wall motion abnl) suggestive of ACS but not specific, as may be seen if old MI
- Coronary angio gold standard for evaluation of CAD

Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (but MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Most frequent between midnight and early morning when vagal tone is highest
- Provocation testing: spasm can be precipitated at angio w/ IC ergonovine or acetylchol. positive test = severe narrowing w/ sx or ECG Δs; nonobstructive CAD typically seen; rarely done as risks include refractory/recurrent spasm or arrhythmia
- Noninvasive testing: hyperventilation, 12-lead Holter, exercise study
- Treatment: often initiated empirically without provocation testing: high-dose CCB (dilt, verap or nifed all roughly ≈) & standing nitrates (+SL prn) ? α-blockers/statins; d/c smoking
avoid high-dose ASA (can inhibit prostacyclin & worsen spasm), nonselect βB, triptans
- Cocaine-induced vasospasm: use CCB, nitrates, ASA; ? avoid βB, but data weak and labetalol appears safe (Archives 2010;170:874; Circ 2011;123:2022)

Likelihood of ACS

| Feature | High (any of below) | Intermediate (no high features, any of below) | Low (no high/inter. features, may have below) |
|---------|--|---|---|
| History | Chest or L arm pain like prior angina, h/o CAD (incl MI) | Chest or arm pain age >70 y, male, diabetes | Atypical sx (eg, pleuritic, sharp or positional pain) |
| Exam | HoTN, diaphoresis, HF, | PAD or cerebrovas- | Pain reproduced on palp. |

| | | | |
|-------------------|--|---|--|
| | transient MR | cular dis. | |
| ECG | New STD (≥ 1 mm) TWI in mult leads | Old Qw , STD (0.5-0.9 mm), TWI (> 1 mm) | TWF/TWI (< 1 mm) in leads w/ dominant R wave |
| Biomarkers | \oplus Tn or CK-MB | Normal | Normal |

(Adapted from ACC/AHA 2007 Guideline Update for **UA/NSTEMI**, *Circ* 2007;116:e148)

Approach to triage

- If **hx** and initial **ECG** & **Tn** non-dx, repeat **ECG** q15-30min \times 1 h & **Tn** 3-6 h after **sx** onset
 - If remain **nl** and low likelihood of **ACS**, search for alternative causes of chest pain
 - If remain **nl**, have ruled out **MI**, *but* if suspicion for **ACS** based on **hx**, then still need to **r/o UA w/** stress test to assess for inducible ischemia (or **CTA** to **r/o CAD**);
- if low risk (eg, age ≤ 70 ; \emptyset prior **CAD**, **CVD**, **PAD**; \emptyset rest angina) can do before **d/c** from **ED** or as outPt w/in 72 h (0% mortality, $< 0.5\%$ **MI**, *Ann Emerg Med* 2006;47:427)
- if not low risk, admit and initiate **Rx** for possible **ACS** and consider stress test or cath

Acute Anti-Ischemic and Analgesic Treatment

| | |
|--|---|
| Nitrates (SL or IV) 0.3-0.4 mg SL q5min $\times 3$, then consider IV if still sx | Use for relief of sx , control HTN or Rx of HF No clear \downarrow in mortality <i>Caution</i> if preload-sensitive (eg, HoTN , AS , sx RV infarct); contraindic if recent PDE5 inhibit use |
| β-blockers eg, metop 25-50 mg PO q6h titrate slowly to HR 50-60 IV only if HTN and no HF | \downarrow ischemia & progression of UA to MI (<i>JAMA</i> 1988;260:2259) STEMI : $\sim 20\%$ \downarrow arrhythmic death or reMI, but 30% \uparrow cardiogenic shock early (espec if signs of HF), & \therefore no Δ overall mortality (<i>Lancet</i> 2005;366:1622) In Pts w/o HF , IV βB prior to 1 $^\circ$ PCI \downarrow infarct size and \uparrow EF (<i>Circ</i> 2013;128:1495) <i>Contraindic.</i> PR > 0.24 sec, HR < 60 , 2 $^\circ/3^\circ$ AVB , severe bron-chospasm, s/s HF or low output, risk factors for shock (eg, > 70 y, HR > 110 , SBP < 120 , late presentation STEMI) |
| CCB (nondihydropyridines) | If cannot tolerate βB b/c bronchospasm; otherwise has similar contraindications as βB Rx |
| Morphine | Relieves pain, \downarrow anxiety, venodilation \rightarrow \downarrow preload \therefore use for persistent sx or CHF . Do not mask refractory sx . May delay onset of antiplatelet Rx (<i>JACC</i> 2014;63:630) |
| Oxygen | Use prn for resp distress or to keep S_aO₂ $> 90\%$? \uparrow infarct size in STEMI w/o hypoxia (<i>Circ</i> 2015;131:2143) |

Other early adjunctive therapy

- **High-intensity statin therapy** (eg, atorvastatin 80 mg qd) ↓ ischemic events w/ benefit emerging w/in wks (*JAMA* 2001;285:1711 & *JACC* 2005;46:1405) ↓ peri-PCI MI (*JACC* 2010;56:1099); ↓ contrast-induced nephropathy (*JACC* 2014;63:71)
- **ACEI/ARB**: start once hemodynamics and renal function stable Strong indication for ACEI if heart failure, EF <40%, HTN, DM, CKD; ~10% ↑ mortality, greatest benefit in ant. STEMI or prior MI (*Lancet* 1994;343:1115 & 1995;345:669)

Start w/ low dose of short-acting (eg, captopril 6.25 mg tid), titrate up as tolerated ARB appear ≈ ACEI (*NEJM* 2003;349:20); give if contraindic to ACEI

- Ezetimibe, aldosterone blockade, and ranolazine discussed later (long-term Rx)
- **IABP**: can be used for refractory angina when PCI not available

NSTE-ACS (*Circ* 2014;130:e344)

Key issues are antithrombotic regimen and invasive vs conservative strategy

Antiplatelet Therapy

Aspirin 162-325 mg × 1, then 81 mg qd (non-enteric coated, chewable) 50-70% ↓ D/MI (*NEJM* 1988;319:1105) Low dose (~81 mg) pref long term (*NEJM* 2010;363:930) If allergy, use clopi and/or desensitize to ASA

P2Y₁₂ (ADP receptor) inhibitor (choose one of the following in addition to ASA). Timing remains controversial. Some data support benefit of clopidogrel preRx prior to angiography (*JAMA* 2012;308:2507). Ticagrelor was given upstream in pivotal study. Prasugrel should be given once PCI planned (ie, anatomy defined). European guidelines recommend P2Y₁₂ inhibitor as soon as possible after presentation (*EHJ* 2011;32:2999).

- **Ticagrelor** 180 mg × 1 → 90 mg bid Reversible binding, but wait 3-5 d prior to surg Use only with ASA <100 mg qd Preferred over clopidogrel More rapid and potent plt inhib c/w clopi 16% ↓ CVD/MI/stroke & 21% ↓ CV death c/w clopi; ↑ non-CABG bleeding (*NEJM* 2009;361:1045) Sensation of dyspnea (S_aO₂ & PFTs nl) and ventricular pauses; perhaps b/c blocks adenosine reuptake
- **Prasugrel** 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery Use at time of PCI; preferred over clopidogrel More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs clopi, but ↑ bleeding (*NEJM* 2007;359:2001), incl fatal bleeds Not sup to clopi if med mgmt w/o PCI (*NEJM* 2012;367:1297) In NSTE-ACS, should be given at time of PCI and not upstream due to ↑ bleeding (*NEJM* 2013;369:999) Contraindic. if h/o TIA/CVA; ? avoid if >75 y

- **Clopidogrel*** 300-600 mg × 1 → 75 mg qd Requires ~6 h to steady state

ASA+clopi → 20% ↓ CVD/MI/stroke vs ASA alone ↑ benefit if given hrs prior to PCI, but then if require CABG, need to wait >5 d after d/c clopi

- **Cangrelor** Only IV P2Y₁₂ inhibitor Rapid onset/offset; t_{1/2} 3-5 min

22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs clopi 300 mg at time of PCI; no significant ↑ bleeding (NEJM 2013;368:1303) Unclear benefit if upstream clopi (NEJM 2009;361:2318) and no data vs prasugrel or ticagrelor

GP IIb/IIIa inhibitors (GPI)

Abciximab: LD 0.25 mg/kg IV, then 0.125 mcg/kg/min
Eptifibatide: LD 180 mcg/kg IV ×2, then 2 mcg/kg/min (½ dose if CrCl <50 mL/min) Tirofiban: LD 25 mcg/kg IV, then 0.15 mcg/kg/min (½ dose if CrCl <30 mL/min)

No clear benefit for routinely starting prior to PCI and ↑ bleeding (NEJM 2009;360:2176). Consider epti or tiro if refractory ischemia despite optimal Rx while awaiting angio. Consider in high-risk Pts (eg, large thrombus burden) at time of PCI, espec if using clopi and not preRx'd. Often administered 18-24 h post PCI, but shorter duration (~2 h) may be as efficacious and with ↓ bleeding (JACC 2009;53:837); D/C eptifibatide/tirofiban ≥2-4 h and abciximab ≥12 h prior to urgent CABG.

*Utility of platelet function testing remains unproven (JAMA 2011;305:1097; NEJM 2012;367:2100), but studies underpowered. ~30% pop has ↓ fxn CYP2C19 allele → ↑ CV events if PCI on clopi compared w/ wild type (NEJM 2009;360:354; JAMA 2010;304:1821).

Anticoagulant Therapy (choose one)

UFH: 60 U/kg IV (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of PCI

24% ↓ D/MI (JAMA 1996;276:811) Titrate to aPTT 1.5-2× control (~50-70 sec) Hold until INR <2 if already on warfarin

Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IV) (qd if CrCl <30) × 2-8 d or until PCI

~10% ↓ D/MI vs UFH (JAMA 2004;292:45,89). Can perform PCI on enox (Circ 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.

Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IV at PCI → 1.75 mg/kg/h

↓ bleeding (espec vs UFH + GPI), ± ↑ early MI (Lancet 2014;384:599). Use instead of UFH if HIT.

Fondaparinux (Xa inhibitor) 2.5 mg SC qd × 2-8 d

C/w enox, 17% ↓ death & 38% ↓ bleeding (NEJM 2006;354:1464). However, ↑ risk of catheter thrombosis; ∴ must supplement w/ UFH if PCI.

Coronary angiography (Circ 2014;130:e344)

- **Immediate/urgent coronary angiography** (w/in 2 h) if refractory/recurrent angina or hemodynamic or

electrical instability

- **Invasive (INV) strategy** = routine angiography w/in 72 h (*NEJM* 2009;360:2165)

Early (w/in 24 h) if: ⊕ **Tn**, **ST Δ**, GRACE risk score (www.outcomes-umassmed.org/grace) >140

Delayed (ie, acceptable anytime w/in 72 h) if no indication for early/immediate cath but has other high-risk predictors incl: diabetes, **EF** <40%, **GFR** <60, post-MI angina , TIMI Risk Score ≥3, GRACE score 109-140, **PCI** w/in 6 mo, prior **CABG**

Invasive strategy leads to 32% ↓ re hosp for **ACS**, nonsignif 16% ↓ **MI**, no Δ in mortality c/w cons. (*JAMA* 2008;300:71); ↑ peri-PCI **MI** counterbalanced by ↓ ↓ in spont. **MI**; mortality benefit seen in some studies, likely only if cons. strategy w/ low rate of angio

↑ risk of death or **MI** if invasive strategy deferred beyond 72 h (*JAMA* 2003;290:1593)

- **Conservative (CONS) strategy** = selective angio. Medical **Rx** with pre-d/c stress test; angio only if recurrent ischemia or ⊕ **ETT**. *Indicated for:* low TIMI Risk Score, **Pt** or physician preference in absence of high-risk features, low-risk women (*JAMA* 2008;300:71).

TIMI Risk Score (TRS) for **UA/NSTEMI** (*JAMA* 2000;284:835)

| Calculation of Risk Score | | Application of Risk Score | |
|---------------------------------------|-------|--|-----------------|
| Characteristic | Point | Score | D/MI/UR by 14 d |
| <i>Historical</i> | | 0-1 | 5% |
| Age ≥65 y | 1 | 2 | 8% |
| ≥3 Risk factors for CAD | 1 | 3 | 13% |
| Known CAD (stenosis ≥50%) | 1 | 4 | 20% |
| ASA use in past 7 d | 1 | 5 | 26% |
| <i>Presentation</i> | | 6-7 | 41% |
| Severe angina (≥2 episodes w/in 24 h) | 1 | Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH , GP IIb/IIIa inhibitors and early angiography (<i>JACC</i> 2003;41:89S) | |
| ST deviation ≥0.5 mm | 1 | | |
| ⊕ cardiac marker (troponin, CK-MB) | 1 | | |

RISK SCORE = Total (0-7) points

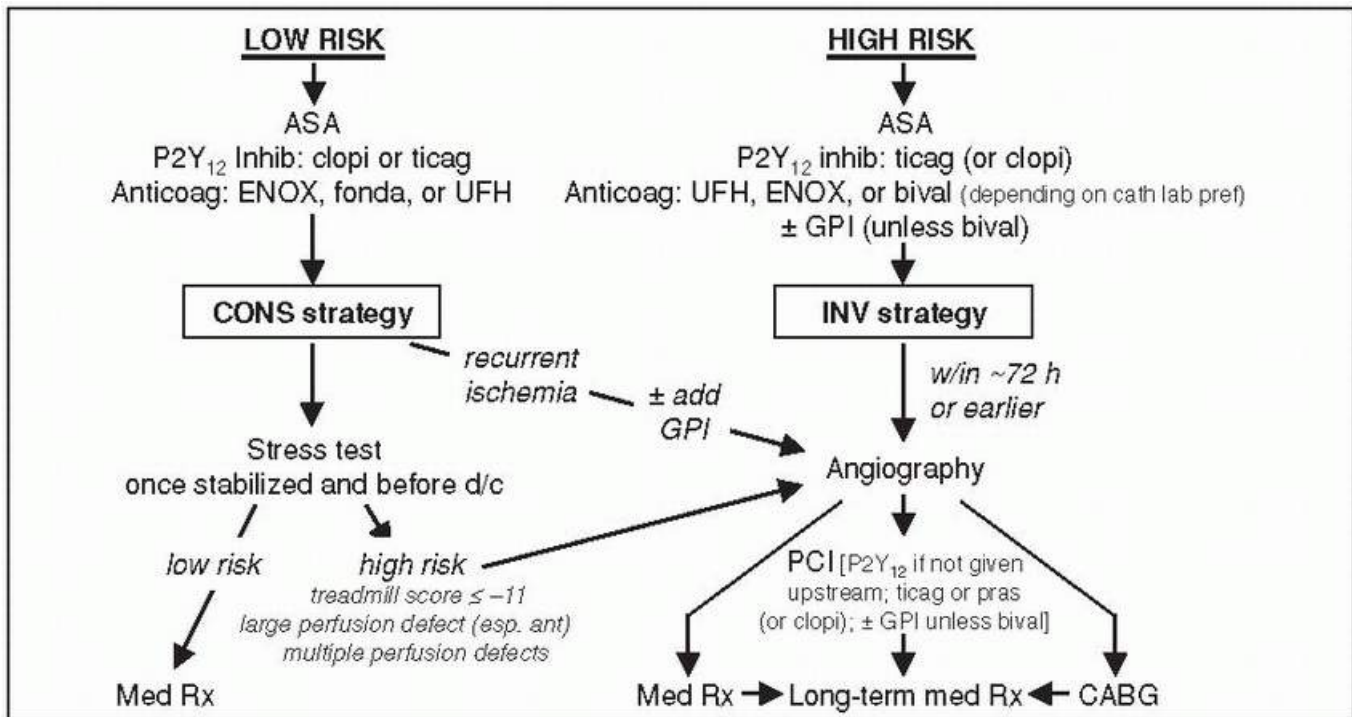


Figure 1-2 Approach to UANSTEMI

STEMI

Requisite STE (at J point)

- ≥ 2 contiguous leads w/ ≥ 1 mm (except for V_2 - V_3 : ≥ 2 mm in ♂ and ≥ 1.5 mm in ♀), or
- New or presumed new LBBB w/ compelling H&P, or
- True posterior MI: ST depression V_1 - V_3 \pm tall Rw w/ STE on posterior leads (V_7 - V_9)

Reperfusion (“time is muscle”)

- Immediate reperfusion (ie, opening occluded culprit coronary artery) is critical
- In PCI-capable hospital, goal should be **primary PCI w/in 90 min** of 1st medical contact
- In non-PCI-capable hospital, consider *transfer* to PCI-capable hospital (see below), o/w **fibrinolytic therapy** w/in 30 min of hospital presentation. If dx confirmed, administration of fibrinolytic in ambulance prior to arrival can be considered
- Do not let decision regarding *method* of reperfusion delay *time* to reperfusion

Primary PCI (NEJM 2007;356:47; JACC 2013;61:e78)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- Indications: STE + sx onset < 12 h; ongoing ischemia 12-24 h after sx onset; shock or severe HF regardless of time
- Superior to lysis: 27% \downarrow death, 65% \downarrow reMI, 54% \downarrow stroke, 95% \uparrow ICH (Lancet 2003;361:13)

- **Transfer** to center for 1° **PCI** superior to lysis (*NEJM* 2003;349:733). ∴. If initially seen at non-PCI capable hosp, transfer for **PCI** if door-in to door-out time can be ≤30 **min** and 1st medical contact to **PCI** time estimated to be ≤120 **min**.
- Thrombus aspiration: small study showed ↓ mortality, but larger studies show no benefit and ↑ stroke (*Lancet* 2008;371:1915; *NEJM* 2013;369:1587 & 2015;372:1389)
- Small studies have demonstrated ↓ **MACE w/** complete revasc vs culprit artery alone (*NEJM* 2013; 369:1115; *JACC* 2015;65:963), large study ongoing; alternatively, could assess ischemia due to residual lesions **w/** imaging stress (*Circ* 2011;124:e574)

Fibrinolysis vs Hospital Transfer for Primary **PCI**: Assess Time and Risk

1. **Time required for transport to skilled **PCI** lab:** door-to-balloon <120 **min** & [door-to-balloon]-[door-to-needle] <1 **h** favors transfer for **PCI**
2. **Risk from **STEMI**:** high-risk Pts (eg, shock) fare better with mechanical reperfusion
3. **Time to presentation:** efficacy of lytics ↓ **w/** ↑ time from **sx** onset, espec >3 **h**
4. **Risk of fibrinolysis:** if high risk of **ICH** or bleeding, **PCI** safer option Adapted from ACC/AHA 2013 **STEMI** Guidelines (*Circ* 2013;127:529)

Fibrinolysis

- Indic: **STE/LBBB** + **sx** <12 **h** + >120 **min** before **PCI** can be performed; benefit if **sx** >12 **h** less clear; reasonable if persist. **sx** & **STE** or hemodyn instability or large territory at risk
- Fibrin-spec lytics (TNK, TPA, RPA) ↑ artery patency vs streptokinase (*JACC* 2013;61:e78)
- Mortality ↓ ~20% in anterior **MI** or **LBBB** and ~10% in **IMI c/w** ∅ reperfusion **Rx**
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (*JAMA* 2000;283:2686)
- ~1% risk of **ICH**; high-risk groups include elderly (~2% if >75 **y**), women, low wt
- Although age not contraindic., ↑ risk of **ICH** in elderly (>75 **y**) makes **PCI** more attractive
- Successful reperfusion gauged by **sx** & **ECG**: sudden **CP** resolution & ≥70% resolution of **STE** indicative of successful reperfusion; conversely, **STE** resolution <50% after 60-90 **min** should prompt consideration of rescue **PCI** (qv)

Contraindications to Fibrinolysis

Absolute contraindications

- Any prior **ICH**
- Intracranial neoplasm, aneurysm, **AVM**

Relative contraindications

- Hx of severe **HTN** or **SBP** >180 or **DBP** >110 on presentation (? absolute contra. if low-risk **MI**)

- Ischemic stroke w/in 3 mo (unless acute w/in 4.5 h) or closed head trauma w/in 3 mo
- Active internal bleeding or known bleeding diathesis
- Head/facial trauma w/in 3 mo
- Head/spinal surgery w/in 2 mo
- Suspected aortic dissection
- Severe uncontrollable HTN
- For SK, SK Rx w/in 6 mo
- Ischemic stroke >3 mo prior
- Dementia
- Recent traumatic or prolonged CPR >10 min
- Trauma or major surgery w/in 3 wk
- Recent internal bleed (w/in 2-4 wk); active PUD
- Noncompressible vascular punctures
- Prior SK exposure (if considering SK)
- Pregnancy
- Current use of anticoagulants

Nonprimary PCI

- Facilitated or pharmacoinvasive PCI = upstream lytic, GPI or GPI + ½ dose lytic before PCI; in general no clear clinical benefit & ↑ bleeding (*Lancet* 2006;367:569; *NEJM* 2013;368:1379)
- Rescue PCI if shock, unstable, failed reperfusion or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (*NEJM* 2009;360:2705);
 ∴ if lysed at non-PCI capable hospital, consider transfer to PCI-capable hospital ASAP espec if high-risk presentation (eg, anterior MI, inferior MI w/ low EF or RV infarct, extensive STE or LBBB, HF, ↓ BP or ↑ HR)
- Late PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy

Aspirin 162-325 mg × 1
(crushed/chewed) then 81 mg qd

23% ↓ in death (*Lancet* 1988;ii:349) Should not be stopped if CABG required

P2Y₁₂ inhibitor Give ASAP (do not wait for angio) Ticagrelor or prasugrel (if PCI) as detailed above
 Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd

Lysis: clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (*NEJM* 2005;352:1179; *Lancet* 2005;366:1607); no data for pras or ticag w/ lytic PCI: prasugrel and ticagrelor ↓ CV events c/w clopi (*Lancet* 2009;373:723 & *Circ* 2010;122:2131) Nb, antiplt effects delayed in STEMI Pts

GP IIb/IIIa inhibitors abciximab, eptifibatide, tirofiban

Lysis: no indication (*Lancet* 2001;357:1905) Peri-PCI: 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

Adapted from ACC/AHA 2013 STEMI Guidelines Update (*Circ* 2013;127:529); *Lancet* 2013;382:633

Anticoagulant Therapy (choose one)

UFH 60 U/kg IV (max 4000

No demonstrated mortality benefit ↑ patency with fibrin-specific lytics

U) 12 U/kg/h (max 1000 U/h initially)

Titrate to aPTT 1.5-2× control (~50-70 sec)

Enoxaparin Lysis: 30 mg **IVB** → 1 mg/kg **SC** bid (adjust for age >75 & CrCl) **PCI**: 0.5 mg/kg **IVB**

Lysis: 17% ↓ **D/MI w/ ENOX** × 7 d vs **UFH** × 2 d (*NEJM* 2006;354:1477) **PCI**: ↓ **D/MI/revasc** and ≈ bleeding vs **UFH** (*Lancet* 2011;378:693)

Bivalirudin 0.75 mg/kg **IVB** → 1.75 mg/kg/hr **IV** (ongoing research on prolonged infusions)

PCI: ↓ bleeding (espec vs **UFH** + **GP IIb/IIIa** inhib), ± ↑ **MI**, ↑ stent thromb (not mitigated by longer infusion), ↓ mortality in some but not all trials (*Lancet* 2014;384:599; *JAMA* 2015;313:1336; *MATRIX NEJM* 2015)

Fondaparinux 2.5 mg **IVB** → 2.5 mg **SC** qd Contraindic if CrCl ≤30 mL/min

Lysis: superior to placebo & to **UFH**, with less bleeding (*JAMA* 2006;295:1519) **PCI**: risk of catheter thromb.; should not be used

Adapted from ACC/AHA 2013 **STEMI** Guidelines (*Circ* 2013;127:529); *Lancet* 2013;382:633

Intraaortic Balloon Pump (IABP) Counterpulsation

- Inflates during diastole and deflates during systole to ↑ coronary flow and ↑ afterload
- *Routine* use in high-risk **STEMI** → ↑ stroke/bleeds w/o Δ in survival, infarct size or **EF** (*EHJ* 2009;30:459; *JAMA* 2011;306:1329)
- In cardiogenic shock, no survival benefit **w/ IABP** if early revasc (*NEJM* 2012;367:1287); 18% ↓ death in Pts **w/** cardiogenic shock treated with lytic (*EHJ* 2009;30:459)

LV failure (~25%)

- Diurese to achieve **PCWP** 15-20 → ↑ pulmonary edema, ↓ myocardial O₂ demand
- ↓ Afterload → ↑ stroke volume & **CO**, ↓ myocardial O₂ demand can use **IV NTG** or nitroprusside (risk of coronary steal) → short-acting **ACEI**
- Inotropes if **HF** despite diuresis & ↓ afterload; use dopamine, dobutamine or milrinone
- **Cardiogenic shock** (~7%) = **MAP** < 60 mmHg, **CI** <2 L/min/m², **PCWP** >18 mmHg; inotropes, mech support [eg, **VAD**, **IABP** (see above)] to keep **CI** >2; pressors to keep **MAP** >60; if not done already, coronary revasc (*NEJM* 1999;341:625)

IMI complications (*Circ* 1990;81:401; *NEJM* 1994;330:1211; *JACC* 2003;41:1273)

- **Heart block** (~20%, occurs because **RCA** typically supplies **AV** node) 40% on present., 20% w/in 24 h, rest by 72 h; high-grade **AVB** can develop abruptly **Rx**: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- **RV infarct** (proximal **RCA** occlusion → compromised flow to **RV** marginal branch) Angiographically in 30-50%, but only ½ of those clinically signif. **HoTN**; ↑ **JVP**, ⊕ Kussmaul's; 1 mm **STE** in V_{4R}; **RA/PCWP** ≥0.8;

Rx: optimize preload (**RA** goal 10-14, *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain **AV** synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (**IABP** or **RVAD**); pulmonary vasodilators (eg, inhaled **NO**)

Mechanical complications (incid. <1% for each; typically occur a few days post-MI)

- **Free wall rupture:** ↑ risk w/ lysis, large **MI**, ↑ age, ♀, **HTN**; p/w **PEA** or hypoTN, pericardial **sx**, tamponade; **Rx:** volume resusc., ? pericardiocentesis, inotropes, **surgery**
- **VSD:** large **MI** in elderly; **AMI** → apical **VSD**, **IMI** → basal septum; 90% w/ harsh murmur ± thrill (*NEJM* 2002;347:1426); **Rx:** diuretics, vasodil., inotropes, **IABP**, **surgery**, perc. closure
- **Papillary muscle rupture:** more common after inf **MI** (**PM** pap. muscle supplied by **PDA** alone) than ant **MI** (**AL** pap. muscle supplied by diags & OMs); 50% w/ new murmur, rarely a thrill, → v wave in **PCWP** tracing; asymmetric pulmonary edema on **CXR** (often worse in RUL due to direction of jet). **Rx:** diuretics, vasodilators, **IABP**, **surgery**.

Arrhythmias post-MI

- Treat as per **ACLS** for unstable or symptomatic bradycardias & tachycardias
- **AF** (10-16% incidence): **βB** or amio, ± digoxin (particularly if **HF**), heparin
- **VT/VF:** lido or amio × 6-24 h, then reassess; ↑ **βB** as tol., replete K & Mg, **r/o** ischemia; early monomorphic (<48 h post-MI) does *not* carry bad prognosis. Beyond 48 h, **VT/VF a/w** worse prognosis → consider wearable defibrillator (qv).
- Accelerated idioventricular rhythm (**AVR**): slow **VT** (<100 bpm), often seen after successful reperfusion; typically self-terminates and does not require treatment
- May consider **backup transcutaneous pacing (TP)** if: 2° **AVB** type I, **BBB**
- **Backup TP or initiate transvenous pacing** if: 2° **AVB** type II; **BBB** + **AVB**
- **Transvenous pacing (TV)** if: 3° **AVB**; new **BBB** + 2° **AVB** type II; alternating **LBBB/RBBB** (can bridge w/ **TP** until **TV**, which is best accomplished under fluoroscopic guidance)

Other Post-MI Complications

| Complication | Clinical features | Treatment |
|-----------------------------|--|---|
| LV thrombus | ~30% incid. (espec lg antero-apical MI) | Anticoagulate × 3-6 mo |
| Ventricular aneurysm | Noncontractile outpouching of LV ; 8-15% incid. (espec ant); persist STE | Surgery or perc repair if HF , thromboemboli, arrhythmia |

| | | |
|-----------------------------------|---|--|
| Ventricular pseudoaneurysm | Rupture → sealed by thrombus and pericardium (espec in inf). Typically w/ narrow neck as c/w true aneurysm; Dx w/ cardiac MRI, CTA, or TEE. | Urgent surgery (or percutaneous repair) |
| Pericarditis | 10-20% incid.; 1-4 d post-MI ⊕ pericardial rub; ECG Δs rare | High-dose ASA > aceta., colchicine, narcotics; minimize anticoag |
| Dressler's syndrome | <4% incid.; 2-10 wk post-MI fever, pericarditis, pleuritis | High-dose aspirin, NSAIDs |

Prognosis

- In registries, in-hospital mortality is 6% w/ reperfusion Rx (lytic or PCI) and ~20% w/o
- Predictors of mortality: age, time to Rx, anterior MI or LBBB, heart failure (Circ 2000;102:2031)

Killip Class

| Class | Definition | Mort. |
|-------|---------------------------|--------|
| I | no CHF | 6% |
| II | ⊕ S3 and/or basilar rales | 17% |
| III | pulmonary edema | 30-40% |
| IV | cardiogenic shock | 60-80% |

(Am J Cardiol 1967;20:457)

Forrester Class Mortality

| | PCWP (mmHg) | |
|----|-------------|-----|
| | <18 | >18 |
| CI | >2.2 | 3% |
| | ≤2.2 | 23% |
| | | 9% |
| | | 51% |

TIMI Risk Score for STEMI

| Characteristic | Points | Characteristic (cont) | Points | Score | 30-d death |
|--------------------|--------|-----------------------|--------|-------|------------|
| Age 65-74/≥75 y | 2/3 | Ant MI or new LBBB | 1 | 0-2 | ~1-2% |
| SBP <100 mmHg | 3 | h/o DM, HTN or angina | 1 | 3-4 | ~4-6% |
| HR >100 bpm | 2 | Wt <67 kg | 1 | 5-6 | ~10-15% |
| Killip class II-IV | 2 | Time to Rx >4 h | 1 | ≥7 | ≥20% |

(JAMA 2001;286:1356)

PREDISCHARGE CHECKLIST AND LONG-TERM POST-ACS MANAGEMENT

Risk stratification

- Stress test if anatomy undefined; consider stress if signif residual CAD post-PCI of culprit
- Assess LVEF prior to d/c; EF ↑ ~6% in STEMI over 6 mo (JACC 2007;50:149)

Medications (barring contraindications)

- **Aspirin:** 81 mg daily
- **P2Y₁₂ inhib** (ticagrelor or prasugrel preferred over clopi): treat for *at least* 12 mo Prolonged Rx beyond 12 mo → ↓ CV death, MI, & stroke (& stent thrombosis) w/ ↑ in bleeding, but no ↑ fatal bleeding or ICH. For Rx beyond 1st 12 mo, comparable efficacy w/ ticagrelor 90 or 60 mg bid, better safety & tolerability with 60 bid (NEJM 2015;372:1791; JACC 2007;49:1982 & 2015;65:2211).

Some PPIs interfere w/ biotransformation of clopi and . . . plit inhibition, but no convincing impact on clinical outcomes (Lancet 2009;374:989; NEJM 2010;363:1909); use w/PPIs if h/o GIB or multiple GIB risk factors (JACC 2010;56:2051)

- **β-blocker:** 23% ↓ mortality after MI
- **Statin:** high-intensity lipid-lowering (eg, atorvastatin 80 mg, NEJM 2004;350:1495)
- **Ezetimibe:** ↓ CV events including MI and ischemic stroke when added to statin (IMPROVE-IT, NEJM 2015;372:1500)
- **ACEI:** lifelong if HF, ↓ EF, HTN, DM; 4-6 wk or at least until hosp. d/c in all STEMI ? long-term benefit in CAD w/o HF (NEJM 2000;342:145 & 2004;351:2058; Lancet 2003;362:782)
- **Aldosterone antag:** 15% ↓ mortality if EF <40% & either s/s of HF or DM; contraindic if renal dysfxn (Cr >2.5 in men, >2 in women) or K >5 (NEJM 2003;348:1309)

- Nitrates: standing if symptomatic; SL **NTG** prn for all
- Ranolazine: inhibits late inward Na current, prevents intracellular Ca overload; ↓ recurrent ischemia (*JAMA* 2007;297:1775)
- Oral anticoagulants: if warfarin needed in addition to **ASA**/clopi (eg, **AF** or **LV** throm-bus), target **INR** 2-2.5. ? stop **ASA** if at high bleeding risk on triple **Rx** (*Lancet* 2013;381:1107). Not FDA approved: low-dose rivaroxaban (2.5 mg bid) in addition to **ASA** & clopi → 16% ↓ **D/MI**/stroke and 32% ↓ all-cause death, but ↑ major bleeding and **ICH** (*NEJM* 2012;366:9).
- NSAIDs/COX2 inhib relatively contraindic **b/c** ? ↑ death, **MI**, **HF**, rupture (*Circ* 2006;113:2906)

ICD (*NEJM* 2008;359:2245)

- If sust. **VT/VF** >2 d post-MI not due to reversible ischemia; consider wearable defibril-lator or **ICD** (*JACC* 2014;130:94)
- Indicated in 1° prevention of **SCD** if post-MI **w/ EF** ≤30-40% (**NYHA** II-III) or ≤30-35% (**NYHA** I); need to wait ≥40 d after **MI** (*NEJM* 2004;351:2481 & 2009;361:1427)

Risk factors and lifestyle modifications (*Circ* 2014;129(Suppl 2):S1 & S76)

- Low chol. (<200 mg/d) & fat (<7% saturated) diet; ? Ω-3 FA
- Traditional LDL-C goal <70 mg/dL; new recs w/o LDL-C target, rather simply high-intensity statin; may change **w/ IMPROVE-IT** trial showing that lower is better (lower **CV** event rate in arm with achieved LDL-C of 54 vs 70 mg/dL)
- **BP** <140/90 and consider <130/80 mmHg (*HTN* 2015;65:1372); smoking cessation
- If diabetic, tailor HbA1c goal based on **Pt** (avoid TZDs if **HF**)
- Exercise (30-60 min 5-7×/wk); cardiac rehab; **BMI** goal 18.5-24.9 kg/m²
- Influenza & pneumococcal vaccination (*Circ* 2006;114:1549; *JAMA* 2013;310:1711); screen for depression

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CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Goal: characterize risk of Pt & procedure → appropriate testing (ie, results will Δ management) and interventions (ie, reasonable probability of → risk of MACE)

Preoperative assessment

- Clinical assessment: evidence of active cardiac disease and/or risk factors
- Functional capacity (**METs**)
- Surgery-specific risk

Clinical Assessment

Active cardiac conditions

- **MI** w/in 30 d or current unstable or severe angina

Clinical risk factors

- **h/o** ischemic heart

- Decompensated HF
- Significant arrhythmia (eg, Mobitz II, high-grade AVB, 3° AVB, new or sx VT, SVT w/ HR >100, sx brady)
- Severe AS or sx MS
- h/o congestive HF
- h/o stroke or TIA
- Diabetes on insulin
- Renal insuffic. (Cr >2 mg/dL)

Functional Capacity

1-4 METs (poor)

- ADLs
- Walk indoors
- Walk 1-2 level blocks

4-10 METs (moderate-to-good)

- Climb a flight of stairs/hill
- Walk briskly; heavy housework
- Golf, doubles tennis

>10 METs (excellent)

- Strenuous sports

Surgery-Specific Risk

High (>5% risk)

- Aortic or other major vascular
- Peripheral vasc.

Intermediate (1-5%)

- Intrathoracic; intraperitoneal; prostate & major urologic
- CEA; head & neck
- Orthopedic

Low (<1%)

- Endoscopic
- Breast; superficial
- Cataract; ambulatory
- Dental

Noninvasive Testing Result

High risk

Ischemia at <4 METs manifested by ≥1 of:

- Horiz/down ST ↓ ≥1 mm or STE
- ≥5 abnl leads or ischemic ECG Δs lasting >3 min after exertion
- SBP ↓ 10 mmHg or typical angina

Intermediate risk

Ischemia at 4-6 METs manifested by ≥ 1 of:

- Horiz/down ST ↓ ≥1 mm
- 3-4 abnl leads
- 1-3 min after exertion

Low risk

No ischemia or at >7 METs w/

- ST ↑ ≥1 mm or
- 1-2 abnl leads

Imaging with excellent NPV, poor PPV. Consider if high-risk patient.

- **Revised Cardiac Risk Index (RCRI):** 6 risk factors = 5 clinical risk factors above and type of surgery

(intrathoracic, intra-abd, or suprainguinal vascular) (*Circ* 1999;100:1043) # of risk factors predicts risk of **MACE**: ≤1 **RF** → <1%, 2 **RFs** → 6.6%, ≥3 **RFs** → 11%

- Comorbidity indices (eg, Charlson index) may predict mortality (*Am J Med Qual* 2011;26:461)

Preoperative testing (*Circ* 2014;130:e278)

- **ECG** if known cardiac disease and possibly reasonable in all, except if low-risk surgery
- **TTE** if any of the following and prior **TTE** > 12 **mo** ago or prior to Δ in **sx**:
 - dyspnea of unknown origin
 - hx** of **HF w/** ↑ dyspnea
 - suspected valvular disease (eg, murmur on exam)
 - ≥moderate stenosis/regurg
- Stress test (usually pharmacologic) if:
 - active cardiac issues where stress testing is indicated (qv), or not low-risk surgery, RCRI ≥2, poor or unknown fxnal capacity, and results *will* Δ *mgmt* (ie, modify or delay surgery, undergo coronary revascularization, etc.)
 - overall low **PPV** to predict periop **CV** events
- Angiography: based on noninvasive stress results for standard indications, although systematic angio ↓ 2-5 **y** mortality in Pts undergoing vascular surgery (*JACC* 2009;54:989)
- ? consider **CXR** & **ECG** in preop evaluation of severely obese Pts (*Circ* 2009;120:86)

Coronary artery disease

- If possible, wait ~60 **d** after **MI** in the absence of revascularization before elective surgery
- After **PCI**: delay elective surgery 14 **d** after balloon angioplasty, 30 **d** after **BMS** implantation, and ideally 6 **mo** after **DES** implantation

P.1-22

- Coronary revascularization should be based on standard indications (eg, **ACS**, refractory **sx**, lg territory at risk). Has not been shown to Δ risk of death or postop **MI** when done prior to elective vasc. surgery based on perceived cardiac risk (*NEJM* 2004;351:2795) or documented extensive ischemia (*AJC* 2009;103:897).

Heart failure

- Decompensated **HF** should be optimally treated prior to elective surgery
- ↓ **EF** (<30%) associated with poor outcomes
- 30-d **CV** event rate: symptomatic **HF** > **asx** **HFrEF** > **asx** **HFpEF** > no **HF**

Valvular heart disease

- If meet criteria for valve intervention (qv), do so before elective surgery (postpone if necessary)
- If severe valve disease and surgery urgent, intra- & postoperative hemodynamic monitoring reasonable (espec for **AS**, since at ↑ risk even if **sx** not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)
- If severe **AS** and **Pt** not eligible for or impractical to do **AVR** prior to noncardiac surgery, balloon aortic valvuloplasty (BAV) and transcatheter aortic valve replacement (**TAVR**) can be considered but not routinely

recommended (*Circ* 2008;118:e523)

Cardiac implantable electronic devices (CIEDs)

- Includes **PPM**, **CRT**, **ICD**
- Should be discussion between surgical team & **CIED** team regarding: need for device (eg, complete heart block) & consequences if interference w/ fxn likelihood of electromagnetic interference consideration of reprogramming, magnet use, etc.

Pre- & perioperative pharmacologic management

- **ASA**: continue in Pts w/ existing indication. Initiation just prior to surgery does not ↓ 30-d ischemic events and ↑ bleeding (*NEJM* 2014;370:1494), but Pts w/ recent stents excluded.
- **Dual antiplatelet therapy** in Pts undergoing urgent surgery: continue 4-6 wk after **PCI** (**BMS** or **DES**) unless risk of bleeding > benefit of prevention of stent thrombosis. If must discontinue ADP receptor blocker, continue **ASA** and restart ADP receptor blocker ASAP.
- **β-blockers** (*Circ* 2009;120:2123; *JAMA* 2010;303:551; *Am J Med* 2012;125:953) Continue **βB** in Pts on them chronically. Do not discontinue **βB** abruptly postop, as may cause sympathetic activation from withdrawal. Use IV agents peri-operatively if Pt unable to take **PO**.

In terms of initiating **βB**, conflicting evidence; may depend on how administered. Some studies show ↓ death & **MI** (*NEJM* 1996;335:1713 & 1999;341:1789), another showed ↓ **MI**, but ↑ death & stroke and ↑ bradycardia/**HoTN** (*Lancet* 2008;371:1839).

? consider initiating if intermed- or high-risk ⊕ stress test, or RCRI ≥3, espec if vasc surgery

Ideally initiate at least 1 wk prior to surgery, use low-dose, short-acting **βB**, and titrate slowly and carefully to achieve desired individual **HR** and **BP** goal (? **HR** ~55-65). Avoid bradycardia and **HoTN**.

- **Statins**: ↓ ischemia & **CV** events in Pts undergoing vascular surg (*NEJM* 2009;361:980); may reduce **AF**, **MI**, **LOS** in statin-naïve Pts (*Arch Surg* 2012;147:181). Consider in Pts w/ a clinical risk factor undergoing non-low-risk surgery.
- **ACEI/ARB**: may cause **HoTN** perioperatively. If held before surgery, restart ASAP.
- Amiodarone: ↓ incidence of postop **AF**

oral (eg, 600 mg qd × 7 d preop, then 200 mg qd until discharge) & IV regimens equivalent but effective only if initiated ≥1 d prior to surgery (*Pacing Clin Electrophysiol* 2013;36:1017)

cardiac surgery: ↓ postop **AF**, length of stay & cost (*NEJM* 1997;337:1785) thoracic surgery: ↓ postop **AF** but not length of stay or cost (*J Thorac CV Surg* 2010;140:45; *Ann Thorac Surg* 2012;94:339; *Eur J Cardiothorac Surg* 2014;45:120). Not advised if severe lung disease or undergoing pneumonectomy (*Ann Thorac Surg* 2011;92:1144).

Postoperative monitoring

- ✓ Postop **ECG** if known **CAD** or high-risk surgery. Consider if >1 risk factor for **CAD**.
- ✓ Postop troponin only if new **ECG** Δs or chest pain suggestive of **ACS**. Elevated **Tn** postop predicts mortality, but may simply be a marker for underlying **CAD** (*Annals* 2011;154:523; *JAMA* 2012;307:2295). Routine ✓ postop in all Pts (even just high-risk Pts) has not been proven to modify outcomes and it is not routinely recommended.

Myocardial, Valvular, and Pericardial Disease

HEART FAILURE

Definitions (*Braunwald's Heart Disease, 10th ed., 2014*)

- Failure of heart to pump blood forward at sufficient rate to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output (\downarrow cardiac output) vs high output (\uparrow stroke volume \pm \uparrow cardiac output)
- Left-sided (pulmonary edema) vs right-sided (\uparrow JVP, hepatomegaly, peripheral edema)
- Backward (\uparrow filling pressures, congestion) vs forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs diastolic (failure to relax and fill normally)
- Reduced (HFrEF) vs preserved (HFpEF) left ventricular ejection fraction
- Some degree of systolic and diastolic dysfxn may occur regardless of ejection fraction

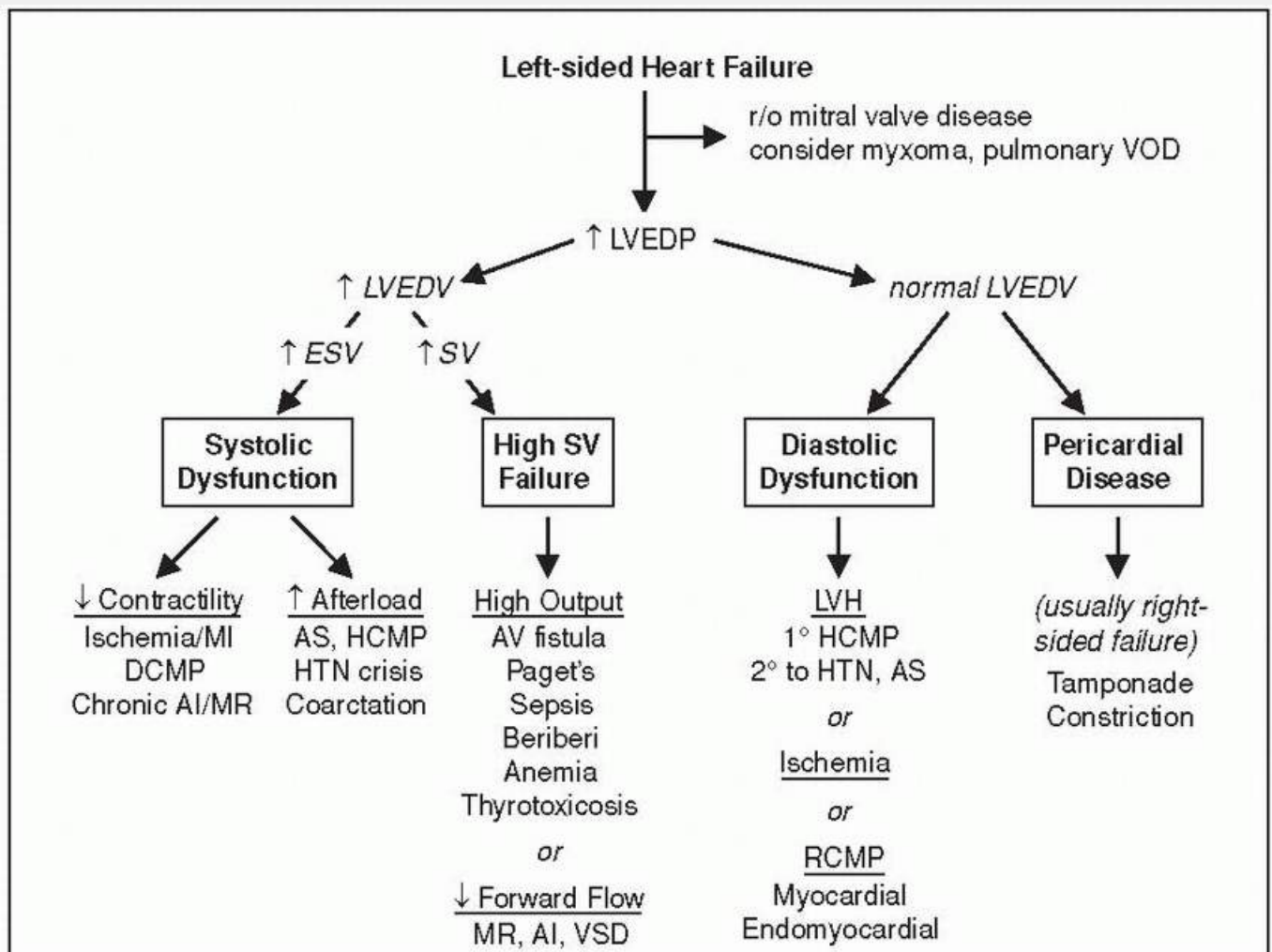


Figure 1-3 Approach to left-sided heart failure

History

- Low output: fatigue, weakness, exercise intolerance, Δ MS, anorexia
- Congestive: dyspnea, weight gain;

left-sided → orthopnea, paroxysmal nocturnal dyspnea

right-sided → peripheral edema, RUQ discomfort, bloating, early satiety

Stages in the Development of Heart Failure (*Circ* 2009;119:e391)

- A: At high risk for HF, but w/o structural heart disease or symptoms of HF
- B: Structural heart disease, but w/o signs or symptoms of HF
- C: Structural heart disease w/ prior or current symptoms of HF
- D: Refractory heart failure requiring specialized intervention

Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity; class III: sx w/ minimal activity; class IV: sx at rest

Physical exam (“2-minute” hemodynamic profile; *JAMA* 1996;275:630 & 2002;287:628)

• Congestion (“dry” vs “wet”)

↑ JVP (~80% of the time RAP > 10 mmHg → PCWP >22 mmHg; *JHLT* 1999;18:1126)

⊕ hepatojugular reflux: ≥4 cm ↑ in JVP that persists for ≥15 sec w/ abdominal pressure Se/Sp 73/87% for RA >8 and Se/Sp 55/83% for PCWP >15 (*AJC* 1990;66:1002)

Abnl Valsalva response: square wave (↑ SBP w/ strain), no overshoot (no ↑ BP after strain) S₃ (in Pts w/ HF → ~40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;345:574) rales, dullness at base 2° pleural effus. (often absent in chronic HF due to lymphatic compensation) ± hepatomegaly, ascites and jaundice, peripheral edema

- Perfusion (“warm” vs “cold”): narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; *JAMA* 1989;261:884); other signs of low perfusion include soft S₁ (↑ dP/dt), pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- Other signs to look for: periodic breathing/Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S₄ (diast. dysfxn), murmur (valvular disease, ↑ MV or TV annulus, displaced papillary muscles), ↓ carotid upstroke

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Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines
- BNP/NT-proBNP can help exclude HF; levels ↑ w/ age, renal dysfxn, AF, ↓ w/ obesity Se ≥95%, Sp ~50%, PPV ~65%, NPV ≥94% for HF in Pts p/w SOB (*BMJ* 2015;350:h910)
- Evidence of ↓ organ perfusion: ↑ Cr, ↓ Na, abnl LFTs
- Echo (see inserts): ↓ EF & ↑ chamber size ↑ systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler → ? diastolic dysfxn; abnl valves or pericardium; ↑ estimated RVSP
- PA catheterization: ↑ PCWP, ↓ CO and ↑ SVR (in low-output failure)

Evaluation of the potential causes of heart failure

- **ECG**: Q waves or **PRWP** (ischemic heart disease); **LVH** (hypertensive heart disease or HCM); low limb lead voltage (NICM or infiltrative); heart block (infiltrative)
- **TTE**: **LV** & **RV** size & function, valvular disease (and whether likely 1° or 2° to **CMP**), findings indicative of infiltrative or pericardial disease
- **Coronary angio** (or noninvasive imaging, eg, **CT** angio); if no **CAD**, **w/u** for NICM
- **Cardiac MRI**: multiparameter evaluation of cardiac structure & function including:
 - LVEF, RVEF and volumes; regional wall motion abnormalities
 - presence, pattern, & extent of myocardial scar (using late gadolinium enhancement, LGE) **w/ Se/Sp** of 100%/96% vs coronary angio for **dx** etiology of **HF** (*Circ* 2011;124:1351)
 - myocardial inflammation or infiltration (eg, myocarditis, sarcoidosis, amyloidosis) restriction vs constrictive pericardial disease

Evaluation of Potential Causes of Heart Failure

| Etiology | ECG Pattern | Imaging Pattern |
|-------------------|---|---|
| Ischemia, infarct | ST segment deviation, Qw | TTE : regional WMA , ± thinning/aneurysm Cor angio/CTA : obstructive CAD MRI : subendocardial or transmural LGE |
| Infiltrative | Low limb lead voltage, ± heart block, pseudoinfarct | TTE : LVH , “starry sky,” ↑ biatrial size → amyloid MRI : inappropriately nulling of myocardium + diffuse LGE → amyloid; patchy LV + RV LGE → sarcoidosis; ↓ T2 star → iron overload |
| Idiopathic DCM | Low limb lead volts, precordial LVH , BBB | TTE : 4 chamber dilation, diffuse hypokinesis MRI : mid-myocardial LGE |
| Tachy-myopathy | Persistent SVT | TTE : diffuse hypokinesis MRI : absent LGE in early stage |
| Myo(pericarditis) | Pseudoischemia/-infarct. Pericard: diffuse concave STE w/ ST : T ratio >0.24 in V ₆ and PR depression | TTE : typically global HK MRI : mid-myocardial + epicardial LGE, ↑ T2 and ↑ T1 ratios (edema) |

Precipitants of acute heart failure

- **Dietary indiscretion or medical nonadherence** (~40% of cases)
- **Myocardial ischemia or infarction** (~10-15% of cases); myocarditis
- **Renal failure** (acute, progression of **CKD**, or insufficient dialysis) → ↑ preload

- **Hypertensive crisis (incl. from RAS), worsening AS** → ↑ left-sided afterload
- **Drugs** (βB, CCB, NSAIDs, TZDs), **chemo** (anthracyclines, trastuzumab), or **toxins** (EtOH)
- **Arrhythmias**; acute valv. dysfxn (eg, endocarditis), espec mitral or aortic regurgitation
- **COPD or PE** → ↑ right-sided afterload; **RV pacing**
- Other: **extreme emotional stress; anemia, systemic infection, thyroid disease**

Treatment of acute decompensated heart failure

| | | Congestion? | |
|----------------|-----|--|---|
| | | No | Yes |
| Low perfusion? | No | Warm & Dry Outpatient Rx | Warm & Wet Diuresis |
| | Yes | Cold & Dry Inotropes (CCU) | Cold & Wet Diuresis, inotropes and/or vasodil (CCU) |

- Assess degree of congestion & adequacy of perfusion

- For **congestion**: “**LMNOP**”

Lasix IV w/ monitoring of UOP; total daily dose 2.5× usual daily PO dose → ↑ UOP, but transient ↑ in renal dysfxn vs 1× usual dose; ∅ clear diff between cont gtt vs q12h dosing (NEJM 2011;364:797)

Morphine (↓ sx, venodilator, ↓ afterload)

Nitrates (venodilator)

Oxygen ± noninvasive vent (↓ sx, ↑ P_aO₂; no Δ mortality; see “Mechanical Ventilation”)

Position (sitting up & legs dangling over side of bed → ↓ preload)

- For **low perfusion**, see below

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- Adjustment of oral meds

ACEI/ARB: hold if HoTN, consider Δ to hydralazine & nitrates if renal decompensation βB: reduce dose by at least ½ if mod HF, d/c if severe HF and/or need inotropes

Overview of Treatment of Heart Failure by Stage

Pt characteristics

Therapy

| | | |
|----------|--|---|
| A | HTN, DM, CAD Cardiotoxin exposure FHx of CMP | Treat HTN, lipids, DM, SVT Stop smoking, EtOH; ↑ exercise ACEI/ARB if HTN/DM/CAD/PAD |
| B | Prior MI, ↓ EF, LVH or asx valvular dis. | All measures for stage A + ACEI/ARB & βB if MI/CAD or ↓ EF. ? ICD. |
| C | Overt HF | All measures for stage A, ACEI, βB, diuretics, Na restrict ↓ EF: aldo antag, ICD, consider CRT, nitrate/hydral, dig. |

D Sx despite max med Rx 4-y mortality >50% All measures for stages A-C Consider IV inotropes, VAD, transplant, end-of-life care

- Utility of BNP-guided Rx remains debated (*Circ* 2013;301:500 & 509)
- Implantable PA pressure sensor in NYHA III → 37% ↓ risk of hosp (23% for HFrEF; 52% for HFpEF) (*Lancet* 2011;377:658)

Treatment of advanced heart failure (*Circ* 2009;119:e391)

- Consider PAC (qv) if not resp to Rx, unsure re: vol status, HoTN, ↑ Cr, need inotropes
- Tailored Rx w/ PAC; goals of MAP >60, CI >2.2 (MVO₂ >60%), SVR <800, PCWP <18
- **IV vasodilators:** NTG, nitroprusside (risk of coronary steal if CAD; prolonged use → cyanide/thiocyanate toxicity); nesiritide (rBNP) not rec for routine use (*NEJM* 2011;365:32)
- **Inotropes:** in addition to ↑ inotropy, consider additional properties:

dobutamine: vasodilation at doses ≤5 mcg/kg/min; mild ↑ PVR; desensitization over time

dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrictor at ≥5 mcg/kg/min; does not enhance decongestion or preserve renal fxn in ADHF (*JAMA* 2013;310:2533)

milrinone: prominent systemic & pulmonary vasodilation; ↑ dose by 50% in renal failure

- Ultrafiltration: similar wt loss to aggressive diuresis, but ↑ renal failure (*NEJM* 2012;367:2296)
- **Mechanical circulatory support (MCS)** (*JHLT* 2013;32:157; *JACC* 2015;65:e7 & 2542)

Temporary MCS: depending on the device (Table), can be placed percutaneously or surgically to support LV or RV, as a bridge to recovery, for periprocedural support, or as a bridge to decision regarding transplant or durable long-term MCS

Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to ↓ impedance to LV ejection of blood, ↓ myocardial O₂ demand & ↑ coronary perfusion

Axial flow pumps (eg, Impella): Archimedes screw principle in LV

Extracorporeal magnetically levitated centrifugal pumps (eg, TandemHeart & CentriMag)

Extracorporeal membrane oxygenation (ECMO, *Circ* 2015;131:676)

Short-Term Mechanical Circulatory Support in Cardiogenic Shock

| Device | IABP | Impella 2.5 & CP | Impella 5.0 | Tandem | CentriMag | ECMO |
|---------------------|------|--------------------------|-------------|--------------------------|--------------------------|------|
| Max support (L/min) | 0.5 | 2.5 & 3-4 | 5.0 | 5.0 | 10 | 6 |
| RV support | N | Y (2 nd dev.) | N | Y (2 nd dev.) | Y (2 nd dev.) | Y |

| | | | | | | |
|------------------|----------------------|---------------------------------|-------|---------------------|----------|----------|
| Support duration | wks | ~4 wk | ~4 wk | <4 wk | mos | wks |
| Percutan? | Y | Y | N | Y | N | Y |
| Contraindic. | ≥ mod AI, severe PAD | LV thrombus, mech AV, severe AS | | coagulop severe PAD | coagulop | coagulop |

(*Circ* 2011;123:533 & 126:1717; *JACC* 2015;65:e7)

Durable Long-term MCS: surgically placed LVAD ± RVAD as bridge to recovery (*NEJM* 2006;355:1873) or transplant (HeartMate II or HeartWare LVAD or Total Artificial Heart if biventricular failure), or as destination Rx (HeartMate I: 52% ↓ 1-y mort. vs med Rx; *NEJM* 2001;345:1435, HeartMate II: 24% ↑ mort. vs HeartMate I; *NEJM* 2009;361:2241)

- **Cardiac transplantation:** curative Rx but supply of organs limited (~2500/y in U.S.) 10% mortality in 1st year, median survival ~10 y

Contraindications: active malignancy or infection, irreversible PHT (TPG>15, PVR>5WU despite pulmonary vasodilator Rx), active substance abuse or lack of social supports

Relative contraindications: age (eg, >70 y), other end organ dysfunction (liver, kidney, lung, unless dual organ transplantation is performed)

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Treatment of Chronic Heart Failure with Reduced Ejection Fraction

Diet, exercise Na <2 g/d, fluid restriction, exercise training in ambulatory Pts

ACEI ↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20-30% in asx but ↓ EF (*NEJM* 1992;327:685 & *Lancet* 2000;355:1575) High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, Kayexalate; patiromer, another K binder, under review; *NEJM* 2015;372:211), cough, angioedema.

ATII receptor blockers (ARBs) Consider as alternative if cannot tolerate ACEI (eg, b/c cough) Noninferior to ACEI (*Lancet* 2000;355:1582 & 2003;362:772) As with ACEI, higher doses more efficacious (*Lancet* 2009;374:1840) Adding to ACEI → ↑ risk of ↑ K and ↑ Cr (*BMJ* 2013;346:f360)

ARNi (ARB + neprilysin inhib) Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides as well as bradykinin & angiotensins. LCZ696 = valsartan + sacubitril (NEPi): ↓ CV mort & HF hosp c/w ACEi; more HoTN and trend to more angioedema (PARADIGM-HF, *NEJM* 2014;371:993).

Hydralazine + nitrates Consider if cannot tolerate ACEI/ARB or in blacks w/ NYHA III/IV 25% ↓ mort. (*NEJM* 1986;314:1547); infer. to ACEI (*NEJM* 1991;325:303) 43% ↓ mort. in blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)

| | |
|--|--|
| β-blocker (data for carvedilol, metoprolol, bisoprolol) | <i>EF will transiently ↓, then ↑. Contraindic. in decompensated HF. 35% ↓ mort. & 40% ↓ re hosp. in NYHA II-IV (JAMA 2002;287:883) Carvedilol superior to low-dose metop in 1 trial (Lancet 2003;362:7), but meta-analysis suggests no diff between βB (BMJ 2013;346:f55).</i> |
| Aldosterone antagonists | <i>Consider if adeq. renal fxn and w/o hyperkalemia; watch for → K 24-30% ↓ mort. in NYHA II-IV & EF ≤35% (NEJM 2011;364:11) 15% ↓ mort. in HF post-MI, EF ≤40% (EPHESUS, NEJM 2003;348:1309)</i> |
| Cardiac resynch therapy (CRT, qv) | <i>Consider if EF ≤35%, LBBB and symptomatic HF 36% ↓ mort. & ↑ EF in NYHA III-IV (CARE-HF, NEJM 2005;352:1539) 41% ↓ mort. if EF ≤30%, LBBB and NYHA III (NEJM 2014;370:1694)</i> |
| ICD (see “Cardiac Rhythm Mgmt Devices”) | <i>Use for 1° prevention if EF ≤30-35% or 2° prevention; not if NYHA IV ↓ mort. in ischemic & non-isch CMP; no Δ mort. early post-MI (NEJM 2004;351:2481 & 2009;361:1427), ∴ wait ≥40 d</i> |
| Diuretics | <i>Loop ± thiazide diuretics (sx relief; no mortality benefit)</i> |
| Digoxin | <i>23% ↓ HF hosp., no Δ mort (NEJM 1997;336:525); ? ↑ mort w/ ↑ levels (NEJM 2002;347:1403); optimal 0.5-0.8 ng/mL (JAMA 2003;289:871)</i> |
| Ivabradine (if blocker w/o ino) | <i>Consider if HR >70, NSR on max βB. 18% ↓ CV mort or HF hosp (Lancet 2010;376:875)</i> |
| ω-3 fatty acids | <i>9% ↓ mortality (included HF with normal LVEF) (Lancet 2008;372:1223)</i> |
| IV iron supplementation | <i>? if NYHA II/III, EF ≤40%, Fe-defic (ferritin <100 or ferritin 100-300 & TSAT <20%). ↓ Sx, ↑ 6MWD, independent of Hct (NEJM 2009;361:2436).</i> |
| Anticoagulation | <i>If AF, VTE, LV thrombus, ± if large akinetic LV segments In SR w/ EF <35%, ↓ isch stroke, but ↑ bleed (NEJM 2012;366:1859)</i> |
| Heart rhythm | <i>Catheter ablation of AF → ↑ in EF, ↓ sx (NEJM 2004;351:2373) No mortality benefit to AF rhythm vs rate cntl (NEJM 2008;358:2667) Pulm vein isolation ↓ sx c/w AVN ablation & CRT (NEJM 2008;359:1778)</i> |
| Meds to avoid | <i>NSAIDs, nondihydropyridine CCB, TZDs</i> |
| Experimental | <i>Serelaxin ± ↓ dyspnea & ? ↓ mortality (Lancet 2013;381:29)</i> |

(Circ 2009;119:e391; NEJM 2010;362:228; Lancet 2011;378:713 & 722)

Heart failure with preserved EF (HFpEF; “Diastolic HF”) (*Circ* 2011;124:e540)

- Epidemiology: ~½ of Pts w/ HF have normal or only **min.** impaired systolic fxn (EF ≥40%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mortality ≈ to those w/ systolic dysfxn.
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCMP infiltrative CMP, RCMP aging, hypothyroidism
- Precipitants of pulmonary edema: *volume overload* (poor compliance of LV → sensitive to even modest ↑ in volume); *ischemia* (↓ relaxation); *tachycardia* (↓ filling time in diastole), AF (loss of atrial boost to LV filling); HTN (↓ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic fxn. Dx supported by evidence of diast dysfxn:
 - (1) echo: **abnl MV** inflow (E/A reversal and Δs in E wave deceleration time) & ↓ myocardial relax. (↑ isovol relax. time & ↓ early diastole tissue Doppler velocities)
 - (2) exercise-induced ↑ PCWP (± ↓ response chronotropic & vasodilator reserve)
- Treatment: diuresis for vol overload, BP control, prevention of tachycardia and ischemia; no benefit to: ACEI/ARB (*NEJM* 2008;359:2456) or PDE5 inhib (*JAMA* 2013;309:1268) spironolactone ↓ CV death & HF hosp (at least in Americas) (*NEJM* 2014;370:1383);
ARNi (*Lancet* 2012;380:1387) and serelaxin (*Lancet* 2013;381:29) under study

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PA CATHETER AND TAILORED THERAPY

Rationale

- Cardiac output (CO) = SV × HR; LV SV depends on LV end-diastolic volume (LVEDV) ∴ manipulate LVEDV to optimize CO while minimizing pulmonary edema
- Balloon at tip of catheter inflated → floats into “wedge” position. Column of blood extends from tip of catheter, through pulmonary circulation, to a point just proximal to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:
 - (1) Catheter tip not in West lung zone 3 (and ∴ PCWP = alveolar pressure ≠ LA pressure); clues include lack of a & v waves and if PA diastolic pressure < PCWP
 - (2) PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)
 - (3) Mean LA pressure > LVEDP (eg, MR, MS)
 - (4) Δ LVEDP-LVEDV relationship (ie, **abnl** compliance, [“nl” LVEDP may not be optimal])

Indications (*Circ* 2009;119:e391; *NEJM* 2013;369:e35)

• Diagnosis and evaluation

Ddx of shock (cardiogenic vs distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs not; espec if trial of diuretic failed or is high risk)

Evaluation of CO, intracardiac shunt, pulmonary HTN, MR, tamponade, cardiorenal syndrome

Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)

• Therapeutics (*Circ* 2006;113:1020)

Tailored therapy to optimize **PCWP**, **SV**, $S_{MV}O_2$, **RAP**, & **PVR**, in heart failure or shock

Guide to vasodilator therapy (eg, inhaled **NO**) in pulm **HTN**, **RV** infarction

Guide to perioperative management in some high-risk Pts, pretransplantation

Guide to candidacy for thoracic organ transplantation and mechanical circulatory support

- **Contraindications**

Absolute: right-sided endocarditis, thrombus/mass or mechanical valve; **PE**

Relative: coagulopathy (reverse), recent **PPM** or **ICD** (place under fluoroscopy), **LBBB** (~5% risk of **RBBB** ↑ **CHB**, place under fluoro), bioprosthetic R-sided valve

Efficacy concerns (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine **PAC** use in high-risk surgery, sepsis, **ARDS**
- No benefit in decompensated **HF** (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ~½ of **CO** & **PCWP** clinical estimates incorrect; **CVP** & **PCWP** not well correl.; ∴ use **PAC** to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

Pulmonary Artery Catheter Features

| Component | cm from distal tip | Function |
|--------------------------------------|--------------------|---|
| Distal lumen | 0 | Sampling of blood for $S_{MV}O_2$ |
| 1.5-mL balloon | 0.5 | Inflation allows flow directed placement & determination of PCWP |
| Thermistor | 4 | Detection of temp Δ for CO calc |
| Proximal injectate port | 26 | Infusions & injection of saline for CO calc |
| <i>Additional Optional Features</i> | | |
| Fiberoptic O ₂ sat sensor | 0 | Allows continuous measurement of $S_{MV}O_2$ |
| Thermal filament | ~10-25 | Allows continuous CO calc by thermodilution |
| Pacing port | ~19 | Allows placement of pacing wire in RV |
| Infusion port(s) | ~30 | Additional infusion port(s) |

Placement

- Insertion site: **R internal jugular** or **L subclavian veins** for “anatomic” flotation into **PA**
- **Inflate** balloon (max 1.5 mL) when **advancing** and to **measure PCWP**
- Use resistance to inflation and pressure tracing to avoid overinflation & risk of **PA** rupture
- Should require 1-1.5 mL air in balloon to float into wedge (<1 mL → pull **PAC** back; no **PCWP** at 1.5 mL → advance)
- **Deflate** balloon when **withdrawing** and at all other times
- **CXR** should be obtained after placement to assess for catheter position and **PTX**
- If catheter cannot be successfully floated (typically if severe **TR** or **RV** dilatation) or if another relative contraindication exists, use fluoroscopic guidance

Complications

- **Central venous access:** pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- **Arrhythmias:** ½ PVCs, 20% **NSVT**, 3% **VT** (minimize time **PAC** tip in **RV**); **RBBB** (5%)

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- **Inability to advance:** difficulty **RA** → **RV** seen w/ lg **RA** and/or severe **TR**; difficulty **RV** → **PA** seen w/ lg **RV**; deflate balloon, withdraw 10 cm, inflate balloon & readvance. *If repeated attempts unsuccessful at bedside, then perform under fluoro* (to avoid **PAC** coiling & potentially knotting, which would require interventional cardiology to extract).
- **PA rupture:** risk factors include prolonged balloon inflation, **PHT**, anticoag. Presents w/ hemoptysis and, if severe, hypoxemia & hypovolemic shock. *Keep balloon inflated, intubate w/ dbl-lumen endotracheal tube, lateral decubitus position with affected side down, STAT interventional radiology and/or thoracic surgery consultation.*
- **Air embolism:** presents w/ dyspnea, chest pain, ↑ R-sided pressures, **HoTN**. *Place in Trendelenburg, high-flow O₂.*
- **Other:** infxn (espec if **PAC** >3 d old); thrombus; pulm infarction; valve/chordae damage

Intracardiac pressures

- Zero the transducer and level it with the right atrium (phlebostatic axis)
- Transmural pressure (≈ preload) = measured intracardiac pressure - intrathoracic pressure
- Intrathoracic pressure (usually slightly ⊖) is transmitted to vessels and heart
- **Always measure intracardiac pressure at end-expiration**, when intrathoracic pressure closest to 0 (“high point” in spont. breathing Pts; “low point” in Pts on ⊕ pressure vent.)
- If ↑ intrathoracic pressure (eg, **PEEP**), measured **PCWP** *overestimates* true transmural pressures. Can approx by subtracting ~½ **PEEP** (× ¾ to convert cm H₂O to mmHg).
- **PCWP:** **LV** preload best estimated at a wave; risk of pulmonary edema from avg **PCWP**

Cardiac output

- **Thermodilution:** saline injected in RA. Δ in temp over time measured at thermistor (in PA) is integrated and is $\approx 1/CO$. Inaccurate if $\downarrow CO$, severe TR or shunt.

- **Fick method:** O_2 consumpt ($[V$ with dot above $O_2]$) (L/min) = CO (L/min) $\times \Delta$ arteriovenous O_2 content

$\therefore CO = [V$ with dot above $O_2] / C(a-v)O_2$

$[V$ with dot above $O_2]$ ideally measured (espec if \uparrow metab demands), but freq estimated (125 mL/min/m²)

$C(a-v)O_2 = [10 \times 1.36 \text{ mL } O_2/\text{g of Hb} \times \text{Hb g/dL} \times (S_aO_2 - S_{MV}O_2)]$

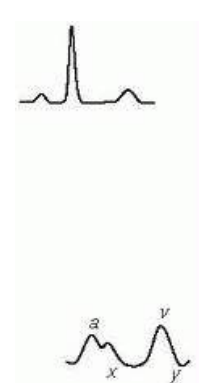
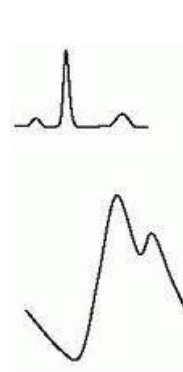
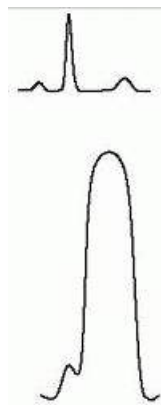
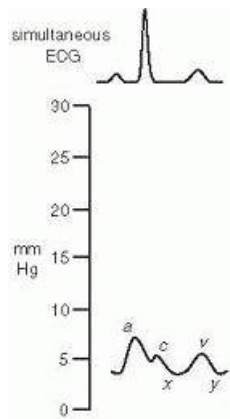
$S_{MV}O_2$ is key variable that Δ s with acute interventions

If $S_{MV}O_2 > 80\%$, consider if the PAC is “wedged” (ie, pulm vein sat), L \rightarrow R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), $\uparrow \uparrow FiO_2$

PA Catheter Waveforms

| Location | RA | RV | PA | PCWP |
|------------------------|---------------|-------------------------|------------------------------------|----------------|
| Distance | ~20 cm | ~30 cm | ~40 cm | ~50 cm |
| Normal Pressure (mmHg) | mean ≤ 6 | syst 15-30 diast 1-8 | syst 15-30 mean 9-18 diast 6-12 | mean ≤ 12 |

Waves



Comment

a = atrial contraction, occurs in PR interval c = bulging of TV back into RA at start of systole x = atrial relaxation and descent of base of heart v = blood entering RA, occurs mid-T wave y = blood exiting RA after TV opens at start of diastole

RVEDP occurs right before upstroke and \geq mean RA pressure unless there is TS or TR

Waveform should contain notch (closure of pulmonic valve). Peak during T wave PA systolic = RV systolic unless there is a gradient (eg, PS). PA diastolic \approx PCWP unless \uparrow trans-pulm gradient (eg, \uparrow PVR).

Similar to RA except dampened and delayed. a wave after QRS, \pm distinct c wave, v wave after T (helps distinguish PCWP w/ large v waves 2° MR from PA).

PCWP waveform abnormalities: large *a* wave → ? mitral stenosis; large *v* wave → ? mitral regurgitation; blunted *y* descent → ? tamponade; steep *x* & *y* descents → ? constriction.

Hemodynamic Profiles of Various Forms of Shock

| Type of shock | RA | PCWP | CO | SVR |
|--|----------|----------|------------------------------------|-----|
| Hypovolemic | ↓ | ↓ | ↓ | ↓ |
| Distributive | variable | variable | usually ↑ (but can be ↓ in sepsis) | ↓ |
| Cardiogenic: 1° L-sided (eg, acute MI) | nl or ↑ | ↑ | ↓ | ↑ |
| Cardiogenic: 1° R-sided (eg, RV infarct; PE) | ↑ | nl or ↓ | ↓ | ↑ |
| Tamponade | ↑ | ↑ | ↓ | ↑ |

Surrogates: JVP ≈ RA; pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2-3 sec) implies ↑ SVR

Tailored therapy and management of shock (Circ 2009;119:e391)

- **Goals:** optimize both MAP and CO to promote end-organ perfusion, while ↓ risk of pulmonary edema & systemic venous congestion $MAP = CO \times SVR$; $CO = HR \times SV$ (depends on preload, afterload and contractility) pulmonary edema when PCWP >20-25 (↑ levels may be tolerated in chronic HF) hepatic and renal congestion when CVP/RAP >15 mmHg
- **Optimize preload** = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (NEJM 1973;289:1263) goal PCWP ~14-18 in acute MI, ≤14 in acute decompensated HF optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve ↑ by giving NS (albumin w/o clinical benefit over NS; PRBC if significant anemia) ↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics
- **Optimize afterload** ≈ wall stress during LV ejection = $[(SBP \times radius) / (2 \times wall\ thick.)]$ and ∴ ∝ MAP and ∝ SVR = $(MAP - CVP / CO)$; goals: MAP >60, SVR 800-1200 MAP >60 & SVR ↑ : vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors MAP <60 & SVR ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below) MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α] or vasopressin [V₁] if refractory)
- **Optimize contractility** ∝ CO for given preload & afterload; goal CI = $(CO / BSA) >2.2$ if too low despite optimal preload & vasodilators (as MAP permits):
 - ⊕ inotropes: eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl

pulm), both proarrhythmic, or epi (strong inotrope & pressor)

mechanical support devices: eg, IABP, percutaneous or surgical VAD (L-sided, R-sided, or both) or ECMO (Circ 2011;123:533)

Vasopressors and Inotropes Used in Shock

| Drug | Receptors | | | Hemodynamics | | | | Comment |
|--------------------------|------------|-----------|-----------|--------------------|------------------|-----------------|----------------|--|
| | α_1 | β_1 | β_2 | SVR | MAP | HR | CO | |
| Phenylephrine | +++ | 0 | 0 | ↑↑↑ | ↑↑ | ↓↓ ^a | ↓ ^a | ↑ PVR |
| Vasopressin ^b | 0 | 0 | 0 | ↑↑↑ | ↑↑ | ↓↓ ^a | ↓ ^a | ↔PVR; ∴ attractive if RV dysfxn or PHT |
| Norepinephrine | +++ | ++ | + | ↑↑↑ | ↑↑ | ↔/↑ | ↔/↑ | Better outcomes than w/ dopa |
| Epinephrine | +++ | +++ | +++ | ↓ / ↑ ^c | ↑ | ↑↑ | ↑ | β predom at low doses |
| Isoproterenol | 0 | +++ | +++ | ↓↓ | ↓ | ↑↑ ↑ | ↑↑ | ⊕ chronotrope |
| Dobutamine | + | +++ | ++ | ↓ | ↔/↓ | ↑↑ | ↑↑ | ↓ PCWP |
| Dopamine ^d | + | ++ | 0 | ↔/↑ ^d | ↔/↑ ^d | ↑↑ ↑ | ↑ | |
| Milrinone ^e | 0 | 0 | 0 | ↓↓ | ↓ | ↔ | ↑↑ ↑ | ↓↓ PCWP; ↓ PVR; ∴ attractive if RV dysfxn or PHT |

^aBradycardia seen due to vagal reflex if hypertension; ↓ CO due to ↑ afterload

^bV₁ agonist

^cLow doses ↓ SVR, high doses ↑ SVR

^dAlso a (D) dopa receptor agonist; 0.5-2 mcg/kg/min → D; 2-10 → D & β_1 ; > 10 → α_1 , β_1 , D

^ePDE₃ inhibitor

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

DILATED CARDIOMYOPATHY (DCM)

Definition and epidemiology (Circ 2013;128:e240; JACC 2013;62:2046)

- Ventricular dilatation and ↓ contractility ± ↓ wall thickness *in the absence of myocardial disease caused by ischemia/infarct, valvular disease or hypertension*
- Ventricular dysfunction usually global but can be regional variation
- May be accompanied by significant MR & TR due to impaired leaflet coaptation
- Incidence: 5-8/100,000/y; prevalence: 1/2500. Most common reason for heart transplant.

Etiologies (JACC 2011;57:1641; Circ Res 2012;111:131)

- **Familial (>35%)**: defined as having DCM and at least 2 closely related family members with otherwise unexplained DCM; usually autosomal dominant pattern of inheritance; ~30 genes identified to date, encoding structural & nuclear proteins *sarcomere*: eg, titin (*TTN*, ~20%; *NEJM* 2012;366:619); β- & α-myosin heavy chain (*MYH7*, *MYH6*, ~5% each); troponin T (*TNNT2*, ~5%)
nuclear envelope: eg, lamin A/C (*LMNA*, ~5%), often w/ conduction system disease (eg, sinus brady, AV block, atrial arrhythmias) (*NEJM* 2009;341:1715)
ion channel: eg, Na channel (*SCN5A*, <5%), same gene as for LQTS & Brugada *Z-disc*: eg, myopalladin (*MYPN*, <5%), ankyrin (*ANKRD1*, <5%) *cytoskeletal*: eg, desmin (*DES*, <1%); dystrophin (*DMD*, <1%)
syndromic disorders: eg, muscular dystrophies (Duchenne/Becker; limb-girdle)
- **Idiopathic (<20%)**: ? undiagnosed infectious, alcoholic or genetic cause (in ~1/4 of Pts w/ “idiopathic” DCM, evidence of DCM found in 1° relative, suggesting undx genetic)
- **Infectious myocarditis** (10-15%, autoimmune response; *Lancet* 2012;379:738)
Viruses (parvoB19 & HHV6 > coxsackie, adeno, echo, CMV, HCV): from subacute (dilated LV; mild-mod dysfxn) to fulminant (nondil., thick, edematous LV; sev dysfxn)
Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB, qv)
HIV: ~8% of asx HIV ⊕; due to HIV, 2° infxns, or antiretrovirals; HIV also associated w/ premature CAD (*JACC* 2012;59:779)
Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*NEJM* 2015;373:456)
- **Toxic**
alcohol (20-35%; *Prog CV Dis* 2010;52:289): typically 7-8 drinks/d × >5 y, but variable; male > female, typical age 30-55, may resolve w/ abstinence
cocaine (primarily myocardial ischemia, but DCM is also seen); amphetamines & ephedra; anabolic steroids
XRT (usually RCM); cobalt; chloroquine anthracyclines: risk ↑ >550 mg/m², may manifest late; usually irreversible cyclophosphamide, taxoids, mitomycin-C, 5-fluorouracil, and interferons trastuzumab: usually reversible
- **Infiltrative (5%)**: often mix of DCM + RCM (qv) with thickened walls sarcoidosis, amyloidosis, hemochromatosis, tumor

- **Autoimmune**

collagen vasc. dis./vasculitis (~5%): **PM**, **SLE**, scleroderma, **PAN**, **RA**, Wegener's;

peripartum (last month → 5 mo postpartum; *EJH* 2015;36:1090): ~1:3000 preg. ↑ risk w/ multiparity, ↑ age, Afr Am; std HF Rx except if preg then select drugs based on safety; ? bromocriptine to ↓ prolactin; 72% normalize EF; predictors of poor recovery include EF <30% & LVEDD ≥6 cm (*JACC* 2015;66:905); even if nl EF, ~30% recur w/ next preg

idiopathic giant cell myocarditis (**GCM**): avg age 42 y, may present as severe HF, high-grade AV block, or VT, historically poor prognosis (<6 mo median transplant-free survival; *NEJM* 1997;336:1860), but with modern immunosuppression 67% achieve HF remission with transplant-free survival of 77% at 1 y (*Circ HF* 2013;6:15)

eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; **STE**, effusion, severe HF)

- **Stress-induced** (Takotsubo = apical ballooning)

typically seen in postmenopausal ♀ after psychological stressor

? due to catecholamine surge → microvasc dysfxn & Ca overload mimics MI (pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis, sometimes w/ cardiogenic shock (caution w/ pressors as can induce LV outflow tract obstruction)

? Rx w/ βB, ACEI, anticoag if LV thrombus (but usually not just for dyskinesis given rapid resolution); usually improves over wks (*JAMA* 2011;306:277)

- **Tachycardia**: likelihood ∝ duration & rate (although avg HR ~120); often resolves w/ rate control, which is only way to definitely make dx, over several mos (*Circ* 2005;112:1092)

- **Arrhythmogenic (right ventricular) cardiomyopathy** (**ACM**, formerly **ARVC**): see below

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- **Metabolic/other**

hypothyroidism, acromegaly, pheo; **OSA**; cirrhosis thiamine, selenium or carnitine deficiency

- **LV noncompaction**: see below

Clinical manifestations

- **Heart failure**: both congestive & poor forward flow sx; signs of L- & R-sided HF diffuse, laterally displaced **PMI**, **S3**, ± **MR** or **TR** (annular dilat., displaced pap. muscle)
- Embolic events (~10%), supraventricular/ventricular arrhythmias, & palpitations
- Chest pain can be seen w/ some etiologies (eg, myocarditis)

Diagnostic studies and workup

- **CXR**: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- **ECG**: may see **PRWP**, Q waves or **BBB**; low-voltage; **AF** (20%); may be normal
- Echocardiogram: LV dilatation, ↓ EF, regional or global LV HK ± RV HK, ± mural thrombi
- Cardiac **MRI**: up to 76% Se, 96% Sp for myocarditis or infiltrative disease (*JACC Imaging* 2014;7:254); nontransmural delayed gadolinium enhancement in noncoronary distribution suggestive of DCM; extent of midwall fibrosis correlated w/ mortality in NICM (*JAMA* 2013;309:896)

- Laboratory evaluation: **TFTs**, iron studies, HIV, **SPEP**, **ANA**; others per clinical suspicion; viral serologies *not* recommended (*JACC* 2012;59:779)
- Stress test: useful to **r/o** ischemia (low false \ominus rate), high false \oplus rate, even **w/** imaging
- Coronary angiography to **r/o CAD** if risk factors, **h/o** angina, **Qw MI** on **ECG**, equivocal **ETT**; consider **CT** angiography (*JACC* 2007;49:2044)
- ? Endomyocardial biopsy (*JACC* 2007;50:1914)
 - yield 10%: of these, 75% myocarditis (for which no proven **Rx**) & 25% systemic disease
 - 40% false \ominus rate (patchy dis.) & false \oplus (necrosis \rightarrow inflammation)
 - \therefore biopsy if: acute & hemodynamic or electrical compromise (**r/o GCM**, ANEM); arrhythmia or **RCMP** features (**r/o** infiltrative); or suspect toxic, allergic, tumor
- Family **hx** & genetic testing (*JAMA* 2009;302:2471; *Circ* 2013;128:e240)
 - family **hx** for ≥ 3 generations; incomplete penetrance and variable expression make **dx** of familial **CMP** challenging
 - sequencing of DCM gene panels now available; typically test most clearly affected person
 - if specific mutation identified, then can screen family using genetic testing
 - if no mutation identified, consider cascade clinical screening (**ECG**, echo) of 1 $^\circ$ relatives every ~ 3 -5 years

Treatment (see “Heart Failure” for standard HF Rx)

- Implantation of devices may be tempered by possibility of reversibility of **CMP**
- Immunosuppression: for giant cell myocarditis (prednisone + **AZA** + cyclosporine), collagen vasc disease, peripartum (? **IVg**), & eosinophilic; no proven benefit for viral myocarditis
- Prognosis differs by etiology (*NEJM* 2000;342:1077): postpartum (best), ischemic/**GCM** (worst)
- Abstain from **EtOH** (for alcoholic **CMP** and reasonable for others)
- Consider **ACEI** and/or **β B** if genotype \oplus but currently phenotype \ominus

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Definition and epidemiology

- **LV** (usually ≥ 15 mm) and/or **RV** hypertrophy disproportionate to hemodynamic load
- Prevalence: 1/500; 50% sporadic, 50% familial, most asymptomatic
- Autosomal-dominant mutations (> 1500) in cardiac sarcomere genes most common genes involved: β -myosin heavy chain (**MYH7**, $\sim 40\%$), myosin-binding protein C (**MYBPC3**, $\sim 40\%$), cardiac troponin T (**TNNT2**, $\sim 5\%$) and **I** (**TNNI3**, $\sim 5\%$) no clear correlation between genotype and clinical course
- Noonan syndrome: HCM, pulmonic stenosis, **ASD**, short stature, pectus, webbed neck
- **Ddx**: **LVH** 2 $^\circ$ to **HTN**, **AS**, elite athletes (wall usually < 13 mm & symmetric and **nl/** \uparrow rates of tissue Doppler diastolic relaxation; **LV** cavity large; no late gadolinium enhancement on **MRI**; *Circ* 2011;123:2723), Fabry dis. (\uparrow **Cr**, skin findings)

Pathology

- Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
- Morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical
- **LVH** evolves over time, typically manifests in adolescence

Pathophysiology

- Subaortic outflow obstruction: narrowed tract 2° hypertrophied septum + systolic anterior motion (**SAM**) of ant. **MV** leaflet (may be fixed, variable or nonexistent) and papillary muscle displacement. Gradient (∇) worse w/ \uparrow contractility (digoxin, β -agonists, exercise, PVCs), \downarrow preload or \downarrow afterload.

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- Mitral regurgitation: due to **SAM** (mid-to-late, post.-directed regurg. jet) and/or **abnl** mitral leaflets and papillary muscles (pansystolic, ant.-directed regurg. jet)
- Diastolic dysfunction: \uparrow chamber stiffness + impaired relaxation
- Ischemia: small vessel dis., perforating artery compression (bridging), \downarrow coronary perfusion
- Syncope: Δ s in load-dependent **CO**, arrhythmias

Clinical manifestations (70% asymptomatic at dx)

- **Dyspnea** (90%): due to \uparrow **LVEDP**, **MR**, and diastolic dysfunction
- **Angina** (25%) even w/o epicardial **CAD**; microvasc. dysfxn (*NEJM* 2003;349:1027)
- **Arrhythmias** (**AF** in 20-25%; **VT/VF**) \rightarrow palpitations, syncope, sudden cardiac death

Physical exam

- Sustained **PMI**, **S₂** paradoxically split if severe outflow obstruction, \oplus **S₄** (occ. palpable)
- **Systolic murmur**: crescendo-decrescendo; **LLSB**; \uparrow w/ **Valsalva** & standing (\downarrow preload)
- \pm mid-to-late or holosystolic murmur of **MR** at apex
- Bifid carotid pulse (brisk rise, decline, then 2nd rise); **JVP** w/ prominent a wave
- Contrast to **AS**, which has murmur that \downarrow w/ Valsalva and \downarrow carotid pulses

Diagnostic studies

- **CXR**: cardiomegaly (**LV** and **LA**)
- **ECG**: **LVH**, anterolateral and inferior pseudo-Qw, \pm apical giant **TWI** (apical variant)
- Echo: no absolute cutoffs for degree of **LVH** but septum/post. wall ≥ 1.3 suggestive, as is septum > 15 mm; other findings include dynamic outflow obstruction, **SAM**, **MR**
- **MRI**: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure ∇ *Brockenbrough sign* = \downarrow pulse pressure post-PVC (in contrast to **AS**, in which pulse pressure \uparrow post-PVC)
- ? Genotyping for family screening, but pathogenic mutation ID'd in $< 1/2$ (*Circ* 2011;124:2761)

Treatment (*Circ* 2011;124:e783 & 2012;125:1432; *Lancet* 2013;381:242; *EHJ* 2014;35:2733)

- Heart failure
 - **inotropes/chronotropes:** nonvasodilating β Bs, **CCB** (verapamil), disopyramide

Careful use of diuretics, as may further \downarrow preload. Vasodilators only if systolic dysfxn. Avoid digoxin.

If **sx** refractory to drug **Rx** + *obstructive* physiology ($\nabla >50$ mmHg):

(a) Surgical myectomy: long-term \downarrow symptoms in 90% (*Circ* 2014;130:1617)

(b) Alcohol septal ablation (*Circ CV Interv* 2011;4:256; *JACC* 2011;58:2322): gradient \downarrow by \sim 80%, only 5-20% remain w/ **NYHA** III-IV **sx**; 14% require repeat ablation or myectomy. Good alternative for older Pts, multiple comorbidities. Complic: transient (& occ. delayed) 3^o **AVB** w/ 10-20% req. **PPM**; **VT** due to scar formation.

No clear benefit of dual-chamber pacing (*JACC* 1997;29:435; *Circ* 1999;99:2927)

If refractory to drug therapy and there is *nonobstructive* pathophysiology: transplant
- Acute **HF**: can be precip. by dehydration or tachycardia; **Rx** w/ fluids, β B, phenylephrine
- **AF**: rate control with β B, maintain **SR** with disopyramide, amiodarone; low threshold to anticoagulate
- **SCD**: **ICD** (*JACC* 2003;42:1687). Risk factors: h/o **VT/VF**, \oplus **FHx SCD**, unexplained syncope, **NSVT**, \downarrow **SBP** or rel **HoTN** (\uparrow **SBP** <20 mmHg) w/ exercise, **LV** wall ≥ 30 mm, extensive **MRI** delayed enhancement. **EPS** *not* useful. Risk 11%/y if h/o **VT/VF**, 4%/y if highrisk w/o h/o **VT/VF** (*JAMA* 2007;298:405).
- Counsel to avoid dehydration, competitive sports & extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;116:1736)
- First-degree relatives: periodic screening w/ echo, **ECG** (as timing of **HCM** onset variable). Genetic testing if known mutation. ? **CCB** for preclinical **HCM** (*JACC HF* 2015;3:180).

RESTRICTIVE CARDIOMYOPATHIES (RCM)

Definition (*Circ* 2006;113:1807)

- Impaired ventricular filling with \downarrow compliance in nonhypertrophied, nondilated ventricles; normal or \downarrow diastolic volumes, normal or near-normal **EF**; must *r/o* pericardial disease

Amyloidosis (*Circ* 2011;124:1079 & 2012:126:1286)

- Extracellular deposition of misfolded proteins in a variety of organs (eg, heart, kidney, liver, autonomic nervous system; deposition leads to morbidity & mortality)
- Age at presentation \sim 60 y; $\text{♂}:\text{♀}$ 3:2
- **AL** (primary; **MM**, light-chain, **MGUS**, **WM**): multiorgan disease (\sim 50% cardiac)
- **ATTR** (familial; mutation in transthyretin, **TTR**; *Circ* 2012;126:1286)
 - V122I variant \rightarrow 2.6 \times \uparrow **HF** risk; 10% carriage in blacks >65 y w/ **HF** (*JACC* 2006;47:1724)
 - V30M variant seen in European & Japanese
 - T60R variant in Europeans, autonomic + peripheral neuropathy common

- **SSA** (senile; normal **TTR**): typically presents at age >70 y, prevalence $>5\%$ beyond age 80, $\text{♂} \gg \text{♀}$ (50:1), heart-only

- Workup

ECG: ↓ QRS amplitude in **AL** (50%), pseudoinfarct pattern (**Qw**), **AVB** (10-20%), hemiblock (20%), **BBB** (5-20%)

Echo: biventricular wall thickening (*yet w/ low voltage on ECG*), granular sparkling texture (30%), biatrial enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic dysfxn, small effusions

Normal voltage & septal thickness has NPV ~90%

Lab: **SPEP**, **UPEP**, serum free light chain ratio (<0.25 or >1.65 κ-to-λ ratio) 91% **Se** for **AL** amyloid (*Clin Chem* 2005;51:878)

MRI: diffuse subendo late gado enhance, ~90% **Se/Sp** vs **bx** (*JACC* 2008;51:1022)

(99m)Tc-pyrophosphate **PET:** ↑ tracer retention in **ATTR** >> **AL** differentiates cardiac amyloid subtypes (*Circ Imaging* 2013;6:195)

Cardiac **bx:** gold standard (~100% **Se** due to widespread amyloid distrib) and permits subtyping of precursor protein. Abd fat pad **bx** 70% sensitivity for **AL**.

- Treatment: judicious loop diuretics often only tolerated **Rx** avoid digoxin (↑ toxicity w/ binding fibrils) and **CCB** (⊖ inotrope)

βB or **ACEI** often poorly tolerated b/c of **HoTN**

cardiac tx usually contraindic. b/c extracardiac involvement, but isolated cardiac **AL** amyloid combined heart/auto stem cell tx yields survival ≈ other RCM (*JHLT* 2014;33:149)

LVADs not appropriate b/c small restricted **LV** and frequent **RV** dysfunction

- Prognosis (median survival after **HF dx**): **AL** <12 mo, **ATTR** ~30 mo, **SSA** ~60 mo

Sarcoidosis

- Noncaseating, granulomatous disorder that can involve any organ
- Recognized cardiac disease in ~5% of those w/ systemic sarcoid, but imaging & autopsy data show myocardial involvement in >50%
- **LV** dysfxn (DCM ≥ RCM); **MR** can be due to involvement of papillary muscles
- **ECG:** **AVB** (75%), can be high grade; **RBBB** (20-60%); atrial & vent. arrhythmias
- Cardiac **MRI:** T2-imaging and early gadolinium detect acute inflammation (edema), nontransmural patchy delayed gado enhancement, particularly in basal and/or midventricular septum detects fibrosis/scar from chronic disease and predicts prognosis (⊕ LGE → 31× risk for adverse cardiac events; *JACC Imaging* 2013;6:501)
- Echo: regional **WMA** (particularly basal septum) with thinning or mild hypertrophy
- Nuclear imaging: thallium perfusion defects in a noncoronary distribution; gallium uptake in areas of active inflammation can guide steroid **Rx**; **PET:** ↑ FDG uptake in areas of active inflammation
- Cardiac **bx** w/ low yield as granulomas patchy
- Treatment: steroids are standard although have not been evaluated in RCTs; 47% of Pts w/ **AV** conduction disease improved w/ steroids (*Can J Cardiol* 2013;29:1034) and retrospective studies suggest ↓ mortality. For steroid-sparing or intolerance, consider **MTX**, **AZA**, chloroquine or anti-TNF drugs. Low threshold for PPM-ICD.

Hemochromatosis

- In middle-aged men (espec Northern European)
- 15% p/w cardiac sx, typically HF and conduction disturbances
- Cardiac MRI: myocardial T2* is reduced (<20 ms) in iron overload disorders and enables tracking of response to Rx
- Treatment w/ phlebotomy or, in one report, chelation has been associated with reversal of LV dysfunction (JACC 1986;8:436)

Other etiologies (Circ 2005;112:2047 & JACC 2010;55:1769)

• Myocardial processes

Autoimmune (scleroderma, polymyositis-dermatomyositis)

Infiltrative diseases (see primary entries for extracardiac manifestations, Dx, Rx)

Storage diseases: Gaucher's, Fabry, Hurler's, glycogen storage diseases

Diabetes mellitus

• Endomyocardial processes

Chronic eosinophilic: Löffler's endocarditis (temperate climates; ↑ eos; mural thrombi that embolize); endomyocardial fibrosis (tropical climates; var. eos; mural thrombi; NEJM 2008;359:43); treat for heart failure, steroids early, anticoagulation for thrombus

Toxins: radiation (also p/w constrictive pericarditis, valvular dis, ostial CAD), anthracyclines

Serotonin: carcinoid, serotonin agonists, ergot alkaloids

Metastatic cancer

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Pathology & pathophysiology

- Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
- ↓ myocardial compliance → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (Circ 2000;101:2490)

- Right-sided > left-sided heart failure w/ peripheral edema ± ascites > pulmonary edema
- Diuretic “refractoriness”
- Thromboembolic events
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP ↑ w/ inspiration, classically seen in constrictive pericarditis)
- Cardiac: ± S₃ and S₄ (usually absent in amyloid b/c atrial dysfxn), ± murmurs of MR and TR

- Congestive hepatomegaly, ± ascites and jaundice, peripheral edema

Diagnostic studies

- **CXR**: normal ventricular chamber size, enlarged atria, ± pulmonary congestion
- **ECG**: low voltage, pseudoinfarction pattern (**Qw**), ± arrhythmias
- Echo: ± symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit. **w/** diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
- Cardiac **MRI/PET**: may reveal inflammation or evidence of infiltration (but nonspecific)
- Initials labs: **SPEP**, **UPEP** & serum free light chains, Fe studies (transferrin sat, HFE mutation), **BNP** (typically higher in RCM than in constrictive pericarditis)
- Cardiac catheterization: atria: **M's** or **W's** (prominent x and y descents)
Ventricles: **dip & plateau** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
Concordance of **LV** and **RV** pressure peaks during respiratory cycle (vs discordance in constrictive pericarditis; *Circ* 1996;93:2007)
- Endomyocardial biopsy if suspect infiltrative process; fat pad **bx** for amyloid
- Restrictive cardiomyopathy vs constrictive pericarditis: see “**Pericardial Disease**”

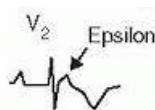
Treatment (in addition to Rx'ing underlying disease)

- Gentle diuresis. May not tolerate **CCB** or other vasodilators. Avoid digoxin in amyloid.
- Control **HR** (but can ↓ **CO**); maintain **SR** (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Inotropes may have limited efficacy due to small ventricular cavity & preserved systolic fxn
- Anticoagulation (particularly with **AF** or low **CO**)
- Transplantation for refractory cases

OTHER CARDIOMYOPATHIES

Arrhythmogenic (right ventricular) cardiomyopathy (ACM, formerly ARVC)

- **RV** or biventricular (~50%) or isolated **LV** (rare) dysfxn due to fatty infiltration and fibrous replacement (small amount of former normal variant) (*Lancet* 2009;373:1289)
- Due to mutations in desmosome (cell-cell coupling): eg, plakophilin 2, desmoglein, desmo-plakin; **abnl** Wnt signaling leads to myocytes → adipocytes
- Naxos syndrome (mutation in plakoglobin): wooly hair, palmar & plantar keratoses, **ACM**
- Clinical phases (*Circ CV Gen* 2015;8:437): (1) subclinical **w/ nl** imaging, but ↑ risk of **SCD**;
(2) **abnl** ventricular fxn on imaging, **sx** ventricular arrhythmias (**VT w/ LBBB** morphology **w/** superior axis), but no **HF**; (3) **RV** failure; (4) ? **LV** failure



- **ECG**: ± **RBBB**, **TWI** V₁-V₃, ε wave
- Dx **w/ MRI**

- Avoid **bx** as septum usually *not* involved (.∗. high false ⊖ rate) and risk of perforation **w/** free wall **bx**
- Major **dx** criteria (*EHJ* 2010;31:806): (1) regional **RV** akinesia/dyskinesia and ↑ RVEDV; (2) fibrous replacement of **RV** free wall; (3) **TWI** V₁-V₃, (4) ε wave
- Treatment (*Circ* 2015;132:441): usual **HF Rx**; **EP** study & **ICD**; **VT** ablation as needed

Ion channelopathies (CMP despite lack of structural abnl; *Circ* 2006;113:1807)

- Defective ionic channel proteins lead to **abnl** cell membrane transit of Na and K ions
- Disorders include: **LQTS**, short-QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT)

LV noncompaction (LVNC; *JACC* 2015;66:578)

- Prominent trabeculae **w/** deep intertrabecular recesses due to intrauterine arrest of compaction of loose interwoven myocardial meshwork
- Debated whether distinct genetic **CMP** vs morphological trait of other CMPs
- Clinical: **HF**, atrial and/or vent arrhythmias, cardioembolic events
- Dx **w/ MRI** > echo; >2:1 ratio of noncompacted to compacted myocardium at end-systole, thickened **LV** wall and prominent deep trabeculae
- Usual **HF Rx**; low threshold to anticoagulate

P.1-35

VALVULAR HEART DISEASE

AORTIC STENOSIS (AS)

Etiology

- **Calcific**: predominant cause in Pts >70 y; risk factors include **HTN**, ↑ chol., **ESRD**
- **Congenital** (ie, bicuspid **AoV w/** premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (**AS** usually accompanied by **AR** and **MV** disease)
- **AS** mimickers: subvalvular (**HCMP** subAo membrane) or supraaortic stenosis

Clinical manifestations (usually indicates AVA <1 cm² or concomitant CAD)

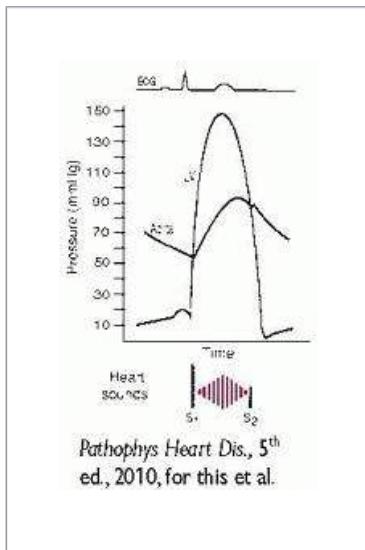
- **Angina**: ↑ O₂ demand (hypertrophy) + ↓ O₂ supply (↓ cor perfusion pressure) ± **CAD**
- **Syncope** (*exertional*): peripheral vasodil. **w/** fixed **CO** → ↓ **MAP** → ↓ cerebral perfusion
- **Heart failure**: outflow obstruct + diastolic dysfxn → pulm. edema; espec lf ↑ **HR/AF** (↓ **LV** fill.)
- Acquired **vWF** disease (~20% of **sev. AS**): destruction of **vWF**; GI angiodysplasia
- Natural **hx**: usually slowly progressive (**AVA** ↓ ~0.1 cm²/y, but varies; *Circ* 1997;95:2262), until **sx** develop; mean survival based on **sx**: angina = 5 y; syncope = 3 y; **CHF** = 2 y

Physical exam

- **Midsystolic crescendo-decrescendo** murmur at **RUSB**, harsh, high-pitched, radiates to carotids, apex (holo-systolic = Gallavardin effect), ↑ **w/** passive leg raise, ↓ **w/** standing & Valsalva. In contrast, dynamic

outflow obstruction (HCM) ↓ w/ leg raise, ↑ w/ standing, Valsalva.

- Ejection click after S₁ sometimes heard with *bicuspid AoV*
- Signs of severity: *late-peaking* murmur, paradoxically split S₂ or inaudible A₂, small and delayed carotid pulse (“*pulsus parvus et tardus*”), LV heave, ⊕ S₄ (occasionally palpable)



Diagnostic studies

- **ECG:** may see LVH, LAE, LBBB, AF (in late disease)
- **CXR:** cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- **Echo:** valve morphology, jet velocity, estim pressure gradient (∇) & calculate AVA, LVEF if concom severe AR: vel & ∇ may be ↑ than typical b/c of ↑ flow, but AVA calc valid if concom severe MR: vel & ∇ may be ↓ than typical b/c of ↓ flow, but AVA calc valid
- **Cardiac cath:** usually to r/o CAD (in ~½ of calcific AS); for hemodyn. if disparity between exam & echo: ✓ pressure gradient (∇) across AoV, calc AVA (underestim. if mod/sev AR)
- **Dobutamine challenge:** in cases with low flow, low ∇, and low LVEF, repeating echo (or cath) during low-dose dobutamine can differentiate:

| Condition | Comment | SV | Jet Vel | ∇ | AVA |
|--------------------------|--|-----------|---------|------|------|
| Afterload mismatch | Low EF 2° to severe AS; EF should ↑ post-AVR | ≥20% ↑ | ↑ | ↑ | no Δ |
| Pseudostenosis | Low AVA artifact of LV dysfxn | ≥20% ↑ | no Δ | no Δ | ↑ |
| Lack contractile reserve | EF prob. will not ↑ w/ AVR | no Δ | no Δ | no Δ | no Δ |

Classification of Aortic Stenosis (*Circ* 2014;129:e521)

| Stage | Sx | Severity | Max Jet Vel (m/s) | Mean Grad (mmHg) | AVA (cm ²) ^a | LVEF |
|-------|----|---|----------------------|---------------------|--|------|
| n/a | N | Normal | 1 | 0 | 3-4 | nl |
| A | N | At risk | <2 | <10 | 3-4 | nl |
| B | N | Mild | 2-2.9 | <20 | >1.5 | nl |
| | | Moderate | 3-3.9 | 20-39 | 1-1.5 | nl |
| C1 | N | Severe | ≥4 | ≥40 | ≤1.0 | nl |
| | | Very severe | ≥5 | ≥60 | ≤0.8 | nl |
| C2 | | Severe + ↓ EF | ≥4 | ≥40 | ≤1.0 | ↓ |
| D1 | | Severe | ≥4 | ≥40 | ≤1.0 | nl |
| D2 | Y | Severe + low flow/▽ + ↓ EF ^b | <4 | <40 | ≤1.0 | ↓ |
| D3 | | Severe + low flow/▽ + nl EF ^c | <4 | <40 | ≤1.0 | nl |

^aAVA indexed to BSA <0.6 cm²/m² also severe;

^bDSE → max jet vel ≥4 & AVA ≤1.0;

^csmall LV w/ ↓ stroke vol.

Treatment (*Circ* 2014;129:e521 & *NEJM* 2014;371:744)

- Management decisions based on *symptoms*: once they develop **AVR** is needed. If **asx**, **HTN** can be cautiously **Rx'd** (probably best w/ **ACEI/ARB** rather than diuretics). Statins have not been proven to ↓ progression.

- **AVR**

Indicated in: **sx severe AS** (ie, stage D1); **asx severe AS + EF <50%** (stage C2); or **asx severe** (stage C1) *and* undergoing other cardiac surgery.

Reasonable if:

asx severe AS (stage C1) *but* either **sx** or ↓ **BP w/ exercise** (can *carefully* exercise **asx AS** to uncover **sx**, do *not* exercise **sx AS**) or **very severe**

sx severe w/ low flow/▽ w/ low EF & response to dobuta (stage D2) or normal **EF** but **AS** felt to be cause of **sx** (stage D3)

asx moderate AS (stage B) *and* undergoing cardiac surgery

- Transcatheter **AoV** replacement (**TAVR**, see below) indicated if surgical risk prohibitive or as reasonable alternative to surgery if high operative risk (STS predicted mortality 8-15%)
- Medical (if not **AVR** candidate or to temporize): careful diuresis prn, control **HTN**, maintain **SR**; digoxin if ↓ **EF** & **HF** or if **AF**; *avoid* venodilators (nitrates) & ⊖ inotropes (**βB/CCB**) if severe; *avoid* vigorous physical exertion once **AS** mod-severe; ? nitroprusside if **p/w CHF w/ sev. AS, EF <35%, CI <2.2, & nl BP** (*NEJM* 2003;348:1756)
- **IABP**: stabilization, bridge to surgery
- Balloon **AoV** valvotomy (BAV): 50% ↑ **AVA** & ↓ peak ▽, *but* 50% restenosis by 6-12 **mo** & ↑ risk of peri-PAV stroke/**AR** (*NEJM* 1988;319:125), ∴ bridge to **AVR** or palliation

TAVR (transcatheter AoV replacement)

- Catheter-based technique for replacing diseased **AoV** with bioprosthetic valve
- Valves: balloon-expandable (Edwards SAPIEN) or self-expanding (Medtronic CoreValve); balloon-expandable **w/ less AR**, less redo, less need for **PPM** (*JAMA* 2014;311:1503)
- Approaches: primarily retrograde via percutaneous transfemoral access; also retrograde via axillary artery or ascending aorta (via small sternotomy & aortotomy); alternatively transapical via direct **LV** apical puncture and antegrade implantation through small thoracotomy (if severe **PAD** or heavily calcified ascending Ao & arch)
- Periprocedural: local anesthesia **w/** conscious sedation or general anesthesia; **RV** pacing (to decrease **SV** during deployment); **TEE** to guide placement
- Peri- & postprocedural complications: low **CO**, annular rupture or coronary occlusion (both rare), local vascular complications, paravalvular leaks & heart block (see below)
- **ASA** lifelong + clopidogrel × 6 **mo**
- Outcomes

in nonoperative Pts vs med **Rx**: 44% ↓ mortality, but still ~20% annual mortality in **TAVR** group illustrating comorbidities in this population (*NEJM* 2012;366:1696; *JACC* 2014;63:1972)

high-risk operative Pts vs surg **AVR** (*NEJM* 2012;366:1686 & 2014;370:1790) postop ≈ **sx** & hemodynamics mortality ≈ (balloon-expandable) or 26% ↓ (self-expanding) **w/ TAVR** vs surgery ↑ vasc complic; ↑ early risk of stroke/**TIA w/** balloon-expandable heart block requiring **PPM** in ~20% **w/** self-expanding; paravalvular leaks in ~7% prelim data in low-risk Pts shows lower mortality & stroke with **TAVR** (*JACC* 2015;65:2184)

AORTIC REGURGITATION (AR)

Etiology (Circ 2006;114:422)

- **Valve disease** (43%)

rheumatic heart disease (usually mixed **AS/AR** and concomitant **MV** disease)

bicuspid AoV: natural **hx**: 1/3 → normal, 1/3 → **AS**, 1/6 → **AR**, 1/6 → endocarditis → **AR infective endocarditis**

valvulitis: RA, SLE; anorectics (fen/phen) & other serotonergics (NEJM 2007;356:29,39), XRT

- **Root disease** (57%)

HTN

aortic aneurysm or dissection, annuloaortic ectasia, Marfan syndrome

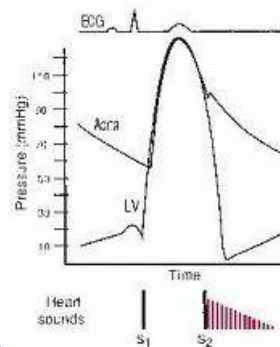
aortic inflammation: giant cell, Takayasu's, ankylosing spond., reactive arthritis, syphilis

Clinical manifestations

- Acute: sudden ↓ forward SV and ↑ LVEDP (noncompliant ventricle) → pulmonary edema ± hypotension and cardiogenic shock
- Chronic: clinically silent while LV dilates (to ↑ compliance to keep LVEDP low) more than it hypertrophies → chronic volume overload → LV decompensation → CHF
- Natural hx: variable progression (unlike AS, can be fast or slow); once decompensation begins, prognosis poor w/o AVR (mortality ~10%/y)

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Physical exam



- **Early diastolic decrescendo murmur at LUSB (RUSB** if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); *Austin Flint murmur*: mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- **Wide pulse pressure** due to ↑ stroke volume, hyper-dynamic pulse → many of classic signs (see table); pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- **PMI** diffuse and laterally displaced; soft S₁ (early closure of MV); ± S₃ (≠ ↓ EF but rather just volume overload in AR)

Classic Eponymous Signs in Chronic AR (South Med J 1981;74:459)

| Sign | Description |
|------------------|---|
| Corrigan's pulse | “water hammer” pulse (ie, rapid rise/fall or distention/collapse) |
| Hill's sign | (popliteal SBP - brachial SBP) >60 mmHg |
| Duroziez's sign | to-and-fro murmur heard over femoral artery w/ light compression |

| | |
|--------------------|---|
| Pistol shot sounds | pistol shot sound heard over femoral artery |
| Traube's sound | double sound heard over femoral artery when compressed distally |
| de Musset's sign | head-bobbing with each heartbeat (low Se) |
| Müller's sign | systolic pulsations of the uvula |
| Quincke's pulses | subungual capillary pulsations (low Sp) |

Diagnostic studies

- **ECG**: can see **LVH**, **LAD**, **abnl** repol; **CXR**: cardiomegaly ± ascending Ao dilatation
- **Echo**: severity of **AR** (in addition to parameters below, severe **AR** requires holodia-stolic flow reversal in proximal abdominal Ao); **LV** size & fxn (chronic severe **AR** requires **LV** dilatation; **LV** dysfxn = **EF** <50% or **LV** end-syst. diam. [**LVEDD**] >50 mm)
- Cardiac **MR** if **TTE** not sufficiently informative

Classification of Aortic Regurgitation

| Severity | Regurg. fraction (%) | Jet width (% of LVOT) | ERO (cm ²) | Angio* |
|----------|----------------------|-------------------------------|-------------------------------|--------|
| Mild | <30 | <25 | <0.1 | 1+ |
| Moderate | 30-49 | 25-64 | 0.1-0.29 | 2+ |
| Severe | ≥50 | ≥65 | ≥0.3 | 3/4+ |

*1+ = incomplete **LV** opac.; 2+ = opac. <Ao root & clears 1 beat; 3+ = **LV** = Ao root opac.; **LV** > Ao root opac.

Treatment (*Circ* 2014;129:e521)

- Acute decompensation (consider ischemia and endocarditis as possible precipitants):
surgery usually urgently needed for acute severe **AR**, which is poorly tolerated by **LV** IV afterload reduction (nitroprusside) and inotropic support (dobutamine) ± chronotropic support (↑ **HR** → ↓ diastole → ↓ time for regurgitation) pure vasoconstrictors and **IABP** contraindicated
- In chronic **AR**, management decisions based on **LV** size and fxn (and before **sx** occur)
- **Surgery** (**AVR**, replacement or repair if possible):
severe and **sx** (if equivocal, consider stress test)
asx and either **EF** ≤50% or **LV** dilation (**LVEDD** >50 mm) or undergoing cardiac surg
- Transcatheter **AoV** replacement (**TAVR**) being explored (*JACC* 2013;61:1577)

- Medical therapy: **vasodilators** (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & Pt not operative candidate or to improve hemodynamics before AVR; no clear benefit on clinical outcomes or LV fxn when used to try to prolong compensation in asx severe AR w/ mild LV dilation & nl LV fxn (NEJM 2005;353:1342)

MITRAL REGURGITATION (MR)

Etiology (Lancet 2009;373:1382; NEJM 2010;363:156)

- **Primary** (degeneration of valve apparatus)

leaflet abnl: myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs, XRT

chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma

papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied by PDA only) vs anterolateral (suppl. by diags & OMs)]

- **Secondary (functional)**: inferoapical papillary muscle displacement due to ischemic LV remodeling or other causes of DCM (JACC 2015;65:1231)

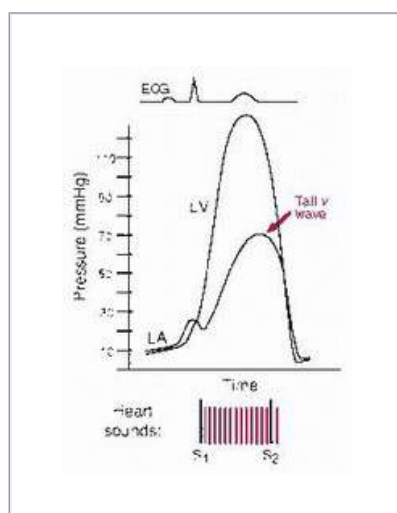
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Clinical manifestations

- Acute: **pulmonary edema**, hypotension, cardiogenic shock (NEJM 2004;351:1627)
- Chronic: typically asx for yrs, then as LV fails → progressive DOE, fatigue, AF, PHT
- Prognosis: 5-y survival w/ medical therapy is 80% if asx, but only 45% if sx

Physical exam

- **High-pitched, blowing, holosystolic murmur at apex**; radiates to axilla; ± thrill; ↑ w/ handgrip (Se 68%, Sp 92%), ↓ w/ Valsalva (Se 93%) (NEJM 1988;318:1572) ant. leaflet abnl → post. jet heard at spine post. leaflet abnl → ant. jet heard at sternum
- ± diastolic rumble b/c ↑ flow across valve
- Lat. displ. hyperdynamic PMI, obscured S₁, widely split S₂ (A₂ early b/c ↓ LV afterload, P₂ late if PHT); ± S₃
- Carotid upstroke brisk (vs diminished and delayed in AS)



Diagnostic studies (*NEJM* 2005;352:875)

- **ECG**: may see **LAE**, **LVH**, ± atrial fibrillation
- **CXR**: dilated **LA**, dilated **LV**, ± pulmonary congestion
- **Echo**: **MV** anatomy (ie, etiol); **MR** severity: jet area (can underestimate eccentric jets), jet width at origin (vena contracta) or effective regurgitant orifice (**ERO**; predicts survival); **LV** fxn (**EF** should be *supranormal* if compensated, [**EF** <60% w/ sev. **MR** = **LV** dysfxn]); **TEE** if **TTE** inconclusive or pre/intraop to guide repair vs replace
- Cardiac **MR** if **TTE** not sufficiently informative
- **Cardiac cath**: prominent **PCWP** c-v waves (not spec. for **MR**), LVgram for **MR** severity & **EF**

Classification of Primary Mitral Regurgitation

| Severity | Regurg. fraction | Jet area (% of LA) | Jet width (cm) | ERO (cm ²) | Angio* |
|----------|------------------|----------------------------|----------------|-------------------------------|--------|
| Mild | <30% | <20 | <0.3 | <0.2 | 1+ |
| Moderate | 30-49% | 20-40 | 0.3-0.69 | 0.2-0.39 | 2+ |
| Severe† | ≥50% | >40 | ≥0.70 | ≥0.40 | 3/4+ |

*1+ = **LA** clears w/ each beat; 2+ = **LA** does not clear, faintly opac. after several beats; 3+ = **LA** & **LV** opac. equal.

†For secondary **MR**, because **ERO** underestimated & likely progressive **LV** dysfxn, **ERO** ≥0.20 is severe

Treatment (*Circ* 2014;129:e521)

- Acute decompensation (consider ischemia and endocarditis as precipitants) IV afterload reduction (nitroprusside), ± inotropes (dobuta), **IABP**, avoid vasoconstrictors *surgery* usually needed for acute severe **MR** as prognosis poor w/o (*JAMA* 2013;310:609)
- **Surgery** (repair [preferred if feasible] vs replacement w/ preservation of mitral apparatus)
for **severe primary MR** indicated if **sx** & **EF** >30% or if **asx** & either **EF** 30-60% or **LV** sys. diam. ≥40 mm **MV repair** reasonable if **asx** & either **EF** >60% + **LVESD** <40 mm or new **AF** or **PHT** if **AF**, maze procedure or pulm vein isolation → ↓ **AF** recurrence, Ø Δ stroke; consider for **sx** cntl or if planning no anticoag (*NEJM* 2015;372:1399)
for **severe secondary MR**: consider if **NYHA** III-IV; replacement results in more durable correction than repair but no difference in clinical outcomes (*NEJM* 2014;370:23)
- In Pts undergoing **CABG** w/ mod-sev fxnal **MR**, annuloplasty ↓ **MR** but longer surgery, ↑ neurologic events, & no impact on fxnal status or mortality (*NEJM* 2014;371:2178)
- Percut. **MV** repair (*Circ* 2014;130:1712): edge-to-edge clip less effective than surgery but consider for

sev. sx nonoperative Pt (*NEJM* 2011;364:1395); perc valve under study (*JACC* 2014;64:1814)

- Medical: Ø clinical benefit in asx Pts; βB preserve LV fxn (*JACC* 2012;60:833); if sx but not operative candidate ↓ preload (↓ HF and MR by ↓ MV orifice): diuretics, nitrates (espec if ischemic/fxnal MR); if LV dysfxn: ACEI, βB, ± BiV pacing; maintain SR

MITRAL STENOSIS (MS)

Etiology (*Lancet* 2012;379:953)

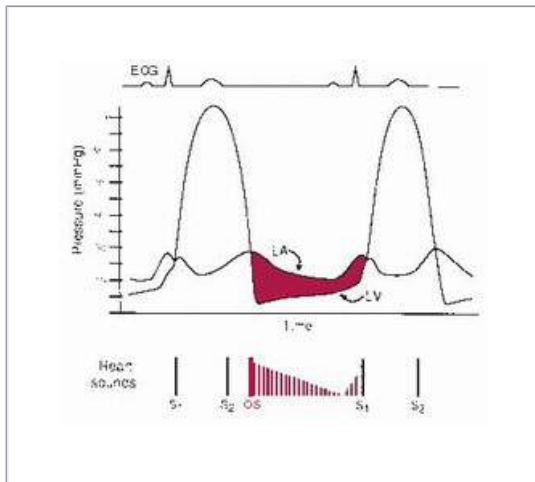
- **Rheumatic heart disease (RHD):** fusion of commissures → “fish-mouth” valve from autoimmune rxn to β strep infxn; seen largely in developing world today
- **Mitral annular calcification (MAC):** encroachment upon leaflets → functional MS
- Congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus
- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

Clinical manifestations (*Lancet* 2009;374:1271)

- **Dyspnea and pulmonary edema** (if due to RHD, sx usually begin in 30s) precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- **Atrial fibrillation:** onset often precipitates heart failure in Pts w/ MS
- **Embolic events:** commonly cerebral, espec in AF or endocarditis

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- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve



Physical exam

- **Low-pitched mid-diastolic rumble at apex** w/ presystolic accentuation (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to duration (not intensity) of murmur
- **Opening snap** (high-pitched early diastolic sound at apex) from fused leaflet tips; MVA proportional to S₂-OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S₁ (unless MV calcified)

Diagnostic studies

- **ECG:** LAE (“P mitrale”), ± AF, ± RVH
- **CXR:** dilated LA (straightening of left heart border, double density on right, left mainstem bronchus elevation)
- **Echo:** estimate pressure gradient (∇), RVSP, valve area, valve echo score (0-16, based on leaflet mobility & thick., subvalvular thick., Ca⁺⁺); exer. TTE (to assess Δ RVSP and ∇) if sx & severity of MS at rest discrepant; TEE to assess for LA thrombus before PMV
- **Cardiac cath:** ∇ from simultaneous PCWP & LV pressures, calculated MVA; LA pressure tall a wave and blunted y descent; ↑ PA pressures

Classification of Mitral Stenosis

| Stage | Mean ∇ (mmHg) | Pressure $\frac{1}{2}$ time | MV area (cm ²) | PA systolic (mmHg) |
|-------------|----------------------|-----------------------------|----------------------------|--------------------|
| Normal | 0 | | 4-6 | <25 |
| Mild-Mod | <5 | 100-149 | 1.6-2 | <30 |
| Severe | 5-9 | 150-219 | 1.1-1.5 | 30-50 |
| Very severe | ≥10 | ≥220 | ≤1 | >50 |

Treatment (*Circ* 2014;129:e521)

- Medical: Na restriction, cautious diuresis, β B, sx-limited physical stress
- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40
- Anticoag if: AF; prior embolism; LA thrombus; ? LA >55 mm or lg LA w/ spont contrast
- Mechanical intervention indicated if heart failure sx w/ MVA ≥1.5; reasonable if asx but very severe (MVA ≤1) and morphology favorable for PMBC; may consider PMBC if MVA >1.5 but hemodyn signif w/ exercise, or if asx but MVA ≤1.5 and new-onset AF
- **Percutaneous mitral balloon commissurotomy (PMBC):** preferred Rx if RHD; MVA doubles, ∇ ↓ by 50%; ≈ MVR if valve score <8, ≤ mild MR, Ø AF or LA clot
- Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5 if PMV unavailable/contraindicated (mod. MR, LA clot), or valve morphology unsuitable
- Pregnancy: if NYHA class III/IV → PMV, o/w medical Rx w/ low-dose diuretic & β B

MITRAL VALVE PROLAPSE (MVP)

Definition and Etiology

- Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
- Leaflet redundancy from myxomatous proliferation of spongiosa of MV apparatus

- Idiopathic, familial and a/w connective tissue diseases (eg, Marfan's, Ehlers-Danlos)
- Prevalence 1-2.5% of gen. population, ♀ > ♂ (*NEJM* 1999;341:1), most common cause of MR

Clinical manifestations (usually asymptomatic)

- MR (from leaflet prolapse or ruptured chordae); infective endocarditis; embolic events
- Arrhythmias, rarely sudden cardiac death

Physical exam

- High-pitched, midsystolic click ± mid-to-late systolic murmur
- ↓ LV volume (standing) → click earlier; ↑ LV volume or afterload → click later, softer

Treatment

- Endocarditis prophylaxis no longer recommended (*Circ* 2007;116:1736)
- Aspirin or anticoagulation if prior neurologic event or atrial fibrillation

TRICUSPID REGURGITATION

- Primary etiol: rheumatic, CTD, radiation, IE, Ebstein's anomaly, carcinoid, tumors
- Fxnal etiol: RV and/or pulm HTN (may be 2° to L-sided dis.), RV dilation and/or infarct

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- Assess based on severity TR, annular dilation, leaflet coaptation (*JACC* 2015;65:2331)
- Consider repair, annuloplasty or replacement for sx and severe TR (eg, ERO ≥ 0.40 cm²)

PROSTHETIC HEART VALVES

Mechanical (60%)

- Bileaflet (eg, St. Jude Medical); tilting disk; caged-ball
- Very durable (20-30 y), but thrombogenic and . require anticoagulation consider if age <~60 y or if anticoagulation already indicated (*JACC* 2010;55:2413)

Bioprosthetic (40%)

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >70 y, lifespan <20 y or Ø anticoag
- If 50-69 y, 2× reop but ½ bleeding or stroke vs mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam

- Normal: **crisp sounds**, ± soft murmur during forward flow (normal to have small ∇)
- Abnormal: regurgitant murmurs, absent mechanical valve closure sounds

Anticoagulation & antiplatelet therapy (*Circ* 2014;129:e521)

- Assess for *high-risk features*: prior thromboembolism, AF, EF<30-35%, hypercoagulable

- **Warfarin:** low-risk mech **AVR:** **INR** 2-3
mech **MVR** or high-risk mech **AVR:** **INR** 2.5-3.5
high-risk bioprosthetic: **INR** 2-3; for 1st 3 **mo**, reasonable in low-risk **MVR**, consider in low-risk **AVR**
- **ASA** (75-100 mg) for all prosthetic valves; avoid adding to warfarin if **h/o GIB**, uncontrolled **HTN**, erratic **INR** or **>80 y**
- If thrombosis, ↑ intensity (eg, **INR** 2-3 → 2.5-3.5; 2.5-3.5 → 3.5-4.5; add **ASA** if not on)

Periprocedural “Bridging” of Anticoagulation in Pts with Mechanical Valve(s)

AVR w/o risk factors d/c warfarin 2-4 before surg; restart 12-24 h after surg

MVR or **AVR w/** risk factors Preop: d/c warfarin, start **UFH** when **INR** <2 4-6 h preop: d/c **UFH**; postop: restart **UFH** & warfarin ASAP

Procedures include noncardiac surgery, invasive procedures, and major dental work

Correction of overanticoagulation (*Circ* 2014;129:e521)

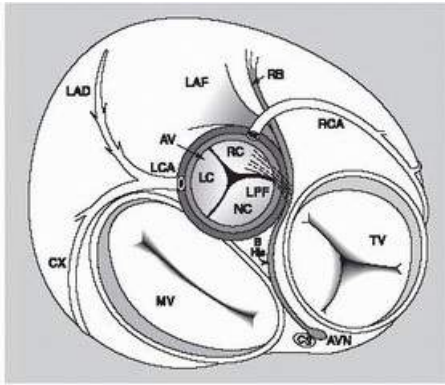
- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding: if **INR** 5-10, withhold warfarin; if **INR** > 10 also give vit K 1-2.5 mg **PO**
- Bleeding: **FFP** or **PCC** ± low-dose (1 mg) vit K IV

Endocarditis prophylaxis: for all prosthetic valves (see “Endocarditis”) Complications

- Structural failure (*r/o* endocarditis); mechanical valves: rare except for Bjork-Shiley; bioprosth: up to 30% rate w/in 10-15 y, mitral > aortic; consider **TAVR** (*JAMA* 2014;312:162)
- Paravalvular leak (*r/o* endocarditis); small *central* jet of regurg is normal in mech. valves
- Obstruction from thrombosis or pannus ingrowth: ✓ **TTE**, **TEE**, and/or fluoroscopy if ? clot significantly *sx* *pannus* ingrowth: remove *w/* surgery
thrombosis: surgery if L-sided valve & either severe *sx* or lg (? ≥0.8 cm) thrombus; lytic often *ineffective* for L-sided thrombosis & 12-15% risk of stroke; consider **UFH** ± lytic (? low-dose tPA via slow infusion, *JACC CV Imaging* 2013;6:206) if mild *sx* & small clot burden or poor surg candidate; lytic reasonable for R-sided
- Infective endocarditis ± valvular abscess and conduction system dis. (see “Endocarditis”)
- Embolization (*r/o* endocarditis); risk ~ 1%/y *w/* warfarin (vs 2% *w/* **ASA**, or 4% *w/o* meds) mech **MVR** 2× risk of embolic events vs mech **AVR** (*Circ* 1994;89:635)
- Bleeding (from anticoag), hemolysis (espec *w/* caged-ball valves or paravalvular leak)

HEART VALVES (superior view, *JAMA* 1976;235:1603)





AV = aortic valve

AVN = AV node

B His = bundle of His

CS = coronary sinus

Cx = circumflex artery

LAD = left anterior descending artery

LAF = left anterior fascicle

LCA = left coronary artery

LPPF = left posterior fascicle

MV = mitral valve

RB = right bundle

RC/LC/NC = right/left/noncoronary cusp

RCA = right coronary artery

TV = tricuspid valve

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CARDIOPULMONARY EXERCISE TESTING

Background, rationale, and measurements performed (*Circ* 2010;122:191)

- In exercise, to meet metabolic demands of active cells, need to ↑ effective ventilation, ↑ cardiac output, and ↓ pulmonary & systemic vascular resistance, ↑ O₂ extraction
- Dyspnea due to insufficient supply to or impaired uptake of O₂ by skeletal muscle
- Ddx of dyspnea:
 - impaired external respiration (ventilation & pulmonary gas exchange)
 - impaired circulatory system (transport of O₂ and CO₂)
 - impaired internal respiration (peripheral capillary gas exchange and O₂ utilization)
- Cardiorespiratory fitness predicts morbidity & mortality
- CPET is an individualized incremental exercise test that combines traditional cardiac stress test parameters: ECG, heart rate, BP quantification of O₂ consumption ($\dot{V}O_2$), CO₂ production ($\dot{V}CO_2$)

above] $\dot{V}O_2$), minute ventilation (V_E) if invasive (radial artery & PA cath): RAP, PAP, & PCWP; arterial & mixed venous sats can be coupled with cardiac imaging (eg, radionuclide ventriculography, TTE)

- Well tolerated even w/ advanced disease, 0.16% adverse event rate (*Circ* 2012;126:2465)

Indications for CPET

- Diagnose etiology of exercise intolerance or dyspnea by defining organ system limiting gas exchange (heart, pulm mechanical, pulm vasculature, muscles/mitochondria)
- Grade severity of advanced heart and lung diseases and predict prognosis

Prioritize Pts for heart/lung transplantation, mechanical support:

Heart transplant candidacy: peak $[\dot{V}O_2]$ <14 ml/kg/min, <12 on βB , \pm <50% predicted LVAD candidacy <12 ml/kg/min (*NEJM* 2001;345:1445)

Determine whether to intervene on valvular disease, shunts/congenital heart disease

- To objectively measure responses to interventions (clinical trials, disability, rehabilitation)

Clinical relevance of measurement patterns

- RER (respiratory exchange ratio) = $[\dot{V}CO_2]/[\dot{V}O_2]$, indicator of volitional effort independent of chronotropic response (goal > 1.05)

- V_E/MVV (max voluntary vent): >70-80% indicates encroachment on pulm mechanical limit

- Peak $[\dot{V}O_2]$: max aerobic capacity at peak exercise; indicator of cardiorespiratory fitness measured with metabolic cart but also represented by the Fick equation:

$$[\dot{V}O_2] = (\text{heart rate} \times \text{stroke volume}) \times [(\text{arterial} - \text{mixed venous}) O_2 \text{ content}]$$

- VAT (ventilatory anaerobic threshold): % of peak predicted $[\dot{V}O_2]$ at which O_2 supply inadequate \rightarrow anaerobic metabolism (normal value >40%); indep. of volitional effort, highly reproducible, and occurs at activity levels often assoc. w/ daily living. Low VAT reflects impaired O_2 delivery \pm utilization but does not localize organ system responsible. In HFrEF, VAT <11 ml/kg/min assoc w/ 5 \times \uparrow in 6-mo mortality (*Circ* 2002;106:3079).

- V_E/VCO_2 slope: ventilation required to exchange 1 L/min of CO_2 in addition, V_E/VCO_2 slope = constant / $[P_aCO_2 \times (1 - V_d/V_t)]$ high level (>36) especially seen in pulm vascular and/or RV dysfunction, where V/Q mismatch & \downarrow pulm perfusion $\rightarrow \uparrow V_d/V_t$, and \uparrow ventilatory drive $\rightarrow \downarrow P_aCO_2$

high levels also indicate poor prognosis (*Circ* 2007;115:2410; *Circ HF* 2008;1:227)

- Exercise oscillatory vent: periodic breathing that reflects circul. delay (ie, low CO) relative to metab needs during exercise; assoc w/ 3 \times \uparrow mort (*JACC* 2010;55:1814; *Circ* 2011;124:1442)
- mPAP/CO slope (serial measurements during exercise define the pulm artery pressure response to increased blood flow through the pulmonary circulation during exercise): mPAP = TPG + LAP mPAP/CO slope >3 indicates either abnl pulm vascular response to exercise or upstream transmission of high LAP (*Circ* 2013;128:1470), with TPG/CO (ie, PVR) that fails to fall and remains > 1.5 indicative of pulmonary vascular dysfunction and

PCWP/CO slope >2 indicative of left-sided failure

- DPG (diastolic pulmonary gradient) = $PAD - LAP$; DPG >5-7 indicates pulm vasc disease and may be preferable to TPG ($mPAP - LAP$) for pulm vasc disease diagnosis b/c it is not significantly influenced by ΔLAP and CO (*Chest* 2013;143:758)

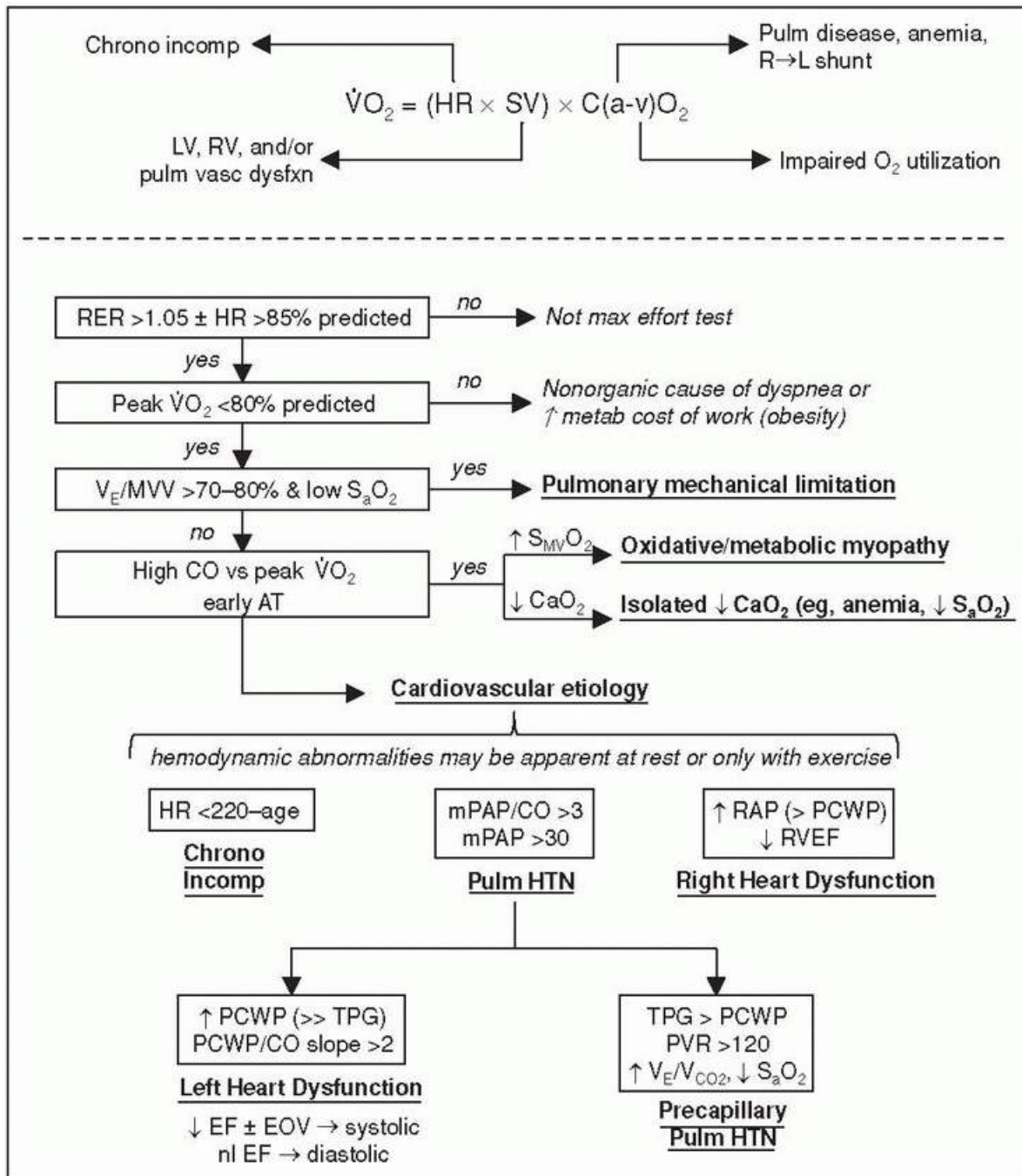


Figure 1-4 Approach to CPET

PERICARDIAL DISEASE

GENERAL PRINCIPLES

Anatomy

- 2-layered (parietal & visceral) tissue sac surrounding heart & proximal great vessels

Disease states

- Inflammation (*w/* or *w/o* fluid accumulation) → pericarditis
- Fluid accumulation → effusion ± tamponade
- Decrease in compliance (sequela of inflammation) → constrictive pericarditis
- Tamponade and constriction characterized by increased ventricular interdependence

PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Acute Pericarditis (*Lancet* 2004;363:717; *Curr Probl Cardiol* 2012;37:75)

| | |
|--|---|
| Idiopathic (~90%) | Most presumed to be undiagnosed viral etiologies |
| Infectious (<5% can be confirmed infectious) | Viral: Coxsackie, echo, adeno, EBV , VZV , HIV, influenza Bacterial (from endocarditis, pneumonia or <i>s/p</i> cardiac surgery): <i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>S. aureus</i> , <i>Borrelia</i> (Lyme); TB Fungal: <i>Histo</i> , <i>Coccidio</i> , <i>Candida</i> ; Parasitic: <i>Entamoeba</i> , <i>Echino</i> |
| Neoplastic (<10%) | <i>Common</i> : metastatic (lung, breast, lymphoma, leukemia, RCC) <i>Rare</i> : primary cardiac & serosal tumors (mesothelioma) |
| Autoimmune | Connective tissue diseases: SLE , RA , scleroderma, Sjögren's Vasculitides: PAN , Churg-Strauss, Wegener's Drug-induced: procainamide, hydralazine, INH , CsA |
| Uremia | ~5-13% of Pts prior to HD ; ~20% occurrence in chronic HD Pts |
| Cardiovascular | Acute STEMI , late post-MI (Dressler's syndrome), but both rare in modern era; proximal AoD ; chest trauma/postpericardiectomy |
| Radiation | >40 Gy to mediastinum; acute or delayed; may be transudative |
| Effusions w/o pericarditis | HF , cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis Transudative |

Clinical manifestations (*NEJM* 2014;371:2410)

- **Pericarditis**: retrosternal chest pain that is pleuritic, positional (↓ by sitting forward), radiates to trapezius; may be *absent* in **TB**, neoplastic, post-XRT and uremic pericarditis; ± fever; ± *s/s* of systemic etiologies
- **Effusion**: ranges from *asx* to tamponade (see below)

Physical exam

- **Pericarditis**: multiphasic **friction rub** best heard at **LLSB w/** diaphragm of stethoscope. Notoriously variable and evanescent leathery sound *w/* up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (*NEJM* 2012;367:e20).
- **Effusion**: distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from

pericardial effusion (Ewart's sign)

Diagnostic studies (*EHJ* 2004;25:587; *Circ* 2006;113:1622 & 2010;121:916)

- **ECG**: may show diffuse **STE** (*concave up*) & **PR** depression (except in aVR: **ST** ↓ & **PR** ↑), **TWI**; classically and in contrast to **STEMI**, **TWI** do not occur until STs normalize Stages: (I) **STE** & **PR** ↓ ; (II) **ST** & **PR** normalize; (III) diffuse **TWI**; (IV) **Tw** normalize **ECG** may show evidence of large effusion w/ low voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis due to swinging heart)
- **CXR**: if large effusion (>250 mL of fluid) → ↑ cardiac silhouette w/ “water-bottle” heart and epicardial halo
- **Echocardiogram**: presence, size, & location of *effusion*; presence of *tamponade physiology*; pericarditis itself w/o spec. *abnl* (., echo can be *nl*), although can see pericardial stranding (fibrin or tumor); can also detect **LV/RV** dysfxn (myocarditis ?)
- **CT** will reveal pericardial effusions, often appearing larger than on echocardiography
- CK-MB or troponin (⊕ in ~30%, *JACC* 2003;42:2144) if myopericarditis. Consider **CRP/ESR**.

Workup for effusion

- *r/o* infxn: usually apparent from Hx & **CXR**; ? value of ✓ acute and convalescent serologies
- *r/o* noninfectious etiologies: **BUN**, **Cr**, **ANA**, **RF**, HIV, screen for common malignancies
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent ✓ cell counts, **TP**, **LDH**, **glc**, Gram stain & Cx, **AFB**, cytology ADA, PCR for **MTb**, and specific tumor markers as indicated by clinical suspicion “exudate” criteria: **TP** >3 g/dL, $\frac{TP_{eff}}{TP_{serum}} >0.5$, $\frac{LDH_{eff}}{LDH_{serum}} >0.6$ or **glc** <60 mg/dL high **Se** (~90%) but *very low Sp* (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial **bx** if suspicion remains for malignancy or **TB**

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Treatment of pericarditis (*Circ* 2013;127:1723)

- High-dose **NSAID** (eg, ibuprofen 600-800 mg tid) or **ASA** (eg, 650-1000 mg tid) × 7-14 d then taper over wks; **ASA** preferred over **NSAID** in acute **MI**; consider **PPI** to ↓ risk of **GIB**
- Add **colchicine** 0.5 mg bid (qd if ≤70 kg) × 3 mo; ↓ risk of refractory or recurrent pericarditis by 50% (*NEJM* 2013;369:1522)
- Steroids (usually systemic; occ. intrapericardial) only for systemic rheum or autoimmune disorder, uremic, preg., contraindication to **NSAID**, or refractory idiopathic dis. Systemic steroids appear to ↑ rate of pericarditis recurrence (*Circ* 2008;118:667).
- Avoid anticoagulants (although no convincing data that ↑ risk of hemorrhage/tamponade)
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Acute idiopathic effusion self-limited in 70-90% of cases
- Recurrent pericarditis (*Circ* 2007;115:2739)
risk factors: subacute, lg effusion/tamponade, T >38°C, lack of **NSAID** response after 7 d treatment: colchicine 0.5 mg bid × 6 mo (*Annals* 2011;155:409 & *Lancet* 2014;383:2232)
- Recurrent effusion: consider pericardial window (percutaneous vs surgical)

PERICARDIAL TAMPONADE

Etiology

- Any cause of pericarditis but espec **malignancy**, **uremia**, **idiopathic**, proximal aortic dissection with rupture, myocardial rupture
- Rapidly accumulating effusions most likely to cause tamponade as no time for pericardium to stretch (eg, to ↑ compliance) and accommodate ↑ intrapericardial fluid volume

Pathophysiology (*NEJM* 2003;349:684)

- ↑ intrapericardial pressure, compression of heart chambers, ↓ venous return → ↓ **CO**
- Diastolic pressures ↑ & equalize in all cardiac chambers → minimal flow of blood from **RA** to **RV** when **TV** opens → blunted **y** descent
- ↑ ventricular interdependence → pulsus paradoxus (pathologic exaggeration of **nl** physio) Inspiration → ↓ intrapericardial & **RA** pressures → ↑ venous return → ↑ **RV** size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ **LV** filling → ↓ **LV stroke volume** & blood pressure.

Clinical manifestations

- **Cardiogenic shock** (hypotension, fatigue) **without pulmonary edema**
- Dyspnea (seen in ~85%) may be due to ↑ respiratory drive to augment venous return

Physical exam (*JAMA* 2007;297:1810)

- **Beck's triad** (present in minority of cases): **distant heart sounds**, ↑ **JVP**, **hypotension**
- ↑ **JVP** (76%) w/ blunted **y** descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), cool extremities
- **Pulsus paradoxus** (**Se** 82%, **Sp** 70%) = ↓ **SBP** ≥10 mmHg during inspiration

⊕ **LR** 3.3 (5.9 if pulsus >12), ⊖ **LR** 0.03

Ddx = **PE**, hypovolemia, severe **COPD**, constriction (~1/3), **RV** infarct

Can be absent if pre-existing ↑ **LVEDP**, arrhythmia, severe **AI**, **ASD**, regional tamponade

- Distant heart sounds (28%), ± pericardial friction rub (30%)
- Tachypnea but clear lungs

Diagnostic studies

- **ECG**: ↓ voltage (seen in 42%), electrical alternans (20%), ± signs of pericarditis
- **CXR**: ↑ cardiac silhouette (89%)
- **Echocardiogram**: ⊕ **effusion**, **IVC** plethora, **septal shift** with inspiration **diastolic collapse** of **RA** (**Se** 85%, **Sp** 80%) and/or **RV** (**Se** <80%, **Sp** 90%) **respirophasic Δ's in transvalvular velocities** (↑ across **TV** & ↓ across **MV** w/ inspir.) postsurgical tamponade may be localized and not easily visible
- Cardiac cath (right heart and pericardial): elevation (15-30 mmHg) and equalization of intrapericardial and

diastolic pressures (RA, RV, PCWP), blunted y descent in RA ↑ in stroke volume postpericardiocentesis = ultimate proof of tamponade if RA pressure remains elevated after drainage, may have effusive-constrictive disease (NEJM 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

Treatment

- Volume (but be careful as overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors as will ↓ stroke volume & potentially ↓ HR
- **Pericardiocentesis** (except if due to aortic or myocardial rupture, in which case consider removing just enough fluid to reverse PEA en route to emergent surgery)

P.1-45

CONSTRUCTIVE PERICARDITIS

Etiology (Circ 2011;124:1270)

- Any cause of pericarditis (~1-2% incidence overall after acute pericarditis)
- Highest risk w/ TB, bacterial, neoplastic, connective tissue, postcardiac surgery
- **Viral/idiopathic**, as most common cause of pericarditis, also account for signif proportion

Pathophysiology

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and *prominent x and y descents*
- Kussmaul sign: JVP does not decrease with inspiration (↑ venous return with inspiration, but negative intrathoracic pressure not transmitted to heart because of rigid pericardium)

Clinical manifestations (NEJM 2011;364:1350)

- Right-sided > left-sided heart failure (systemic congestion > pulmonary congestion)

Physical exam

- ↑ JVP with prominent y descent, ⊕ Kussmaul sign (Ddx: tricuspid stenosis, acute cor pulmonale, RV failure and RV infarct, RCMP)
- Hepatosplenomegaly, ascites, peripheral edema. Consider on Ddx of idiopathic cirrhosis.
- PMI usually not palpable, **pericardial knock**, usually no pulsus paradoxus

Diagnostic studies

- ECG: nonspecific, AF common (up to 33%) in advanced cases
- CXR: calcification (MTb most common), espec in lateral view (although not specific)
- Echocardiogram: ± thickened pericardium, “**septal bounce**” = abrupt displacement of septum during rapid filling in early diastole

- Cardiac catheterization: atria **w/ Ms** or **Ws** (prominent x and y descents) ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)
discordance between **LV** & **RV** pressure peaks during respiratory cycle (*Circ* 1996;93:2007)
- **CT** or **MRI**: thickened pericardium (>4 mm; **Se** ~80%) **w/** tethering (*Circ* 2011;123:e418)

Treatment

- Diuresis for intravascular volume overload; surgical pericardiectomy in advanced cases
- ? **MRI** able to predict reversibility with anti-inflammatory agents (*Circ* 2011;124:1830)

Constrictive Pericarditis vs Restrictive Cardiomyopathy

| Evaluation | Constrictive pericarditis | Restrictive cardiomyopathy |
|---|--|---|
| Physical exam | ⊕ Kussmaul sign Absent PMI ⊕ Pericardial knock | ± Kussmaul sign Powerful PMI , ± S ₃ and S ₄ ± Murmurs of MR , TR |
| ECG | ± Low voltage | Low voltage if infiltrative myopathy ± Conduction abnormalities |
| Echocardiogram | Respirophasic variation (25-40%): inspir. → ↑ flow across TV and ↓ flow across MV E' (tissue velocity) nl/↑ (> 12) Expir. hepatic vein flow reversal Septal bounce during early diastole Normal wall thickness | <10% respirophasic variation Slower peak filling rate Longer time to peak filling rate E' ↓ (<8 cm/sec) Inspir. hepatic vein flow reversal Biatrial enlargement ± ↑ wall thickness |
| CT/MRI | Thickened pericardium | Normal pericardium |
| NT-proBNP | Variable | Typically ↑ /↑ ↑ (<i>JACC</i> 2005;45:1900) |
| Prominent x and y descents Dip-and-plateau sign | | |
| Cardiac catheterization | LVEDP = RVEDP RVSP <55 mmHg (Se 90%, Sp 29%) RVEDP > 1/3 RVSP (Se 93%, Sp 46%) Discordance of LV & RV pressure peaks during respiratory cycle Systolic area index (ratio of RV to LV pressure-time area in inspir vs expir) >1.1 (Se 97%, Sp 100%) | LVEDP > RVEDP (esp. w/ vol.) RVSP >55 mmHg RVEDP <1/3 RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (<i>JACC</i> 2008;51:315) |

Endomyocardial biopsy
Usually normal

± Specific etiology of RCMP
(fibrosis, infiltration,
hypertrophy)

Vascular Disease

HYPERTENSION

| Category | Classification | |
|-------------|-----------------|------------------|
| | Systolic (mmHg) | Diastolic (mmHg) |
| Normal | <120 | <80 |
| Pre-HTN | 120-139 | 80-89 |
| Stage 1 HTN | 140-159 | 90-99 |
| Stage 2 HTN | ≥160 | ≥100 |

Average ≥2 measurements >1-2 min apart. Confirm stage 1 w/in 1-4 wk; can Rx stage 2 immediately. ✓ q2y (if nl) or yearly (if pre-HTN). (*J Clin HTN* 2014;16:14)

| Setting | Ambulatory Thresholds | |
|----------------|-----------------------|------------------|
| | Systolic (mmHg) | Diastolic (mmHg) |
| 24-hr average | 135 | 85 |
| Day* (awake) | 140 | 90 |
| Night (asleep) | 125 | 75 |

*Threshold of hypertension for home readings should be same as daytime ambulatory

Epidemiology (*Circulation* 2012;125:e2)

- Prevalence 33.5% in U.S. adults; >75 million affected (prevalence equal for men and women, highest in African American adults at 44%)
- ↑ Age → ↓ arterial compliance → systolic HTN
- Only 48% of patients with dx of HTN have adequate BP control

Etiologies

- **Essential** (95%): onset 25-55 y; ⊕ FHx. Unclear mechanism but ? additive microvasc renal injury over time w/

contribution of hyperactive sympathetics (*NEJM* 2002;346:913). Both genetic (*Nature* 2011;478:103) & environmental risk factors (Na, obesity, inactivity) Blacks more likely to be salt sensitive and have less activation of renin-angiotensin system, explaining preference for thiazides & CCB over ACEI or ARB

- **Secondary:** Consider if Pt <20 or >50 y or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension

| Diseases | Suggestive findings | Initial workup |
|---|--|---|
| Renal parenchymal (2-3%) | h/o DM, polycystic kidney disease, glomerulonephritis | CrCl, albuminuria See "Renal Failure" |
| RENAL Renovascular (1-2%, qv) Athero (90%) FMD (10%, women) PAN , scleroderma | ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (<i>NEJM</i> 2009;361:1972) | MRA (>90% Se & Sp , less for FMD), CTA , duplex U/S , angio, plasma renin (low Sp) |
| Hyperaldo or Cushing's (1-5%) | Hypokalemia Metabolic alkalosis | See "Adrenal Disorders" |
| ENDO Pheochromocytoma (<1%) | Paroxysmal HTN, H/A, palp. | |
| Myxedema (<1%) | See "Thyroid Disorders" | TFTs |
| Hypercalcemia (<1%) | Polyuria, dehydration, Δ MS | iCa |
| Obstructive sleep apnea (qv) | | |
| OTHER Medications: OCP , steroids, licorice; NSAIDs (espec COX-2); Epo; cyclosporine | | |
| Aortic coarctation: \downarrow LE pulses, systolic murmur, radial-femoral delay; abnl TTE , CXR | | |
| Polycythemia vera: \uparrow Hct | | |

Standard workup (*J Clin HTN* 2014;16:14)

- Goals: (1) identify **CV** risk factors or other diseases that would modify prognosis or **Rx**;
(2) reveal 2° causes of hypertension; (3) assess for target-organ damage
- History: **CAD**, **HF**, **TIA/CVA**, **PAD**, **DM**, renal insufficiency, sleep apnea, preeclampsia; \oplus **FHx** for **HTN**; diet, Na intake, smoking, alcohol, prescription and OTC meds, **OCP**
- Physical exam: \checkmark **BP in both arms**; funduscopic exam; **BMI** & waist circumference; cardiac (**LVH**, murmurs) including signs of **HF**, vascular (bruits, radial-femoral delay); abdominal (masses or bruits); neuro exam

- Testing: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, or peripheral edema), ? renin, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): predictive of CV risk and ↑ Se & Sp for dx of HTN vs office BP (HTN 2005;46:156). Consider for suspected episodic or white coat HTN, resistant HTN, HoTN sx on meds, or suspected autonomic dysfxn. Rec by some guidelines to confirm HTN dx, so utilization may expand (BMJ 2011;342:d3621 & 343:d4891).

Complications of HTN

- Each ↑ 20 mmHg SBP or 10 mmHg DBP → 2× → CV complications (Lancet 2002;360:1903)
- Neurologic: TIA/CVA, ruptured aneurysms, vascular dementia

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- Retinopathy: stage I = arteriolar narrowing; II = copper wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: CAD, LVH, HF, AF
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, renal failure

Treatment (JAMA 2014;311:507; J Clin HTN 2014;16:14; JACC 2015;65:1998)

- Goal: in general, <140/90 mmHg

In elderly: data sparser, but benefit, albeit w/ less strict BP target (NEJM 2008;358:1887); thus, consider <150/90 mmHg if either (a) ≥80 y and w/o DM or CKD (ASH/ISH rec), or (b) ≥60 y (but no need to downtitrate if <140/90 & tolerating meds) (JNC 8 rec)

In Pts w/ prior MI or stroke: reasonable to consider <130/80 (HTN 2015;65:1372)

In Pts w/ DM and/or CKD: prior targets of <130/80 not supported by data (and harm if target <120; NEJM 2010;362:1575), but may consider if CKD & albuminuria for renal protection (ASH/ISH rec based on NEJM 1994;330:877)

- Treatment results in 50% ↓ HF, 40% ↓ stroke, 20-25% ↓ MI (Lancet 2014;384:591)
- **Lifestyle modifications** (each ↓ SBP ~5 mmHg) weight loss: goal BMI 18.5-24.9; aerobic exercise: ≥30 min exercise/d, ≥5 d/wk diet: rich in fruits & vegetables, low in saturated & total fat (DASH, NEJM 2001;344:3) sodium restriction: ≤2.4 g/d and ideally ≤1.5 g/d (NEJM 2010;362:2102) maintain adequate potassium intake through diet counseling (~120 mEq of dietary potassium) if no predisposition to hyperkalemia (NEJM 2007;356:1966)
limit alcohol consumption: ≤2 drinks/d in ♂; ≤1 drink/d in ♀ & lighter-wt Pts avoid exacerbating exposures (eg, NSAID use)
- **Pharmacologic options** for HTN or pre-HTN w/ comorbidity (nb, pre-HTN w/o DM, CKD, CV disease, or other end organ dysfunction treated w/ lifestyle alone) **Pre-HTN:** ARB prevents onset of HTN, no ↑ in clinical events (NEJM 2006;354:1685) **HTN:** choice of therapy controversial, concomitant disease and stage may help guide **Rx uncomplicated:** CCB, ARB or ACEI, or thiazide (chlorthalidone preferred) are 1st line (NEJM 2009;361:2153); βB not 1st line (Lancet 2005;366:1545).

For non-black Pts <60 y: reasonable to start w/ ARB or ACEI, then add CCB or thiazide if needed, and then add remaining class if still needed

For black, elderly, and ? obese Pts (all of whom more likely to be salt sensitive): reasonable to start with

CCB or thiazide, then add either the other 1st choice class or ARB or ACEI if needed, and then all 3 classes if still needed

+CAD (*Circ* 2015;131:e435): ACEI or ARB (*NEJM* 2008;358:1547); ACEI+CCB superior to ACEI+thiazide (*NEJM* 2008;359:2417) or βB+diuretic (*Lancet* 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, βB ± ACEI/ARB ± aldo antag (see “ACS”)

+HF: ACEI/ARB, βB, diuretics, aldosterone antagonist (see “Heart Failure”)

+2° stroke prevention: ACEI (*Lancet* 2001;358:1033); ? ARB (*NEJM* 2008;359:1225)

+diabetes mellitus: ACEI or ARB; can also consider thiazide or CCB

+chronic kidney disease: ACEI or ARB (*NEJM* 1993;329:1456 & 2001;345:851 & 861)

• Tailoring therapy

lifestyle Δs typically complementary rather than alternative to drug Rx [although if low risk (stage 1, no end-organ damage or risk factors), could start with lifestyle]

if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo (eg, ACEI + CCB; *NEJM* 2008;359:2417), as most will require ≥2 drugs

typically start drug at ½ maximal dose; after 2-3 wk either titrate up or add new drug

Resistant hypertension (*JAMA* 2014;311:2216)

- BP > goal on ≥3 drugs incl diuretic, ~12-13% of hypertensive population (*HTN* 2011;57:1105)
- Differentiate between true & *pseudoresistance*, w/ latter due to: inaccurate measurement or use of wrong cuff size poor dietary compliance (Na/K intake, can assess w/ 24-hr urine for Na, K and Cr) suboptimal med dosing (eg, <50% of max dose) or poor med compliance volume expansion (inadequate diuretic dosing) white coat HTN (consider ABPM) 2° causes or external drivers (eg, OSA, steroids, NSAIDs, alcohol) (*Lancet* 2010;376:1903)

- True resistance = uncontrolled BP confirmed by ABPM despite compliance w/ optim. doses

- Treatment considerations:

Persistent ↑ volume may contribute even if on standard HCTZ (*Archives* 2008;168:1159).

Effective diuretic dosing required for most to achieve control (*HTN* 2002;39:982).

Chlorthalidone over HCTZ (if renal function preserved). Loop diuretic favored over thiazide for initial Rx if eGFR <30; however, adding thiazide to loop can ↑ diuresis if insufficient response to loop alone.

Adding aldosterone antagonist (if renal function preserved) (*PATHWAY-2*, *ESC* 2015)

Adding β-blocker (particularly vasodilating ones such as labetalol, carvedilol, or nebivolol), centrally acting agent, α-blocker, or direct vasodilator

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Other Rx under investigation: renal denervation (see below); carotid baroreceptor stimulation; central AV anastomosis ↑ SBP by ~23 mmHg (*Lancet* 2015;385:1634)

- **Renal denervation:** catheter-based RF ablation of renal nerves modifying sympathetic outflow. Had appeared beneficial in unblinded and/or uncontrolled studies, but no effect on BP in controlled trial, so not currently an option in routine care (*NEJM* 2014;370:1393).

Special situations

- **Secondary causes**

Renovascular (qv)

Renal parenchymal disease: salt and fluid restriction, ± diuretics

Endocrine etiologies: see “Adrenal Disorders”

- **Pregnancy:** methyldopa, labetalol, nifedipine, hydralazine; avoid diuretics; Ø ACEI/ARB

HYPERTENSIVE CRISES

- **Hypertensive emergency:** ↑ BP → acute target-organ ischemia and damage

neurologic: encephalopathy (insidious onset of headache, nausea, vomiting, confusion), hemorrhagic or ischemic stroke, papilledema

cardiac: ACS, HF/pulmonary edema, aortic dissection

renal: proteinuria, hematuria, acute renal failure; scleroderma renal crisis

microangiopathic hemolytic anemia; preeclampsia-eclampsia

- **Hypertensive urgency (severe asymptomatic HTN):** SBP >180 or DBP >120 (?110) w/ minimal or no target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (espec clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine
- Cerebral injury: do *not* treat HTN in acute ischemic stroke unless Pt getting lysed, extreme BP (>220/120), Ao dissection, active ischemia or HF (*Stroke* 2003;34:1056)

Treatment (Chest 2007;131:1949)

- Tailor goals to clinical context (eg, more rapid lowering for Ao dissection)
- Emergency: ↓ MAP by ~25% in mins to 2 h w/ IV agents (may need arterial line for monitoring); goal DBP <110 w/in 2-6 h, as tolerated
- Urgency: ↓ BP to ≤160/100 in hrs using PO agents; goal normal BP in ~1-2 d
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

Drugs for Hypertensive Crises

| | | |
|----|---|---|
| | Nitroprusside* 0.25-10 mcg/kg/min | Nitroglycerin 5-1000 mcg/min |
| | Labetalol 20-80 mg IVB q10min or 0.5-2 mg/min | Esmolol 0.5 mg/kg load → 0.05-0.2 mg/kg/min |
| IV | Fenoldopam 0.1-1.6 mcg/kg/min | Hydralazine 10-20 mg q20-30 min |

Nicardipine 5-15 mg/h

Clevidipine 1-16 mg/h

Phentolamine 5-15 mg bolus q5-15min

Enalaprilat 1.25 mg

Captopril 12.5-100 mg tid

Labetalol 200-800 mg tid

PO

Clonidine 0.2 mg load → 0.1 mg qh

Hydralazine 10-75 mg qid

*Metabolized to cyanide → Δ MS, lactic acidosis, death. Limit use of very high doses (8-10 mcg/kg/min) to <10 min. Monitor thiocyanate levels. Hydroxocobalamin or sodium thiosulfate infusion for treatment of cyanide toxicity.

Treatment Considerations for Specific Clinical Settings

| Clinical | Setting Note | Treatment |
|---|--|--|
| Acute stroke | BP ↓ must be balanced w/ risk of worsening ischemia | Consult stroke team |
| Aortic dissection (qv) | ✓ BP in both arms and treat higher value | βB first, then add vasodilator (eg, nitroprusside) if needed |
| Acute pulm edema | Avoid ⊖ inotropes (eg, βB) if LV dysfxn, unless ischemia | Vasodilator (eg, NTG) and loop diuretic |
| Antihypertensive withdrawal | Suspect if abrupt d/c of symp. blocker (eg, clonidine) | Restart d/c'd drug or consider labetalol or nitroprusside |
| Sympathetic activity (pheo, auton dysfxn, cocaine, MAO + tyramine-containing foods) | Avoid βB as could → unopposed α in vasculature → vasoconstriction and further ↑ BP | Phentolamine (pheochromocytoma), nitroprusside |

RENOVASCULAR DISEASE

Pathophysiology

- ↑ renal perfusion → activation of RAA system → vasoconstriction, ↑ aldo & vasopressin, ↑ sympathetic activity → volume retention & HTN → progressive renal dysfxn and CV risk

- Unilateral stenosis ↑ HTN
- Bilateral (or unilat involving solitary functioning kidney) → HTN & progressive renal insuffic

Etiologies

- **Atherosclerosis** (~90%): usually involving ostial or prox segments. Often incidental finding as common in Pts w/ established athero (eg, CAD, PAD) but uncommon cause of HTN.
- **Fibromusclar dysplasia (FMD)**, ~10%): nonathero medial fibroplasia usually mid/distal female-predominant (85-90%); mean age 52 y (*Circ* 2012;125:3182) characteristic “string of beads” appearance (or concentric smooth stenosis) on angio usually > 1 territory involved (eg, carotid in ~65%), explaining sx of HA, dizziness, tinnitus
- Other (uncommon): vasculitis (Takayasu's, GCA, PAN or eosinophilic granulomatosis w/ polyangiitis) often w/ ↑ inflammatory markers, systemic s/s; scleroderma; local aneurysm or dissection; embolism; retroperitoneal fibrosis

Diagnosis

- Consider testing if any of the following *and* if finding would modify treatment:

Clinical picture consistent w/ secondary HTN w/ no other compelling etiology Severe HTN (SBP ≥180 and/or DBP ≥120 mmHg) and/or flash pulm edema/CHF Progressive renal insufficiency w/ bland sediment, unilateral small kidney (≤9 cm), renal asymmetry > 1.5 cm, or acute sustained Cr ↑ by ≥30% w/in 1 wk of starting ACEI/ARB

Testing for Renovascular Disease (*Am Fam Physician* 2009;80:273)

| Modality | Se | Sp | Notes |
|-----------------------------|---------------|------|--|
| Duplex Doppler US | 85% | 92% | Pt habitus & operator dependent. May be preferred if renal dysfxn. Allows quantification of resistive index.* |
| CTA | 88-96% | 97% | Less sensitive (~30%) for distal disease such as FMD Contrast agent nephrotoxic |
| MRA | 88-100% | >95% | Less sensitive (~30%) for distal disease such as FMD Risk of nephrogenic systemic fibrosis if mod-sev CKD |
| Angiography (DSA) | gold standard | | Allows measurement of gradients Invasive, contrast agent nephrotoxic |
| Plasma Renin Activity (PRA) | 50-80% | low | Not 1 st line. Can ↑ Se by measuring 1 hr after capto administration |
| Captopril Renal Scan | 75-100% | n/a | Not 1 st line, but can determine hemodynamic signif of stenosis. Not reliable in bilateral RAS or poor renal fxn. |

*Resistive index = [(peak syst vel - end diast vel) / peak syst vel].

- Monitoring: for athero, repeat imaging only necessary if Δ in clinical status that would lead to intervention; for **FMD** image q6-12mo to assess for progression

Treatment

- If due to atherosclerosis, risk factor modification: quit smoking, ↓ chol
- Antihypertensive **Rx** effective for most Pts: diuretic + **ACEI/ARB** (watch for ↑ **Cr**) or **CCB**
- Revascularization (typically percutaneous **w/** stenting):

Had considered if refractory **HTN**, recurrent flash pulm edema, worsening **CKD**

However, clinical trials enrolling stable Pts **w/** mod stenosis (50-70%) and **HTN** on ≥ 2 agents showed no benefit on # of **BP** meds, renal fxn or **CV** outcomes (*NEJM* 2000;342:1007; 2009;361:1953; 2014;370:13). Unknown if beneficial in more severe stenoses or in higher-risk Pts (eg, recent **CHF**, >3 meds).

Resistive index >80 on **U/S** implies intrinsic renal damage and thus less likely to benefit from revasc, so may predict outcome after intervention (*NEJM* 2001;344:410). Operator dependent and some studies have not replicated findings, so not utilized broadly.

Renal vein renin measurements, PRA, captopril renogram may provide supportive evidence as to hemodynamic significance of **RAS**, but limited utility due to low **Se**

For **FMD** (usually more distal lesions): **PTA** \pm bailout stenting

- Surgery (very rare): resection of pressor kidney
- Bilateral **RAS**: 20-46% of Pts **w/** **RAS**. Associated **w/** higher creatinine and worse **CV** outcomes. In addition to anti-**HTN** **Rx**, consider revasc if likely to benefit (failure of meds, recurrent pulmonary edema, progressive renal failure). Trials including Pts **w/** bilateral **RAS** did not show benefit but included moderate stenoses.

P.1-50

AORTIC ANEURYSMS

Definitions

- **True** aneurysm ($\geq 50\%$ dilation of all 3 layers of aorta; <50% called ectasia) vs **false or pseudoaneurysm** (rupture contained by adventitia)
- **Location**: root (annuloaortic ectasia), thoracic aortic aneurysm (**TAA**), thoracoabdominal aortic aneurysm (**TAAA**), abdominal aortic aneurysm (**AAA**)
- **Type**: fusiform (circumferential dilation) vs saccular (localized dilation of aortic wall)

Epidemiology (*Circ* 2010;121:e266, 2011;124:2020 & 2013;127:e6; *Nat Rev Cardiol* 2011;8:92)

- In U.S., ~15,000 deaths/y from aortic ruptures; overall ~50,000 deaths/y from Ao disease
- **TAA**: 10/100,000 Pt-yrs, ♂:♀ 2:1; ~60% root/ascending; 40% descending

- **AAA**: ~4-8% prev in those >60 y (although may be ↓ ; *Circ* 2011;124:1118); 4-6× more common in ♂ vs ♀; mostly infrarenal
- Arch & TAAA rarer

Pathophysiology (*NEJM* 2009;361:1114; *Nat Med* 2009;15:649)

- Medial degeneration and/or ↑ wall stress
Medial degeneration = muscle apoptosis, elastin fiber weakening, mucoid infiltration
Wall stress $\propto [(\Delta P \times r) / (\text{wall thickness})]$, LaPlace's law
- **TAA**: most commonly medial degeneration; seen w/ connective tissue disorders & aortitis
- **AAA**: most commonly long-standing HTN + athero/inflammation → medial weakening

Risk factors

- Classic: **HTN**, **atherosclerosis**, **smoking**, **age**, **male sex**
- **Marfan syndrome** (mutations in fibrillin-1, *FBN-1*): cardinal features are Ao root aneurysm & ectopia lentis. Other suggestive signs include: tall stature; arachnodactyly w/ *thumb sign* (entire distal phalanx of adduct. thumb extends beyond ulnar border of palm) and/or *wrist sign* (tip of thumb covers 5th finger fingernail when wrapped around contralat wrist); pectus deformities; scoliosis; dural ectasia; spontaneous **PTX**; **MVP**.
- **Loeys-Dietz syndrome** (mutation in TGF-β receptors 1 or 2, *TGFBR1/2*): triad of arterial tortuosity & aneurysms, widely spaced eyes, bifid uvula or cleft palate. Also w/ velvety & hyperlucent skin and bluish sclera.
- Vascular **Ehlers-Danlos syndrome** (mutation in type III procollagen, *COL3A1*): easy bruising; thin, translucent skin w/ visible veins (but not excessively stretchable); acrogeria (aged appearance of hands & feet); flexible digits; uterine or intestinal rupture; distinctive facial features (protruding eyes, thin nose & lips, sunken cheeks, small chin)
- Other genetic disorders: **bicuspid AoV**; Turner syndrome (45X; short stature, ovarian failure, Ao coarctation); other familial aortopathies (mutations in smooth muscle myosin & actin genes including MYH11 and ACTA2)
- **Aortitis**: Takayasu's, **GCA**, spondyloarthritis, IgG4-related disease
- **Infection** (ie, mycotic aneurysm): salmonella, **TB**, syphilis

Screening (*Circ* 2010;121:e266 & 2011;124:2020; *Annals* 2014;161:281; *JAMA* 2015;313:1156)

- **TAA**: if bicuspid **AoV** or 1° relative w/: (a) TAA or bicuspid valve, (b) Marfan, Loeys-Dietz, Turner; known relevant genetic mutation (see above)
- **AAA**: ✓ for pulsatile abd mass; **U/S** ♂ >60 y w/ **FHx** of **AAA** & ♂ 65-75 y w/ prior tobacco

Diagnostic studies (*Circ* 2010;121:e266 & 2011;124:2020)

- **Contrast CT**: quick, noninvasive, high **Se** & **Sp** for all aortic aneurysms
- **TTE/TEE**: **TTE** most useful for root and proximal Ao; **TEE** can visualize other sites of TAA
- **MRI**: preferred over **CT** for aortic root imaging for TAA; also useful in **AAA** but time-consuming; noncontrast "black blood" **MR** to assess aortic wall

- **Abdominal U/S:** screening and surveillance test of choice for infrarenal AAA

Treatment principles (*Circ* 2006;113:e463; 2008;117:1883; 2010;121:1544 & e266)

- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- **Smoking cessation:** smoking associated w/ ↑ rate of expansion (*Circ* 2004;110:16)
- **Statin** (to achieve LDL-C <70 mg/dL): ↓ death and stroke & possibly ↓ rate of expansion (*Eur J Vasc Endovasc Surg* 2006;32:21)
- **BP control: βB** (↓ dP/dt) ↓ aneurysm growth (*NEJM* 1994;330:1335)
ACEI a/w ↓ risk of rupture (*Lancet* 2006;368:659)
ARB may ↓ rate of aortic root growth in Marfan (*NEJM* 2008;358:2787)
βB and **ARB** similar ↓ rate of Ao root growth in children and young adults w/ Marfan (*NEJM* 2014;371:2061)

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- Moderate cardiovascular exercise okay, but no burst activity/exercise requiring Valsalva maneuvers (eg, heavy lifting)
- **Indications for intervention** (surgery/endovascular repair)
 Individualize based on **FHx**, body size, gender, anatomy, surgical risk
TAA (*Circ* 2010;121:1544 & e266) symptoms
 ascending Ao ≥5.5 cm (4-5 cm if Marfan, bicuspid **AoV**, Loeys-Dietz, vascular EDS, or other genetic/familial disorder)
 descending >6 cm ↑ >0.5 cm/y
 aneurysm >4.5 cm and planned **AoV** surgery
AAA (*NEJM* 2002;346:1437 & 2014;371:2101) symptoms infrarenal ≥5.5 cm, but consider ≥5.0 cm in ♀ ↑ >0.5 cm/y; inflam/infxn

Surgery (*Circ* 2010;121:e266; *EHJ* 2014;25:2873)

- Ascending aorta
 No root involvement: resection & replacement w/ Dacron tube graft
 Root involvement: need to address **AoV** integrity; depending on **AoV** itself: modified Bentall: Dacron Ao root + prosthetic **AoV**, reattach coronaries valve-sparing: reimplant native **AoV** in Dacron Ao graft; reattach coronaries
- Arch: high-risk, complex surgery because of the arch branches; variety of combinations of partial/complete resection, stent graft & bypass of arch vessels
- Descending thoracic aorta: resection & grafting vs endovascular repair (qv)

Endovascular repair (EVAR) (*NEJM* 2008;358:494; *Circ* 2011;124:2020 & 2015;131:1291)

- Depends on favorable aortic anatomy
- TEVAR (thoracic **EVAR**) for descending TAA ≥5.5 cm may ↑ periop morbidity and possibly mortality (*Circ* 2010;121:2780; *JACC* 2010;55:986; *J Thorac CV Surg* 2010;140:1001 & 2012;144:604)
- **AAA**

Guidelines support open repair or **EVAR** for infrarenal **AAA** in good surg candidates ↓ short-term mort., bleeding, **LOS**; but long-term graft complic. (3-4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no proven Δ in overall mortality in trials, except ? in those <70 y (*NEJM* 2010;362:1863, 1881 & 2012;367:1988)

In observational data, **EVAR** assoc w/ ↑ survival over 1st 3 y, after which survival similar. Rates of rupture over 8 y 5.4% w/ **EVAR** vs 1.4% w/ surgery (*NEJM* 2015;373:328)

In Pts unfit for surgery or high periop risks: ↓ aneurysm-related mortality but no Δ in overall mortality over medical **Rx** (*NEJM* 2010;362:1872). **EVAR** noninferior (? superior) to open repair in ruptured **AAA** w/ favorable anatomy (*Ann Surg* 2009;250:818).

- **Pt** selection for endovascular includes requirement to comply with long-term surveillance

Complications (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92)

- **Pain**: gnawing chest, back or abdominal pain; new or worse pain may signal rupture
- **Rupture**: risk ↑ w/ diameter, ♀, current smoking, **HTN**
TAA: ~2.5%/y if <6 cm vs 7%/y if >6 cm
AAA: ~1%/y if <5 cm vs 6.5%/y if 5-5.9 cm rupture p/w severe constant pain and hemorrhagic shock; ~80% mortality at 24 h
- **Aortic insufficiency (TAA)** and **CHF**
- **Acute aortic syndromes** (qv)
- **Thromboembolic ischemic events** (eg, to **CNS**, viscera, extremities)
- **Compression of adjacent structures** (eg, **SVC**, trachea, esophagus, laryngeal nerve)

Follow-up (*Circ* 2010;121:1544 & e266; *Nat Rev Cardiol* 2011;8:92; *JAMA* 2013;309:806)

- Expansion rate ~0.1 cm/y for **TAA**, ~0.3-0.4 cm/y for **AAA**
- **AAA**: <4 cm q2-3 yrs; 4-5.4 cm q6-12 mos; more frequent if rate of expansion >0.5 cm in 6 mo
- **TAA**: 6 mo after **dx** to ensure stable, and if stable, then annually (*Circ* 2005;111:816)
- Screen for **CAD**, **PAD** and aneurysms elsewhere, espec popliteal. About 25% of Pts w/ **TAA** will also have **AAA**, and 25% of **AAA** Pts will have a **TAA**: consider pan-Ao imaging.
- Patients with endovascular repair require long-term surveillance for endoleak & to document stability of aneurysm

P.1-52

ACUTE AORTIC SYNDROMES

Definitions (*Circ* 2005,112:3802 & 2010;121:e266; *Eur Heart J* 2012;33:26)

- **Aortic dissection (AoD)**: intimal tear → blood extravasates into Ao media (creates false lumen). Rate 3-16/100,000 Pt-yrs. False lumen acts as “wind sock,” ↑ in size and compressing true lumen (patency of false lumen associated with outcome).
- **Intramural hematoma (IMH)**: vasa vasorum rupture → medial hemorrhage that does not communicate with aortic lumen; 6% of aortic syndromes; clinically managed as **AoD**

- **Penetrating ulcer (PAU):** atherosclerotic plaque penetrates elastic lamina → medial hemorrhage. PAU in setting of IMH assoc. w/ similar outcomes as AoD. Outcomes for isolated PAU less well defined but considered AAS. Rx depends on clinical context.

Classification (proximal twice as common as distal)

- **Proximal:** involves ascending Ao, regardless of origin (= Stanford A, DeBakey I & II)
- **Distal:** involves descending Ao only, distal to L subclavian art. (= Stanford B, DeBakey III)
- **Other Considerations:** isolated to arch generally treated as proximal; distal with involvement of subclavian depends on overall clinical picture.

Risk factors

- **Classic** (in older Pts): **hypertension** (h/o HTN in >70% of dissections); **age** (60s-70s), **male sex** (~70% ♂); **smoking**

- **Genetic or acquired predisposition** (may present younger; see “Aortic Aneurysms”):

Connective tissue disease/congenital anomaly: Marfan, Loeys-Dietz, vascular Ehlers-Danlos, bicuspid AoV, coarctation (eg, in Turner's), other familial aortopathies, PCKD

Aortitis: Takayasu's, GCA, Behçet's, syphilis

Pregnancy: typically 3rd trimester

- Other environmental factors:

Trauma: blunt, deceleration injury

Cardiovascular procedures: IABP, cardiac or aortic surgery, cardiac catheterization

Acute ↑ BP: cocaine, Valsalva (eg, weightlifting)

Clinical Manifestations and Physical Exam* (JAMA 2000;283:897)

| Feature | Proximal | Distal |
|---|----------------------|------------------------|
| “Aortic” pain (abrupt, severe, tearing or ripping quality, maximal at onset [vs crescendo for ACS]) | 94% (chest, back) | 98% (back, chest, abd) |
| Syncope (often due to tamponade) | 13% | 4% |
| HF (usually due to acute AI) | 9% | 3% |
| CVA | 6% | 2% |
| HTN | 36% | 70% |
| HoTN or shock (tamponade, AI, MI, rupture) | 25% | 4% |

| | | |
|---|------------|-----------|
| Pulse deficit (if involves carotid, subclavian, fem) | 19% | 9% |
| AI murmur | 44% | 12% |

*S/S correlate w/ affected branch vessels & distal organs; may Δ as dissection progresses.

Initial evaluation (*Circ* 2010;121:e266)

- H&P, including bilateral **BP** and radial pulses for symmetry

High-risk conditions: Marfan, **CTD**, **FHx AoD**, recent Ao manip., **AoV** dis., Ao aneurysm

High-risk pain features: chest, back or abd pain described as [both (abrupt onset or severe intensity) and (ripping, tearing, sharp or stabbing) (absence ⊖ **LR** 0.3)]

High-risk exam features:

perfusion deficit [pulse deficit (⊕ **LR** 5.7), systolic **BP** differential (>20 mmHg), or focal neuro deficit + pain (⊕ **LR** >6)], or

murmur of **AI** (new or not known to be old and in conjunction w/ pain), or hypotension or shock

- 12-lead **ECG**: often **abnl** but non-dx; may show **STE** if prox **AoD** involving coronary
- **CXR**: **abnl** in 60-90% [↑ mediast. (absence ⊖ **LR** 0.3), L pl effusion] but *cannot r/o AoD*
- *Obtain expedited Ao imaging if:* ≥2 high-risk features, 1 high-risk feature w/o clear alternative **dx**, or 0 features but unexplained **HoTN** or widened mediastinum on **CXR**

Diagnostic studies (*Circ* 2010;121:e266; *JACC CV Img* 2014;7:406)

- **CT**: quick, noninvasive, readily available, **Se** ≥93% & **Sp** 98%; however, if ⊖ & high clin. suspicion → additional studies (2/3 w/ **AoD** have ≥2 studies; *AJC* 2002;89:1235)
- **MRI**: **Se** & **Sp** >98%, but time-consuming test & not readily available
- Axial studies (**CT**, **MRI**) should be gated to **ECG** to evaluate Ao root; if high index of suspicion, study should include entire aorta (chest, abd, & pelvis)

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- Echo

TTE: low **Se** (∴ not **dx** study) but can show effusion, **AI**, & dissection flap (if proximal)

TEE: **Se** >95% prox, 80% for distal; can assess cors/peric/**AI**; “blind spot” behind trachea

- **Aortography**: **Se** ~90%, time-consuming, cannot detect **IMH**; can assess branch vessels
- **D-dimer**: **Se/NPV** ~97%; ? <500 ng/mL to **r/o** dissec (*Circ* 2009;119:2702) but not in Pts at high clinical risk (doi:10.1016/j.annemergmed.2015.02.013); does not **r/o** **IMH**

Initial medical treatment (*Lancet* 2008;372:55; *Circ* 2010;121:1544; *JACC* 2013;61:1661)

- ↓ **dP/dt** targeting **HR** <60 & central **BP** <120 (or lowest that preserves perfusion; **r/o** pseudohypotension, eg, arm **BP** ↑ due to subclavian dissection; use highest **BP** reading)

- **First with IV β B** (eg, esmolol, labetalol) to blunt reflex \uparrow HR & inotropy that would occur in response to vasodilators; verap/dilt if β B contraindic.
- **Then \downarrow SBP with IV vasodilators** (eg, nitroprusside)
- **HTN** control may require multiple agents (median of 4 in one study; *J Hum Hypertens* 2005;19:227). If unable to control readily: 1st evaluate for complication (eg, visceral ischemia); Rx pain w/ MSO₄; if no complication, then consider other drivers (eg, EtOH withdrawal).
- **If HoTN**: urgent surgical consultation, IVF to achieve euvoemia, pressors to keep MAP 70 mmHg; r/o complication (eg, tamponade, contained rupture, severe AI)

Treatment of proximal AoD (*Circ* 2010;121:1544; *Lancet* 2015;385:800)

- **Acute**: all cases should be considered for emergent surgery
root replacement; valve sparing unless bicuspid or valve involvement
acute stroke should not necessarily dissuade from surgery (mortality w/o surgery \sim 100%, *Circ* 2013;128:S175)
prior AoV surgery postulated to be protective from complications, but most would operate
need for preop coronary angio debatable as procedure nontrivial in setting of dissection and likelihood of performing concomitant CABG low
- **Chronic**: consider surgery if complicated by progression, AI or aneurysm

Treatment of distal AoD (*Circ* 2010;121:1544; *JACC* 2013;61:1661; *Lancet* 2015;385:800)

- Intervention warranted if complication (see below)
- Endovascular intervention (fenestrate flap to decompress false lumen, open occluded branch, stent entry tear) may be preferred over surgery due to possible \uparrow mort. (*JACC* 2013;61:1661 & *Circ* 2015;131:1291)
- Stent graft for *uncomplicated* cases may \downarrow risk of aorta-related complications and adverse remodeling (*Circ Cardiovasc Interven* 2013;6:407)

Complications (occur in \sim 20%; *Circ* 2003;108:II-312 & 2010;121:e266)

- **Monitor all Pts w/ frequent assessment (sx, BP, UOP), pulse exam, labs (Cr, Hb, lactic acid), imaging (\sim 7 d or sooner if sx or significant lab Δ)**
- **Uncontrolled BP despite intensive IV Rx or continued or \rightarrow pain may indicate complication**
- **Progression**: propagation of dissection, \uparrow aneurysm size, \uparrow false lumen size
- **Rupture**: pericardial sac \rightarrow tamponade (avoid pericardiocentesis unless PEA); blood in pleural space, mediast., retroperitoneum; \uparrow in hematoma on imaging portends rupture
- **Malperfusion** (partial or complete obstruction of branch artery) can be *static* (avulsed/thrombosed) or *dynamic* (Δ s in pressure in true vs false lumen) coronary \rightarrow MI (usually RCA \rightarrow IMI, since dissection often along outer Ao curvature) innominate/carotid \rightarrow CVA, Horner intercostal/lumbar \rightarrow spinal cord ischemia/paraplegia innominate/subclavian \rightarrow upper extremity ischemia; iliac \rightarrow lower extremity ischemia celiac/mesenteric \rightarrow bowel ischemia (can be subtle w/ nonspecific GI sx, anorexia, pain) renal \rightarrow acute renal failure or gradually \uparrow Cr, refractory HTN
- **AI**: due to annular dilatation or disruption or displacement of leaflet by false lumen
- **Mortality** (*Circ* 2013;127:2031; *JACC* 2015;66:350)

~50% prior to hospital

historically ~1%/h × 48 h for acute prox AoD who survive to hospital w/ 47% subseq mort at 30 d; more recent data w/ 22% in-hospital mortality

13% at 30 d for acute distal overall but 25% if complications mortality similar for proximal and distal that survive to discharge: ~85% at 5 y

Long-term monitoring

- Major concern is progression to aneurysm or recurrent dissection
- Treat BP, risk factors aggressively
- **Serial imaging for all** (CT or MRI, latter may be preferred to lower cumulative radiation exposure) at 1, 3, and 6 mo, and then annually (18 mo, 30 mo, etc.)
- Pts treated endovascularly need close follow-up to monitor for complication (eg, endoleak)
- Partial thrombosis of false lumen associated with worse outcomes/mortality (*NEJM* 2007;357:349)
- In patients who present at young age or other indications of predisposing factor, consider genetic evaluation and screening of family members

P.1-54

PERIPHERAL ARTERY DISEASE (PAD)

Epidemiology and risk Factors

- Prev. ↑ w/ age: <1% if <40 y, ~15% if ≥70 y; risk factors incl. **smoking**, **DM**, **HTN**, chol
- More frequent in Pts w/ other symptomatic atherosclerotic disease (eg, coronary, carotid)
- Associated w/ ↑ risk of CV events (*JAMA* 2007;297:1197)
- If **sx**, 3-y risk of stroke ~3%, acute limb ischemia ~4%, periph revasc ~22% (*Circ* 2013;112:679)

Clinical Features

- **Asymptomatic** (~35%) or **atypical sx** (~40%): often undertreated in terms of risk factor modifying therapy (*Circ* 2011;124:17)
- **Claudication** (~25%): dull ache, often in calves precip by walking & relieved by stopping (vs spinal stenosis, qv)
Leriche syndrome (aortoiliac occlusive disease): buttock & thigh claudication, ↑ or ∅ femoral pulses, & erectile dysfxn
- **Critical limb ischemia** (CLI, 1-2%): 1 or more of the following 3 manifestations
 - rest pain**: ↑ w/ elevation b/c ↓ perfusion
 - ulcer**: typically at pressure foci, often dry (in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition)
 - gangrene**: more typically “dry” (ie, distal limb, dry shrunken and dark red, lack of pus) as a manifestation of ischemia due to impaired blood flow rather than “wet” (ie, infected, pus present, fetid smell), which may occur in the setting of infection or injury may be chronic (ie, **sx** >2-wk duration) vs acute limb ischemia, which is a

vascular emergency (see below)

a/w poor outcome: 45% amputation & 20% mortality at 6 mo (J Vasc Surg 2000;31:S1)

- Blue toe syndrome: most likely atheroembolic disease with occlusion of digital arteries

PAD Clinical Symptom Classification

| Rutherford | | Fontaine | | Typical ABI* |
|------------|---|----------|--|--------------|
| Stage | Definition | Stage | Definition | |
| 0 | Asx | 1 | Asx | 0.9-1.0 |
| 1 | Mild claudication | 2a | Sx at distance >650 ft | 0.4-0.9 |
| 2 | Mod claudication | | | |
| 3 | Severe claudication | 2b | Sx at distance <650 ft | |
| 4 | Rest pain | 3 | Nocturnal or rest pain | <0.4 |
| 5 | Ischemic ulceration not exceeding ulcer on digits of foot | 4 | Necrosis (death of tissue) and/or gangrene of limb | |
| 6 | Severe ischemic ulcers or frank gangrene | | | |

*ABI is generally, but not absolutely correlated w/ clinical measures of lower extremity fxn & sx

Diagnosis

- Ddx includes

nonvascular:

neurogenic claudication (spinal stenosis): pain w/ standing, relieved by sitting, lying, or forward flexion; a/w neurologic abnl (weakness, sensory Δs, h/o deg. disc disease)

musculoskeletal/arthritis: joint pain, morning stiffness, associated joint pathology or instability, crepitus or effusion

Baker's cyst: posterior knee pain, knee stiffness, mass behind knee, discomfort w/ prolonged standing, impairment of bending

non-athero vascular:

venous claudication (uncommon): pain w/ walking in setting of proximal venous obstruction & no arterial obstruction

dissection, embolism, aneurysm, or vasculitis

popliteal artery entrapment (exercise-induced lower leg pain)

- Physical exam: ↓ peripheral pulses ± femoral bruits if severe: pallor of feet w/ elevation, dependent rubor, cyanosis other signs of chronic PAD: hair loss/shiny or cool skin, skin atrophy, nail hypertrophy

Testing

- **Ankle:brachial index (ABI):** nl 1-1.4; borderline 0.91-0.99; abnl ≤0.90; if > 1.4, non-dx, likely due to calcified/noncompressible vessel
 - **Toe:brachial index (TBI)** helpful if noncompressible (toe artery less likely to calcify); but ranges different than ABI (>0.7 nml, 0.5-0.7 mild, 0.35-0.5 mod, <0.35 mod-severe, severe if toe pressure <30 mmHg)
-
- P.1-55
- **Segmental pressures** to determine level of disease (20 mmHg gradient between segments indicates stenosis)
 - **Pulse volume recording (PVR)** done w/ segmental pressures: determine site and severity of disease. Abnormal waveform can indicate disease in noncompressible vessel, but pressures used over waveform if vessels are compressible.
 - If ⊕ sx but nl ABI: ✓ **exercise ABI** (some consider even in asx Pt w/ risk factors for PAD if will modify therapy)
 - Treadmill study (or 6-min walk test) to quantify magnitude of functional limitation
 - **Imaging** (Duplex arterial U/S; CTA w/ distal run-off; MRA or angio) if dx in question or considering intervention. Some do routine Duplex U/S to monitor graft/stent patency.

Medical treatment (JACC 2013;61:1555; JAMA 2013;309:453; Circ Res 2015;116:1579)

- **Treat risk factors:** smoking cessation, high-intensity statin, control HTN & DM, smoking cessation (JACC 2010;56:2105). βB OK if indicated for another reason (eg, CAD, AF).
- **Antiplatelet Rx:** benefit shown primarily for ↑ CV risk (BMJ 2002;324:71)
If asx: benefit of antiplt Rx unclear espec if ABI only borderline (JAMA 2010;303:9)
If sx:ASA or clopidogrel
ASA: 23% ↓ risk of major CV events seen in meta-analysis of older studies (mostly ASA but also other antiplatelet Rx) (BMJ 2002;324:71)
Clopidogrel: superior to ASA, but single, older study (Lancet 1996;348:1333)
ASA+clopi may be better than ASA alone, but only posthoc data (EHJ 2009;30:1992)
Vorapaxar (PAR-1 antag.) further ↓ risk on top of ASA or clopidogrel (Circ 2013;112:679)
- Anticoagulation w/ warfarin not beneficial (NEJM 2007;357:217)
- **ACEI/ARB** to ↓ CV risk (NEJM 2000;342:145)
- **Improve claudication**
Supervised exercise: sx-limited, ≥3x/wk, ≥30-45 min/session, ↑ as tolerated; beneficial including ↑ walking time 50-200% (Cochrane 2014;7:CD990); structured exercise more effective than home-based, but home-based still effective (JAMA 2013;310:57)
ACEI & statins may ↓ sx (Circ 2003;108:1481)
Cilostazol (nb, interacts w/ diltiazem & omeprazole; may cause headache or diarrhea; do not use in Pts w/

CHF); pentoxifylline likely less effective

- **Limb preservation:** foot exams for ulcers/wounds, revasc (qv), vorapaxar (PAR-1 antag) ↓ acute limb ischemia (*Circ* 2013;112:679), statin use assoc. w/ ↓ amput (*EHJ* 2014;35:2864)

Revascularization

- Consider if limiting **sx** despite exercise/medical **Rx** or if CLI; also consider as 1st-line **Rx** for isolated aortoiliac disease given high rate of long-term patency (*Circ* 2013;128:2704)
- **Endovascular** (angioplasty or stenting) usually favored over **surgical** (bypass or endarterectomy), but depends on lesion complexity & location (aortoiliac or “inflow” vs infrainguinal or “outflow”) and **Pt** comorbidities
- Decision for stent vs angioplasty alone depends on lesion length & complexity, location (eg, over joints) (*J Vasc Surg* 2007;33:S1)
- Angioplasty w/ paclitaxel-coated balloon associated with ↑ primary patency vs regular balloon for femoropopliteal disease (*NEJM* 2015;373:145)
- Durability of endovascular revascularization depends in part on location, with greater longterm patency for iliac vs femoral interventions (*JACC* 2006;47:e1)
- Dual antiplatelet (**DAPT**, **ASA** + clopidogrel) commonly prescribed after endovascular intervention for 1-3 **mo**, but no prospective data. **DAPT** after bypass surgery not beneficial overall but possibly in subgroup w/ prosthetic grafts (*J Vasc Surg* 2010;52:825).
- Anticoagulation with warfarin does not improve patency (*NEJM* 2007;357:217), but may be indicated in subgroups with high thrombotic risk
- Stents not ferromagnetic, so **MRI** safe, but both **MRI** & **CT** may have artifact. Duplex **U/S** useful to assess stent patency and is used by some for serial routine monitoring of stent or graft patency, even in **asx** Pts.
- If coronary angiography needed, avoid access through CFA stent or femoral bypass

Acute limb ischemia (ALI)

- Sudden decrement in limb perfusion that threatens viability; *viable* (no immed threat of tissue loss): audible art. Doppler signals, sensory & motor OK *threatened* (salvage requires prompt **Rx**): loss of arterial Doppler signal, sensory or motor
- Etiologies: embolism > acute thrombosis (eg, athero, APLA, HITT), trauma to artery
- Clinical manifestations (**6 Ps**): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: thorough pulse & neuro exam; arterial Doppler; angiography, either **CT** w/ bilateral run-off through feet or arteriography
- Urgent consultation w/ vascular medicine and/or vascular surgery
- Treatment: immediate anticoagulation ± intra-arterial lytic; angioplasty or surgery

CEREBROVASCULAR DISEASE

EXTRACRANIAL DISEASE

Pathobiology

- Involving portions of carotid or vertebral arteries outside skull. Most commonly at carotid bifurcation but may involve common (CCA), internal (ICA), or external carotid (ECA).
- Most common etiology is athero; others include **FMD**, vasculitis, dissection, & radiation
- Associated **w/** ↑ risk of systemic **CV** events including ipsilateral **TIA/stroke**
- Progressive narrowing, thrombosis or unstable plaque in CCA or ICA → embolization and/or ↑ distal perfusion → ischemia → **TIA/stroke**
- *Asx chronically occluded* vessel associated **w/** low risk, as no embolization and Circle of Willis provides collateral flow

Diagnosis (*Circ* 2011;124:354)

- Stenosis defined as % lumen diameter at most severe stenosis relative to either ICA, probable lumen diameter at site of stenosis, or proximal common carotid (*J Neuroimaging* 1994;4:222). Significant stenosis is >50%.
- Carotid bruit suggestive but not sensitive
- **Duplex U/S**: **Se** >80%, **Sp** ~85%; 1st-line test
Peak systolic velocity (PSV) for severity
↑ end diastolic velocity (**EDV**), spectral broadening, carotid index (ratio of PSV in ICA vs CCA) and echolucent plaque each associated **w/** ↑ risk
PSV >200 cm/s + **EDV** > 140 cm/s + carotid index > 4.5 has **Se** 96% for significant stenosis (*Stroke* 1996;27:1965; *Mayo Clin Proc* 2000;75:1133)
- Transcranial Doppler (TCD) as adjunct to **U/S** may show severe stenosis, evidence of occlusion (collateral flow), or microemboli by high-intensity signal transients (HITS)
- If significant but nonsevere stenosis, repeat study at 6 **mo** to determine if stable and then annually thereafter
- If stenosis appears severe (≥70%) or requires further characterization, then either **CT** angio (**Se** ~90%, **Sp** ≥95%) or **MRA** (**Se** ~95%, **Sp** ≥95%). Caution with contrast & risk of either renal dysfxn (**CTA**) or nephrogenic systemic fibrosis (**MRA**).
- Angiography gold standard but invasive and assoc **w/** risk of stroke

Asx carotid stenosis (*Curr Treat Opt CV Med* 2013;252:63; *Expert Rev CV Ther* 2014;12:437)

- Cause of <15% of strokes and risk <1% annually in Pts on standard med **Rx** (see below)
- General management
lifestyle intervention (smoking cessation, diet modification, exercise)
antiplatelet therapy: **ASA** 75-325 mg/d or clopidogrel 75 mg/d if **ASA** allergic (*Circ* 2011;124:354)
high-intensity statin (see “Lipids”) and **BP control** (see “HTN”)
- **Revascularization** (see options below) for selected Pts **w/** ≥70% stenosis
older trials have shown ↓ stroke risk vs med **Rx** alone, but not compared to modern med **Rx** (*NEJM*)

1993;328:221; *JAMA* 1995;273:1421; *Lancet* 2004;363:1491)

due to low rate of associated stroke, absolute risk reduction likely small and benefit of intervention debated
consider Pt preference, risk of procedure, overall life expectancy (eg, ≥ 5 y), gender (benefit less certain in women), lesion characteristics of \uparrow stroke risk (eg, echolucent plaque, TCD evidence of microemboli)

Symptomatic carotid stenosis (*NEJM* 2013;369:12)

- Symptomatic stenosis indicative of severe/unstable plaque and associated w/ \uparrow risk of stroke. \therefore determination of sx important regarding treatment plan.
- Defined as recent (< 6 mo) focal neurologic sx, sudden in onset, referable to carotid distribution. May include TIA or minor stroke [incl amaurosis fugax (transient monocular blindness)]. Vertigo & syncope unlikely related and generally not considered sx.
- For acute treatment for stroke, see “Stroke”
- All Pts w/ sx stenosis should receive med Rx as above
- Revascularization (*NEJM* 1991;325:445; *Lancet* 2004;363:915)
recommended for 70-99% stenosis, generally w/in 2 wk unless severe comorbidity w/ limited lifespan, severe ipsilateral stroke w/ persistent deficit, occluded carotid, or high operative risk ($\geq 6\%$)
consider for 50-69% stenosis, depending on Pt-specific factors
not indicated if $< 50\%$ stenosis

P.1-57

Revascularization options

- **Carotid endarterectomy (CEA)**: gold standard. Risk of procedural stroke or death $< 3\%$ for asymptomatic disease and $< 6\%$ for sx disease in experienced centers.
- Carotid artery stenting (CAS; *JACC* 2014;64:722): compared w/ CEA, periprocedural risk of stroke \uparrow (espec in elderly) & MI \uparrow (although many asx), subsequent rates of stroke similar (*NEJM* 2010;363:11; *Lancet* 2010;376:1062). Consider if not surgical candidate (anatomy or comorbidities). Generally requires DAPT (ASA + clopidogrel) for 30 d.

INTRACRANIAL DISEASE

- Cerebral and basilar arteries and distal branches thereof
- Most common etiology is athero & assoc w/ traditional athero risk factors (*Circ* 2014;1407:14); others include: dissection, FMD, vasoconstriction, vasculitis, moyamoya
- Estimated to cause 5-10% of ischemic strokes and more prevalent among blacks, Hispanics and Asians (*Stroke* 1995;26:14)
- Diagnosis: MRA, CTA, or TCD vs angio (see above); duplex U/S not useful
- Medical treatment similar as in extracranial; however, consider ASA+clopidogrel for sx disease for 90 d (*NEJM* 2011;365:993)
- Stenting and intracranial bypass not shown to be beneficial and not routinely recommended (*NEJM* 2011;365:993; *JAMA* 2015;313:1240)

PHARMACOLOGIC SECONDARY STROKE PREVENTION

Antiplatelet therapy (*NEJM* 2012;366:1914)

- In general monotherapy preferred to multiagent therapy for long-term prevention due to ↑ ICH risk w/ multiagent therapy
 - **ASA**: ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (*NEJM* 2001;345:1444)
 - **Clopidogrel**: marginally superior to **ASA**, slightly ↑ ICH (*Lancet* 1996;348:1329)
 - **Multiagent antiplatelet therapy**:
 - ASA + clopi**: not more effective than **ASA** alone and ↑ bleeding & ICH (*Lancet* 2004;364:331; *NEJM* 2012;367:817). In *minor stroke/TIA*, **ASA + clopi** × 21 d → clopi monoRx vs **ASA** monoRx resulted in ↓ stroke w/o ↑ ICH (*NEJM* 2013;369:11).
 - ASA + dipyrimadole**: superior to **ASA** (*Lancet* 2006;367:1665), but ↑ ICH and poor compliance
- Addition of vorapaxar to **ASA** or **ASA+clopi** ↑ first stroke in Pts w/ athero, but contra-indicated in patients w/ prior stroke due to ICH risk (*NEJM* 2012;366:1404; *Stroke* 2013;691:8)

Anticoagulation

- Not routinely indicated. Anticoag if cardiac/paradoxical emboli (except bacterial endocarditis) or hypercoag state. See “**AF**” and “**VTE**” for details.
- **Hold off on anticoag** in large strokes for ~2-4 wk given risk of hemorrhagic conversion.

Risk factor management

- **BP** (see “**HTN**”): long-term **SBP** target 120-139 mmHg (*JAMA* 2011;306:2137)
- **LDL**: high-intensity statin therapy (*Circ* 2014;129(Suppl 2):S1)

OTHER CEREBROVASCULAR DISEASES

Cervical artery dissection

- May involve intracranial or extracranial arteries. Manifests as luminal stenosis, thrombo-embolism or aneurysm. ~20% of ischemic strokes in young Pts (primarily embolic).
- Etiologies: trauma, physical activity, ? neck manip.; can be spontaneous (if assoc cond.)
- **FMD** most common assoc. condition (seen in 15-20%). Others infrequent: vascular EDS, Marfan, osteogenesis imperfect, homocystinuria, PKD, α_1 -AT.
- Most (>60%) report **HA** or neck pain, Horner's in ~25%, tinnitus, rarely eye pain
- Imaging may show “crescent sign” of hematoma, string sign, tapering stenosis, flap or dissected aneurysm. Duplex **U/S** can be initial screen but lower **Se** (68-95%) and limited utility at skull base. **CTA** & **MRA** w/ similar **Se** & **Sp**; angio if inconclusive noninvasive imaging.
- Treatment: if stroke, see “Stroke.” In general, thrombolysis should not be withheld if indicated. If **SAH**, manage accordingly.
- Antithrombotic therapy: either anticoagulation (AC) or antiplatelet **Rx** may be considered for extracranial dissection; however, large meta-analysis showed no benefit of AC over antiplatelet **Rx** (*Neurology* 2012;79:686). If AC chosen, typically for 3-6 mo, then Δ to antiplatelet. Intracranial dissection treated with antiplatelet monotherapy and not AC.

- Endovascular therapy or surgery considered for selected Pts, particularly if recurrent ischemia; however, no trials to demonstrate benefit.

Patent foramen ovale (PFO; in ~27% of population) (NEJM 2005;353:2361)

- ↑ stroke risk: ≥4-mm separation, R → L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- If PFO & stroke/TIA: no benefit of warfarin over ASA (Circ 2002;105:2625), but consider if at high risk for or has DVT/PE. No sig benefit shown for PFO closure so far, albeit studies small & w/ favorable trends (NEJM 2012;366:991; 2013:1083 & 1092).

Intracranial aneurysm (Stroke 2015;46:2368)

- Prevalence of saccular aneurysms 3.2%, w/ equal sex ratio (Lancet Neurol 2011;10:626); 20-30% having > 1 aneurysm
- Associated with family hx, hereditary syndromes (eg, EDS, polycystic kidney), smoking, HTN, aortic coarctation, ? estrogen deficiency (female preponderance after menopause) (Stroke 2001;32:606)
- Clinical presentations: most commonly incidental finding on brain imaging may be found in those presenting with SAH, which typically presents as “worst headache of my life,” ± syncope, nausea, vomiting, meningismus (Neurology 1986;36:1445) rarely unruptured aneurysms become symptomatic (eg, headache, visual change, cranial neuropathy, facial pain)
- Diagnosis: CTA or MRA
- Instruct Pt to avoid smoking, heavy EtOH use, illicit drugs, straining/Valsalva
- Treatment requires consideration of size, location, Pt age and comorbidities. In general: if sx or SAH → repair if no sx/SAH and ≥7-10 mm, consider repair if <7 mm observe (CTA or MRA q6mo and every 2-3 y once showing no Δ) endovascular coiling ↑ periprocedural morbidity & mortality vs surgical clipping, but ↑ risk of recurrence

Extracranial aneurysm

- Rare (<1% of arterial aneurysms) (Surgery 1983;93:319)
- True aneurysm may be associated with athero, trauma, dissection (qv), infection, vasculitis or radiation. Male:female predominance (2:1).
- Infected pseudoaneurysm may occur at site of prior carotid intervention.
- Clinical presentation: TIA/stroke; less likely mass effect or rupture
- Diagnosis: see approach for carotid disease above
- Instruct Pt to avoid smoking, heavy EtOH use, illicit drugs, straining/Valsalva
- Treatment: sx disease should be repaired; consider repair if asx and >2 cm, w/ thrombus, or ≤2 cm but ↑ 'ing. Surgical and endovascular options depending on anatomy & Pt risk.

Cerebral venous thrombosis (CVT) (Circ 2012;125:1709)

- Uncommon (<2/100,000/yr); female predominance (3× more common)
- >85% w/ risk factor including: hypercoagulable state, OCP, pregnancy, malignancy, infection, prior trauma, vasculitis, other inflammatory states (eg, IBD), hematologic disorders, nephrotic syndrome

- Clinical presentation variable and includes HA (~90%), seizure, focal deficits, encephalopathy, sx of isolated intracranial hypertension (HA ± vomiting, papilledema, visual problems) may occur if hemorrhage or edema
- Diagnose w/ MR venography or CT venography (traditional head CT normal in ~30% of CVT). D-dimer may be elevated but does not reliably exclude.
- Acute treatment
 - treat elevated ICP
 - consider antiseizure Rx if seizure on presentation or otherwise high risk
 - anticoagulation (UFH or LMWH; see VTE for dosing) if no contraindication (nb, presence of ICH not absolute contraindication)
 - consider endovascular venous recanalization with direct thrombolysis if progressive neurologic worsening despite anticoagulation
- Chronic treatment
 - anticoagulation w/ VKA w/ INR 2-3 for 3-6 mo if provoked or 6-12 if unprovoked
 - consider indefinite duration if recurrent, complicated by DVT or PE, or severe thrombophilia
 - if occurred in setting of OCP, change to nonestrogen-based contraception
- Monitoring: imaging at 3-6 mo after dx to assess for recanalization

VENOUS THROMBOEMBOLISM (VTE)

Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT)
 - Proximal: thrombosis of iliac, femoral, or popliteal veins (nb, “superficial” femoral vein part of deep venous system)
 - Distal: calf veins below knee; lower risk of PE/death than prox (*Thromb Haem* 2009;102:493)
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

Risk factors

- Virchow's triad for thrombogenesis
 - stasis:** bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h (*NEJM* 2001;345:779)
 - injury to endothelium:** trauma, surgery, prior DVT, inflammation, central catheter
 - thrombophilia:** APC resistance, protein C or S deficiency, APS, prothrombin gene mutation, ↑ factor VIII, hyperhomocysteinemia, HIT, OCP, HRT, tamoxifen, raloxifene
- Malignancy (12% of “idiopathic” DVT/PE)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

- Statin therapy ↑ risk (*NEJM* 2009;360:1851)

Thromboprophylaxis (*Chest* 2012;141:e195S, 227S, 278S)

| Patient & situation | Prophylaxis |
|--|---|
| Low-risk med; same-day surg & <40 y | Early, aggressive ambulation |
| Minor surgery in mobile Pt | Mechanical Ppx |
| High-risk medical (eg, immobilized, h/o VTE, thrombophilia or cancer) Most surgery Pts | UFH 5000 U SC bid or tid, or LMWH, or fonda (if HIT ⊕), or mech Ppx (espec if high bleed risk) |
| High-risk surg (eg, trauma, recent stroke or spinal cord injury, h/o VTE or thrombophilia) | [LMWH or UFH SC] + mech Ppx |
| Orthopedic surgery | LMWH [or fonda, direct oral anticoag (qv) or warfarin (INR 2-3)] + mech Ppx Start before or shortly after (<12 h) surgery & cont. up to 35 d (hip) or 10-14 d (knee). LMWH or fonda favored over UFH or VKA. Direct oral anticoagulants overall appear favorable vs LMWH. |

For enoxaparin, 30 mg bid for highest risk or 40 mg qd for moderate risk or spinal/epidural anesth. Dose adjust: qd in CrCl <30 mL/min, ↑ 30% if BMI >40 (*Ann Pharmacother* 2009;43:1064).

- Direct oral anticoagulants vs LMWH (*Annals* 2012;156:710)

Dabigatran (approved in Europe & Canada; 110 mg 1-4 h after surgery & hemostasis or 220 mg if not initiated on day of surgery; 220 mg qd maintenance) noninferior to LMWH after hip and knee surgery (*Lancet* 2007;370:949)

Rivaroxaban (10 mg qd 6-10 h postop) ↓ VTE by ~25-50% vs enox 40 mg qd, with ≈ bleeding after hip or knee replacement (*NEJM* 2008;358:2765 & 2776; *Lancet* 2009;373:1673)

Apixaban (2.5 mg bid 12-24 h postop) ↓ VTE by ~50% vs enox 40 mg qd, with ≈ bleeding after hip replacement (*NEJM* 2010;363:2487)

Edoxaban (30 mg qd 6-24 h after surgery) ↓ VTE vs enox 20 mg qd, but no comparison to standard dose enox (*Thromb Res* 2014;134:1198)

- Evolving role for Ppx in ambulatory cancer Pts w/ low bleeding risk and additional VTE risk factors (*NEJM* 2012;366:601). Khorana score (cancer site, plt & WBC counts, Hb, BMI) risk predictor (*Blood*

2008;111:4902). Semuloparin (ultra LMWH) ↓ VTE by ~2/3 w/o ↑ major bleeding in Pts w/ met. or locally adv. cancer receiving chemo (NEJM 2012;366:601).

Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord, ⊕ Homan's sign (calf pain on dorsiflexion, seen in <5%)
- *Phlegmasia cerulea dolens*: massive proximal DVT → stagnant blood → edema, cyanosis, pain, compartment syndrome → can lead to limb loss or death
- 50% of Pts with sx DVT have asx PE
- Palpable tender superficial veins c/w superficial thrombophlebitis rather than DVT
- Popliteal (Baker's) cyst: related to knee pathology, may result in calf pain & may lead to DVT due to compression of popliteal vein

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“Simplified Wells” Pretest Probability Scoring of DVT (JAMA 2006;295:199)

| Clinical variable | Point score |
|--|-------------|
| ○ Active cancer (Rx ongoing or w/in 6 mo or palliative) | 1 |
| ○ Paralysis, paresis, or recent immobilization of lower extremities | 1 |
| ○ Recently bedridden for ≥3 d or major surgery w/in 12 wk | 1 |
| ○ Localized tenderness along distribution of deep venous system | 1 |
| ○ Entire leg swelling | 1 |
| ○ Calf ≥3 cm larger than asx calf (at 10 cm below tibial tuberosity) | 1 |
| ○ Pitting edema confined to sx leg | 1 |
| ○ Collateral superficial veins (nonvaricose) | 1 |
| ○ Previous DVT | 1 |
| ○ Alternative dx at least as likely as DVT | -2 |

Pretest Probability Assessment

| Score ≤0 | Score 1 or 2 | Score ≥3 |
|----------------------|----------------------------|------------------------|
| Low probability (5%) | Moderate probability (17%) | High probability (53%) |

- For UE DVT, + 1 point each for venous cath, local pain, & unilateral edema, -1 if alternative dx. ≤1 = unlikely; ≥2 = likely. U/S if likely or if unlikely but abnl D-dimer (Annals 2014;160:451).

Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (Annals 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower for asx DVT); survey whole leg rather than just proximal if ≥mod prob (JAMA 2010;303:438); venography rarely used

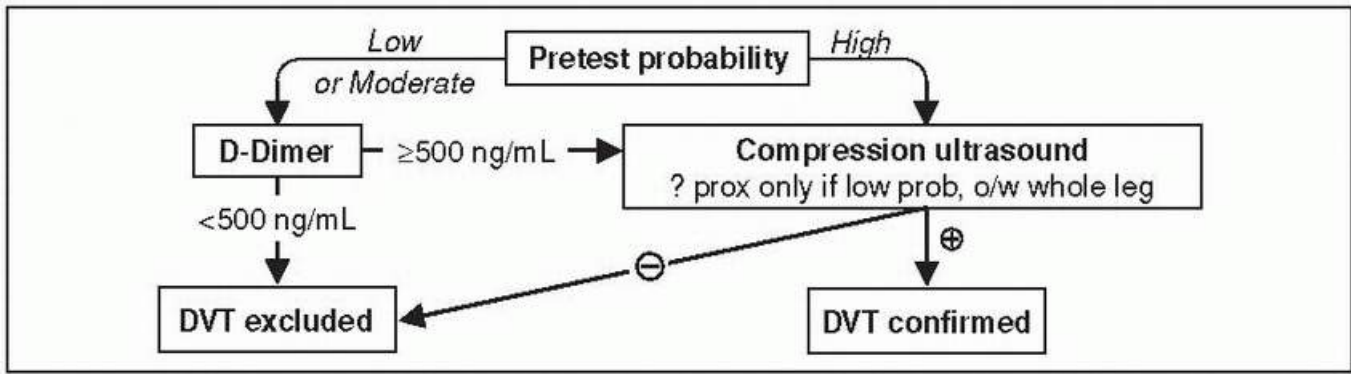


Figure 1-5 Approach to suspected DVT (*Chest* 2012;141:e351S)

Clinical manifestations—PE

- Dyspnea (73%), pleuritic chest pain (66%), cough (37%), hemoptysis (13%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P₂
- *Massive*: syncope, HoTN, PEA; ↑ JVP, R-sided S3, Graham Steell (PR) murmur

Simplified Wells Pretest Probability Scoring for PE (*Annals* 2011;154:709)

- Prior PE or DVT
- Active cancer
- Immobilization (bed rest ≥3 d) or surgery w/in 4 wk
- Alternative dx less likely than PE
- Clinical signs of DVT
- HR >100 bpm
- Hemoptysis

Dichotomized Wells Probability Assessment

≤1 Variable = “Unlikely” (13% probability)

> 1 Variable = “Likely” (39% probability)

Diagnostic studies—PE (*NEJM* 2010;363:266)

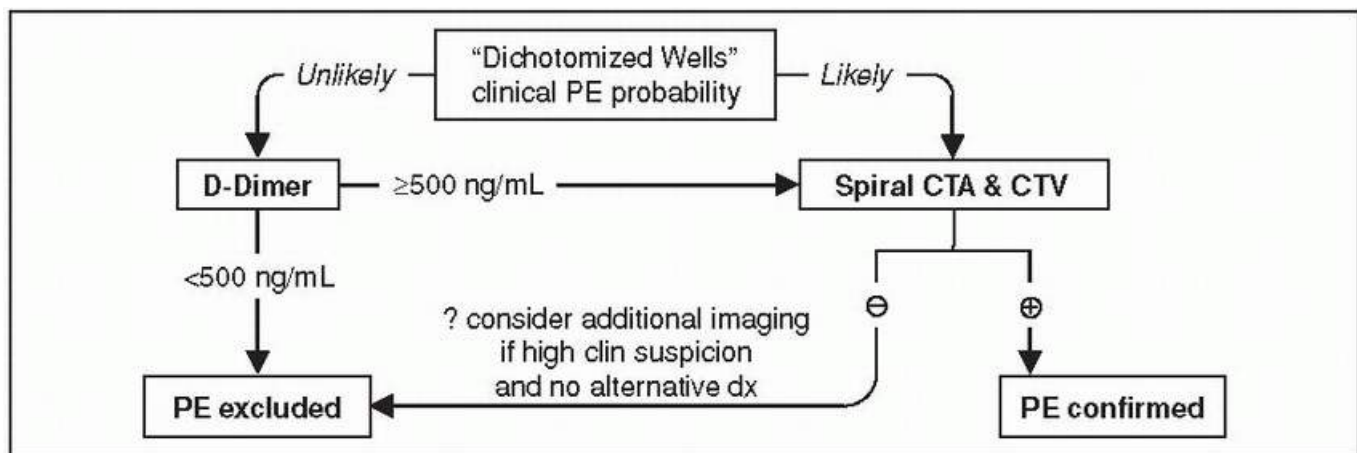
- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, S₁Q_{III}T_{III} & TWIV₁-V₄ (McGinn-White pattern; *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78), 18% w/ room air P_aO₂ 85-105 mmHg, 6% w/ nl A-a gradient (*Chest* 1991;100:598)
- D-dimer (*JAMA* 2015;313:1668): high Se, poor Sp (~25%); ⊖ ELISA has >99% NPV ∴ use to r/o PE if “unlikely” pretest prob. (*JAMA* 2006;295:172) consider age-specific cutpoint: 500 if <50 y, 10× age if ≥50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (~98%), low Sp (~10%). Sp improves to 97% for high prob VQ. Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low prob VQ, but 4% false ⊖

(*JAMA* 1990;263:2753).

- **CT angiography (CTA)**; see Radiology inserts; *JAMA* 2015;314:74): **Se** ~90% & **Sp** ~95% w/ MDCT (*NEJM* 2006;354:2317); **PPV** & **NPV** >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant ([need to consider both]); **CT** may also provide other **dx**
- Lower extremity compression **U/S** shows **DVT** in ~9%, sparing **CTA**, but when added to **CTA**, does not Δ outcomes (*Lancet* 2008;371:1343)

P.1-61

- Pulmonary angio: ? gold standard (morbidity 5%, mortality <0.5%), infrequently performed
- **MR** angiography: **Se** 84% (segmental) to 100% (lobar) (*Lancet* 2002;359:1643); if add **MR** venography, **Se** 92%, **Sp** 96% (*Annals* 2010;152:434)



Based on data from *NEJM* 2005;352:1760 & 2006;354:22; *JAMA* 2005;293:2012 & 2006;295:172

Figure 1-6 Approach to suspected PE using CTA

Workup for idiopathic VTE

- **Thrombophilia workup**: ✓ if ⊕ **FH**, may be helpful but consider timing as thrombus, heparin and warfarin Δ results. May not be helpful for **Pt** if will not change management (eg, plan for long-term anticoagulation regardless), although could be of use to relatives (*JAMA* 2005;293:2352; *Blood* 2008;112:4432; *Am J Med* 2008;121:458).
- **Malignancy workup**: 12% **Pts** w/ "idiopathic" **DVT/PE** will have malignancy; ageappropriate screening adequate; avoid extensive **w/u** (*NEJM* 1998;338:1169 & 2015;373:697)

Risk stratification for Pts with PE

- **Clinical**: hypotension and/or tachycardia (~30% mortality), hypoxemia
- **CTA**: **RV / LV** dimension ratio >0.9 (*Circ* 2004;110:3276)
- **Biomarkers**: ↑ troponin & ↑ **BNP** a/w ↑ mortality; w/ ⊖ **Tn**, decomp extremely unlikely (*Circ* 2002;106:1263 & 2003;107:1576; *Chest* 2015;147:685)
- **Echocardiogram**: **RV** dysfxn (even if normal troponin) (*Chest* 2013;144:1539)
- Simplified **PE** Severity Index: 0 **RFs** → 1.1% mort.; ≥1 → 8.9% mort (*Archives* 2010;170:1383) **RFs**: age >80 **y**; **h/o** cancer; **h/o** **HF** or lung disease; **HR** ≥110; **SBP** <100; **S_aO₂** <90%

Whom to treat (*Lancet* 2012;379;1835; *Chest* 2012;141:e419S)

- **Superficial venous thrombosis:** elevate extremity, warm compresses, compression stockings, NSAIDs for *sx*. *Anticoag* if high risk for *DVT* (eg, ≥ 5 cm, proximity to deep vein ≤ 5 cm, other risk factors) for 4 *wk* as $\sim 10\%$ have *VTE* w/in 3 *mo* (*Annals* 2010;152:218).
- **LE *DVT*:** proximal \rightarrow anticoag. If distal: anticoag if severe *sx*, o/w consider serial imaging over 2 *wk* and anticoag if extends (although if bleeding risk low, many would anticoag).
- **UE *DVT*:** anticoagulate (same guidelines as LE; *NEJM* 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- **PE:** anticoagulate

Anticoagulation options (*Chest* 2012;141:e419S; *JAMA* 2014;311:717)

- *Initiate immediately if high clinical suspicion or intermed but dx test results delayed for ≥ 4 h*
- Either (a) initial parenteral anticoag \rightarrow long-term oral anticoagulant (eg, warfarin or Xa inhibitor) or (b) solely with an oral Xa inhibitor
- **LMWH** (eg, enoxaparin 1 mg/kg *SC* bid or dalteparin 200 IU/kg *SC* qd)
Preferred over **UFH** (espec in *cancer*) except: renal failure (CrCl < 25), ? extreme obesity, hemodynamic instability or bleed risk (*Cochrane* 2004;CD001100)

No need to monitor anti-factor Xa unless concern re: dosing (eg, renal insuffic.)

Attractive option as outPt bridge to long-term oral anticoagulation

- If cancer, **LMWH** \downarrow recur. & mort. *c/w* **UFH** & warfarin (*NEJM* 2003;349:146; *Lancet Oncol* 2008;9:577; *JAMA* 2015;314:677); \checkmark head **CT** for brain mets if melanoma, renal, thyroid, chorioCA
- **Fondaparinux:** 5-10 mg *SC* qd (*NEJM* 2003;349:1695); use if **HIT** \oplus ; avoid if renal failure
- **DVT** & low-risk **PE** can be treated completely as outPt (*Lancet* 2011;378:41)
- **IV UFH:** 80 U/kg bolus \rightarrow 18 U/kg/h \rightarrow titrate to **PTT** 1.5-2.3 \times cntl (eg, 60-85 *sec*); preferred option when contemplating thrombolysis or catheter-based **Rx** (qv)
- IV Direct thrombin inhibitors (eg, argatroban, lepirudin) used in **HIT** \oplus Pts
- **Warfarin** (goal **INR** 2-3): start same day as parenteral anticoag unless instability and ? need for lytic, catheter-based **Rx** or surgery; overlap ≥ 5 *d w/* parenteral anticoag & until **INR** $\geq 2 \times \geq 24$ *h*
- **Oral Xa inhibitor:** effect wears off w/in 24 *h*, but not easily immediately reversed

Can give as sole anticoag (nb, initial doses higher than for **AF**): **rivaroxaban** (15 mg bid for 1st 3 *wk* \rightarrow 20 mg/d) as good/better than **LMWH** \rightarrow warfarin in preventing recurrent **VTE**, \downarrow bleeding (*NEJM* 2010;363:2499 & 2012;366:1287); **apixaban** (10 mg bid \times 7 *d* \rightarrow 5 bid) \approx **LMWH** \rightarrow warfarin in preventing recurrent **VTE**, \downarrow bleeding (*NEJM* 2013;369:799)

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Can initiate after ≥ 5 d of parenteral anticoag (1st dose when *d/c* IV **UFH** or w/in 2 *h* before when next **LMWH** dose would have been due): both **dabigatran** (150 mg bid) & **edoxaban** (60 mg qd) \approx warfarin but *w/* \downarrow bleeding (*NEJM* 2009;361:2342 & 2013;369:1406)

Systemic thrombolysis (*Chest* 2012;141:e419S)

- Typically TPA 100 mg over 2 *h* or wt-adjusted TNK bolus

- Indications & efficacy below; risk of **ICH** ~1.5%, ↑ **w/** age; see contraindications in “**ACS**”
- **Massive PE** (hemodynamic compromise): ↓ death and recurrent **PE** each by ~50% (*Circ* 2004;110:744; *JAMA* 2014;311:2414; *EHJ* 2015;36:605) & lower **PVR** long term (*JACC* 1990;15:65)
- **Submassive PE** (hemodyn. stable but **RV** dysfxn on echo or enlargement on **CTA**, or ? marked dyspnea or severe hypoxemia): ↑ death & ↑ bleeding; may consider if low bleed risk (see lytic contra-indic.; *EHJ* 2015;36:605). Benefit/risk may be more favorable if <75 y (*NEJM* 2014;370:1402; *JAMA* 2014;311;2414). Some centers prefer catheter-directed **Rx** (qv).
- **Moderate PE w/ large clot burden** (≥2 lobar arteries or main artery on **CT** or high prob VQ **w/** ≥2 lobes **w/** mismatch): *low-dose lytic* (50 mg if ≥50 kg or 0.5 mg/kg if >50 kg; for both 10 mg bolus → remainder over 2 h) ↓ pulm **HTN w/** ≈ bleeding vs heparin alone; await further validation (*Am J Cardiol* 2013;111:273)
- **DVT**: consider if all are present (a) acute (< 14 d) & extensive (eg, iliofemoral), (b) severe symptomatic swelling or ischemia (phlegmasia cerulea dolens), (c) catheter-directed **Rx** not available, and (d) low bleeding risk

Mechanical intervention

- **Catheter-directed therapy** (fibrinolytic & thrombus fragmentation/aspiration)
 - Consider if extensive **DVT** (see above) and to ↓ post-thrombotic synd (*Lancet* 2012;379:31)
 - Consider if **PE w/** hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy (*Circ* 2011;124:2139). Preferred to systemic lytic by some centers.
 - U/S-assisted → improves hemodynamics & **RV** fxn vs anticoag alone (*EHJ* 2015;36:597)
- **Thrombectomy**: if large, proximal **PE** + hemodynamic compromise + contra. to lysis; consider in experienced ctr if large prox. **PE** + **RV** dysfxn (*J Thorac CV Surg* 2005;129:1018)
- **IVC filter**: use instead of anticoagulation if latter contraindicated
 - No benefit to adding to anticoag (including in submassive) (*JAMA* 2015;313:1627)
 - Consider removable filter for temporary indications
 - Complications: migration, acute **DVT**, ↑ risk of recurrent **DVT** & **IVC** obstruction (5-18%), which may lead to worsening LE **sx** (*Archives* 1992;152:1985)

Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 **wk**
- 1st prox **DVT** or **PE** 2^o reversible/time-limited risk factor or distal **DVT**: 3-6 **mo**
- 1st *unprovoked* prox **DVT/ PE**: ≥3 **mo**, then reassess; benefit to prolonged **Rx** (see below). Consider bleeding risk, **Pt** preference and intensity of extended **Rx**.
- 2nd **VTE** event or cancer: indefinite (or until cancer cured) (*NEJM* 1997;336:393 & 2003;348:1425)
- Does *not* appear that can rely on D-dimer testing to guide **d/c** (*Annals* 2015;162:27)

Extended antithrombotic strategies (*JAMA* 2015;314:72)

- After ≥6 **mo** of anticoag, following strategies have been compared **w/ no extended Rx**:
- Full-dose dabigatran, rivaroxaban, or apixaban: 80-90% ↓ recurrent **VTE**, 2-5× bleeding, but no signif excess

in major bleeding (*NEJM* 2010;363:2499; 2013;368:699 & 709)

- Full-dose warfarin: 85% ↓ reduction in recurrent **VTE** (*JAMA* 2015;314:31)
- Low-intensity warfarin (**INR** 1.5-2.0): 64% ↓ reduction in recurrent **VTE** (*NEJM* 2003;348:1425)
- Low-intensity apixa (2.5 mg bid): 80% ↓ recur. **VTE**, w/o signif ↑ bleeding (*NEJM* 2013;368:699)
- Aspirin: 32% ↓ recurrent **VTE** (*NEJM* 2012;366:1959 & 367:1979)

Other therapeutic interventions

- Early ambulation
- For **DVT**: fitted graduated compression stockings (min 20-30 mmHg → 30-40 mmHg) for **sx** & to ↓ risk of postthrombotic synd (occurs in 23-60%; *J Thromb Thrombolysis* 2009;28:465)
- Leg elevation and exercise (use of calf muscle pump) also may be helpful
- Anticoag teaching: avoidance of high-risk activities, med alert bracelet, dietary instructions

Complications & prognosis

- Post-thrombotic syndrome (23-60%): thrombosis → injury to vein/valves → pain, edema, venous ulcers (*J Thromb Thrombolysis* 2009;28:465)
- Recurrent **VTE**: 1%/y (after 1st **VTE**) to 5%/y (after recurrent **VTE**) after only 6 mo of **Rx**: 5%/y & > 10%/y, respectively

predictors: **abnl** D-dimer 1 mo after **d/c** anticoag (*NEJM* 2006;355:1780); ⊕ **U/S** after 3 mo of anticoag (*Annals* 2002;137:955); thrombin generation >400 nM (*JAMA* 2006;296:397)
- Chronic thromboembolic **PHT** after acute **PE** ~3.8% (*NEJM* 2004;350:2257), consider thromboendarterectomy
- Mortality: ~10% for **DVT** and ~10-15% for **PE** at 3-6 mo (*Circ* 2008;117:1711)

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PULMONARY HYPERTENSION (PHT)

PA mean pressure ≥25 mmHg at rest

Pathobiology (*NEJM* 2004;35:1655)

- Smooth muscle & endothelial cell proliferation; mutations in bone morphogenic protein receptor 2 (**BMPR2**) in ~50% familial & ~26% sporadic cases of **IPAH** (*NEJM* 2001;345:319)
- Imbalance between vasoconstrictors and vasodilators
↑ vasoconstrictors: thromboxane A₂ (TXA₂), serotonin (5-HT), endothelin-1 (ET-1)
↓ vasodilators: prostacyclin (PGI₂), nitric oxide (**NO**), vasoactive peptide (VIP)
- *In situ* thrombosis: ↑ TXA₂, 5-HT, PAI-1; ↓ PGI₂, **NO**, VIP, tissue plasminogen activator

Etiologies of Pulmonary Hypertension (Revised WHO Classification)

Pulmonary arterial **HTN**

- Idiopathic (**IPAH**): mean age of onset 36 y (♂ older than ♀); ♀:♂ = ~2:1,

| | |
|--|---|
| <p>(PAH) (group 1)</p> | <p>usually mild ↑ in PAP</p> <ul style="list-style-type: none"> • Familial (FPAH) • Associated conditions (APAH) Connective tissue disorders: CREST, SLE, MCTD, RA, PM, Sjögren Congenital: L→R shunts: ASD, VSD, PDA, 1° PHT of newborn Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) HIV; drugs & toxins: anorexic agents, rapeseed oil, L-tryptophan • Pulmonary veno-occlusive disease: ? 2° chemo, BMT; orthopnea, pl eff, nl PCWP; art vasodil. worsen pulm edema (AJRCCM 2000;162:1964) • Pulmonary capillary hemangiomatosis |
| <p>Left heart disease (group 2)</p> | <ul style="list-style-type: none"> • Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR > AS/AR) • Congenital: left-sided inflow/outflow obstruction, CMP |
| <p>Lung diseases and/or chronic hypoxemia (group 3)</p> | <ul style="list-style-type: none"> • COPD • ILD • Sleep apnea • Alveolar hypoventilation (eg, NM disease) • Chronic hypoxemia (eg, high altitude) • Developmental abnormalities |
| <p>Chronic thrombo-embolic dis (group 4)</p> | <ul style="list-style-type: none"> • Prox or distal PEs; ~½ w/o clinical h/o PE (Circ 2014;130:508) • Nonthrombotic emboli (tumor, foreign body, parasites) |
| <p>Miscellaneous (group 5)</p> | <ul style="list-style-type: none"> • Sarcoidosis, histiocytosis X, LAM, schistosomiasis • Metab: thyroid, glycogen storage, Gaucher • Heme: chronic hemolytic anemia, myeloprolif d/o, splenectomy • Other: compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT); HHT (multifactorial) <p>(Circ 2013;62:25S)</p> |

Clinical manifestations

- Dyspnea, exertional syncope (hypoxia, ↓ CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II = sx w/ ord. activ.; III = sx w/ min activ.; IV = sx at rest

Physical exam

- PHT: prominent P₂, R-sided S₄, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (Circ 2014;130:1820)

- IPAH yearly incidence 1-2 per million, ∴ r/o 2° causes

- High-res chest CT: dil. & pruning of pulm arteries, ↑ RA and RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE (“P pulmonale”), RVH (Se 55%, Sp 70%)
- PFTs: disproportionate ↓ D_Lco, mild restrictive pattern; r/o obstructive & restrict. lung dis.
- ABG & polysomnography: ↓ P_aO₂ and S_aO₂ (espec w/ exertion), ↓ P_aCO₂, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but estimate over/under by ≥10 mmHg in ½ of PHT Pts; *Chest* 2011;139:988)
 - ↑ RA, RV (RV:LV area >1) and PA size; TR, PR
 - ↑ RVSP → interventricular septum systolic flattening (“D” shape)
 - ↑ RAP → interatrial septum bowing into LA
 - ↓ RV systolic fxn: TAPSE (tricuspid annular plane systolic excursion) < 1.6 cm; lateral-septal tissue-Doppler imaging disparity (reflecting relatively more systolic dysfxn of RV lateral wall vs septum, which is shared with LV)
 - ↑ PA impedance ↑ RVOT Doppler notching
 - r/o LV dysfxn, MV or AoV disease, and congenital heart disease
- RHC: ↑ RA, RV, & PA pressures; ✓ L-sided pressures and for shunt if PAH: nl PCWP, ↑ transpulm gradient (mean PAP-PCWP > 12-15), ↑ PVR, ± ↓ CO if 2° to L-heart disease: PCWP (or LVEDP) > 15; if PVR nl → “passive PHT”; PVR >240 suggests mixed picture: if ↓ PCWP → ↓ PVR, then “reactive” PHT; if no Δ, then “fixed”

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- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH), ± pulmonary angiogram: r/o PE and chronic thromboembolic disease
- Vasculitis labs: ANA (~40% ⊕ in PAH), RF, anti-Scl-70, anticentromere, ESR
- LFTs & HIV: r/o portopulmonary and HIV-associated PAH
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Differentiating Left Heart Disease from Alternative PHT Etiologies

| Feature | Favors Left Heart Disease | Favors Alternative Etiology |
|---------|--|--|
| History | Prior MI, CMP, AoV or MV disease, CV risk factors (HTN, diabetes), ↑ age | Family hx PHT, connective tissue disorder, pulm, liver or hematologic disease, HIV, h/o VTE |
| PEx | L-sided S3, S4 L-sided murmurs Displaced apical impulse Coarse rales | Cyanosis, clubbing Fine rales; signs of COPD Raynaud's, sclerodactyly, telangiectasia Splenomegaly, spider angiomas |
| ECG | Q waves, LVH, LBBB | Isolated RAE, RVH, S ₁ Q _{III} T _{III} pattern |

| | | |
|------|--|--|
| Echo | LV systolic or diastolic dysfxn LVH, ↑ LA size ≥ Moderate MV or AoV disease | Isolated RV or RA enlargement Interventricular septum systolic flattening and/or interatrial septum bowing into LA ↓ RV systolic fxn |
| RHC | ↑ L-sided filling pressures Abrupt ↑ PCWP (to > 20-25) w/ exercise or volume loading | PCWP <15 mmHg Exercise PCWP <20-25 mmHg |

Treatment (JACC 2013;62:25S & 2015;65:1976)

- Principles

- 1) prevent and reverse vasoactive substance imbalance and vascular remodeling
- 2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq. systemic DBP

- Supportive

Oxygen: maintain S_aO_2 >90-92% (reduces vasoconstriction)

Diuretics: ↓ RV wall stress and relieve RHF sx; gentle b/c RV is preload dependent

Digoxin: control AF, ? counteract neg. inotropic effects CCB

Dobutamine and inhaled NO or prostacyclin for decompensated PHT

Anticoagulation: ↓ VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mortality benefit even if in NSR, no RCTs (*Circ* 1984;70:580; *Chest* 2006;130:545)

Supervised exercise training (*Eur Respir J* 2012;40:84)

- Vasodilators (right heart catheterization prior to initiation) *acute vasoreactivity test*: use inhaled NO, adenosine or prostacyclin to identify Pts likely to have a long-term response to oral CCB (⊕ vasoreactive response defined as ↓ PAP ≥10 mmHg to a level <40 mmHg with ↑ or stable CO); ~10% Pts are acute responders; no response → still candidates for other vasodilators (*NEJM* 2004;351:1425)

Vasoactive agents

Comments (data primarily in Group 1 PAH)

Oral CCB
Nifedipine,
diltiazem

If ⊕ acute vasoreactive response; <½ will be long-term responder (NYHA I/II & near-nl hemodynamics) & have ↓ mortality. Side effects: HoTN, lower limb edema (*NEJM* 1992;327:76; *Circ* 2005;111:3105).

IV Prostacyclin
Epoprostenol
(Flolan)

Vasodilation, ↓ plt agg, ↓ smooth muscle proliferation; benefits ↑ w/ time (? vascular remodeling). ↑ 6MWT, ↑ QoL, ↓ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn (*NEJM* 1996;334:296 & 1998;338:273; *Annals* 2000;132:425).

Prostacyclin analogues
Iloprost (inhaled)
Treprostinil (IV, inh, SC)
Beraprost (PO)

Same mechanism as prostacyclin IV, but easier to take, ↓ side effects, and w/o risk of catheter infxn, ↓ sx, ↑ 6MWT; trend to ↓ clinical events w/ iloprost but not treprostinil. Beraprost w/o sustained outcome improvement (n/a in U.S.) (*NEJM* 2002;347:322; *AJRCCM* 2002;165:800).

Endothelin receptor antagonists (ERAs)
Bosentan, ambrisentan, macitentan

↓ Smooth muscle remodeling, vasodilation, ↓ fibrosis, ↓ **sx**, ↑ 6MWT, ↓ worsening PAH or need for prostanoids **w/** trend for ↓ PAH mortality (**w/** macitentan). Side effects: ↑ **LFTs**, headache, anemia, edema, teratogen (*NEJM* 2002;346:896; *JACC* 2005;46:529; *Circ* 2008;117:3010; *NEJM* 2013;369:809).

PDE-5 Inhibitor
Sildenafil, tadalafil

↑ cGMP → vasodilation, ↑ smooth muscle proliferation, ↓ **sx**, ↑ 6MWT, no data on clinical outcomes. Low side-effect profile: **HA**, vision Δ's, sinus congestion (*NEJM* 2009;361:1864).

Soluble guanylate cyclase stimulator
Riociguat

NO-independent ↑ cGMP → vasodilation, ↑ smooth muscle proliferation, ↓ **sx**, ↑ 6MWT in PAH; ↓ **sx**, ↓ **PVR**, ↑ 6MWT in **CTEPH** (*NEJM* 2013;369:319 & 330)

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- Up front combination **Rx** (tadalafil + ambrisentan vs monotherapy): ↓ **sx**, ↓ NT-BNP, ↑ 6MWT, ↓ hospitalizations (*NEJM* 2015;373:834)
- Treat underlying causes of 2° **PHT**; can use vasodilators, although little evidence beyond riociguat use for **CTEPH** as described above
- Refractory **PHT**:
balloon atrial septostomy: R→L shunt causes ↑ **CO**, ↓ S_aO_2 , net ↑ tissue O_2 delivery lung transplant (single or bilateral); heart-lung needed if Eisenmenger physiology

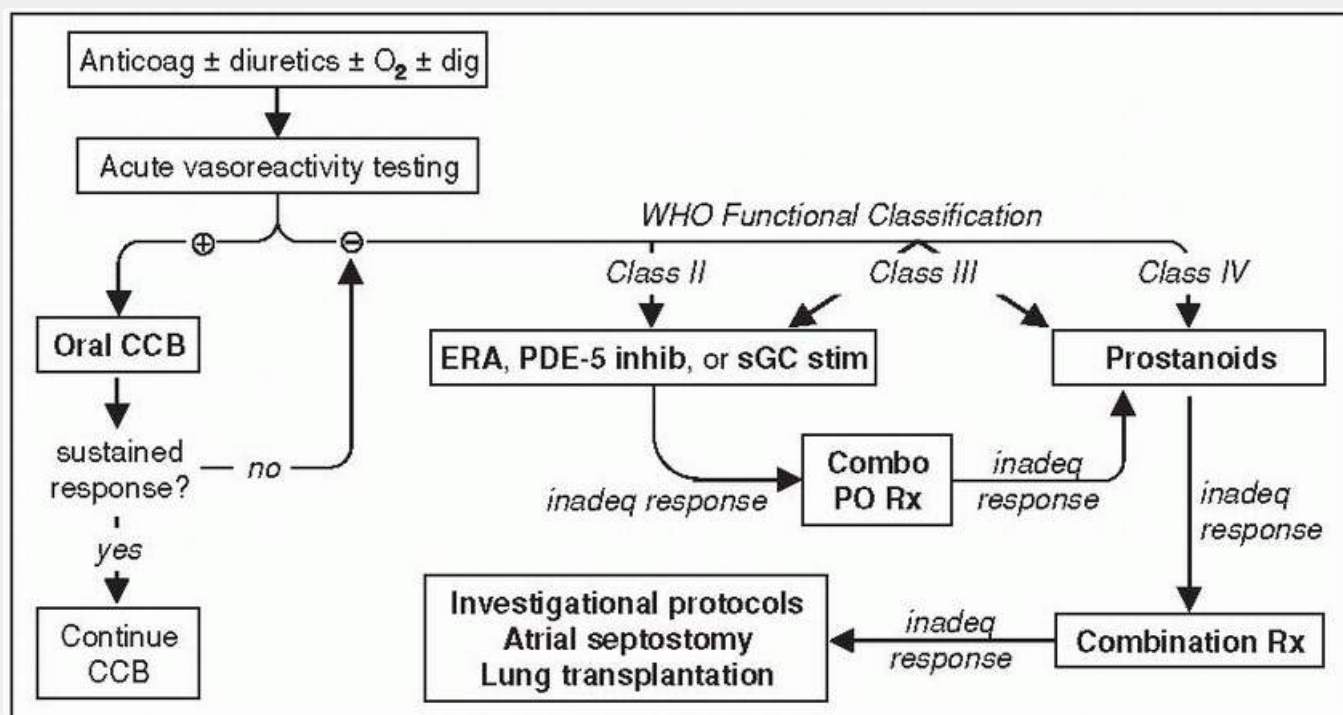


Figure 1-7 Treatment of PAH (modified from *JACC* 2009;54:S78)

Management of ICU patient

- Avoid overly aggressive volume resuscitation
- Caution with vasodilators if any L-sided dysfunction
- May benefit from inotropes/chronotropes
- Mechanical RV support (RVAD, ECMO) (*Circ* 2015;132:526)
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

Prognosis

- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78-S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT <300 m, peak VO₂ <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)
- Lung transplant: 1-y survival 66-75%; 5-y survival 45-55% (*Chest* 2004;126:63-S)

Arrhythmias

BRADYCARDIA AND AV BLOCK

BRADYCARDIAS

Sinus bradycardia (SB) (*NEJM* 2000;342:703)

- Etiologies: **meds** (incl β B, CCB, amio, Li, dig), → **vagal tone** (incl. in athletes, sleep, IMI), **metabolic** (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no **sx**, none; atropine, β_1 agonists or long-term permanent pacing if **sx**
- Most common cause of sinus pause is *blocked premature atrial beat*

Sick sinus syndrome (SSS)

- Features may include: periods of unprovoked SB, SA arrest, paroxysms of SB and atrial tachyarrhythmias (“tachy-brady” syndrome), chronotropic incompetence w/ ETT
- Treatment: meds alone usually fail (adeq. control of tachy → unacceptable brady); usually need **combination of meds** (β B, CCB, dig) for tachy & PPM for brady

Pseudobradycardia

- Intermittent PVCs (with low stroke volume and hence low pulse wave) followed by compensatory pause can cause ascertainment of HR by palpation of radial pulse to be artifactually low

AV BLOCK AND AV DISSOCIATION

AV Block

| Type | Features |
|--------------------------|--|
| 1° | Prolonged PR (>200 ms), all atrial impulses conducted (1:1) |
| 2° Mobitz I (Wenckebach) | Progressive ↑ PR until impulse not conducted (↑ “grouped beating”) Due to AV node conduction delay: ischemia (IMI), inflammation (myocarditis, MV surgery), high vagal tone (athletes), drug-induced QRS duration most often normal AVB usually worsens w/ carotid sinus massage, improves w/ atropine & exercise Often paroxysmal/nocturnal/asymptomatic; no Rx required |
| 2° Mobitz II | Occasional or repetitive blocked impulses w/ consistent PR interval. Nb, do not confuse with APBs in bigeminal pattern; to dx AVB, atrial rate should be <i>regular</i> and P waves should be the <i>same</i> . Due to His-Purkinje conduction delay: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/valve surgery QRS duration most often prolonged AVB usually improves w/ carotid sinus massage, worsens w/ atropine & exercise (both of which should be <i>avoided</i> if dx suspected) Risk of progression to 3° AVB. Zoll at bedside when recognized; temp pacing wire or PPM often required. |

3° (complete) No AV conduction, with ventricular rhythm slower than atrial rhythm. Escape, if present, is regular and can be narrow (jxnal) or wide (vent.) Urgent temporary pacing as bridge to permanent pacing is appropriate in most scenarios, especially when syncope is present.

Nb, if 2:1 block, cannot distinguish type I vs II 2° AVB (no chance to observe PR prolongation); usually categorized based on other ECG & clinical data. High-grade AVB usually refers to block of ≥2 successive impulses. All categories above assume SR in atrium, criteria do not apply during rapid atrial rates, such as in atrial flutter or tachycardia.

AV dissociation

- *Default:* slowing of SA node allows subsidiary pacemaker (eg, AV junction) to take over
- *Usurpation:* acceleration of subsidiary pacemaker (eg, AV junctional tach, VT)
- *3° AV block:* atrial pacemaker unable to capture ventricles, subsidiary pacemaker emerges; distinguish from *isorhythmic dissociation* (A ≈ V rate, some P waves nonconducting)

Temporary pacing wires

- Consider w/ bradycardia with hemodynamic instability or unstable escape rhythm when permanent pacemaker not readily available. Risks: RV perforation, VT, PTX, CHB if existing LBBB, etc.
- Consider instead of PPM for *symptomatic* bradycardia due to reversible cause (βB/CCB O/D, Lyme, myocarditis, SBE, s/p cardiac surgery/trauma), TdP, acute MI (*symptomatic* brady, high-grade AVB)

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SUPRAVENTRICULAR TACHYCARDIAS

PALPITATIONS

Etiologies

- PACs, PVCs; SVT, AF, VT, respiratory sinus arrhythmia; pauses; noncardiac

Workup

- History: duration & frequency; initiating & aggravating factors: exercise, alcohol, stimulants (caffeine, pseudoephedrine, other prescription & recreational drugs); h/o presyncope or syncope; FHx of arrhythmia, CMP, SCD
- Structural evaluation w/ echo; consider ETT if exercise-induced or other RF; TFTs
- Ambulatory cardiac monitoring: *must monitor during symptoms to diagnose!* Holter (worn continuously): if *symptomatic* typically occur within a 24-48-hr period. Looping event monitor (worn continuously): if *symptomatic* fleeting. Nonlooping event monitor (put on during *symptomatic*): if rarer episodes lasting minutes

Treatment (for SVT and VT, see respective sections)

- Simple ectopy in structurally normal heart: reassurance, βB, CCB. If refractory, frequent *symptomatic* with poor QoL, antiarrhythmic drug, such as flecainide, can be tried in consultation w/ electrophysiologist. Rarely catheter ablation for frequent PVCs.

- If NICM and > 13% PVCs, elim of ectopy w/ catheter ablation can significantly ↑ EF (JACC 2013;62:1195). However, risk of *developing* CMP due to frequent PVCs not established.

SUPRAVENTRICULAR TACHYCARDIAS (SVTS)

Arise above the ventricles, ∴ **narrow QRS** unless aberrant conduction or pre-excitation

Common Etiologies of SVT (NEJM 2006;354:1039 & 2012;367:1438)

| Type | Features |
|--|--|
| Sinus tachycardia (ST) | Caused by pain, fever, hypovolemia, hypoxia, anemia, anxiety, β-agonists, etc. |
| Atrial tachycardia (AT) | Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig. |
| Atrial | |
| Multifocal atrial tachycardia (MAT) | ↑ automaticity at multiple sites in the atria. Seen with underlying pulmonary disease. |
| Atrial flutter (AFL) | Macroreentry, usually w/in right atrium |
| Atrial fibrillation (AF) | Chaotic atrial activation and rapid, irregular bombardment of AVN |
| AV nodal reentrant tach (AVNRT) | Reentrant circuit using dual pathways w/in AVN |
| AV reciprocating tachycardia (AVRT) | Reentrant circuit using AVN antegrade and accessory pathway retrograde. When in sinus rhythm may show pre-excitation (WPW) or not (concealed accessory pathway). |
| AV Jxn | |
| Paroxysmal junctional reciprocating tachycardia (PJRT) | Reentry using AVN & slowly conducting concealed posterosept acc path. More common in peds, at times w/ tachy-induced CMP. |
| Nonparoxysmal junctional tachycardia (NPJT) | ↑ jxnal automaticity. May see retrograde P's & AV dissociation. A/w myo/endocarditis, cardiac surg, IMI, dig. |

Diagnosis of SVT Type (NEJM 2006;354:1039 & 2012;367:1438)

Onset Abrupt on/off argues against sinus tachycardia

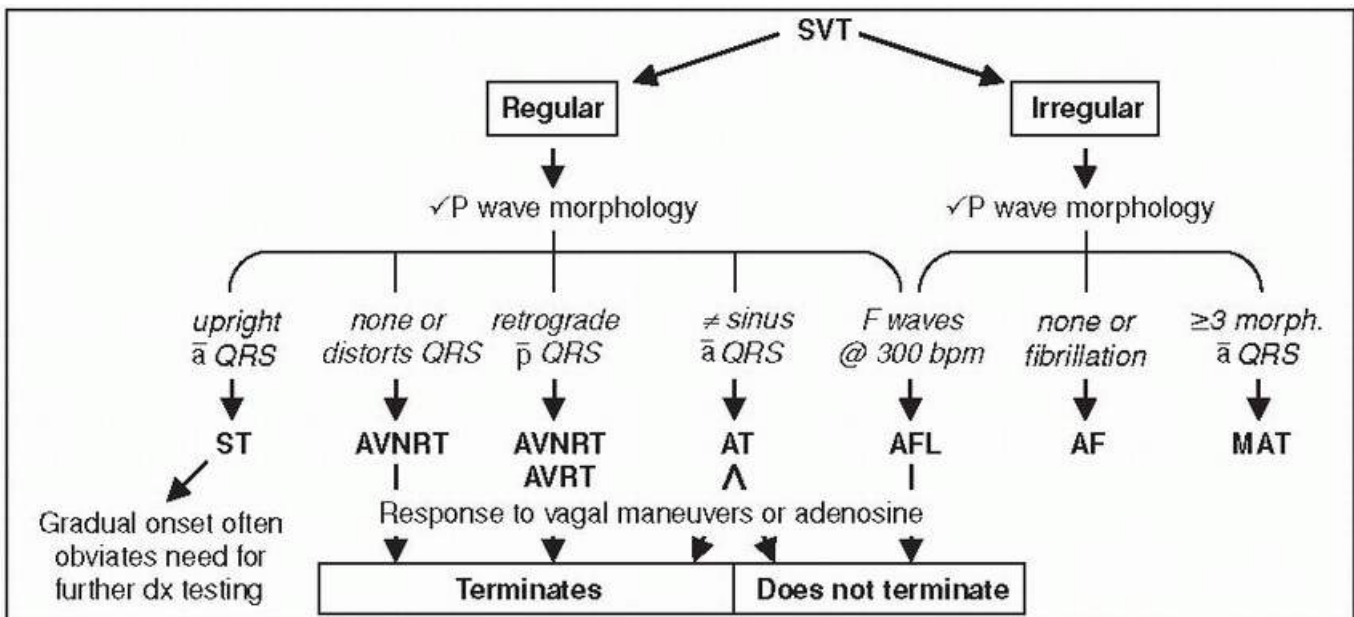
Rate Not dx as most can range from 140-250 bpm, *but*: **ST** usually <150; **AFL** often conducts 2:1 → vent. rate 150; **AVNRT** & **AVRT** usually >150

Rhythm Irregular → **AF**, **AFL w/** variable block, or **MAT**

P wave Long RP: **ST** (P same as sinus), **AT**, **MAT** (≥3 morphologies), **PJRT** Short RP, P inverted in inf. leads → *retrograde* atrial activation via **AVN AVNRT**: buried in or distort terminal portion of QRS (pseudo-RSR' in V₁) **AVRT**: slightly after QRS (RP interval > 100 ms favors **AVRT** vs **AVNRT**) **NPJT**: either no P wave or retrograde P wave similar to **AVNRT** *Fibrillation or no P waves* → **AF** *Saw-toothed "F" waves* (best seen in inferior leads & V₁) → **AFL**

Response to vagal stim. or adenosine Slowing of **HR** often seen with **ST**, **AF**, **AFL**, **AT**, whereas reentrant rhythms (**AVNRT**, **AVRT**) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ **AT** may terminate. **AFL** & **AF** → ↑ **AV** block → unmasking of "F" waves or fibrillation

Short RP: P wave closer to preceding than following QRS (ie, RP < PR). Long RP: P wave closer to following than preceding QRS (ie, PR < RP).



(Adapted from NEJM 2012;367:1438)

Figure 1-8 Approach to SVT

Treatment of SVT

| Rhythm | Acute treatment | Long-term treatment |
|----------|-------------------------------|---------------------|
| Unstable | Cardioversion per ACLS | n/a |

| | | |
|------------------|--|--|
| ST | Treat underlying stressor(s) | n/a |
| AT | β B, CCB or amiodarone; ? vagal maneuvers or adenosine | β B or CCB, \pm antiarrhythmics, possibly radiofrequency ablation (RFA) |
| AVNRT or AVRT | Vagal maneuvers Adenosine (caution in AVRT*) CCB or β B | For AVNRT (see next section for AVRT): RFA . CCB or β B (chronic or prn) \pm Class IC antiarrhythmics (if nl heart) |
| NPJT | CCB, βB, amiodarone | Rx underlying dis. (eg, dig tox, ischemia) |
| AF | βB, CCB, digoxin, AAD | See "Atrial Fibrillation" |
| AFL | βB, CCB, digoxin, AAD | RFA; β B or CCB \pm antiarrhythmics |
| MAT | CCB or β B if tolerated | Treat underlying disease process AVN ablation + PPM if refractory to meds |

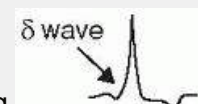
*Avoid adenosine & nodal agents if accessory pathway + preexcited tachycardia, see below (JACC 2003;42:1493)

- **Catheter ablation:** high overall success rate (AFL/AVNRT ~95%, AVRT ~90%, AF ~80%) Complications: stroke, MI, bleeding, perforation, conduction block (JAMA 2007;290:2768)

ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)

Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting atria & ventricles, allowing impulses to bypass normal AVN delay
- **Preexcitation (WPW) pattern:** \downarrow PR interval, \uparrow QRS width w/ δ wave (slurred onset, *can be subtle*), ST & Tw abnl (can mimic old IMI);
only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde then ECG will be normal during SR; "concealed" bypass tract)
PAC can exaggerate preexcitation if AV node conduction slowed
- **WPW syndrome:** accessory pathway + paroxysmal tachycardia



Classic tachycardias of WPW

- **Orthodromic AVRT:** narrow-complex SVT (typically), conducting \uparrow AVN & \uparrow accessory pathway; requires retrograde conduction and \therefore can occur w/ concealed bypass tracts
- **Antidromic AVRT** (less common): wide-complex regular tachycardia, conducting \downarrow accessory pathway & \uparrow

AVN. Can meet many **ECG** morphology criteria for **VT**. Requires antegrade conduction and .*. should see **WPW** pattern during **SR**.

- **AF w/** rapid conduction down accessory pathway; .*. wide-complex irregular **SVT**; requires antegrade conduction; .*. should see **WPW** pattern in **SR**. Rarely can degenerate into **VF**.

Treatment

- **AVRT:** vagal, β B; caution w/ adenosine (can precip. **AF**); *have defibrillator ready*
- **AF/AFL w/** conduction down accessory pathway: need to **Rx** arrhythmia *and* \uparrow pathway refractoriness; use **procainamide**, **ibutilide**, or **DCCV**; avoid **CCB** & β B, dig/adenosine (can \downarrow refractoriness of pathway \rightarrow \uparrow vent. rate \uparrow **VF**)
- **Long term:** **Rx sx** tachycardias w/ **RFA**, antiarrhythmics (**IA**, **IC**) if not candidate for **RFA**.
Consider **RFA** if **asx** but **AVRT** or **AF** inducible on **EPS** (*NEJM* 2003;349:1803) or if rapid conduction possible (\checkmark w/ **EPS** if preexcitation persists despite exercise testing).
Risk of **SCD** related to how short **RR** interval is in **AF** and # of accessory pathways present. Exercise testing to look for loss of pre-excitation can be used as a proxy for short **RR** interval in **AF**: if pathway still present at peak exercise, more concerning.

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ATRIAL FIBRILLATION

Classification (*Circ* 2014;130:2071)

- **Paroxysmal** (terminates spontaneously or w/ **Rx** w/in 7 d) vs **persistent** (sustained >7 d) vs **long-standing persistent** (>1 y) vs **permanent** (no plan to restore or maintain **SR**)
- **Nonvalvular** (**AF** absent rheumatic **MS**, prosthetic valve or mitral valve repair) vs **valvular**
- **Lone AF** = age <60 y and w/o clinical or echo evidence of cardiac disease (including **HTN**)

Pathophysiology

- Disorganized atrial electrical activity \rightarrow ineffective atrial mechanical contraction
- For paroxysmal **AF**, >90% triggered by rapid firing in pulmonary veins (*NEJM* 1998;339:659)

Epidemiology and etiologies (*Annals* 2008;149:ITC5-2)

- 1-2% of pop. has **AF** (8% of elderly); lifetime risk 25%; mean age at presentation \sim 75 y
- Acute (up to 50% w/o identifiable cause)

Cardiac: **HF**, myo/pericarditis, ischemia/**MI**, hypertensive crisis, cardiac surgery

Pulmonary: acute pulmonary disease or hypoxia (eg, **COPD** flare, **PNA**), **PE**, **OSA**

Metabolic: high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis

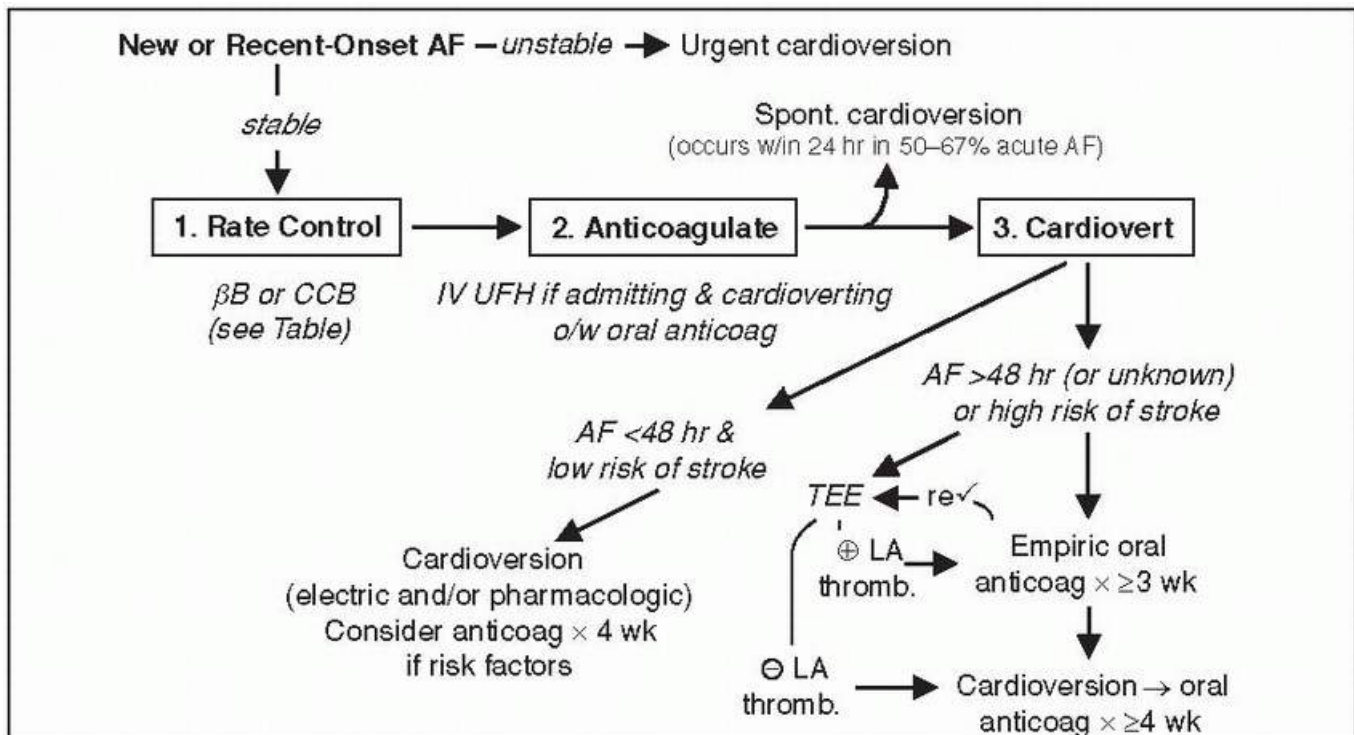
Drugs: alcohol (“holiday heart”), cocaine, amphetamines, theophylline, caffeine

Neurogenic: subarachnoid hemorrhage, ischemic stroke

- Chronic: \uparrow age, **HTN**, ischemia, valve dis. (**MV**, **TV**, **AoV**), **CMP**, hyperthyroidism, obesity

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), K, Mg, FOBT before anticoag, TFTs; r/o MI not necessary unless other ischemic sx



(Adapted from *NEJM* 2004;351:2408; *JACC* 2006;48:e149)

Figure 1-9 Approach to acute AF

Rate control

- If sx, goal HR <80; if asx & EF >40%, goal HR <110 at rest (*NEJM* 2010;362:1363)
- AV node ablation + PPM if pharmacologic Rx inadequate (*NEJM* 2001;344:1043; 2002;346:2062)

Rate Control for AF

| Agent | Acute (IV) | Maint. (PO) | Comments |
|-------------------|--|-------------------------------|--|
| Verapamil | 5-10 mg over 2' may repeat in 30' | 120-360 mg/d in divided doses | ↓ BP (Rx w/ Ca gluc) Can worsen HF Preferred if severe COPD Can ↑ dig levels |
| CCB | | | |
| Diltiazem | 0.25 mg/kg over 2' may repeat after 15' 5-15 mg/h infusion | 120-360 mg/d in divided doses | |
| βB | | | |
| Metoprolol | 2.5-5 mg over 2' may repeat q5' × 3 | 25-100 mg bid or tid | ↓ BP (Rx w/ glucagon) Preferred if CAD Risks: HF & bronchospas. |

| | | | |
|---------------------------------|---------------------------------------|----------------------------------|---|
| Digoxin* (onset >30 min) | 0.25 mg q2h up to 1.5 mg | 0.125-0.375 mg qd (adj for CrCl) | Consider in HF or low BP Poor exertional HR ctrl |
| Amiodarone | 300 mg over 1 h → 0.5-1 mg/min × 24 h | 100-200 mg QD | Consider in HF or low BP Long-term potential tox |

IV β B, CCB and digoxin **contraindicated** if evidence of **WPW** (ie, pre-excitation or **WCT**) since may facilitate conduction down accessory pathway leading to **VF**; ∴ use procainamide, ibutilide or amiodarone

*Many meds incl. amio, verapamil, quinidine, propafenone, macrolides & azole antifungals ↑ digoxin levels.

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Cardioversion

- Consider pharm or electrical cardioversion w/ 1st **AF** episode or if **sx**; if **AF** >48 h, 2-5% risk stroke w/ cardioversion (*pharmacologic or electric*) ∴ either **TEE** to *r/o* thrombus or ensure therapeutic anticoagulation for ≥3 **wk** prior if need to cardiovert urgently, anticoagulate acutely (eg, IV **UFH**)
- Likelihood of success ∝ **AF** duration & atrial size; control precip. (eg, vol status, thyroid)
- Consider pre-Rx w/ antiarrhythmic drugs (eg, ibutilide), espec if 1st cardioversion fails
- For pharmacologic cardioversion, class III and **IC** drugs have best proven efficacy
- If **SR** returns (spont. or w/ Rx), atria may be *mech. stunned*; also, high risk of recurrent **AF** over next 3 **mo**. ∴ **Anticoag postcardioversion ≥ 4 wk** (? unless <48 h and low risk).

Rhythm control (*Lancet* 2012;379:648; *Circ* 2014;130:2071)

- No clear survival benefit or ↓ stroke risk vs rate control (*NEJM* 2002;347:1825 & 2008;358:2667)
- Consider if *symptomatic* w/ rate control (eg, heart failure), difficult to control rate, or tachycardia-mediated cardiomyopathy

Antiarrhythmic Drugs (**AAD**) for **AF** (*Circ* 2011;123:104 & 2012;125:381; *EHJ* 2012;33:2719)

| Agent | Conversion | Maintenance | Comments |
|-------------|--|--|--|
| Amiodarone | 5-7 mg/kg IV over 30-60' → 1 mg/min, 10 g load | 200-400 mg qd (most effective AAD for SR) | ↑ QT, but TdP rare Low rate of acute conversion. May convert wks after load, ∴ attention to anticoag Pulm, liver, thyroid toxicity ✓ PFTs, LFTs , TFTs Potentiates warfarin, ∴ → warfarin by ~50% |
| Dronedarone | n/a | 400 mg bid | ↓ side effects but also ↓ effic. <i>c/w</i> amio; |

contraindic. in perm AF or sx HF / ↓ EF; risk of liver toxicity

III

| | | | |
|------------|---------------------------------|----------------|--|
| Ibutilide | 1 mg IV over 10' may repeat × 1 | n/a | Contraindic. if ↓ K or ↑ QT ↑ QT, 3-8% risk of TdP Mg 1-2 g IV to ↓ risk TdP Lasts 4-6 h |
| Dofetilide | 500 mcg PO bid | 500 mcg mg bid | ↑ QT, ↑ risk of TdP; renal adj |
| Sotalol | n/a | 80-160 mg bid | ✓ for ↓ HR, ↑ QT; renal adj |
| Flecainide | 300 mg PO × 1 | 100-150 mg bid | PreRx w/ AVN blocker Contraindic. if structural or ischemic heart disease |

IC

| | | |
|-------------|---------------|----------------|
| Propafenone | 600 mg PO × 1 | 150-300 mg tid |
|-------------|---------------|----------------|

IA

| | | | |
|--------------|-------------------------|-----|-----------------------------------|
| Procainamide | 10-15 mg/kg IV over 1 h | n/a | ↓ BP; ↑ QT ± PreRx w/ AVN blocker |
|--------------|-------------------------|-----|-----------------------------------|

Underlying disease

Maintenance AAD of choice

None or minimal (incl HTN w/o LVH)

class IC (“pill in pocket”), sotalol, dronedarone

HTN w/ LVH

amiodarone

CAD

sotalol, dofetilide, amiodarone, dronedarone

HF

amiodarone, dofetilide

Radiofrequency ablation (JAMA 2015;314:278)

- **Rationale:** Controlling triggers in pulmonary veins can control AF when little atrial scar present. As progress to persistent and permanent, LA substrate more complex due to scarring and is likely harder to ablate with pulmonary vein isolation alone.
- **Indication:** reasonable alternative to AAD in structurally normal heart
- **Approach:** for paroxysmal AF, circumferential pulm. vein isolation done via ablation in LA myocardium (ablation in PVs causes stenosis) w/ ~80% success (Lancet 2012;380:1509). In AF w/o ↑↑ LA or ↓ EF, RFA still superior to AAD, but lower success rate w/ AF recurring in ~1/2 over 2 y and 2nd RFA often required to prevent LA flutter (NEJM 2012;367:1587; JAMA 2014;311:692). Utility of upfront additional lines of block unclear (NEJM 2015;372:1812).
- Often performed on uninterrupted/minimally interrupt. warfarin or Xa inhib (Circ 2014;129:1688)

- **Risks and complications**

→ arrhythmia & pericarditis during healing post ablation

left atrial flutters may persist and need additional “touch up” ablation

rarer complications (1-2%): stroke, tamponade, phrenic nerve injury, **PV** stenosis, LA-esophageal/mediastinal communication (~3 wk after procedure, severe dysphagia, fever, **CNS** signs of thromboembolism; **dx w/ CT** scan or barium study, **no TEE**; **emergent** thoracic surgery)

- Surgical “maze” procedure (70-95% success rate) option if undergoing cardiac surgery

P.1-71

Oral anticoagulation (Circ 2014;130:2071; JAMA 2015;313:1950)

- **All valvular AF** (ie, rheum **MS**, valve prosthesis or repair), as stroke risk very high
- **Nonvalvular AF (NVAf)**: stroke risk ~4.5%/y, but varies depending on patient; anticoagulation → 68% ↓ stroke but carries risk of bleeding; ∴ use a risk score to guide **Rx**
- **CHA₂DS₂-VASc**: **CHF** (1 point), **HTN** (1), **Age ≥75 y** (2), **DM** (1), **Stroke/TIA** (2), **Vascular disease (MI, PAD, or aortic plaque)** (1), **Age 65-74 y** (1), ♀ **Sex category** (1) annual risk of stroke (*Lancet* 2012;379:648): at low end, ~1% per point: 0 → ~0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑ ↑ (5 → 6.7%, ≥6 → ≥10%)
- Anticoagulation recommendations: **score ≥2 → anticoagulate**
score 1 → consider anticoagulation or antiplatelet **Rx** (? latter reasonable if risk factor 65-74 y, vascular disease or ♀) or no **Rx**
score 0 → reasonable to not anticoagulate
- **HAS-BLED** (*Chest* 2010;138:1093)
HTN (1 point if >160 mmHg), **Abnl renal/liver fxn** (1 for each), **Stroke** (1), **Bleeding hx** or predisposition (eg, anemia), **Labile INR** (time in therapeutic range <60%), **Elderly** (eg, age >65, frailty), **Drugs/alcohol concom** (1 point for antiplt or **NSAID**; 1 for alcohol)
≥3 → ↑ risk for bleeding, ∴ consider closer monitoring or different drug/dose selection
- Special situations in Pts **w/** indication for anticoagulation:
plan for rhythm control: continue anticoagulation
Pt refuses anticoag: **ASA** + clopi or, even less effective, **ASA** alone (*NEJM* 2009;360:2066) underwent **PCI**: ? **Rx w/** anticoagulant & clopidogrel, omit **ASA** (*Lancet* 2013;381:1107)
- **Anticoagulant options**: **factor Xa** or **direct thrombin inhib** (**NVAf** only) or **warfarin** (**INR** 2-3; **w/ UFH** bridge if high risk of stroke)
- Periop rate of arterial embolization in **AF** (w/o mech valve) <0.5%; ∅ benefit to bridging anticoag **w/ LMWH** & ↑ bleeding **c/w** stopping warf 5 d before (*NEJM* 2015;373:823)

Novel Oral Anticoagulants for Nonvalvular AF

Anticoag

Dosing

Efficacy & safety vs warfarin

| | | |
|--|---|---|
| Dabigatran (Direct thromb inhib) | 150 mg bid (110 not avail in U.S.) (75 mg bid if CrCl 15-30) | 150 mg: ↓ ischemic stroke & ICH 110 mg: ≈ ischemic stroke & ↓ major bleed/ICH Risks: GI side effects, ↑ MI c/w warfarin |
| Rivaroxaban (FXa inhib) | 20 mg qd (15 mg qd if CrCl 15-50) w/ pm meal | ≈ ischemic stroke & ↓ major bleed incl ICH |
| Apixaban (FXa inhib) | 5 mg bid (2.5 mg bid if ≥2 risks: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL) | ≈ ischemic stroke & ↓ major bleed incl ICH, 11% ↓ death. In Pts felt not cand for warfarin, apixa 55% ↓ stroke w/o ↑ bleed vs ASA alone. |
| Edoxaban (Fxa inhib) | 60 mg qd if CrCl 51-95 (30 mg if CrCl 15-50) (30/15 mg regimen not available in U.S.) | 60/30 mg: ≈ ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death 30/15 mg: ↑ ischemic stroke & ↓ ↓ major bleed incl ICH, 15% ↓ CV death |

- Rapid onset (w/in several hrs) and offset. Consequently do not need to bridge when starting. However, missing 1 dose could lead to inadequate protection.
- No monitoring required
- Require dose adjustment based on renal fxn, which should be monitored while on drug
- Difficult to reverse if bleeding. Prothrombin complex concentrate or recombinant FVIIa needed. Dabi can be reversed w/ idarucizumab (Ab frag; *NEJM* 2015;373:511).

(*NEJM* 2009;361:1139; 2011;364:806; 365:883 & 981; 2013;369:2063; *Lancet* 2014;383:955)

Nonpharmacologic stroke prevent (ACC/HRS/SCAI 2015 Overview, JACC 2015)

- Percutaneous occlusion of left atrial appendage (LAA) w/ watchman device (nitinol cage w/ polyethylene membrane). Postprocedure: warfarin × ~45 d followed by clopi × ~4.5 mo and ASA lifelong. In NVAf w/ CHADS₂ ≥1-2, c/w warfarin, ≈ stroke (↓ hemorrhagic, ↑ ischemic), ≈ bleeding (↑ procedural, ↓ non-proc), ↓ CV death (*JACC* 2015;65:2614). Does not address issue of high-risk anticoag Pt w/ existing LAA thrombus.
- Epicardial snare to ligate LAA (lariat device). High rate of initial technical success (*JACC* 2013;62:108), but long-term clinical outcomes & safety to be defined.
- Surgical LAA resection reasonable if another indication for cardiac surgery. Resection superior to ligation, which can recanalize.

Atrial flutter

- Macroreentrant atrial loop typically involving cavotricuspid isthmus (usually counter-clockwise w/ flutter waves ⊖ in inf leads & ⊕ in V₁, but can be clockwise).
- Risk of stroke similar to that of AF; ∴ same mandate for stroke prevention.
- Ablation of cavotricuspid isthmus has 95% success rate w/ only 0.5% complication rate. Pts remain at risk for atrial fibrillation.

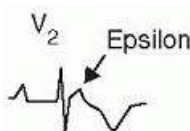
WIDE-COMPLEX TACHYCARDIA (WCT)

Etiologies (*Lancet* 2012;380:1520)

- **Ventricular tachycardia (VT)**: accounts for 80% of **WCT** in unselected population
- **SVT conducted with aberrancy**: either fixed **BBB**, rate-dependent **BBB** (usually **RBBB**), conduction via an accessory pathway or atrially triggered ventricular pacing

Monomorphic ventricular tachycardia (MMVT)


- All beats look similar; predominantly upward in V_1 = **RBBB**-type vs downward = **LBBB**-type
- Most commonly in obviously **structurally abnormal heart**: **prior MI** (scar); **CMP**
mechanism is most commonly re-entry around areas of electrically silent scar tissue with slow myocardial conduction through adjacent areas of surviving myocytes
focal arrhythmias also occur (**RVOT**, Ao root, fascicles, papillary muscles)
re-entry utilizing the Purkinje system is also seen (Bundle Branch Reentry); “typical” form occurs in Pts **w/ LBBB** in sinus and **VT w/** very similar morphology to sinus



- May occur in **apparently nl heart that is actually diseased**:
Arrhythmogenic (RV) CMP (**ACM**, **qv**): incomplete **RBBB**, ϵ wave (terminal notch in QRS) & **TWI** in V_1 - V_3 on resting **ECG**, **LBBB**-type **VT**, **dx w/ MRI** (*Lancet* 2009;373:1289)
subtle **HCMP** sarcoid; myocarditis (incl giant cell); anom coronary
- In structurally **normal heart w/ nl** resting **ECG** (prog generally good):
RVOT VT: **LBBB**-type **VT w/** inferior axis; often seen immediately after exercise; can suppress with **CCB** or **β B** or ablate
idiopathic LV VT: **RBBB**-type **VT w/** superior axis; responds to verapamil or can ablate

Polymorphic ventricular tachycardia (PMVT)

- QRS morphology and/or axis changes from beat to beat
- Etiologies: **ischemia**; **CMP**
torsades de pointes (TdP) (“twisting of the points,” **PMVT** + \uparrow **QT**): \uparrow **QT** **acquired** (meds, lytes, stroke; see “**ECG**”) **w/** risk \uparrow **w/** \uparrow **HR**, freq PVCs (pause dependent) or **congenital** (K/Na channelopathies) **w/** resting **Tw abnl** & **TdP** triggered by sympa-thetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750)

Brugada syndrome (Na channelopathy): $\text{♂} > \text{♀}$; pseudo-**RBBB**  **w/ STE** in V_1 - V_3 (provoked **w/** class **IA** or **IC**) on resting **ECG**

catecholaminergic (CPVT): familial; mutations in ryanodine receptor or calsequestrin 2; presents during emotional or physical stress

Diagnostic clues that favor VT (assume until proven otherwise)

- **Prior MI**, **CHF** or **LV dysfxn** best predictors (90%) that **WCT** is **VT** (*Am J Med* 1998;84:53)

- Hemodynamics and rate do *not* reliably distinguish VT from SVT
- MMVT is regular, but may have initial “warmup period” and may be slightly irregular (as compared w/ SVT, which is extremely regular); grossly irregularly irregular rhythm suggests PMVT or AF w/ aberrancy
- More the QRS morphology is like QRS morphology in SR, more likely SVT
- ECG features that favor VT (*Circ* 1991;83:1649; *EHJ* 2007;28:589)

AV dissociation (independent P waves, capture or fusion beats) proves VT; physical exam correlates: variable S₁ and cannon a waves on JVP

very wide QRS (> 140 ms in RBBB-type or > 160 in LBBB-type)

extreme axis deviation; RBBB-type w/ LAD; LBBB-type w/ RAD; shift in axis >40°; initial R wave in aVR

QRS morphology atypical for BBB

RBBB-type: absence of tall R' (or presence of monophasic R) in V₁, r/S ratio <1 in V₆

LBBB-type: onset to nadir >60-100 ms in V₁, q wave in V₆ longest RS interval in any precordial lead > 100 ms and R wider than S ratio of voltage Δ in initial 40 msec to Δ in terminal 40 ms ≤1

concordance (QRS in all precordial leads w/ same pattern/direction)

Acute management

- If stable: conscious sedation & sync cardioversion; if unstable (↓ BP, angina, ΔMS, HF): emergent cardioversion; if pulseless → ACLS w/ CPR & cardioversion
- Refractory: consider amiodarone, procainamide, and lidocaine (if suspect ischemia)
- If suspect PPM-mediated tachycardia → place magnet (switches device to VOO or DOO)
- If ICD: should deliver Rx, but do not rely on for VT resolution. If stable, can interrogate ICD. If repeated, appropriate & successful shocks → antiarrhythmics to suppress arrhythmia. If repeated shocks (approp or inapprop) w/o arrhythmia term → disable device (magnet).

Long-term management (JACC 2006;48:1064)

- Workup: echo to ✓ LV fxn, cath or stress test to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? EP study to assess inducibility

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- ICD: 2° prevention after documented VT/VF arrest (unless due to reversible cause) 1° prev. if high risk, eg, EF <30-35%, ACM, Brugada, certain LQTS, severe HCM. See “Cardiac Rhythm Management Devices.” ? Wearable vest if reversible etiology while waiting for ICD (*Circ* 2013;127:854).

Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock

- Meds: βB, antiarrhythmics (eg, amio, mexiletine) to suppress VT, which could trigger shock
- If med a/w TdP → QT >500 ± VPBs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- Radiofrequency ablation if isolated VT focus or if recurrent VT triggering ICD firing; ablation before ICD implantation ↓ discharge rate by 40% (*Lancet* 2010;375:31)

SUDDEN CARDIAC DEATH (SCD)

Definition

- Sudden cessation of cardiac activity with hemodynamic collapse
- Technically sudden cardiac arrest (SCA) or “aborted SCD” if resuscitated
- Frequently due to sustained VT/VF

Etiologies

- **Coronary artery disease** (~60-70%)
acute ischemia: ACS; spasm; congenital coronary artery anomaly
scar from prior MI
- **Structurally abnormal heart or vasculature** (~10-15%)
cardiomyopathy: DCM, HCM, ACM; myocarditis
valvular heart disease
myocardial rupture, tamponade, Ao dissection
PE
- **Apparently structurally normal heart** (~10-15%)
LQTS (acquired or congenital); Brugada syndrome; catecholaminergic polymorphic VT
ACM or infiltrative cardiomyopathy
Wolff-Parkinson-White (typically w/ antegrade conduction of AF → VF)
complete heart block
commotio cordis (*NEJM* 1995;333:337)

Precipitants

- Ischemia
- Drugs: antiarrhythmics, QT-prolonging, diuretics
- Electrolytes (usually not sufficient to cause SCD; always search for underlying cause)

Workup (*JACC* 2006;48:1064)

- Hx (usually very limited): may have had prodrome c/w ACS or HF; PMH; meds; FHx
- Exam: signs of cardiovascular disease
- ECG: ischemia, infarction, conduction block, QT, pre-excitation, abnormal V₁-V₃ (eg, pseudo-RBBB + STE, ε wave + TWI), LVH
- Echocardiogram; MRI if echo unrevealing and no other obvious cause
- Coronary angiography (? or CT angio)
if STE or ? chest pain prodrome, urgent angio (unless poor neurologic prognosis)
even w/o STE, 33-40% will have evidence of acute occlusion (*NEJM* 1997;336:1629 & *JACC Intv* 2015;8:1031)

- **EP** study (qv) if above workup unrevealing, programmed stimulation to look for accessory pathway, drug infusions to provoke arrhythmia from CPVT, **LQTS**, Brugada
- Exercise testing to provoke CPVT or assess resolution of pre-excitation to risk stratify **WPW**
- If genetic or unexplained **SCD**, evaluation of family members

SYNCOPE

Definition

- Sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then **SCD** (qv) and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without **LOC**

Epidemiology

- Incidence ↑ w/ age, particularly above 70 y; similar in men & women
- Lifetime incidence ~1 in 3

Etiologies (*NEJM* 2002;347:878; *JACC* 2006;47:473; *EHJ* 2009;30:2631)

- **Neurocardiogenic** (a.k.a. vasovagal, ~25%; *NEJM* 2005;352:1004)
 - ↑ sympathetic tone → vigorous contraction of **LV** → mechanoreceptors in **LV** trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ **HR** (cardioinhibitory) and/or ↓ **BP** (vasodepressor)
 - cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants
 - carotid sinus hypersensitivity is a related disorder w/ an exaggerated vagal resp to carotid massage
- **Cardiovascular** (~20%, more likely in men than women)
 - Arrhythmia* (15%): challenging to **dx** as often transient
 - Bradyarrhythmias: **SSS**, high-grade **AV** block (Stokes-Adams attack), ⊖ chronotropes, **PPM** malfunction
 - Tachyarrhythmias: **VT**, **SVT** (syncope rare unless structural heart disease or **WPW**)
 - Mechanical* (5%)
 - Endocardial/Valvular: **AS**, **MS**, **PS**, prosthetic valve thrombosis, atrial myxoma
 - Myocardial: outflow obstruction from **HCMP** (can also cause **VT**), **MI** (more likely **VT**)
 - Pericardial: tamponade
 - Vascular: **PE**, **PHT**, aortic dissection, ruptured **AAA**, subclavian steal
- **Orthostatic hypotension** (~10%) hypovolemia/diuretics, deconditioning; vasodilat. (espec if combined w/ ⊖ chronotropes) autonomic neuropathy
 - 1° = Parkinson's, Shy-Drager, Lewy body dementia, postural orthostatic tachycardia syndrome (**POTS**, dysautonomia in the young)
 - 2° = **DM**, **EtOH**, amyloidosis, **CKD** (*NEJM* 2008;358:615)
- **Neurologic** (~10%): vertebrobasilar insufficiency (occlusion, dissection or steal), impaired perfusion to all

cerebral vessels (very rare), SAH

- Remainder of cases with unknown etiology
- Misc. causes of LOC (but not syncope): seizure, TIA/stroke, migraine, hypoglycemia, hypoxia, anemia, anaphylaxis, narcolepsy, psychogenic

Workup (etiology cannot be determined in ~40% of cases)

- H&P incl. orthostatic VS have highest yield and most cost-effective (Archives 2009;169:1299)
- **History** (from Pt and witnesses if available) activity and posture before the incident precipitating factors:
 - exertion → AS, HCMP PHT
 - positional Δ → orthostatic hypotension
 - stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, NV, cough/micturition/defecation/swallowing ↑ vasovagal
 - head turning or shaving → carotid sinus hypersensitivity arm exercise → subclavian steal
 - prodrome: sx such as diaphoresis, nausea, blurry vision for >5 sec suggests vasovagal; abrupt onset suggests cardiac or seizure
 - associated sx: chest pain (MI), palpitations (tachycardia)
 - neuro: aura prior to event, neuro sx, postictal state, bowel/bladder incontinence, & lateral tongue biting suggestive of seizure; brief convulsive activity for < 10 sec may occur w/ syncope & mimic seizure, but true tonic then clonic activity is indicative of seizure
- **PMH:** prior syncope, previous cardiac or neurologic dis.; no CV disease at baseline → 5% cardiac, 25% vasovagal; CV disease → 20% cardiac, 10% vasovagal (NEJM 2002;347:878)
- **Medications that may act as precipitants** vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep. diuretics; ⊖ chronotropes (eg, βB and CCB)
 - proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics (see “ECG”) psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- **Family history:** CMP, SCD, syncope (vasovagal may have genetic component)

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• Physical exam

VS including orthostatics (⊕ if supine → standing results in >20 mmHg ↓ SBP, >10 mmHg ↓ DBP, or > 10-20 bpm ↑ HR), BP in both arms

persistently abnormal VS concerning

cardiac: HF (↑ JVP, displ. PMI, S₃), murmurs, LVH (S₄, LV heave), PHT (RV heave, ↑ P₂)

vascular: ✓ for asymmetric pulses, carotid/vertebral/subclavian bruits

carotid sinus massage to assess for carotid hypersensitivity (if no bruits and no h/o TIA or stroke); ⊕ if asystole >3 sec or ↓ SBP >50 mmHg

neurologic exam: focal findings, evidence of tongue biting; FOBT

- **ECG** (abnormal in ~50%, but only definitively identifies cause of syncope in <10%)

Conduction abnl: SB <40 bpm, repetitive sinus pauses >3 sec, AVB (partic. Mobitz II 2° or 3°), IVCD or BBB

(partic. bifascicular block or alternating BBB) (*EHJ* 2009;30:2631)

Arrhythmia: ectopy, ↑ (or ↓) QT, preexcitation (WPW), Brugada, ε wave (ACM), SVT/VT Ischemic changes (new or old): atrial or ventricular hypertrophy

- Place on telemetry while diagnostic workup ongoing
- Lab: glc, Hb, preg test (child-bearing age ♀), ? D-dimer, ? troponin (low yield w/o other s/s)

Life-threatening dx

- *Arrhythmia*: VT, high-grade AVB, long sinus pauses
- *Cardiovascular structural disease*: critical AS, HCMP tamponade, aortic dissection, PE
- *Massive hemorrhage* (eg, large GIB, Ao rupture, splenic rupture, ectopic preg, RP bleed)
- *Neurologic*: SAH (headache + syncope)

High-risk features (*J Emerg Med* 2012;42:345)

- Advanced age (? >60 y), h/o CAD, HF/CMP, valvular or congenital heart disease, arrhythmias, or FHx SCD
- Syncope c/w cardiac cause (lack of prodrome, exertional, supine, or resultant trauma) or recurrent syncope (risk of recurrence if ≥2 prior episodes >50%)
- Complaint of chest pain or dyspnea; abnl VS or cardiac, pulmonary or neuro exam
- Abnormal ECG suggesting arrhythmia, conduction abnormality, ischemia/infarction; Pt w/ PPM/ICD (unless interrogated and found to have no arrhythmia)

Disposition

- High-risk Pts should usually be admitted w/ telemetry and further testing (qv)
- Low-risk Pts may be discharged with follow-up testing
- Obvious vasovagal syncope can be discharged

Other diagnostic studies (consider based on results of H&P and ECG)

- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope

Holter monitoring (continuous ECG 24-48 h): useful if frequent events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)

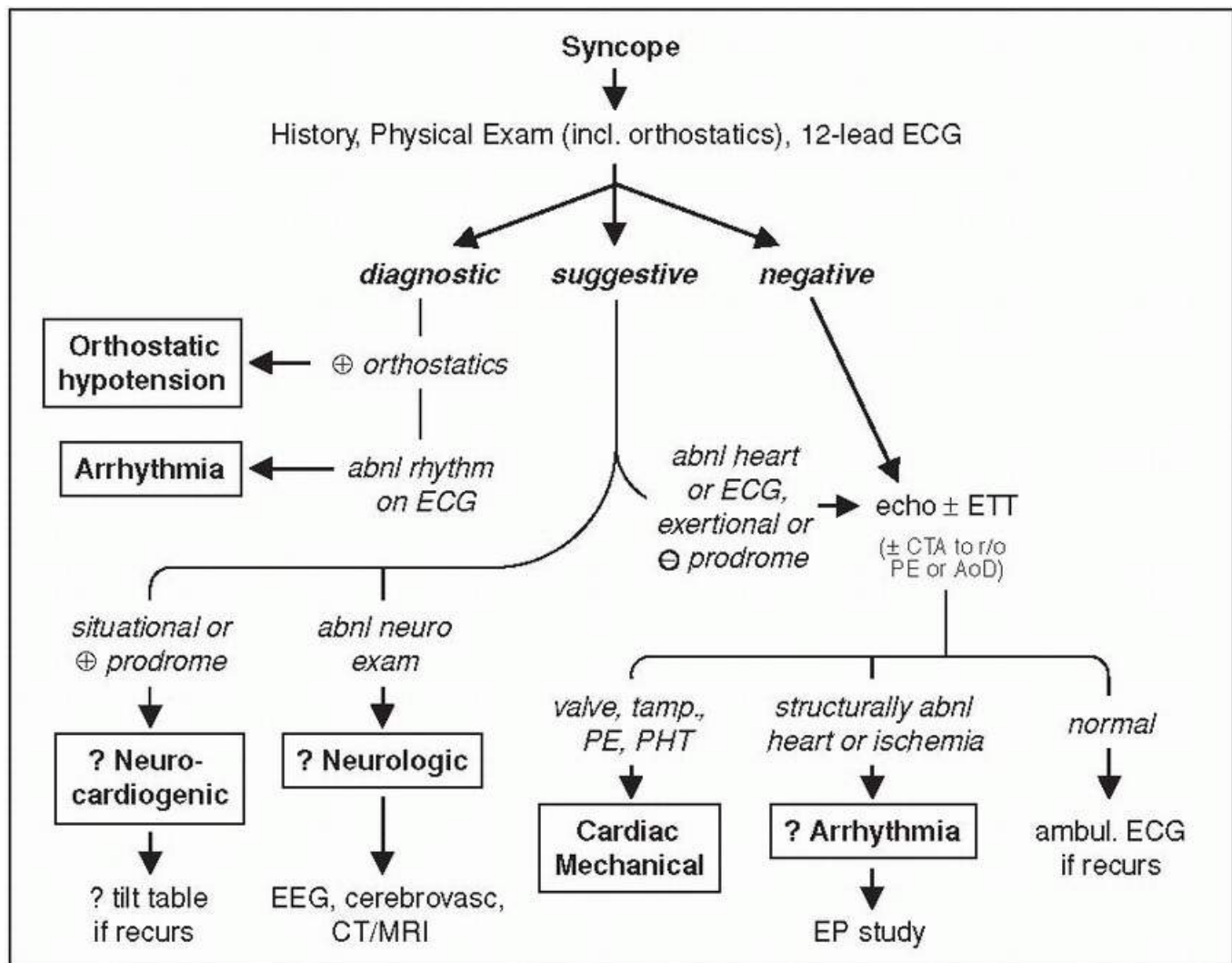
Event recorder (activated by Pt to record rhythm strip): limited role, as only useful if established prodrome (because must be Pt activated)

External intermittent loop recorders (continuously saves rhythm, .*. can be activated after an event): useful for episodes (including w/o prodrome) likely to occur w/in 1 mo

Implantable loop recorders (inserted SC; can record up to 3 y): useful for infrequent episodes (< 1/mo); recommended for recurrent syncope w/o prodrome. Appears to establish a dx (often bradycardia) more frequently (55% vs 19%) than conventional testing (external loop recorder, tilt table, etc.; *Circ* 2001;104:46)

- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ACM], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT: espec w/ exertional syncope; r/o ischemia- or catecholamine-induced arrhythmias

- Cardiac catheterization: consider if noninvasive tests suggest ischemia
- Electrophysiologic studies (EPS, qv): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected but cannot be confirmed;
 - 50% **abnl** (inducible **VT**, conduction abnormalities) if heart disease, but ? significance
 - 3-20% **abnl** if **abnl ECG**; <1% **abnl** if normal heart and normal **ECG** (*Annals* 1997;127:76)
- ? Tilt table testing: utility is debated due to poor **Se/Sp**/reproducibility; consider only if vasovagal **dx** suspected but cannot be confirmed by **hx**
- Cardiac **MRI**: helpful to **dx ARVC** if suggestive **ECG**, echo (**RV** dysfxn) or ⊕ **FHx** of **SCD**
- Neurologic studies (cerebrovascular studies, **CT**, **MRI**, EEG): if H&P suggestive; low yield



(Adapted from *JACC* 2006;47:473)

Figure 1-10 Approach to syncope

Treatment

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder
- Vasovagal syncope (*Int J Cardiol* 2013;167:1906): benefit for midodrine, **SSRI**
 - ? 16 oz of H₂O before at-risk situations (*Circ* 2003;108:2660)

No proven benefit w/ β B (*Circ* 2006;113:1164) or tilt training

No benefit w/ PPM in RCT comparing active pacemaker vs pacemaker programmed in backup mode only. However, guidelines permit implant if ≥ 3 episodes/2y & loop recorder w/ asystole > 3 sec (*Circ* 2012;125:2566).

No data for fludrocortisone, disopyramide

- Orthostatic syncope: volume replete (eg, 500 mL PO q a.m.); if chronic \rightarrow rise from supine to standing slowly, compressive stockings, midodrine, atomoxetine (*HTN* 2014;64:1235), fludrocortisone, high Na diet

Prognosis (*Ann Emerg Med* 1997;29:459; *NEJM* 2002;347:878)

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope: 2-fold \uparrow in mort., 20-40% 1-y SCD rate, median survival ~ 6 y
- Unexplained syncope w/ 1.3-fold \uparrow in mort., but noncardiac or unexplained syncope w/ nl ECG, no h/o VT, no HF, age < 45 \rightarrow low recurrence rate and $< 5\%$ 1-y SCD rate
- Vasovagal syncope: Pts not at increased risk for death, MI or stroke
- \checkmark state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

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ANTIARRHYTHMIC DRUGS (AAD)

Procainamide (class IA = moderate Na channel blocker)

| | |
|---------------------|--|
| Dose | 10-15 mg/kg IV over 1 h; 1-2 g bid (oral form not available in U.S.) |
| Uses | Converting AF & maint. SR; emergent Rx of VT or WCT of ? etiology |
| Side effects | \rightarrow QT, TdP. HoTN (w/ IV use); lupus-like synd. Metab by hepatic N-acetylation. NAPA K channel blocker and renally cleared; \checkmark proc & NAPA levels. |

Quinidine (class IA = moderate Na channel blocker)

| | |
|---------------------|---|
| Dose | 200-648 mg tid (slowly uptitrate); can be given IV |
| Uses | Prevention of VT (used mainly in refractory cases). Blocks I_{TO} (Rx VF storms in Brugada syndrome). |
| Side effects | \rightarrow QT, TdP. Diarrhea often limiting. Moderate anticholinergic effects. α blockade \rightarrow HoTN. Tinnitus, hemolytic anemia, thrombocytopenia. |

Disopyramide (Norpace) (class IA = moderate Na channel blocker)

Dose 200-600 mg bid (slowly uptitrate)

Uses Rx for AF in HCMPP Rx for HCMPP(b/c ⊖ inotrope)

Side effects → QT, TdP. Marked anticholinergic effects. ⊖ inotrope (∴ contraindic in Pts w/ ↓ EF).

Lidocaine (class IB = mild Na channel blocker)

Mech Blocks activated & inactivated but not resting Na channels; ∴ selectively blocks ischemic arrhythmogenic tissue

Dose 100 mg IVB, subsequent 50 mg IVB prn × 2; infusion 1-4 mg/min

Uses Emergent treatment of VT/VF

Side effects Δ MS, slurred speech, twitching; ✓ lido levels, toxicity can manifest as seizure

Other **Mexiletine**: IB that can be given PO (200-300 tid) to suppress VT/VF

Flecainide (Tambocor) (class IC = marked Na channel blocker)

Dose 50-150 mg bid (slowly uptitrate); 200-300 mg × 1 (pill-in-pocket)

Uses Maintenance of SR (PAF, PSVT); acute cardioversion (test in-hosp first!) PreRx with AV nodal blocker to prevent rapid ventricular conduction.

Side effects → mortality if structural heart disease (∴ *contraindic if ischemic or structural heart disease*). Metallic taste, negative inotropy.

Other **Propafenone** (Rhythmol): similar indications & contrindic. Also βB. 150-300 mg tid or 225-425 bid (slowly uptitrate); 450-600 mg × 1 (pill-in-pocket).

Amiodarone (Cordarone) (class III = K channel blocker)

| | |
|---------------------|--|
| Mech | Primarily K channel blocker, but also Na channel blocker, β B, & CCB |
| Dose | IV load: 150 mg over 10 min \rightarrow 1 mg/min \times 6 h \rightarrow 0.5 mg/min \times 18 h \rightarrow cont IV drip or Δ PO load for total \sim 10 g. PO load: 400 mg tid \rightarrow total \sim 10 g Maintenance: 200 (for AF) to 400 (for VT) qd Emergent Rx of VT/VF: 300 mg IVB \pm another 150 mg IVB if persists/recurs |
| Uses | Cardioversion of AF & maintenance of SR; treatment & suppression of VT/VF |
| Side effects | HoTN when given IV; bradycardia. Hypo- (\sim 10%) or hyper- (\sim 3%, typically in iodine-defic Pts) thyroidism. \uparrow LFTs; pneumonitis or pulmonary fibrosis. |
| Other | Dronedaron : noniodine-containing derivative of amio w/ \downarrow efficacy but better tolerability. Used for paroxysmal AF (400 mg bid). Contraindic if HF or perm AF. |

Sotalol (Betapace) (class III = K channel blocker)

| | |
|---------------------|---|
| Mech | K+ blocker, and nonselective β B d and l isomers, respectively |
| Dose | Start 80 mg bid, \uparrow to 120 and then up to 160 mg bid as needed. |
| Uses | Maintenance of SR in Pts w/ AF, prevention of VT in pts with ICD |
| Side effects | \rightarrow QT (contraindic if QTc $>$ 450 msec, adjust dose to keep $<$ 500 ms), TdP. \therefore monitor in hospital for \geq 3 days on maintenance dose. Renally cleared. |

Ibutilide (Convert) (class III = K channel blocker)

| | |
|---------------------|--|
| Dose | 1 mg IV over 10 min, may repeat \times 1. Mg 2 g IV routinely during infusion. |
| Uses | Conversion of AF |
| Side effects | \rightarrow QT, TdP (\sim 5%). Replete K & Mg before Rx. Continuous ECG monitoring (including for several hrs after last dose) and be prepared to defibrillate. |
| Other | Dofetilide (Tikosyn): maintenance of SR in Pts w/ AF. 0.5 mg bid. \uparrow QT, TdP. |

ELECTROPHYSIOLOGY STUDY (EPS)

Indications

- Syncope (w/ high-risk features or abnl ECG); identification of unsuspected tachyarrhythmias; distal

conduction disease (not good for ruling out paroxysmal sinus node dysfunction)

- Determination of mechanism of narrow [eg, **AVNRT** (dual **AV** node physiology), **AVRT** (bypass tract), ectopic atrial tachycardia] and wide complex tachycardias
- Diagnosis in Pts post cardiac arrest
- Risk stratification for **SCD** (ie, inducibility of **VT/VF**) in structural heart disease

Preprocedural evaluation

- Coronary angiography to *r/o* signif **CAD** (either as cause of ischemia-induced arrhythmia and/or to fix before inducing **VT**)
- **TEE** to *r/o* **LA** clot before left atrial procedures

Commonly used catheters and measurements

- Most often electrode catheters placed via femoral vein and placed at high right atrium (HRA), His bundle (HBE) and right ventricular apex (RVA). For **SVT**, also have a catheter in coronary sinus (**CS**), coursing to left side of heart around mitral annulus.

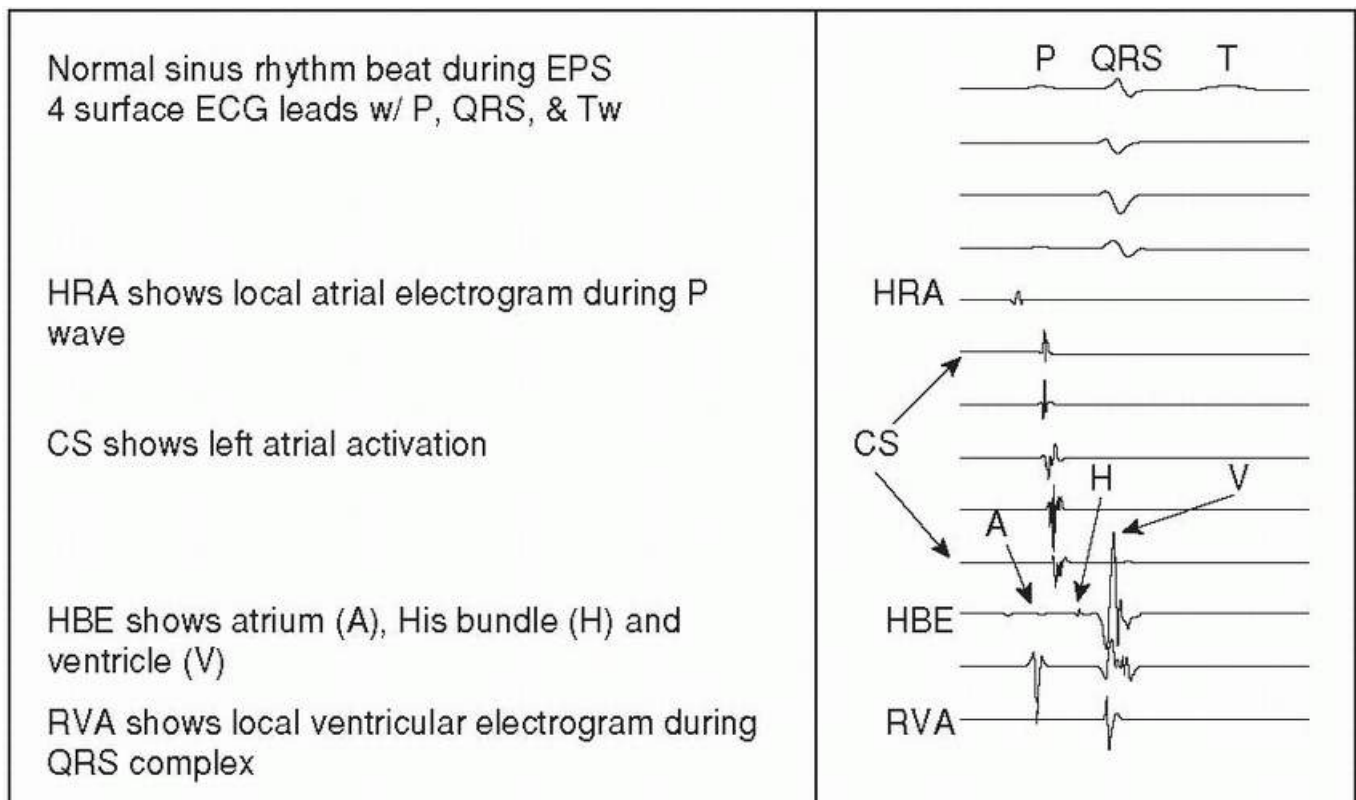


Figure 1-11 Tracing from **EPS**

- His bundle electrogram allows measurement of **AVN** conduction (AH interval) and distal conduction system (HV interval, **nl** 35-55 ms):
 - HV interval <35 ms: pre-excitation (**WPW**)
 - HV interval >35 ms: conduction system disease. **LBBB** typically 55-65 ms, > 70 ms w/ syncope needs **PPM**, > 100 ms needs **PPM**
- Current driven through electrodes used to pace heart and introduce extra beats following 8-beat drive train (programmed electrical stimulation, PES) usually done at HRA and RVA

- Atrial PES can be used to reveal evidence of dual AVN pathways or accessory pathways. Can also be used to induce SVT, AF, AFL.
- Ventricular PES can be used to reveal evidence of concealed accessory pathways, assess inducibility of VT/VF (and thereby risk of SCD), particularly in ischemic heart disease.
- Drug infusions (eg, epinephrine, procainamide) can help to dx LQTS, CPVT and Brugada

Complications

- Vascular injury at site of access
- Damage to tricuspid valve
- Arrhythmias
- Cardiac chamber perforation ± tamponade
- If ablation:
 - heart block ± need for PPM
 - chamber perforation ± tamponade for AF ablation: PV stenosis, phrenic nerve injury, atrio-esophageal fistula

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CARDIAC RHYTHM MANAGEMENT DEVICES

Pacemaker Code

| A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive | 1 st letter | 2 nd letter | 3 rd letter | 4 th letter |
|---|------------------------|------------------------|-------------------------|------------------------|
| | Chamber paced | Chamber sensed | Response to sensed beat | Program features |

Common Pacing Modes

| | |
|--------------------|--|
| VVI | Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia. |
| DDD | A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & triggers V pacing → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF. |
| Mode Switch | In atrial tachyarrhythmia (usually atrial flutter or fibrillation), pacemaker switches from DDD to nontracking mode (like VVI) in order to prevent pacing the ventricle at the upper rate limit (max rate at which PPM will pace ventricle) in an attempt to track the rapid atrial arrhythmia |

Magnet (place over generator) Pacemaker will pace at fixed rate regardless of intrinsic activity (= VOO/DOO). **ICD**: no detection/shock, but pacing programming preserved. Indications: ✓ ability to capture; ✓ battery life (to which rate will be proportional; uses less energy than programmer and does not require a programmer); during surgery w/ electrocautery; hemodynamic instability due to inappropriate **PPM** inhib, failure to **mode** switch or PM-mediated tachy; inapprop **ICD** shocks.

Indications for Permanent Pacing (*Circ* 2012;126:1784)

AV block 3° or type II 2° **AVB** a/w **sx** or w/ either **HR** <40 or asystole ≥3 **sec** (≥5 **sec** if in **AF**) while awake; ? **asx** 3° or type II 2° **AVB**; bifascicular or alternating left & right **BBB**

Sinus node **SB**, pauses, chronotropic incompet a/w **sx** or ? if **sx** w/o clear assoc

Tachy-arrhythmia Most common: **AF** w/ **SSS**, where pacing permits rate support of sinus rhythm in setting of rate controlling drugs for episodes of **AF** Pacing after **AV** junctional ablation for uncontrolled rates in **AF** Sustained pause-dependent **VT** Selected Pts w/ congenital long QT may benefit from pre-emptive pacing from their **ICD**

Syncope Carotid sinus hypersensitivity with asystole >3 **sec** ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi/trifascicular block and not likely 2° to other causes

Pacing Complications (Pacemaker or **ICD**)

| Issue | Manifestation | Description |
|--------------------|---|---|
| Failure to pace | Bradycardia | Oversensing (ie, inappropriate inhibition) due to noise from lead fracture or set screw problem, myopotentials, EMI source outside body such as electrocautery or metal detector Sensitivity too low Battery depletion |
| Failure to capture | Pacing impulses delivered, but no P waves or QRS evoked | Elevated pacing threshold due to lead dislodgement, local tissue reaction or injury |
| Failure to sense | Inapprop. pacing | Lead dislodgment or disease of local myocardium (measured electrogram from leads too small to sense) or sensing threshold too high |
| PM- | WCT at device | Seen w/ DDD. VA retrograde conduction; sensed by A lead → |

| | | |
|----------------------|-----------------|---|
| mediated tachycardia | upper rate | triggers V pacing → etc. |
| PM syndrome | Palpit, HF | Seen w/ VVI in Pts w/ intact AV conduction, due to loss of AV synchrony |
| SVC syndrome | Facial plethora | Thrombosis acutely or scarring a/w chronic intravascular lead(s) |
| Infection | Fever, ⊕ BCx | See below |

Cardiac resynch therapy (CRT)/Biventricular (BiV) pacing (*Circ* 2012;126:1784)

- LBBB and standard RV apical pacing w/ resultant LBBB-like morphology causes dyssynchrony: LV septum activated before LV lateral wall. Wasted myocardial energy due to: prolonged time of contraction (sometimes continuing after AoV closure), sequential rather than simultaneous activation of papillary muscles → functional MR.
- 3-lead pacemaker (RA, RV, coronary sinus to LV lateral wall - LV lead can also be placed surgically by thoracotomy); pre-excites LV lateral wall in attempt to overcome dyssynchrony. R>S in V₁ & predominantly negative in I suggests approp LV capture. QRS width depends on degree of LV pre-excitation; can be narrower or wider than baseline.
- **Indications:** LVEF ≤35% + NYHA II-IV despite med Rx + SR + LBBB ≥150 (? ≥120) ms; mortality benefit only if LBBB (regardless of QRS width) (*NEJM* 2014;370:1694) can also consider in AF, but rate control or AVN ablation necessary to allow ventricular capture, as the greater proportion of time paced, the greater the CRT effect;
 - ? NYHA I w/ LVEF ≤30% + LBBB ≥150 ms;
 - ? EF ≤50% w/ AVB + indic for PPM (*NEJM* 2013;368:1585)

• Benefits

acutely: simultaneous contraction of LV walls and reduction in MR

after 3-6 mo: improvement in one NYHA class in 2/3 of Pts; some “super-responders” will normalize EF

clinically: ↓ HF sx, ↓ HF hosp., ↑ survival (*NEJM* 2005;352:1539; 2010;363:2385)

ineffective when LV lead location poor or LV scarring prevents pacing and/or improvements in wall motion

Implantable cardiac defibrillator (ICD) (*NEJM* 2003;349:1836; *JACC* 2009;54:747)

- RV lead: pacing and sensing like pacemaker lead, coils plus outside housing of ICD can participate in shocking circuit (± antitachycardia pacing [ATP] = burst pacing faster than VT rate to stop VT w/o painful shocks); ± RA lead for dual chamber pacing
- Uninterrupted warfarin at time of ICD (or PPM) placement ↑ risk of pocket hematoma vs bridging with UFH (*NEJM* 2013;368:2084)
- Subcutaneous ICD contains only shocking function (no ATP, no pacing) implanted in the left parasternal area with pulse generator in left lateral thoracic area. Reasonable for those with poor central access and those w/o

pacing requirement (*Circ* 2013;127:854).

- Wearable defibrillator vest can act as a “bridge” for Pts who cannot have an implanted defibrillator for weeks to a few months due to infection or other issue. Not yet demonstrated benefit as a bridge for those who do not yet meet guidelines for ICD (eg, early post MI or new NICMP (*JACC* 2013;62:2000). Data do not support home AED for these Pts either (*NEJM* 2008;358:1793).
- **Pt selection** (*NEJM* 2004;350:2151 & 351:2481; 2005;352:225; 2009;361:1427; *Circ* 2012;126:1784)
 - 2° prevention: survivors of VF arrest, unstable VT w/o reversible cause (*NEJM* 1997;337:1576); structural heart disease & spontaneous sustained VT (even if asx)
 - 1° prevention:
 - LVEF ≤30% & post-MI or LVEF ≤35% & NYHA II-III or LVEF ≤40% & inducible VT/VF wait ≥40 d if post-MI, >9 mo after dx of NICM, or if presumed reversible; however, consider ICD if hemodyn signif VT/VF w/in window (& >48 h after AMI) (*Circ* 2014;130:94)
 - consider for HCM, ARVC, Brugada, sarcoid, LQTS, Chagas or congenital heart disease if risk factors for SCD *life expectancy must be > 1 y*
- **Benefits:** ↓ mortality from SCD c/w antiarrhythmics or placebo
- **Risks:** inapprop shock in ~15-20% at 3 y (most commonly due to misclassified SVT); lead fracture
- ICD discharge: ✓ device to see if approp; r/o ischemia, other proximate cause; if recurrent VT, ? drug Rx (eg, amio + βB; *JAMA* 2006;295:165) or VT ablation (*NEJM* 2007;357:2657); ablation at time of ICD ↑ risk of VT by 40% (*Lancet* 2010;375:31)
- Telemonitoring may improve outcomes (*Lancet* 2014;384:583)

Device infection (*Circ* 2010;121:458; *JAMA* 2012;307:1727; *NEJM* 2012;367:842)

- Presents with one or more of the following: *pocket infection* (warmth, erythema, tenderness), *fever*, *bacteremia* and/or *sepsis*
- Incidence ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%
- More common a complication of generator change
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Treatment: abx and *removal of system* if evidence of pocket infection or GPC bacteremia (*Heart Rhythm* 2009;7:1085)
- Prophylaxis: no recommendation for routine abx prior to invasive procedure