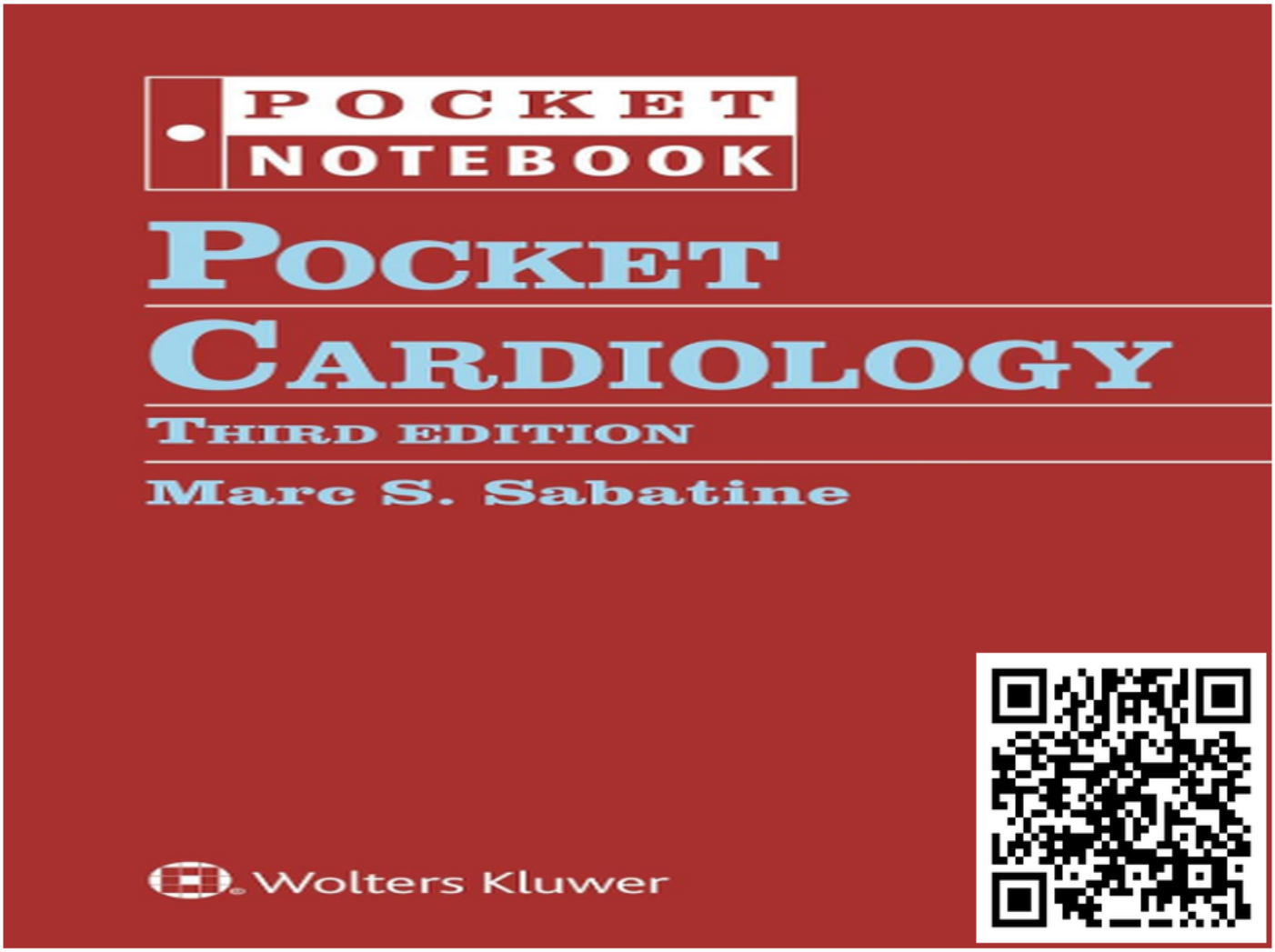

POCKET NOTEBOOK

POCKET CARDIOLOGY

THIRD EDITION

Marc S. Sabatine

Wolters Kluwer

POCKET NOTEBOOK

Pocket CARDIOLOGY

Third Edition

Edited by

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PREFACE

To my parents, Matt and Lee Sabatine, to their namesake grandchildren Matteo and Natalie, and to my wife Jennifer

With this third edition of *Pocket Cardiology* come several major improvements. We have updated every topic thoroughly. Just a few examples include adding a chapter on weight management, incorporating the latest algorithm for patients presenting with chest pain, and updating the recommendations for coronary revascularization reflecting the newest guidelines. We also added sections on molecular therapies for HCM and amyloid cardiomyopathy, transcatheter interventions for TR, and new approaches to AF ablation and physiologic pacing. We have also added new chapters for congenital coronary anomalies and genetic syndromes.

As always, 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. This edition builds on the work of the contributors to the first two editions of *Pocket Cardiology* as well as portions from several sections from the eighth edition of *Pocket Medicine*. We welcome any suggestions for further improvement.

Of course, cardiology is far too vast a field to ever summarize in a textbook of any size. Long monographs have been devoted to many of the topics discussed herein. *Pocket Cardiology* is meant only as a starting point to guide one during the initial phases of diagnosis and management until one has time to consult more definitive resources. Although the recommendations herein are as evidence-based as possible, medicine is both a science and an art. As always, sound clinical judgment must be applied to every scenario.

I am grateful for the support of the house officers, fellows, and attendings at Brigham and Women's Hospital. It is a privilege to work with such a knowledgeable, dedicated, and compassionate group of physicians. I am grateful to the many outstanding clinical cardiology mentors and role models I have had at both Brigham and Women's Hospital and the Massachusetts General Hospital, including Bill Dec, Mike Fifer, Eric Isselbacher, Jim Kirshenbaum, Pat O'Gara, the late Peter Yurchak, and the late Roman DeSanctis, perhaps the most skilled and compassionate clinical cardiologist I have ever known.

This edition would not have been possible without the help of Kate Brennan, my academic coordinator. She shepherded this 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.

Lastly, special thanks to my parents for their perpetual encouragement and love and, of course, to my wife, Jennifer Tseng, who, despite being a surgeon, is my closest advisor, my best friend, and the love of my life.

I hope the information contained within *Pocket Cardiology* proves useful in your quest to deliver the best possible care to your cardiology patients.

MARC S. SABATINE, MD, MPH

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 V_1–V_6, ST ↑/↓ or T-wave Δs)

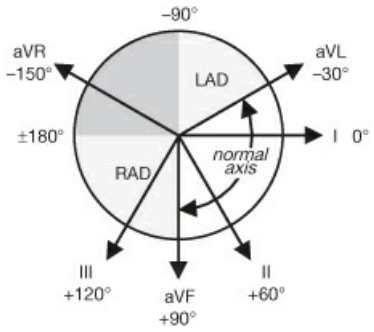
Left axis deviation (LAD)

- **Definition:** axis beyond −30° (S > R in lead II)
- **Etiologies:** LVH, LBBB, inferior MI, WPW
- **Left anterior fascicular block (LAFB):** vide infra

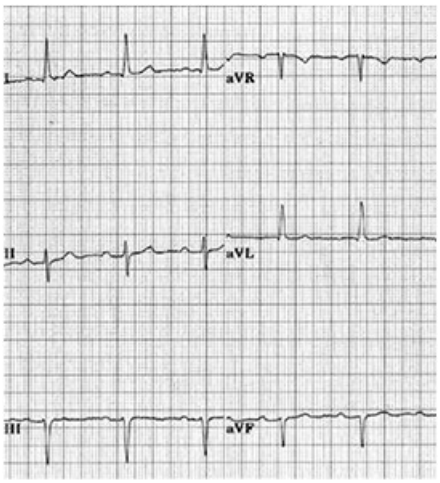
Right axis deviation (RAD)

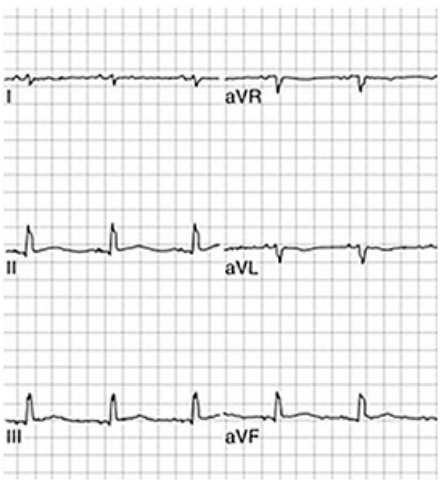
- **Definition:** axis beyond +90° (S > R in lead I)
- **Etiologies:** RVH, PE, COPD (usually not >+110°), septal defects, lateral MI, WPW, limb lead reversal
- **Left posterior fascicular block (LPFB):** vide infra

Figure 1-1 QRS axis



Fascicular Blocks (*Pathophysiology of Heart Disease*, 7th ed, 2021)	
Left Anterior Fascicular Block (LAFB)	**Left Posterior Fascicular Block (LPFB)**
1. LAD (−45 to −90°) 2. qR in aVL 3. QRS <120 ms 4. No other cause of LAD (eg, IMI)	1. RAD (90–180°) 2. rS in I & aVL *and* qR in III & aVF 3. QRS <120 ms 4. No other cause of RAD





Bundle Branch Blocks (*Circ* 2009;119:e235)		
Normal		Initial depol. is left-to-right across septum (r in V_1 & q in V_6; nb, absent in LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB)
LBBB		1. QRS ≥120 ms (110–119 = incomplete) 2. Broad, slurred, monophasic R in I, aVL, V_5–V_6 (± 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. ± PRWP, LAD, Qw's in inferior leads LBBB pattern commonly seen with RV pacing
RBBB		1. QRS ≥120 ms (110–119 = incomplete) 2. rSR′ in R precordial leads (V_1, V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads Does *not* cause right axis deviation
IVCD	QRS ≥110 ms w/o criteria for RBBB/LBBB or w/ features of both	

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 → corrected w/ Bazett's formula: (RR in sec, can be estimated by 60/HR), overcorrects at high HR and undercorrects at low HR (normal QTc <440 ms ♂ and <460 ms ♀)
- Fridericia's formula preferred at very high or low HR: $QTc = QT/\sqrt[3]{RR}$
- QT prolongation associated with ↑ risk TdP (espec, >500 ms); perform baseline/serial ECGs if using QT prolonging meds, no established guidelines for stopping Rx if QT prolongs
- Etiologies:

  Antiarrhythmics: class Ia (procainamide, disopyramide), class III (amiodarone, sotalol, dofetilide)

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

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

atazanavir

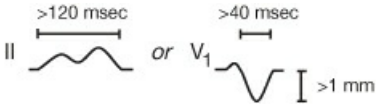
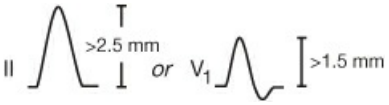
Other: antiemetics (droperidol, 5-HT_3 antagonists), alfuzosin, methadone, ranolazine

Electrolyte disturbances: hypoCa (nb, hyperCa a/w ↓ QT), ± 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

Atrial Abnormalities		
ECG P-wave Criteria	**Left Atrial Abnormality (LAA)**	**Right Atrial Abnormality (RAA)**
		

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

- Etiologies: HTN, AS/AI, CMP (HCM, Fabry), 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 ms	1
Delayed intrinsicoid deflection (QRS onset to R peak) in V_5 or V_6 >50 ms	1

Sokolow–Lyon: S in V_1 + R in V_5 or V_6 ≥35 mm or R in aVL ≥11 mm

Cornell: R in aVL + S in V_3 >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 V_1 or R in V_1 ≥7 mm, S in V_5 or V_6 ≥7 mm, drop in R/S ratio across precordium
  - RAD ≥+110° (LVH + RAD *or* prominent S in V_5 or V_6 → *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular enlargement: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCM
- Myocardial injury: posterior MI (anterior Rw = posterior Qw; often w/ inferior or lateral

MI)
- Abnormal depolarization: RBBB (QRS >120 ms, rSR′); WPW (↓ PR, δ wave, ↑ QRS)
- Other: dextroversion; Duchenne muscular dystrophy; lead misplacement; nl variant

Poor R-wave progression (PRWP) (*AHJ* 2004;148:80)

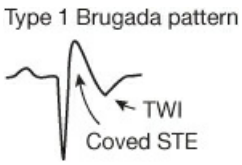
- Definition: loss of anterior forces w/o frank Q waves (V_1–V_3); R wave in V_3 ≤3 mm
- Possible etiologies (nonspecific):
  - old anteroseptal MI (usually w/ R wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3)
  - cardiomyopathy
  - LVH (delayed RWP with prominent left precordial voltage), RVH,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

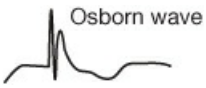
Pathologic Q waves

- Definition: ≥30 ms (≥20 ms 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 ± TWI) or prior MI with persistent STE
- **Coronary spasm** (Prinzmetal's angina): *transient* STE in a coronary distribution
- **Pericarditis** (qv): diffuse, upward concavity STE; a/w PR ↓; Tw usually upright, lack of Qw
- **HCM, Takotsubo CMP, LV aneurysm**, cardiac contusion, myocarditis
- **Pulmonary embolism**: occ. STE V_1–V_3; classically a/w TWI V_1–V_4, RAD, RBBB, $S_IQ_{III}T_{III}$
- **Repolarization abnormalities**
  - LBBB (↑ QRS duration, STE discordant from QRS complex). Dx of STEMI in setting of LBBB challenging but possible (see "ACS").
  - LVH (↑ QRS amplitude, a/w J-point elevation)
  - Brugada pattern (qv)
    - rSR′, downsloping STE V_1–V_2
    - Na^+ channelopathy associated with SCD
  - Hyperkalemia (see below)
  - Hypothermia: Osborn waves
    - ⊗ deflection at J-point, typically in R precordial leads proportional to degree of hypothermia





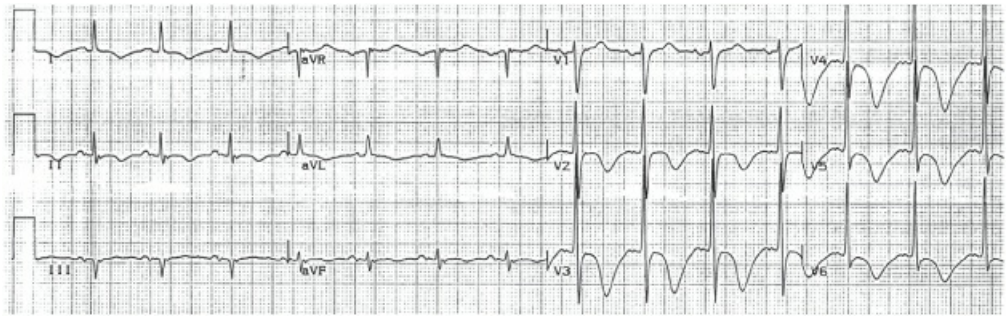
- **aVR:** STE >1 mm a/w ↑ mortality in STEMI; STE aVR > V_1 a/w left main disease
  - May also represent diffuse ischemia, such as w/ multivessel disease & noncardiac HoTN
  - STE >1 mm aVR w/ STD in ≥8 leads suggests left main or mutivessel CAD
- **Early repolarization:** most often seen in V_2–V_5 in young adults (*JACC* 2015;66:470)
  - 1–4 mm elevation of peak of notch or start of slurred downstroke of R wave (ie, J-point); ± up concavity of ST & large Tw (∴ ratio of STE/T wave <25%; may disappear w/ exercise)
  - ? early repolarization in inferior leads may be associated with ↑ risk of VF (*NEJM* 2009;361:2529; *Circ* 2011;124:2208)

ST depression (STD)

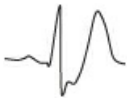
- **Myocardial ischemia** (± Tw abnormalities) or **acute posterior STEMI** (V_1–V_3)
- Digitalis effect (downsloping ST ± Tw abnormalities, does *not* correlate w/ dig levels)
- Hypokalemia (± U wave)
- Repolarization abnormality a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL)
  - Cannot reliably interpret STD as a sign of ischemia in setting of LBBB or PPM unless possibly if concordant w/ direction of QRS or discordant but ≥5 mm

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 *The Washington Manual Cardiology Subspecialty Consult*, 3rd ed, 2014)

- DeWinter's sign (upsloping STD V_2–V_6 w/ hyperacute Tw suggests  proximal LAD occlusion)
- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec. if TWI V_1–V_4)
- Repolarization abnormality is associated with LVH/RVH ("strain pattern"), BBB
- Post-tachycardia or postpacing ("T-wave memory")
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually asymmetric w/ ↑ QT)
- Normal variant in children (V_1–V_4) and leads in which QRS complex predominantly ⊖

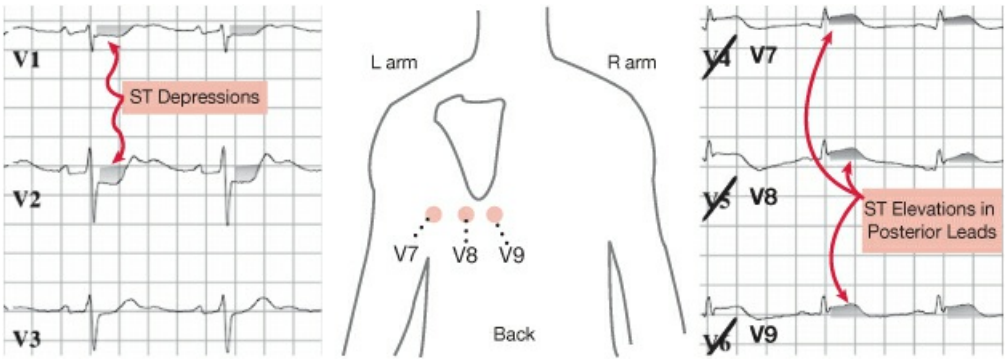
• Isolated TWI in lead III normal

True posterior MI (posterior STE appearing as anterior STD)

• STD ± ↑ R wave in leads V_1–V_4 may correspond to acute posterior "ST elevation" MI

• ✓ Posterior ECG leads; manage as a STEMI with rapid reperfusion

Anterior leads w/ ST depression	*Placement of posterior ECG leads*	*Posterior leads s/ STE*



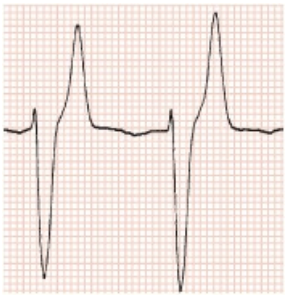
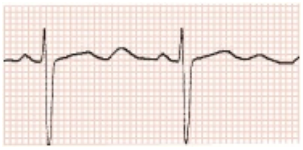
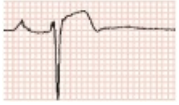
(Modified from *A Visual Guide to ECG Interpretation*, 2nd ed, 2017)

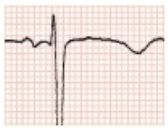
Low voltage

• Can be seen in limb leads, precordial leads, or both

• Defined as QRS amplitude (R + S) <5 mm in limb leads and <10 mm in precordial leads (variably as either the average of the leads or required to be in all of the leads)

• Etiologies: COPD (precordial leads only), pericardial effusion, myxedema, obesity, pleural effusion, restrictive or infiltrative CMP, diffuse CAD

Electrolyte Abnormalities		
↑ **K**	Tented Tw, ↓ QT Small Pw, ↑ PR, AVB Wide QRS → sinusoidal pattern STE (typically V_1–V_2)	
↓ **K**	Flattened Tw U waves (⊕ deflection after T) ST depression Ectopy; ↑ QT & TdP	
↑ **Ca**	↓ QT, flattened Tw & Pw J-point elevation	
↓ **Ca**	↑ QT; Tw Δs	



(*Marriott's Practical Electrocardiography*, 13th ed, 2021)

ECHOCARDIOGRAPHY

General principles

- Technique: based on emission and detection of sound waves with frequencies between 1.5 and 7.5 MHz. Higher frequencies lead to smaller wavelength, higher spatial resolution, but decreased depth of penetration.
- Major advantages: safe, portable, low cost, noninvasive, high temporal resolution
- Limitations: acquisition operator dependent, limited tissue characterization, limited windows in Pts who are obese, have lung disease or chest wall deformities

Types of echo imaging (see Photo Inserts)

- **M-mode**: U/S waves emitted/received along a single line. Image reports depth (y-axis) vs. time (x-axis). High sampling rate allows for excellent temporal resolution. Therefore, useful for rapidly moving structures, such as valves.
- **2D**: U/S waves emitted/received along a range of lines (sector) in a single plane. Useful for assessing cardiac morphology and function.
- **3D**: U/S waves emitted/received along a range of lines (sector) in a pyramidal scan volume. Allows for better assessment of volume and mass and simultaneous assessment of function in different regions. Limited spatial and temporal resolution compared with 2D.
- **Doppler imaging**: based on the change in U/S frequency when reflected by moving targets, such as blood (red blood cells) or tissue (myocardium)
  - *Continuous wave (CW)*: measures highest velocity along a single line. Separate crystals for continuous transmission and receiving U/S waves. Cannot localize peak velocity.
  - *Pulsed wave (PW)*: same crystals transmit and detect U/S wave after a delay matched to area of interest. Due to time delay needed for U/S detection, this technique can only detect velocities up to a certain limit, called the Nyquist limit.
  - *Color*: Velocities and direction of blood flow are encoded with color in a 2D or 3D image. Velocities toward the transducer are represented in shades of red and velocities away from the transducer are displayed in shades of blue.

Main indications

- **Structure**: evaluate chamber sizes, wall thickness, valve structure (including vegetations), anatomy (eg, congenital heart disease), cardiac masses, including thrombus, and pericardial effusions
- **Function:** evaluate valvular hemodynamics and ventricular function (systolic and diastolic)

Standard echo view

- Specific transducer positions on the chest wall to produce standard echo views
- Main TTE views obtained from the left parasternal (long axis and short axis), apical (4Ch, 3Ch, 2Ch), and subcostal positions (see Photo Inserts)
- Additional views can be obtained for specific indications (eg, suprasternal to evaluate the aorta or right parasternal for aortic valve gradients)

LV systolic function

- Methods for assessing LVEF can be divided into linear, 2D, and 3D
- Linear (eg, Teichholz and Quinones): simple mathematical calculation based on mid-cavity diameter of LV in systole and diastole and assumption that LV is a prolate ellipsoid. Should be avoided due to extensive volumetric assumptions.
- 2D: **Simpson's method** is most widely used for LVEF assessment. Endocardial border is traced in A4C and A2C views. Model of disks that are summated to create end-systolic and diastolic volumes. Foreshortening of the LV apex can significantly impair LVEF assessment.
- 3D: no volumetric assumptions; instead uses semi-automated identification of endocardial borders. Limited by low temporal and spatial resolution compared with 2D.
- Both 2D and 3D methods are highly dependent on image quality
- Assessment of **regional wall motion abnormalities** is done by a comprehensive evaluation using multiple different planes (eg, anterior wall on short axis & 2Ch)
- Clear endocardial visualization is essential to global & regional assessment of LV function. Looking for LV wall thickening in systole, not just movement in space. Contrast agents indicated when ≥2 segments are not well visualized.
- **Stress echocardiography**: Pt exercises (treadmill or bicycle) or is given dobutamine. Look for development of new or worsening regional wall motion abnormalities at or immediately after peak exercise.

LV diastolic function

- Assessment primarily focused on evaluation of left-sided filling pressures. With impaired relaxation, higher diastolic pressures are needed to fill the LV. Also see "HFpEF."
- Parameters for assessment of diastolic function and filling pressures
  - *Mitral annular velocities (e')*: determined by LV relaxation and less by filling pressure. Assess by using tissue Doppler. Normal values: septal ≥7 cm/s; lateral ≥10 cm/s.
  - *Mitral E velocity*: reflects gradient between LA and LV pressure in early diastole
  - *E/e'*: as diastolic function worsens and filling pressure increases, *e'* will ↓ and *E* will ↑. *E*/*e'* ≥14 used as a marker of elevated left-sided filling pressures.
  - *E/A ratio*: classified into four general patterns

Diastolic Dysfunction			
Pattern	**E/A**	**e′ (cm/s)**	**E/e′**
Normal	1–2	≥10	<8
Impaired relaxation	<0.8–1	<8	Variable

Pseudonormal	1–1.5	<8	>14 indicates elevated left-sided filling pressures
Restrictive	>1.5–2.0	<8 (usually ≤5)	

Left atrial enlargement: a marker of chronically elevated left atrial pressure

TR velocity: a measurement of ≥2.8 m/s suggests elevated left atrial pressure

RV evaluation

- Anatomy: inlet, body, and outlet
- Dimensions and function evaluated best in A4C view
- On visual assessment, normal RV size should be <2/3 of the LV and should not form part of the ventricular apex
- Quantitative parameters for RV function:
  - Tricuspid annular plane systolic excursion (TAPSE): measured using M-mode to quantify amount of systolic longitudinal displacement of lateral tricuspid annulus toward the apex; normal ≥17 mm
  - Tricuspid annular velocity ≥10 cm/s
  - RV fractional area change: normal ≥35%
- TAPSE and tricuspid annular velocity are measures of longitudinal function, the predominant motion in RV systolic function. However, they may not be reflective of global RV function and are dependent on the imaging angle.
- Can estimate RA pressure based on IVC >2.1 cm and % collapse <50%

RA Pressure Estimation		
IVC Diameter (cm)	**Collapse on Inspiration**	**RA Pressure (mmHg)**
Small (<1.5)	>>50%	≤5
Normal (1.5-2.1)	>50%	6–9
	<50%	10–15
Dilated (>2.1)	<50%	>15

Modified from *Textbook of Clinical Echocardiography*, 2000

Valvular heart disease (qv)

- Can assess morphology, degree of stenosis, and degree of regurgitation
- Pressure gradients: velocity of blood flow is a function of the pressure gradient, which can be estimated using the modified Bernoulli equation: $\Delta P = 4v^2$
- Valve area
  - Aortic valve area can be estimated using the continuity equation. Flow through LVOT = flow through AVA. Flow can be estimated as product of area and velocity (or, better still, velocity time integral). $A_1 \times V_1 = A_2 \times V_2$. LVOT area × VTI_{LVOT} = AVA × VTI_{AoV}.
    $\therefore$ AVA = LVOT area × (VTI_{LVOT}/VTI_{AoV})
  - Mitral valve area can be estimated using pressure half-time method (see “MS”)
- Regurgitant volume: estimated using principle that inflow in diastole = outflow in systole
  - For MR: inflow into LV in diastole (across MV) = outflow of LV in systole (forward through AoV + regurgitant through MV). $\therefore$ regurgitant volume = MV inflow − LVOT outflow.

For AR: inflow into LV in diastole (forward through MV + regurgitant through AoV) = outflow of LV in systole (across AoV). ∴ regurgitant vol. = LVOT outflow − MV inflow.

Can use hydraulic orifice formula (volume = area × velocity time integral) to calculate various volumes and solve for regurgitant volume

Pericardial disease

- Pericardium composed of 2 distinct structures: a more rigid fibrous pericardium and the serous pericardium, which is divided into the visceral (continuous with epicardium) and parietal layers
- Pericardial effusion: echolucent space between the visceral and parietal pericardium
- Size classification: small (<10 mm); medium (10–20 mm); large (>20 mm)
- Echodense material within the effusion may indicate an exudative component (hemorrhagic, inflammatory) or fibrinous material from chronic effusion
- Differential diagnosis includes pleural effusion: if posterior to the descending aorta → pleural effusion; if anterior to the descending aorta → pericardial effusion
- Localized posterior pericardial effusions (eg, post-op) may only be seen w/ TEE/CT
- Pericardial tamponade (qv) is a clinical dx; echo findings of ↑ intrapericardial pressures:
  - RA collapse in systole; RV collapse in diastole
  - Dilated IVC with <50% reduction in diameter with inspiration
  - Ventricular interdependence: inspiration ↑ RV filling at expense of ↓ LV filling
    - Respirophasic change in mitral (>25%) and tricuspid (>40%) peak inflow velocities
    - Respirophasic septal motion

Transesophageal echocardiography (TEE)

- Improved image quality relative to TTE
  - ↓ U/S penetration depth, which allows ↑ frequency and ↑ spatial resolution
  - Less intervening tissue (air/bone) between probe and cardiac chambers
- Limitations
  - Anterior structures may be better imaged by TTE (eg, LV apex, TV, PV)
  - Doppler alignment in the direction of flow may be challenging (eg, AS)
  - Major complications, such as death, esophageal perforation, or major bleeding, occur in <0.1% of cases
- Indications
  - Endocarditis: confirm/exclude diagnosis and/or evaluate for complications
  - Comprehensive valvular evaluation when TTE not definitive; planning transcatheter interventions; prosthetic valve evaluation
  - LAA thrombus: rule out prior to cardioversion or catheter ablation
  - Evaluation of potential cardioembolic sources of stroke/systemic embolism
  - Delineation of cardiac anatomy in cardiac shunts: ASD/PFO, VSD, anomalous PV
- Patient preparation
  - Fasting prior to procedure to minimize aspiration risk
  - Contraindications: esophageal stricture or rupture, obstructive esophageal mass, active upper GI bleeding, recent esophageal surgery. Coagulopathies should be corrected prior to TEE. Therapeutic anticoagulation is acceptable. History of

dysphagia may require GI workup prior to TEE.

EXERCISE ELECTROCARDIOGRAPHY

Indications

- Diagnose obstructive CAD
- Evaluate exercise capacity
- Evaluate symptoms and vital sign changes during exercise
- Evaluate for exercise-induced arrhythmias
- Evaluate prior to cardiac rehabilitation

Exercise protocols

- Typically via treadmill

Protocol	Description
Standard Bruce	↑ speed & incline q3min until limiting symptoms
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 medications (eg, nitrates, βB, CCB, ranolazine) if trying to dx obstructive CAD, but continue medications when assessing if ischemia on current medical regimen

Results

- **HR**: must achieve ≥85% of max pred HR [220 − age] for exercise test to be diagnostic
- **BP** response: SBP should ↑ ≥20 mmHg
- **Peak double product** = HR × SBP; normal >20–25k
- HR recovery: $HR_{peak} - HR_{1\ min\ later}$; normal >12
- **Max exercise capacity** achieved (METS or min on specific protocol)
- Occurrence of **symptoms** (at what level of exertion and similarity to presenting sx)
- **ECG Δs**
  - *Downsloping* or *horizontal* ST ↓ (≥1 mm) 80 ms after j-point predictive of ischemia
  - Upsloping ST ↓ w/ rapid return to baseline usually due to ↑ HR & atrial repolarization
  - In general, ST depressions more specific if:
    - downsloping
    - last long into recovery
    - multiple leads (especially precordial leads)
  - Less specific if baseline ECG abnormal, rapid recovery postexercise
  - Lead V_5 most sensitive
  - If Δs only in inferior leads may be artefact
  - Location of ST ↓ does *not* localize ischemic territory
  - STE: highly predictive of CAD & localizes; ST ↑ aVR suggests LM CAD; nonspecific

if in leads w/ prior Q waves

Diagnosis and prognosis

- Se ~65% and Sp ~80% for CAD
- **Duke treadmill score** = exercise min − (5 × max ST dev) − (4 × angina index) [angina index = 0 none, 1 nonlimiting sxs, 2 limiting sxs]

Category	CAD	1-yr Mort	5-yr 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	≥3%	65%

NUCLEAR CARDIOLOGY

Indications

- Diagnosis of ischemia & prognosis
- Myocardial function & viability
- Diagnosis of infiltrative cardiomyopathies (amyloidosis and sarcoidosis)
- Diagnosis of endocarditis (PET)

Techniques

- **Single-photon emission computed tomography (SPECT)**

  Perfusion-based tracers

  Thallium-201 ($t_{½}$ 73 hrs) or technetium-99m ($t_{½}$ 6 hrs), such as sestamibi or tetrofosmin, emit γ rays

  Spatial localization done by collimators, which accept/reject photons based on the direction of emission

  Conversion into light via scintillation and photomultiplier tubes (conventional Anger cameras) or solid-state detectors (improved sensitivity)

  Protocols

  1-day: low-dose rest followed by high-dose stress

  1-day: stress first; if normal → no need for rest; if abnormal → add rest images at 3× resting dose

  2-day: high dose; for obese Pts

- **Positron emission tomography (PET)**

  Perfusion (rubidium-82 or ammonia-13) or **metabolic** (fluoro-2-deoxyglucose-18) tracers emit a positron, which travels a short distance before annihilation w/ electron → 2 γ photons

  These 2 high-energy photons (511 keV) are emitted at 180° from each other. PET imaging is based on detection of coincident photons.

  Flurpiridaz F-18 is a novel perfusion tracer w/ longer half-life (110 min) compared w/ rubidium-82 (75 sec) and ammonia-13 (10 min), which may increase availability of PET perfusion and allow combination w exercise (*JACC* 2023;82:1598)

Quantification of ischemia & scar

- **Fixed defect**: scar, hibernating myocardium, or artefact
- **Reversible defect**: ischemia
- Quantification of ischemia is based on 17-segment model. Each segment is scored 0–4 according to defect severity (0, normal; 1, mild reduction in counts; 2, moderate reduction in counts; 3, severe reduction in counts; 4, absent counts).
- Results are quantified by adding scores of all segments. % of abnormal myocardium is derived from dividing total score by denominator 68 (17 segments × 4).
  SRS (summed rest score): extent and severity of scar/hibernating myocardium
  SSS (summed stress score): extent and severity of scar/hibernating myocardium *and* ischemia
  SDS (summed difference score): extent and severity of ischemia

Ischemic Category	SDS	% Myocardium
Normal	0	0%
Mild	1–3	1–4%
Moderate	4–7	5–9%
Severe	≥8	≥10%

- Imaging signs of multivessel disease include:
  transient ischemic dilatation (TID) of the LV
  increased RV tracer uptake during exercise
  ↓ EF from rest to stress

Quantification of LV function

- Gated images used to calculate LV volume and systolic function, including regional wall motion abnormalities
- SPECT: gated "stress" images are obtained poststress
- PET: gated "stress" images obtained during peak vasodilation, and thus more likely to identify stress-induced wall motion abnormalities or ↓ EF during stress

Limitations

- Based on *relative* difference in perfusion. ∴ may underestimate extent of CAD; false negative due to "balanced ischemia" may occur in setting of severe multivessel disease.
- To avoid missing high-risk disease, integrate data on exercise capacity, ECG Δs, sx, coronary calcification, high-risk imaging signs (vide supra), and quantitative flow (only available for PET)
- Equivocal results may occur due to artefacts, such as motion or attenuation (eg, breast → anterior "defect" and diaphragm → inferior "defect")
- Limited spatial resolution relative to stress CMR or stress echo
- PET more accurate, but more costly and less available. Need cyclotron for N-13 or generator for producing Rb-82.

PET perfusion (*Circ* 2015;13:19; *JACC* 2018;72:2625)

- PET has improved sensitivity, better spatial resolution, and more robust attenuation correction (PET-CT) compared w/ SPECT
- Allows for dynamic acquisition and calculation of myocardial blood flow (MBF) at rest and stress and myocardial flow reserve (MFR= ratio of MBF stress / MBF rest)

• MBF (mL/min/g) and MFR improved diagnosis + prognostic value
  Global MFR >2.0 → favorable prognosis; excludes high-risk anatomy (NPV ~97%)
  DDx of ↓ MFR: focal epicardial stenosis, diffuse atherosclerosis, microvascular disease
  Measurements of MBF & MFR only possible using pharmacologic testing. ∴ if data on exercise needed (which w/ PET is challenging; only w/ N-13), do separate ETT.

MBF & MFR especially useful for	• Enhanced diagnosis & prognosis • Known or suspected multivessel CAD • Suspect microvascular disease (signs or symptoms of ischemia with no obstructive CAD) • Heart transplant, evaluation of vasculopathy
MBF & MFR less helpful in	• Post-CABG (diffuse reduction in MBF even when patent grafts) • Known large transmural infarcts, where ↓ resting flow, and thus small ↑ in stress MBF, leads to normal MFR • Severe LV dysfunction

(*J Nucl Cardiol* 2016;23:1187)

Radionuclide angiography (*EHJ* 2016;37:2768)

• Tracers used to label blood pool and evaluate EF
• Validated method that is reproducible
• Used for serial evaluation of LVEF in patients undergoing chemotherapy with doxorubicin
• ↓ LVEF by >10% and to a value <50% identifies cardiotoxicity

Infiltrative cardiomyopathies

• **Sarcoidosis** (qv)
  18F-FDG PET used to identify presence and amount of myocardial inflammation in Pts w/ known or suspected cardiac sarcoidosis
  Adequate preparation critical for diagnostic study quality: high-fat / no-carb diet for at least 2 meals, followed by fast of ≥12 hrs; avoid any dextrose infusions
  Goal is to switch myocyte metabolism entirely to fatty acids. With adequate suppression of glc metabolism, 18F-FDG uptake is attributed to inflammation. FDG uptake not specific to cardiac sarcoidosis. DDx includes myocarditis (eg, tuberculosis), other forms of inflammatory cardiomyopathy, hibernating myocardium (if obstructive CAD), incomplete FDG suppression.
  Degree of inflammation (including extracardiac) by 18F-FDG can guide need of immunosuppressive Rx. Extracardiac uptake may also identify site for bx.
  Quantification of inflammatory activity for serial assessment is done by calculating maximum standardized uptake value (SUV); must have *exact* same protocol
  18F-FDG uptake is also compared with perfusion images to detect sarcoid-related scar. Of note, important to exclude obstructive CAD in some Pts, as hibernating myocardium may be 18F-FDG avid as well.
• **Amyloidosis** (qv; *JAMA Cardiol* 2016;1:880)
  Tc-99m pyrophosphate (PYP) imaging has high sensitivity (>90%) and specificity (>90%) for ATTR amyloidosis

SPECT-CT is preferred over planar imaging. Fusion of CT and SPECT images avoids false-positive results related to blood pool or bone uptake (eg, rib fractures).

Grading of Tc-99m uptake: 0 (no uptake); 1 (myocardial < rib uptake); 2 (myocardial = rib uptake); 3 (myocardial > rib uptake)

Grades 2 or 3 specific for ATTR amyloid if AL amyloid is excluded. Important to rule out AL amyloid with light chains and testing for monoclonal gammopathies.

Infection (*J Nucl Cardiol* 2019;26:922; *Clin Infect Dis* 2020;70:583)

- 18F-FDG PET can be used to detect inflammation in the setting of suspected endocarditis
- Especially useful if implanted cardiac devices or prosthetic valves
- Sensitivity and specificity are robust in patients with prosthetic valves (Se ~90% & Sp ~90%). Sensitivity much lower in patients with native valves.

CARDIAC CT

Different types of cardiac CT scans

- Coronary artery calcium (CAC) score
- Coronary CT angiography (CCTA)
- Cardiac CT, noncoronary indications: evaluate for pulmonary vein anatomy/stenosis, LAA thrombus or LAA dimension prior to closure device, prior to TAVR/TMVR, valvular heart disease (especially mechanical valves not well seen by TTE/TEE), cardiac masses, pericardial disease, congenital heart disease (especially shunts, eg, ASD/PFO/VSD) and anomalous origin of coronary arteries

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Coronary Artery Calcium (CAC) Testing

Technique & rationale

- ECG-gated, noncontrast CT
- Used to estimate presence & amount of calcified coronary plaque
- CAC, measured via Agatston score, provides useful surrogate of overall amount of *plaque* (but not % stenosis)
- Advantages: simple, reproducible, low cost, predicts risk better than many traditional risk factors
- Limitations: does not change w/ Rx, may slightly increase w/ statins, no large RCTs available evaluating hard outcomes, not useful in young Pts (avoid if <40 yrs, except for selected cases)

Indications

- Improved risk assessment among asx Pts, if information will enhance preventive care
- In intermediate-risk or selected borderline-risk adults (ie, 10-yr ASCVD risk of 5–20%), if decision about statin use remains uncertain, reasonable to use CAC score to withhold, postpone, or initiate statin therapy

- May be useful in selected low-risk sx Pts: CAC=0 → low risk; CAC >0 → further testing may be useful; also may be added w/ SPECT or PET MPI (see "Nuclear Cardiology")

Interpretation

- Higher plaque burden → higher risk of future ASCVD events
- CAC=0 can "derisk" (ie, reclassify to lower risk). When 10-yr risk of ASCVD <20% this can be used among individuals who prefer to avoid/defer statin Rx.

CAC Score	Amount of Calcified Coronary Plaque	Potential Clinical Management Implications
0	No CAC	Low risk (unless signif. risk factors, ASCVD >20%)
1–99	Mild amount	Favors statin therapy
100–299	Moderate amount	Statin therapy recommended/consider ASA
≥300	Severe amount	High-intensity statin, ASA, ? other 2° prevention Rx
≥1000	Extreme amount	High-intensity statin, ASA, other 2° prevention Rx

- If severe or extreme CAC, stress testing (ETT or PET) may be considered; invasive coronary angiography never appropriate next step

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Coronary CT Angiography

Technique

- *Gated* CT of heart timed during peak contrast enhancement in coronary arteries
- NTG given to dilate coronary arteries. β-Blockers commonly used to lower HR.
- Images usually obtained during diastole, but if information on function or valves also needed, can obtain data throughout cardiac cycle (multiphase dataset)
- Limitations: image quality lower if morbid obesity (eg, BMI >40), heavy calcifications, motion, HR >65–70 bpm (depends on scanner), irregular rhythm, inability to breath hold 5 sec
- Difficult to evaluate small (<1.5 mm) vessels or stents
- Like invasive angiography, functional significance of certain lesions uncertain, and thus may need further testing (~10–20% of lesions)
- Requires high-end CT scanners (eg, high spatial and temporal resolution)
- Photon counting CT (PCCT) detectors offer ability to significantly improve spatial resolution and improve diagnostic accuracy. Traditional scintillation detectors produce visible light that is converted into an electrical signal. With PCCT detectors, X-ray quanta are absorbed by a semiconductor and converted into electrical signals. The magnitude of signal pulses is proportional to the absorbed energy of the X-rays. The improved image quality is especially advantageous when imaging Pts w/ calcifications (ie, less calcium blooming with PCCT) or coronary stents.

Stenosis Severity		
CAD-RADS	**Max Stenosis (%)**	**Interpretation**
0	0	No CAD (no plaque or stenosis)
1	1–24	Minimal plaque
2	25–49	Mild plaque

3	50–69	Moderate stenosis
4A	70–99	Severe stenosis
4B	LM >50% or 3VD >70%	
5	100	Total coronary occlusion
Plaque score	P1 P2 P3 P4	Mild amount of plaque Moderate amount of plaque Severe amount of plaque Extensive amount of plaque

Plaque amount (*JCCT* 2022;16:536)

- Critical for risk stratification and optimization of preventive therapies
- In some studies, plaque burden more prognostic than % stenosis (*JACC* 2020;76:2803)
- CAD-RADS 2.0 classifies as mild (P1), moderate (P2), severe (P3), or extensive (P4)
- Different methods to quantify plaque amount: visual assessment, CAC (requires non-contrast acquisition), segment involvement score (SIS) = # coronary segments w/ plaque
- Plaque quantification software is available for clinical & research use. It remains unclear how much quantification will add to current semi-quantitative assessments.

Methods to Categorize Overall Amount of Coronary Plaque

CAD-RADS	Overall Plaque Amount	Visual Assessment	CAC	SIS
P1	Mild	1–2 VD w/ mild plaque	1–100	≤2
P2	Moderate	1–2 VD w/ mod. plaque; 3VD w/ mild plaque	101–300	3–4
P3	Severe	3VD w/ mod. plaque; 1VD w/ severe plaque	301–999	5–7
P4	Extensive	2–3 VD w/ severe plaque	≥1000	≥8

Classify according to highest risk feature (visual, CAC, or SIS) found. VD, vessel disease.

High-risk plaque features

- Positive remodeling, low-attenuation plaque, spotty Ca, napkin ring sign
- These features (especially if multiple ones) associated w/ higher future ASCVD risk and also lesion-specific ischemia

CT-FFR

- Noninvasive estimation of lesion-specific ischemia
- Uses computational fluid dynamics to estimate invasive FFR (qv)
- May be useful if uncertain functional significance (eg, 40–70% lesions) of focal lesions
- CT-FFR >0.8 suggests safe to defer revascularization (*JACC* 2018;72:2123)
- CTA + selective use of FFR vs. usual testing → 76% ↓ in invasive catheterization w/o obstructive CAD (*JAMA Cardiol* 2023;8:904)

Stable chest pain (w/o known CAD)

- CCTA useful to identify coronary plaque and stenosis, as well as guide the need for further management decisions
- Consider overall amount of plaque when deciding on intensity of preventive therapies. Decision to send for invasive angiography/revascularization also depends on frequency & severity of angina and results of stress testing/CT-FFR (if available).

Interpretation of CCTA in Stable Chest Pain		
CAD-RADS	**Further Evaluation**	**Recommended Management**
0	None	Reassurance. Consider non-atherosclerotic causes of CP.
1	None	Consider non-athero causes of CP. Consider preventive Rx and risk factor modification, more aggressive if more extensive plaque.
2	None	
3	Consider functional assessment	Consider sx-guided anti-ischemic Rx; preventive Rx and risk factor modification as per GDMT
4A	Consider ICA or functional assessment	As above; other treatments (including options of revascularization) should be considered per GDMT
4B	ICA	
5	ICA and/or viability assessment	

ICA, invasive coronary angiography

- If classified by overall plaque burden
  P1 or P2: Risk factor modification and preventive pharmacotherapy
  P3 or P4: *Aggressive* risk factor modification and preventive pharmacotherapy
- PROMISE trial (*NEJM* 2015;372:1291): CCTA vs. functional testing (SPECT, stress echo, ETT). ↑ rate of invasive angiography (12 vs. 8%) but no difference in risk of primary endpoint (death, MI, UA hospitalization, major procedural complication) over median f/up 25 mos. Possibly lower rate of death/MI in Pts w/ DM (*JACC* 2019;73:893).
- SCOT-HEART trial (*NEJM* 2018;379:924): CCTA + standard of care vs. SOC alone (ETT in ~85%). No Δ in invasive angiography or revascularization, but more preventive Rx in CCTA arm. CCTA reduced risk of CHD death or MI by 41% over median f/up 4.8 yrs.

Acute chest pain (w/o known CAD)

- Among Pts w/ acute chest pain or low-risk ACS, who have no known CAD, CCTA useful to exclude coronary plaque or stenosis, and identify those who can be safely discharged
- Presence of plaque sensitive (100%) but not specific for ACS, ∴ NPV 100%, low PPV
- CCTA vs. noninvasive testing → ↓ time to dx & LOS (less so in era of hsTn), but ↑ probability of cath/PCI (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880)

Interpretation of CCTA in Acute Chest Pain		
CAD-RADS	**ACS Probability**	**Recommended Management**
0	Highly unlikely	No further evaluation required; consider other etiologies
1 or 2	Unlikely	Consider evaluation of non-ACS etiology. If Tn negative and no ECG Δs, consider referral for outPt f/up for preventive Rx & risk factor modification.
3	Possible	Consider hospital admission w/ cardiology consultation, fxnal testing and/or ICA for eval and management. Other Rx should be considered if presence of hemodynamically significant lesion.
4	Likely	Consider hospital admission with cardiology consultation. Further evaluation with ICA and revascularization as appropriate.
5	Highly likely	Expedited ICA if acute occlusion

In CADS-RADS 3/4/5: hospital admission recommended; in addition to above management suggestions, also recommend anti-ischemic and preventive management as well as risk factor modification

ICA, invasive coronary angiography

- CCTA may help evaluate other causes of chest pain, although concomitant evaluation of PE or aortic dissection usually requires special protocols
- Limitation of RCTs of CCTA in ED is inclusion of low-risk Pts. In selected higher risk Pts (eg, ⊗ Tn or low-risk NSTEACS) CCTA may be useful to exclude obstructive CAD in ~30% (VERDICT, *JACC* 2020;75:453).

Patients with prior revascularization

- Prior CABG: CCTA useful to evaluate bypass grafts, but may be limited for evaluating native vessels that may be heavily calcified
- Prior stents: CCTA unable to visualize small or overlapping stents; avoid unless large proximal stents

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Cardiac CT for Valvular & Structural Heart Disease

Left atrial appendage (LAA)

- Delayed imaging (45–60 sec) obtained to differentiate thrombus vs. slow filling of LAA
- Excellent Se (~98%) & Sp (~100%) for dx of LAA thrombus (*JAHA* 2021;10:22505)
- May be used for pulmonary vein anatomy prior to catheter ablation of AF; for LAA sizing prior to percutaneous closure; for post-LAA transcatheter closure to assess peri-device leak and device-related thrombus

Valvular heart disease

- Protocol must include multiphase data, typically covering all of RR interval
- May be used for suspicion of endocarditis, to identify vegetations and perivalvular extension (abscess, pseudoaneurysms, fistula, dehiscence), particularly for prosthetic valves or if contraindications to TEE; Se is increased by adding PET-CT
- Indicated for planning of TAVR and TMVR

Other information

- Chamber sizes, wall thickness, shunts, pericardium, coronary veins, Ao & PA, pulm vv
- Ancillary noncardiac findings: lung disease, nodules w/in field of view

CARDIAC MRI

Main applications of cardiac MRI (CMR)

- Quantification of left and right ventricular systolic function and volumes
- Tissue characterization
  - evaluation of edema, inflammation, and fibrosis
  - identification of infiltrative heart disease (eg, amyloidosis, sarcoidosis)
  - differentiation of scar vs. viable myocardium
  - MINOCA: scar from MI vs. myocarditis vs. stress cardiomyopathy

- Valvular heart disease: phase contrast & volumetric assessment of stroke volume to quantify severity of valvular disease
- Calculation of shunt (ie, Qp:Qs ratio)
- Pericardial disease: pericarditis (thickness & inflammation); constriction (physiology & fibrosis); pericardial cysts
- Cardiac masses: anatomy and tissue characterization to identify benign etiology vs. tumor (most helpful for masses >1 cm)
- Stress CMR: first-pass perfusion using gadolinium during pharmacologic stress

Basic physics

- A strong magnet of 1.5T or 3T aligns the intrinsic magnetic spins of H^+ ions into axis of main magnetic field (Bo). For context, 1.0T = 10,000G = 20,000× Earth's magnetic field.
- Pulse sequences are a series of magnetic gradients and radiofrequency (RF) pulses, applied to the magnetic field to generate the desired slices and imaging properties
- The RF pulse displaces the net magnetization vector away from Bo and into the transverse (xy) plane. After RF is turned off, the net magnetization vector starts relaxation:
  Back into the Bo direction: → T1 relaxation
  Loss of transverse (xy) magnetization: → T2 relaxation
- Pulse sequences can be designed to reflect T1 or T2 differences in tissue:
  T1-weighted: eg, postcontrast images, such as perfusion and LGE
  T2-weighted: eg, evaluation of edema/inflammation
  T2*-weighted: eg, evaluation of iron overload

MRI safety

- The MRI magnet is *always on*
- Thorough patient screening needed. Risks: peripheral nerve stimulation (magnetic gradients); heating (RF energy); noise.
- Risk if implanted devices, especially ferromagnetic. "Conditional" devices must be scanned under specific device/scanner conditions.
- Nephrogenic systemic fibrosis (NSF) is a rare life-threatening systemic multiorgan fibrotic disease linked to linear gadolinium-based contrast agents (GBCA) in Pts w GFR <30. No cases reported with macrocyclic GBCA and avoiding GBCA if GFR <30.

Late gadolinium enhancement

- LGE imaging is based on shortening of T1 by GBCA
- Pulse sequences are designed to "null" signal from normal myocardium; areas of myocardial injury or fibrosis will be bright (increased signal)
- The location and pattern of LGE can help differentiate etiology of cardiomyopathies
  Ischemic: subendocardial or transmural LGE in a *coronary distribution*
  Non-ischemic CMP: LGE in *noncoronary distribution*

Pattern	Etiologies
Subendocardial	Amyloidosis, hypereosinophilic syndrome (apical)
Subepicardial	Myocarditis, sarcoidosis (common in basal septum/lateral wall, usually multifocal)

Diffuse, with abnormal gadolinium kinetics	Amyloidosis
Mid-myocardial	Sarcoidosis, myocarditis, Fabry (basal inferolateral), dilated CMP
Patchy mid-myocardial, in areas of focal hypertrophy	Hypertrophic cardiomyopathy
RV insertion points	Nonspecific pattern of ↑ ventricular loading conditions

- LGE images are sensitive for detection of both acute and chronic MI. Acute MI may show edema on T2 imaging and/or areas of microvascular obstruction. Chronic MI: wall thinning.
- The extent of LGE is an independent prognostic marker in ischemic and non-ischemic cardiomyopathies

Parametric mapping

- LGE can image focal replacement fibrosis, but is less sensitive to interstitial fibrosis or diffuse processes, such as cardiac amyloidosis. Similarly, T2-weighted sequences image focal edema, but limited for diffuse inflammation.
- T1 and T2 mapping can quantify T1 and T2 times in the myocardium; main clinical use is in amyloidosis and myocarditis, especially if diagnosis is uncertain based on LGE
- Pre- (native) and postcontrast T1 mapping can calculate extracellular volume % (ECV)

Parameter	Myocarditis	Amyloidosis	Interstitial Fibrosis	Iron Overload*	Fabry
Native T1	↑	↑↑	↑	↓	↓
ECV	↑	↑↑	↑	–	–
T2	↑	–	–	↓	–

Marked decrease in T2 times (vide supra)

Velocity encoding

- Specific pulse sequences “encode” spins with different phases based on velocity of flow
- Used to compute flow *volume* or flow *velocity*
- Velocities can be used to determine peak gradients in stenotic lesions, similar to echo
- Volumes can be used to quantify shunts and volume of regurgitant lesions. Examples:
  - Qp:Qs: pulmonic outflow volume / aortic outflow volume
  - Direct aortic regurgitation volume
  - Indirect aortic regurgitation volume: aortic outflow volume − pulmonic outflow volume
  - Indirect mitral regurgitation volume: (LVEDV − LVESV) − aortic outflow volume

Typical Findings on Cardiac MRI	
Acute or subacute MI	Regional WMA; subendocardial or transmural LGE. Myocardial edema on T2-weighted imaging or T2 mapping. Impaired perfusion; microvascular obstruction/intramyocardial hemorrhage.
Old MI	Regional WMA; subendocardial or transmural LGE. No edema. Degree of transmurality predictive of myocardial recovery w/ revasc (viability).
Non-ischemic	Variable pattern of mid-myocardial or subepicardial LGE; typical pattern is mid-wall linear LGE in interventricular septum

DCM	
Acute myocarditis	Focal or diffuse increase in T1-time & abnormal ECV. Mid-myocardial or subepicardial LGE. Edema on T2-weighted imaging or T2 mapping.
Acute pericarditis	Pericardial LGE. ↑ pericardial thickness; pericardial edema on T2-weighted images. May have associated effusion and/or myocarditis.
Constrictive pericarditis	Ventricular interdependence (respirophasic septal shift). Dilated IVC. Pericardial adhesions (tagging sequences) ± pericardial thickening/LGE. Pericardial effusion (if effusive-constrictive).
HCM	Asymmetric LV hypertrophy. Mid-myocardial LGE, most prominent in areas of hypertrophy and in RV insertion points. Associated MV abnl such as SAM. Apical aneurysm in mid-cavity obstructive phenotype.
Cardiac sarcoidosis	Multifocal, non-ischemic LGE; contiguous involvement of LV & RV ("hook sign"). T2-weighted images may identify inflammation, but FDG PET ↑ Se.
Cardiac amyloidosis	↑ ventricular wall thickness. Diffuse ↑ ECV and T1-time. Abnl gadolinium kinetics (premature nulling of myocardium); diffuse myocardial LGE (subendocardial or transmural); LA/RA/RV LGE.
Thrombus	Mass w/o perfusion or LGE. Long TI images w/o any LGE (dark).

ECV, extracellular volume; LGE, late gadolinium enhancement; WMA, wall motion abnormality

CARDIOPULMONARY EXERCISE TESTING

Rationale (*Circ* 2013;127:1157; *JACC HF* 2016;4:607)

- To meet metabolic demands of exercise, the body needs to ↑ effective ventilation, ↑ cardiac output, ↓ pulmonary & systemic vascular resistance, and ↑ O_2 extraction
- Etiologies of exertional dyspnea:
  impaired external respiration (ventilation & pulmonary gas exchange)
  impaired circulation (transport of O_2 and CO_2)
  impaired internal respiration (peripheral capillary gas exchange and O_2 utilization)
- Cardiorespiratory fitness predicts morbidity & mortality

Testing

- CPET is an exercise testing strategy that couples breath-by-breath gas exchange to standard exercise variables to generate an integrated assessment of cardiorespiratory fitness. The following outputs can be measured:
- ECG, heart rate, BP
- Quantification of O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), minute ventilation (V_E)
- Addition of radial arterial line and PA catheter (invasive or advanced CPET) enables detailed assessment of exercise hemodynamics: RAP, PAP, & PCWP; arterial & mixed venous sats
- Can be coupled with cardiac imaging (eg, radionuclide ventriculography, TTE)

Indications

- Evaluate etiology of exercise intolerance or dyspnea by defining organ system limiting gas exchange (heart, pulmonary mechanical, pulmonary vasculature, muscles/mitochondria)
- Grade severity of advanced heart and lung diseases, and predict prognosis:
  Identify Pts to be considered for heart/lung transplantation, durable mechanical

circulatory support: high risk (>20% 1-yr mortality) defined by peak $\dot{V}O_2$ <14 ml/kg/min (or <12 ml/kg/min on β-blockers) with maximal volitional effort

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

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

Derived CPET variables and clinical importance

- RER (respiratory exchange ratio) = $\dot{V}CO_2/\dot{V}O_2$, ratio between volume of CO_2 produced vs. O_2 consumed. Indicator of volitional effort independent of chronotropic response (goal ≥1.0, ideally ≥1.1 indicating maximal effort).
- Maximum voluntary ventilation (MVV): largest volume of air that can be moved into and out of the lungs during a 10–15 sec interval with voluntary effort. MVV = ~FEV_1 × 40.
- V_E/MVV: measure of ventilatory reserve. Normal <60–70%; >60–70% (ie, minute ventilation close to maximum possible ventilation) indicates pulmonary mechanical limit to exercise.
- Peak $\dot{V}O_2$: maximum aerobic capacity at peak exercise and indicator of cardiorespiratory fitness. Defined as CO multiplied by difference in arterial vs. venous O_2 content: peak $\dot{V}O_2$ = (heart $rate_{max}$ × stroke $volume_{max}$) × [(arterial − mixed venous) O_2 content]$_{max}$
- Ventilatory threshold (VT), also known as anaerobic threshold (AT): % of peak predicted $\dot{V}O_2$ at which O_2 supply inadequate, thereby leading to anaerobic metabolism. Several methods to determine including examining when V_E starts to ↑ nonlinearly or when ↑ in $\dot{V}CO_2$ is greater than ↑ in $\dot{V}O_2$. Independent of volitional effort and highly reproducible. Normal value >40%. Low AT reflects impaired O_2 delivery ± utilization but does not localize organ system responsible. In HFrEF, VT <11 ml/kg/min associated w/ 5× ↑ in 6-mo mortality (*Circ* 2002;106:3079).
- $V_E/\dot{V}CO_2$ slope

  measure of ventilatory efficiency (ie, ventilation required to exchange 1 L/min of CO_2)

  $V_E/\dot{V}CO_2$ slope = $863/[P_aCO_2 \times (1 - V_d/V_t)]$, where V_d = dead space vent., V_t = tidal vol.

  In HF, reduced cardiac output and circulatory delay as well as rising filling pressures during exercise result in ↑ ventilatory drive → ↓ P_aCO_2

  Lung hypoperfusion from impaired RV function/pulmonary vascular disease leads to V/Q mismatch and elevated fractional dead space → ↑ V_d/V_t

  Accordingly, elevated $V_E/\dot{V}CO_2$ slope (>34–36) is a correlate of HF severity and powerful predictor of events (above and beyond peak $\dot{V}O_2$). High levels also indicate poor prognosis (*Circ* 2007;115:2410; *Circ HF* 2008;1:227).
- Exercise oscillatory ventilation (EOV): periodic breathing during exercise that reflects circulatory delay (ie, low CO) relative to metabolic needs during exercise. Associated w/ 3× ↑ mortality (*JACC* 2010;55:1814; *Circ* 2011;124:1442).
- O_2 pulse: $\dot{V}O_2$/HR is a rough surrogate for stroke volume; should increase at start of

exercise before reaching a plateau.

- O_2 uptake efficiency slope (OUES): relationship between $\dot{V}O_2$ and log(V_E) throughout exercise. Highly reproducible, even at submaximal effort. Potent predictor of outcome: 2-fold ↑ in mortality in HFrEF for values <1.47 (*JACC* 2000;36:194).
- mPAP/CO slope
  - Serial measurements during exercise define the pulmonary artery pressure response to increased blood flow through the pulmonary circulation during exercise
  - mPAP/CO slope >3 indicates *either* abnormal pulmonary vascular response to exercise *or* upstream transmission of high left atrial pressure (*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

Interpretation of results (see figure)

- Step 1: Is this a maximal effort? RER >1.05 ± HR >85% predicted
  - If not → nondiagnostic test, consider deconditioning/inadequate effort or chronotropic incompetence (low peak HR + high $\dot{V}O_2$/HR)
  - For submaximal test, V_E/VCO_2 & OUES may still be interpretable and prognostically important
- Step 2: Is peak $\dot{V}O_2$ abnormal (ie, <80–85% predicted)?
  - If not, consider nonorganic cause of dyspnea (eg, anxiety/hyperventilation), ↑ metabolic cost of work (ie, obesity), or early cardiopulmonary disease
- Step 3: Is ventilatory reserve abnormal (V_E/MVV >60–70%)?
  - If so, consider pulmonary mechanical limit (eg, COPD or restrictive lung disease)
- Step 4: Is the ventilatory (anaerobic) threshold reduced (ie, <40%)?
  - If so, consider cardiovascular limit

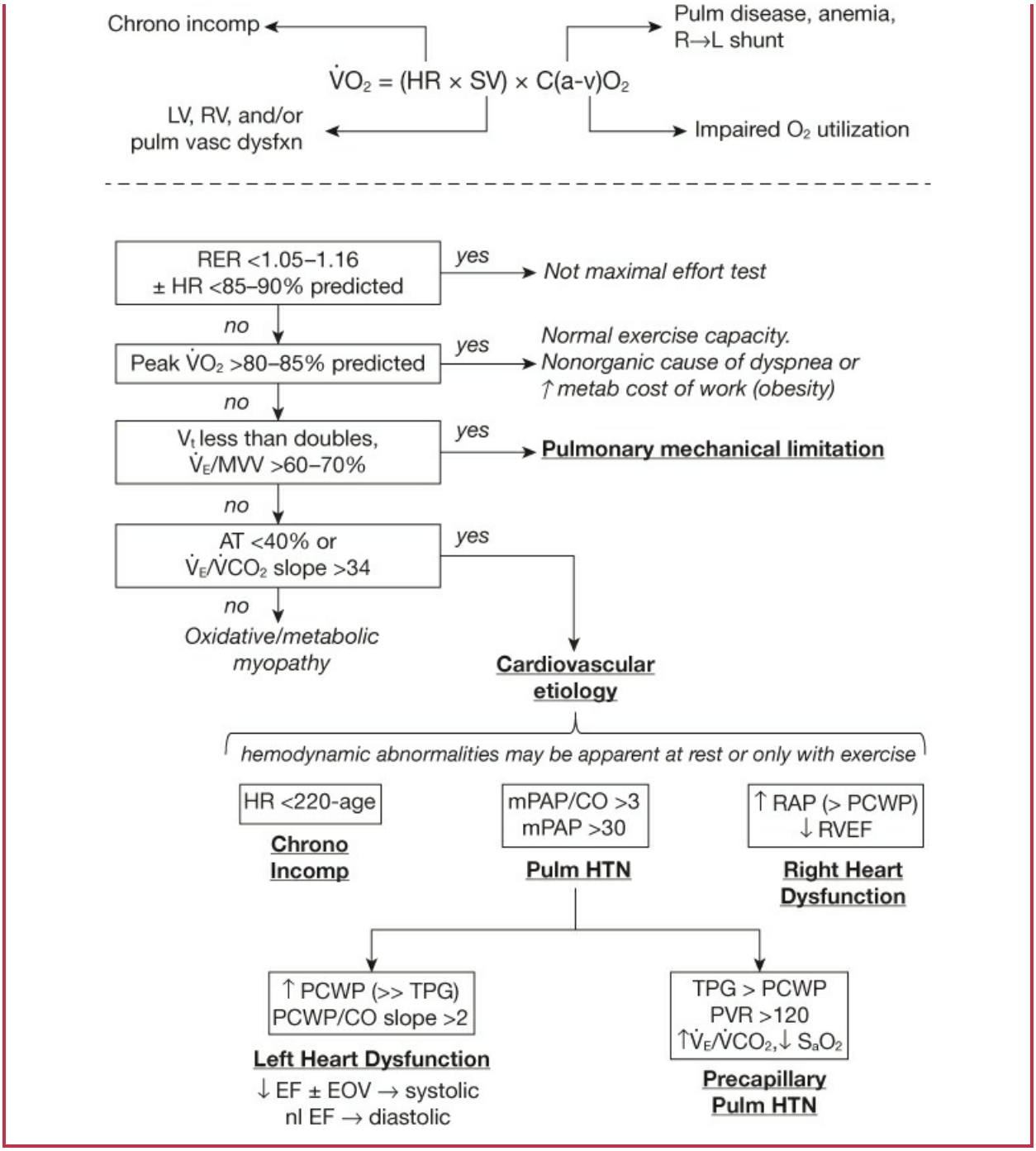
Risk stratification for advanced HF

- Transplant/MCS consideration typically based on peak $\dot{V}O_2$
  - ≤14 ml/kg/min on maximal test for those who are β-blocker intolerant
  - ≤12 ml/kg/min for those tolerating β-blockers
- For young Pts (<50), women, and those with high or low BMI, can use $\dot{V}O_2$ <50% predicted
- In morbidly obese, consider adjustment of $\dot{V}O_2$ for lean body mass (<19 ml/kg/min associated with high risk)
- If effort is submaximal, consider selection based on $V_E/\dot{V}CO_2$ >35 or OUES <1.47

Typical CPET Patterns in Common Disease States (*AJRCCM* 2003;167:212)

Metric	HF	COPD or ILD	Pulm Vascular Disease	Obesity	Deconditioned
Peak $\dot{V}O_2$	↓	↓	↓	↓	↓
AT	↓	nl/↓	↓	nl	nl/↓
Peak HR	variable	nl/↓	nl/↓	nl/↓	nl/↑
O_2 pulse	↓	nl/↓	↓	nl	↓
V_E/MVV	nl/↑	nl/↑	nl	nl/↑	nl
$V_E/\dot{V}CO_2$ (at AT)	↑	↑	↑	nl	nl
V_d/V_t	↑	↑	↑	nl	nl
P_aO_2	nl	nl/↓	↓	nl/↑	nl
$P_{(A-a)}O_2$	usually nl	nl/↑	↑	nl/↓	nl

Figure 1-2 Approach to CPET Interpretation



(Based on *Circ* 2010;122:191 & UpToDate)

HYPERTENSION

ACC/AHA Classification for Office-Based BP (*HTN* 2018;71:e13)		
Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Normal	<120	<80
Elevated	120–129	<80
Stage 1 Hypertension	130–139	80–89
Stage 2 Hypertension	≥140	≥90

- Categories based on SPRINT trial and ACC/AHA 2017 GL (*NEJM* 2015;373:2103). Nb, ESC, & ISH define HTN as office-based SBP ≥140 or DBP ≥90 mmHg with SBP 130–139 or DBP 85–89 called high-normal (*J HTN* 2023;41:1874; *HTN* 2020;75:1334).
- If disparity in a category between systolic and diastolic, higher value determines stage
- Average ≥2 measurements on ≥2 occasions & confirm with out-of-office measurements
- Confirm stage 1 w/in 1–4 wks. Rx for stage 1 depends on risk. Low risk (no ASCVD & 10-yr risk <10%) → lifestyle for 3–6 mos and then Rx if still uncontrolled. High-risk stage 1 and all stage 2 → treat immediately (*HTN* 2021;77:e58).
- ✓ at 1 mo after starting treatment, 3–6 mos (if treating but at goal), q1y (if normal)

Ambulatory Thresholds for Hypertension		
Setting	**Systolic (mmHg)**	**Diastolic (mmHg)**
24-hr mean	≥125	≥75
Day* (awake)	≥130	≥80
Night (asleep)	≥110	≥65

*Threshold of hypertension for home readings should be same as daytime ambulatory on a 24-hr ambulatory monitor (see next). ESC uses 24-hr mean ≥130 systolic or ≥80 diastolic or a daytime mean ≥135 systolic or ≥85 diastolic (*EHJ* 2018;39:3021).

Correlation of SBP & DBP by Mode of Measurement (*HTN* 2018;71:e13)				
Clinic	**Home Monitor**	**Daytime ABPM**	**Nighttime ABPM**	**24-hr ABPM**
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

Measurement & diagnosis

- Measure yearly in adults with normal BP and semiannually if elevated or risk factors
- Avoid caffeine, exercise, or smoking 30 min prior; take BP w/ Pt sitting w/ feet on floor
- First visit measure in *both* arms

- Automated cuff more accurately predicts awake ABPM vs. manual (*JAMA IM* 2019;179:351)
- Obtain after 5 min of rest, ≥2 times, 1–2 min apart, reporting average
- Elevated office BP should be confirmed with out-of-office (ABPM or home cuff) to confirm
- *White coat* (≥ Stage 1 in office but < at home) at heightened risk of developing HTN
- *Masked* (< Stage 1 in office but ≥ at home), if persistent, treat as hypertension
- 24-hr ambulatory BP preferred method for confirming HTN (including white coat & masked)

Epidemiology (*Circ* 2023;147:e93)

- Prevalence: 47% in U.S. adults; >122 million affected. In individuals <65 yrs, more prevalent in men than women, reverse if ≥65 yrs; highest in Black adults (~58%).
- ↑ Age → ↓ arterial compliance → systolic HTN
- 39% of U.S. adults are not aware they have HTN and only 48% of Pts with dx of HTN have adequate BP control

Primary hypertension

- Accounts for 95% of cases
- Onset typically 25–55 yrs of age
- Unclear mechanism with mosaic theory hypothesized with interplay of kidney, vasculature, and CNS (*Circ Res* 2021;128:847)
- Risk factors include age, obesity, diet (Na intake), alcohol, physical inactivity, ⊕ FHx, sleep disorders (*J Hypertens* 2023;41:63), social determinants (*Hypertens Res* 2022;45:1575)
- Genetic predisposition, but can be offset by lifestyle (*Nat Genet* 2017;49:403; *Circ* 2018;137:653)
- Black individuals more likely to be salt sensitive and have less activation of renin–angiotensin system, explaining preference for thiazides & CCB over ACEI or ARB

Secondary hypertension

- Consider if Pt <20 or >50 yrs old or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension

Diseases		Suggestive Findings	Initial Workup
RENAL	**Renal parenchymal** (2–3%)	h/o DM, polycystic kidney disease, glomerulonephritis	eGFR, albuminuria
	Renovascular (1–2%, qv) Athero (90%) FMD (10%, women) PAN, scleroderma	ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (*NEJM* 2009;361:1972)	MRA (>90% Se & Sp, less for FMD), CTA, duplex U/S, angio, plasma renin (low Sp)
ENDO	**Hyperaldo or Cushing's** (1–5%)	Hypokalemia Metabolic alkalosis	See below
	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
	Hypothyroidism (<1%)	Weakness, fatigue, cold intolerance, constipation	TFTs
	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv)		
	Medications: OCP, steroids, licorice, NSAIDs, decongestants, Epo, cyclosporine, oncologic therapies, angio inhibitors (bevacizumab) & TKIs (eg, sunitinib), illicit drugs		
	Aortic coarctation: ↓ LE pulses, systolic murmur, radial–femoral delay; abnl TTE, CXR		
	Polycythemia vera: ↑ Hct		

Adrenal disorders as secondary causes

- **Hyperaldosteronism**
  - Etiologies: 1° (adrenal disorders), 2° (renin dependent, typically from RAS [qv]), or non- aldo mineralocorticoid excess (11β-HSD deficiency, black licorice, Liddle's syndrome)
  - Clinical: headache, muscle weakness, polyuria, polydipsia; no peripheral edema; classically **hypokalemia** (but often normal), metabolic alkalosis, mild hypernatremia
  - Diagnosis: *aldo* (>15–20 ng/dl) and *plasma aldo:renin ratio* (>20 if 1°). Obtain 8 a.m. paired values, Se & Sp >85%. Must be off spironolactone & eplerenone for 6 wks. ACEI/ARB, diuretics, CCB, & βBs can Δ PAC/PRA ratio; ∴ avoid. α-Blockers generally best to control HTN during dx testing. Confirm with sodium suppression test (fail to suppress aldo after sodium load).
- **Hypercortisolism**
  - Etiologies: Cushing's disease (ACTH-secreting pituitary adenoma or hyperplasia), adrenal tumor, ectopic ATCH (eg, lung cancer)
  - Clinical: **glucose intolerance or DM**, central obesity, dorsocervical fat pads, proximal myopathy, rounded facies, wide purple striae, oligo- or amenorrhea, osteoporosis
  - Diagnosis: *dexamethasone suppression test* or *24-hr urinary free cortisol*; if ⊕, ✓ACTH
- **Pheochromocytoma**
  - Etiologies: neuroendocrine neoplasm
  - Clinical (the 5 P's): **pressure** (HTN, paroxysmal in 50%), **pain** (headache, chest pain), **palpitations** (tachycardia, tremor, wt loss, fever), **perspiration**, **pallor** (vasoconstrictive spell)
  - Diagnosis: 24° urinary fractionated metanephrines (85–97% Se, 69–95% Sp; screening test of choice if low risk) or plasma-free metanephrines (89–100% Se, 79–97% Sp; screening test of choice if high risk); if ⊗ then adrenal CT

Standard workup (*HTN* 2018;71:e13)

- Goals
  (1) Identify ASCVD, elevated CV risk, 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; ⊗ FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: 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. Current

guidelines recommend confirmation of in-office diagnosis with out-of-office measurement (ie, ABPM) (*HTN* 2018;71:e13; *J HTN* 2023;41:1874).

Complications of HTN

- Mendelian randomization analyses: each (lifelong) 10 mmHg ↑ in genetically proxied SBP or DBP associated with 49% ↑ in incident CVD (*Hypertension 202*1;77:2004)
- Systolic hypertension more predictive of adverse outcomes but diastolic also important (J- curve relationship) with consistent relationship at lower thresholds (*NEJM* 2019;381:243)
- **LVH and heart failure** (*JAMA* 1996;275:1557)
- Neurologic: **TIA/CVA**, ruptured aneurysms, vascular dementia
- Retinopathy: stage I = arteriolar narrowing; II = copper wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: **CAD, AF**
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, **renal failure**

TREATMENT

Overview (*HTN* 2018;71:e13)

- Goal: in general, <**130/<80 mmHg**
- In higher CV risk Pts, office SBP 120 vs. 134 or 127 vs. 136 mmHg → ↓ MACE, but w/ ↑ HoTN & syncope, and possibly AKI & electrolyte abnl (*NEJM* 2021;384:1921 & 385:1268)
- In Pts w/ CKD not on dialysis, target SBP <120 mmHg (*Annals* 2021;174:1270)
- However, for low CV risk Pts, more liberal targets can be considered (eg, <135/<85 out of office or <140/<90 in office)

Lifestyle modification

- Should be used in ***all patients*;** each can ↓ SBP ~5 mmHg
- **Weight loss**: goal BMI 18.5–24.9 with benefit independent and synergistic with sodium restriction; 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**: ≤2.4 g/d and ideally ≤1.5 g/d (*NEJM* 2010;362:2102)
  - ↓ Na by ~1 tsp (2.3 g) per day → ↓ in SBP of 6 mmHg (*JAMA* 2023;330:2258)
  - Use of salt substitute with 25% potassium chloride vs. 100% NaCl over ~5 yrs → 10–15% ↓ stroke, MACE, & death (*NEJM* 2021;385:1067)
- 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 Y; ≤1 drink/d in X & lighter-wt Pts
- Avoid exacerbating exposures (eg, NSAID use)

Pharmacologic therapy

- Typically lowers SBP by ~5 mmHg. Each 5 mmHg ↓ in SBP results in ~10% ↓ in risk of ischemic heart disease, stroke, and HF (*Lancet* 2021;397:1625). Nb seasonal variation in BP may impact control/tolerability (*J HTN* 2020;38:1235).
- Indicated if:
  - office BP ≥130/80 *and* ASCVD, HF, CKD, T2DM, ≥65 yrs old, or 10-yr ASCVD risk ≥10%, or if lower risk but remains uncontrolled after 3–6 mos of lifestyle

intervention
office BP ≥140/90 or ambulatory BP ≥135/85

- Elevated (previously "pre-HTN") w/o any of the above features treated w/ lifestyle alone. ARB prevents onset of HTN, no ↓ in clinical events (*NEJM* 2006;354:1685).
- *Choice* of drug: concomitant disease and stage may help guide Rx
- **Uncomplicated:** CCB, ARB or ACEI, and thiazide are 1st line (*NEJM* 2009;361:2153)
  - *For most Pts <60 yrs*: 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) U.S. guidelines note 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
  - βB not 1st line in ACC/AHA guidelines but remains an option in ESH guidelines
- **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:** RASi, βB, diuretics, aldosterone antagonist (see "HFrEF" & "HFpEF")
- **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. Recommended to start with combo Rx if ≥20 mmHg above SBP goal or ≥10 mmHg above DBP goal.
  - Typically start each drug at ½ maximal dose; after 2–3 wks either titrate up or add new drug. Trial of fixed-dose quadruple quarter-dose combination achieved 7 mmHg lower SBP than max dose ARB monoRx (*Lancet* 2021;398:1043).
- **Pregnancy:** methyldopa, labetalol, nifedipine; avoid diuretics; ∅ ACEI/ARB

Resistant hypertension (*HTN* 2018;72:e53)

- BP > goal on ≥3 drugs incl diuretic; ~12–13% of hypertensive population
- 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)
  - non-adherence to therapy (*J Hum HTN* 2016;30:83)
  - suboptimal med dosing (eg, <50% of max dose) or poor med compliance
  - volume expansion (inadequate diuretic dosing)
  - white coat HTN (confirm with ABPM)
  - 2° causes or external drivers (eg, OSA, steroids, NSAIDs, alcohol, some cancer Rx)
- True resistance = uncontrolled BP confirmed by ABPM despite compliance w/ optim. doses
- Treatment considerations:

Ensure volume status well controlled as may contribute even if on standard HCTZ (*Archives* 2008;168:1159). Effective diuretic dosing required for most to achieve control (*HTN* 2002;39:982). 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) (*Lancet* 2015;386:2059). Aldosterone synthase inhibition under investigation and may ↓ office SBP by 8–10 mmHg (*JAMA* 2023;330:1140).

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

Aprocitentan (endothelin-1 blocker) ↓ office SBP by ~4 mmHg; most common side effect is fluid retention w/ edema, which occurred in 7% more Pts (*Lancet* 2022;400:1927)

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

- **Renal denervation** (RDN)**:** catheter-based RF or ultrasound ablation of renal nerves modifying sympathetic outflow. Sham-controlled trials necessary to define benefit. Role in management of HTN evolving.

RF RDN

Pts w/ HTN not on meds: ~4 mmHg ↓ in 24-hr SBP and 6.5 mmHg ↓ in office-based SBP (SPYRAL HTN-OFF MED, *Lancet* 2020;395:1444)

Pts w/ treated but not resistant HTN: ~7 mmHg ↓ in 24-hr SBP at 6 mos (primary endpoint) and ~10 mmHg at 36 mos (SPYRAL HTN-ON MED, *Lancet* 2022;399:1401)

Pts w/ resistant HTN (SBP >160 mmHg despite ≥3 meds): no Δ at 6 mos (primary endpoint). In post hoc analyses, ~15 mmHg ↓ ambulatory SBP at 36 mos (*Lancet* 2022;400:1405).

Ultrasound RDN in Pts w/ resistant HTN (SBP >140 mmHg despite ≥3 meds)

4–5 mmHg ↓ ambulatory SBP at 2 mos (RADIANCE-HTN TRIO *Lancet* 2021;397:2476), but when med titration then permitted, no Δ in BP at 6 mos (*JAMA Cardiol* 2022;7:1244)

If withdraw anti-HTN meds before randomization → ~6 mmHg ↓ ambulatory SBP at 2 mos (similar to what anti-HTN meds would achieve) (RADIANCE II, *JAMA* 2023;329:651)

HYPERTENSIVE CRISES (*NEJM* 2019;381:1843)

Definitions & epidemiology

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

Neurologic: encephalopathy (insidious onset of headache, nausea, vomiting, confusion), hemorrhagic or ischemic stroke (~40%), papilledema

Cardiac: ACS, HF/pulmonary edema (~30%), aortic dissection (<5%)

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.
- Incidence: urgency/emergency seen in ≤1% of ED visits. Most commonly with HF (32%), ischemic stroke (29%), ACS (18%), hemorrhagic stroke (11%), and acute aortic syndrome (2%) (*J HTN* 2020;38:1203).

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

Workup

- ECG, CXR, basic metabolic panel, UA, cardiac biomarkers, selected imaging (head CT or MRI if neuro sx, nausea or vomiting; chest CT if sx of dissection or pulse deficit)

Treatment—tailor to clinical condition (*Circ* 2018;138:e426)

- AoD, eclampsia/severe preeclampsia, pheo: target SBP <140 (<120 for AoD) in **1 hr**
- Emerg w/o above: ↓ BP by ~25% in 1 hr; to 160/100–110 over next 2–6 hrs, then nl over 1–2 d
- Acute ischemic stroke (within 72 hrs from sx onset): <185/110 before lysis planned, o/w target <220/120 (same SBP goal for ICH)
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

IV Drugs for Hypertensive Emergency (*Circ* 2018;138:e426; *Stroke* 2018;49:46)

Drug	Dose	Preferred for
Labetalol	20–80 mg IVB q10min or 0.4–2 mg/min	AoD, ACS, Stroke, Eclampsia
Esmolol	0.5–1 mg/kg load → 50–200 µg/kg/min	AoD, ACS
Nitroprusside*	0.25–10 µg/kg/min	Pulm edema
Nitroglycerin	5–500 µg/min	Pulm edema, ACS
Nicardipine	5–15 mg/hr (can η 2.5 mg/hr q5min)	Stroke, AKI, Eclampsia, Pheo
Clevidipine	1–32 mg/hr (can titrate q5–10min)	Stroke, Pulm edema, AKI, Pheo
Fenoldopam	0.1–1.6 µg/kg/min	AKI
Hydralazine	10–20 mg q20–30min prn	Eclampsia
Phentolamine	5–15 mg bolus q5–15min	Pheo
Enalaprilat	1.25–5 mg q6h	

*Metabolized to cyanide →Δ MS, lactic acidosis, death. Limit use of very high doses (8–10 µg/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; may tolerate BP up to 185/110
Aortic dissection (qv)	✓ BP in both arms and treat higher value	**βB first**, then add vasodilator (eg, nitroprusside) if needed. Target systolic <100–120 mmHg; HR ≤60 bpm.
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, autonomic dysfxn, cocaine, MAO + tyramine-containing foods)	**Avoid βB** as could → unopposed α in vasculature → vasoconstriction and further ↑ BP	Phentolamine (pheochromocytoma), nitroprusside
Renal emergency (acute nephrosclerosis)	Hematuria may be present; acute lowering may worsen function	Consult renal team; fenoldopam may ↓ risk of ↓ renal fxn (*Crit Care* 2015;19:449)

DYSLIPIDEMIA

Lipoproteins

- Macromolecular complexes composed of lipids and proteins that serve to transport poorly soluble lipids through the body
- Core of hydrophobic lipids (triglycerides [TG] & cholesteryl esters) surrounded by shell of hydrophilic lipids (phospholipids & unesterified cholesterol) and proteins (called apolipoproteins)
- Include: chylomicrons, chylomicron remnants, VLDL, IDL, LDL, Lp(a) (a subtype of LDL that has special attributes, vide infra), HDL

Lipoprotein metabolism

- **Exogenous pathway**: primarily TG along w/ apoB-48, apoC's, and apoE packaged into *chylomicrons* in enterocytes and enter circulation via lymphatics & thoracic duct. Bring TG to adipocytes & myocytes where lipoprotein lipase (LPL) hydrolyzes TG, liberating free fatty acids. As hydrophobic core depleted of TG, resultant particles are called *chylomicron remnants* and rapidly taken up by the liver (via LDL receptor [LDLR]).
- **Endogenous pathway**: primarily TG along w/ cholesteryl esters, apoB-100, phospholipids, & vitamin E packaged in liver by microsomal TG transfer protein (MTP) into *VLDL* and secreted into circulation. Bring TG to adipocytes and myocytes where LPL hydrolyzes TG, liberating free fatty acids. Resultant particles, now with roughly equal amounts of TG and cholesterol, are called *IDL*. ~½ IDL taken up by liver (via LDLR) and other ~½ remodeled by hepatic lipase (depleting TG and removing all apolipoproteins except apoB-100) to form cholesterol-rich *LDL*. LDL taken up by liver via LDLR.
- **Reverse cholesterol transport**: liver & intestine secrete nascent *HDL* containing unesterified cholesterol & apoA1. Circulates and takes up unesterified cholesterol from cells, VLDL, or chylomicrons. Cholesterol transported to liver directly (HDL taken up by liver) or indirectly (cholesteryl esters transferred to VLDLs [which become LDLs] in exchange for TG by cholesteryl ester transfer protein [CETP] and LDL cleared by LDLR).
- Thus, chylomicrons & VLDL are TG-rich lipoproteins that deliver energy to cells, LDL is a cholesterol-rich lipoprotein that is the by-product of TG removal from VLDL, and HDL facilitates reverse cholesterol transport and excretion

Lipid measurements

- Lipoproteins can be measured by ultracentrifugation or NMR, but not done in routine practice. Instead, lipid content of blood is measured.
- Total cholesterol (cholesterol in all lipoproteins) measured by enzymatic reaction
- TG (TG content in all lipoproteins; surrogate for concentration of TG-rich lipoproteins) measured by enzymatic reaction; levels affected by eating, ∴ measure after 12-hr fast
- HDL-C (cholesterol in HDL particles; surrogate for concentration of HDL particles) measured by enzymatic reaction after removing apoB-containing particles
- LDL-C (cholesterol in LDL particles; surrogate for concentration of LDL particles) typically estimated by Friedewald equation: LDL-C = TC − HDL-C − (TG/5)
  - last term assumes TG:cholesterol ratio in VLDL particles is 5
  - as formula uses TG, should measure fasting (but underestimation typically <10 mg/dl)
  - levels stable up to 24 hrs after ACS and other acute illnesses, then ↓ and may take 6 wks to return to baseline ("inverse acute phase reactant")
  - underestimates true LDL-C if TG >400 or LDL-C <70 mg/dl
  - contemporary NIH equation likely most accurate (*JAMA Cardiol* 2020;5:540)
  - ideally directly measure LDL-C (direct assay or ultracentrifugation)
- Non–HDL-C (TC − HDL-C) and apoB are alternative nonfasting measures of risk that encompass all atherogenic lipoproteins, are better risk predictors than LDL-C, and are increasingly being incorporated into risk prediction scores and treatment guidelines

Metabolic syndrome

- Constellation of metabolic abnormalities associated with ↑ risk of CV disease
- May largely be driven by ↑ central adiposity → insulin resistance, ↑ TG, ↓ HDL-C, HTN
- Consensus definition requires central adiposity + ≥2 other criteria (*Circ* 2009;120:1640)
  - central obesity: waist ≥40″ (or 37″) in men or ≥35″ (or 31.5″) in women
  - TG >150 mg/dl
  - HDL <40 mg/dl in men or <50 mg/dl in women
  - SBP ≥130 or DBP ≥85 mmHg or dx of HTN
  - fasting glc ≥100 mg/dl or dx of DM

Lipoproteins and clinical risk

- All apoB-containing lipoproteins (ie, LDL, IDL, VLDL) can promote atherogenesis; risk appears proportional to # of particles, not chol. or TG content *per se* (*JAMA* 2019;321:364)
- Imaging studies of coronary atheroma show growth when LDL-C exceeds ~70 mg/dl and regression when below, with rate of growth or regression proportional to how much LDL- C is above or below that threshold (*JAMA* 2007;297:499)
- High levels of TG (>500 mg/dl) can cause pancreatitis

More common primary dyslipidemias

- Familial hypercholesterolemia (1:250): loss-of-fxn mutations in LDLR → ↓ LDL hepatic uptake & ∴ ↑↑ LDL-C in circulation & ↑ risk premature CAD. Familial defective apoB-100 (↓ ability of apoB in LDL to bind to LDLR) and autosomal dominant hyperchol. type 3 (gain-of-fxn mutations in PCSK9 → ↓ recycling of LDLR to hepatocyte

surface) have similar phenotypes. LDL-C >190 mg/dl should prompt consideration of genetic etiology.
- Polygenic FH: multiple small effect genetic variants without one causal gene (1:7)
- Familial combined hyperlipidemia (1:200): polygenic; ↑ LDL-C, ↑ TG, ↓ HDL-C; ↑ CAD
- Familial hypertriglyceridemia (FHTG, 1:500): polygenic; ↑ TG, ↓ HDL-C; ↑ pancreatitis

Physical exam findings

- Tendon xanthomas: seen on Achilles, elbows, and hands; implies high LDL-C
- 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

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

Treatment of LDL-C (*EHJ* 2020;41:111; *JACC* 2022;80:1366)

- Every 1 mmol (~39 mg/dl) ↓ LDL-C → 22% ↓ major vascular events in individuals w/ & w/o CAD in data from statin trials with median treatment of 4–5 yrs (*Lancet* 2010;376:1670)
- Similar clinical benefit also seen w/ nonstatin Rxs that upregulate LDLR when taking into account magnitude and duration of LDL-C lowering (*JAMA* 2016;316:1289 & *EHJ* 2018;39:2540)
- Consistent CV benefit *even* when starting w/ LDL-C <70 mg/dl (*JAMA Cardiol* 2018;3:823)
- No evidence to suggest harm at very low LDL-C levels <20 mg/dl (*Lancet* 2017;390:1962)
- **Therapeutic lifestyle modification:** avoidance of trans fat, saturated fat; increased dietary fiber, reduced dietary cholesterol (animal products), plant-based diets, reduced body weight, daily exercise
- **Statins**
  - ↓ cholesterol synthesis by HMG Co-A reductase inhibition → ↑ hepatic LDLR activity
  - ↓ LDL-C by 20–60%, ↓ TG by 10–40%
  - myalgias in ~10%, but ~90% of these appear to be nocebo effect (*NEJM* 2020;383:2182; *Lancet* 2022;400:832); myopathy (ie, myalgias + ↑ CK) <0.1% & rhabdomyolysis <0.01%, both dose dependent (*ATVB* 2019;39:e38)
  - ↑ ALT in ~1% (dose dependent); hepatotoxicity ~0.001%; ✓ ALT before starting and then after as clinically indicated
  - ↑ risk of DM, more so with high-intensity statins; typically preexisting pre-DM → DM (*Lancet D&E* 2024;12:306); screen if risk factors
  - ↓ MACE in secondary & primary prevention populations (*Lancet* 2016;388:2532)

Cardiovascular features

- Bicuspid aortic valve, coarctation, and other left-sided obstructive lesions
- Aortic dissection can occur at lower diameter, should be indexed to body surface area
- ↑ risk for premature CAD & stroke due to ↑ prevalence of ASCVD risk factors

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Chromosome 22q11.2 Deletion (1 in 5000 live births)

Genetics

- Deletion at chromosome 22q11.2 → defective development of pharyngeal pouch system
- Includes **DiGeorge** & **velocardiofacial** syndromes
- Autosomal dominant pattern, consider in strong family history of TOF

Noncardiac features

- Hypoplastic thymus → immune deficiency
- Hypoparathyroidism → hypocalcemia
- Prominent upper jaw, underdeveloped lower jaw, cleft palate

Cardiovascular features

- Conotruncal abnl: interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, ASD, VSD

Williams (1 in 7500 live births)

Microdeletion in elastin (ELN) gene; autosomal dominant

Noncardiac features

- Broad forehead, narrow chin (Elfin facies)
- Outgoing ("cocktail party") personality, difficulty with visual-spatial tasks
- ↑ risk for hypercalcemia, kidney & urinary tract abnl, hearing loss, hyperextensible joints

Cardiovascular features

- Supravalvular AS, peripheral PA stenoses, supravalvular PS, other peripheral artery stenoses, abnormal coronary arteries

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Holt–Oram (Heart–Hand) Syndrome (1 in 100,000 live births)

Mutation in TBX5; autosomal dominant

Noncardiac features

- Upper limb malformations, including radius aplasia

Cardiovascular features

- Ostium secundum ASD, VSD, heart block

ACHD CLASSIFICATION

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