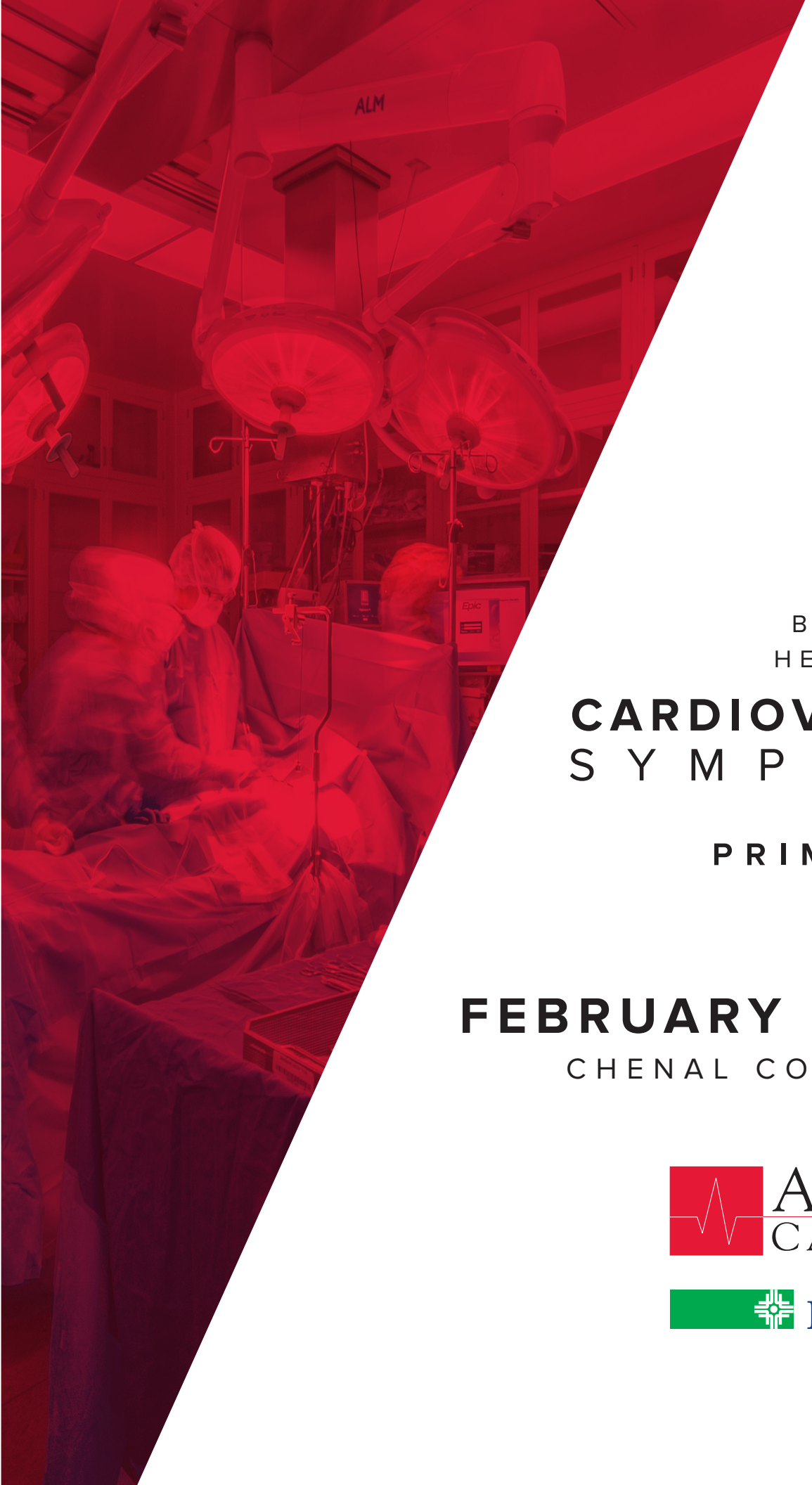

9TH ANNUAL
BAPTIST HEALTH
HEART INSTITUTE

# CARDIOVASCULAR SYMPOSIUM

FOR THE
**PRIMARY CARE PROVIDER**

## FEBRUARY 24, 2023

CHENAL COUNTRY CLUB

ARKANSAS CARDIOLOGY

Baptist Health
HEART INSTITUTE
A Department of Baptist Health

9TH ANNUAL BAPTIST HEALTH HEART INSTITUTE CARDIOVASCULAR SYMPOSIUM FOR THE PRIMARY CARE

Friday, February 24, 2023
Chenal Country Club

# Agenda

| | |
|---|---|
| **7:00 a.m.** | ***Registration, Continental Breakfast, and Exhibits*** |
| **7:50 a.m.** | ***Welcome and Opening Remarks, Invocation***<br>Jay Geoghagan, M.D., F.A.C.C.<br>David Jones, M.D., F.A.C.C.<br>Steve Greer, MD, FACC, FACP |
| **8:00 a.m.** | ***ECG Review***<br>Steve Greer, MD, FACC, FACP |
| **8:30 a.m.** | ***Cardiac Murmurs***<br>David Jones, MD, FACC |
| **9:00 a.m.** | ***Pitfalls of Blood Pressure Management***<br>Aaron Strobel, MD, FACC, FSCAI |
| **9:30 a.m.** | ***Morning Break and Exhibits*** |
| **9:45 a.m.** | ***Prevention Strategies for Heart Disease***<br>Wesley Fiser, MD, FACC |
| **10:15 a.m.** | ***Cardiac Pharmacology: Novel Agents and Emerging Trends***<br>Tom Conley, MD, FACC, FSCAI |
| **10:45 a.m.** | ***Non-Statin Lipid Management***<br>Faheem Beg, MD, FACC, RPVI |
| **11:15 a.m.** | ***HF Update: 2022 Heart Failure Classifications***<br>Anusha Sunkara, MD |
| **11:45 a.m.** | ***Lunch and Exhibits*** |
| **12:30 p.m.** | ***Counter Point with Dr. David Jones and Dr. Jay Geoghagan*** |
| **12:45 p.m.** | **Non-Surgical Structural Options**<br>Ernesto Ruiz-Rodriguez, MD, FACC |
| **1:15 p.m.** | ***Emerging roles for Cardiac CT/MR***<br>Ramey Marshell, MD |
| **1:45 p.m.** | ***Not All Edema is HF***<br>Dwight Chrisman, MD, FACC |
| **2:15 p.m.** | ***Afternoon Break and Exhibits*** |
| **2:30 p.m.** | ***Common Therapies that Increase CV Risk***<br>Kapil Yadav, MD, FACC, RPVI |
| **3:00 p.m.** | ***Sports Cardiology***<br>Jay Geoghagan, MD, FACC |
| **3:30 p.m.** | ***Adjourn*** |

# ECG Review

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# ECG Review

Steve Greer, MD, FHRS, FACC, CCDS

February 24, 2023

## Disclosures

- None

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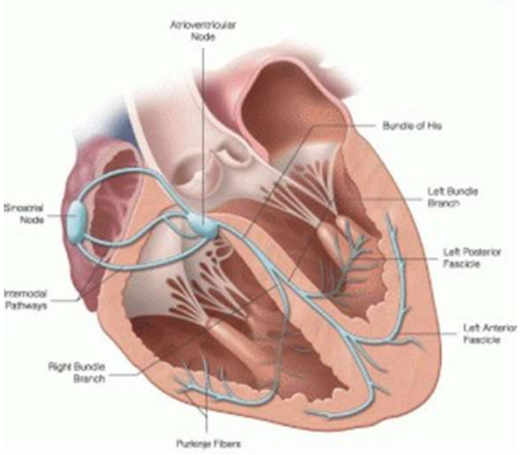
# Normal AV conduction system

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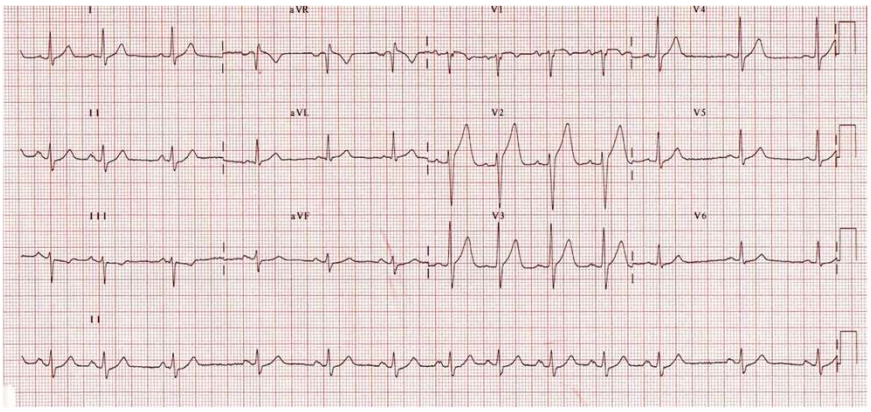
# Normal Sinus Rhythm



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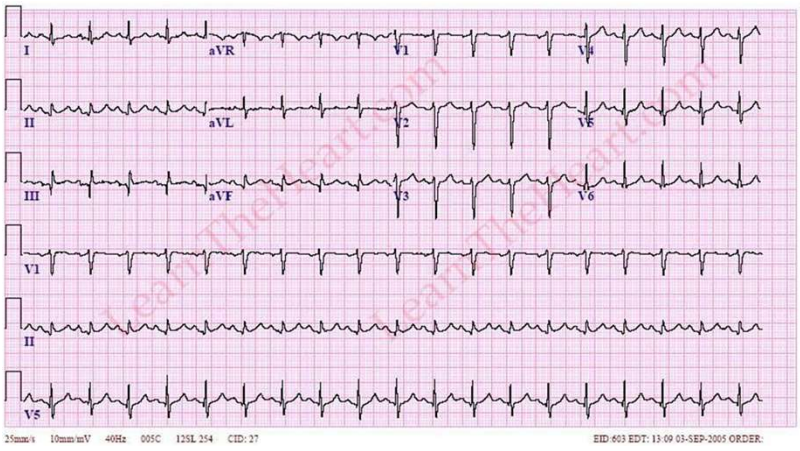
# Sinus Tachycardia

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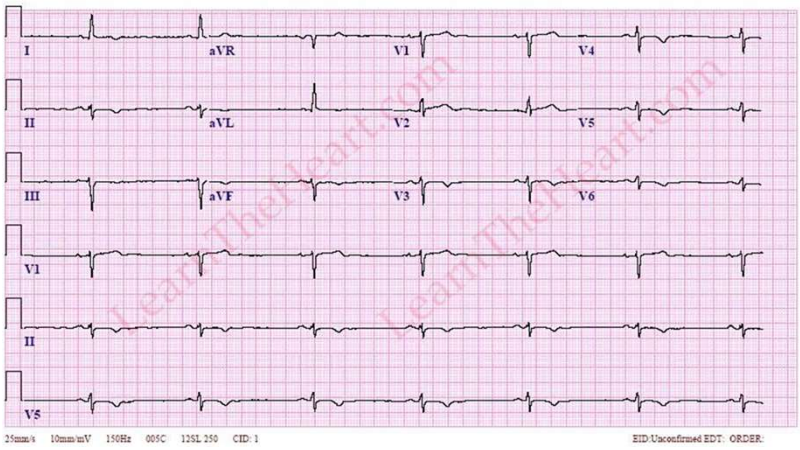
# Sinus Bradycardia

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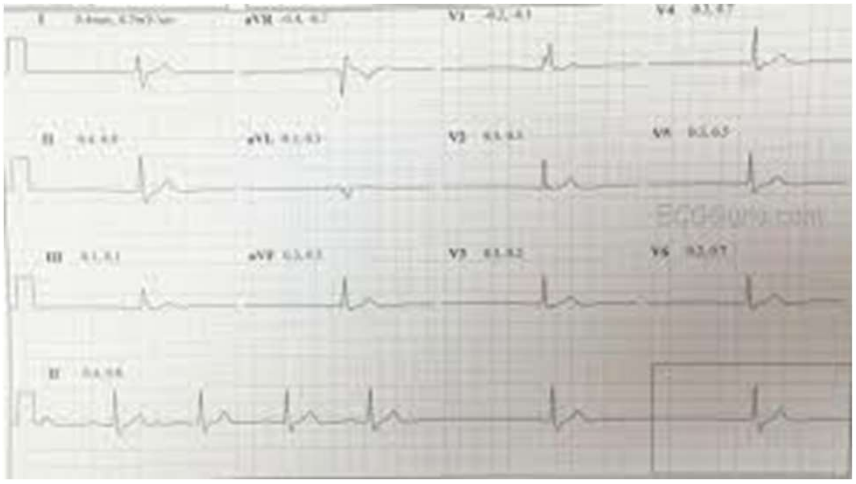
## Sinus Arrest



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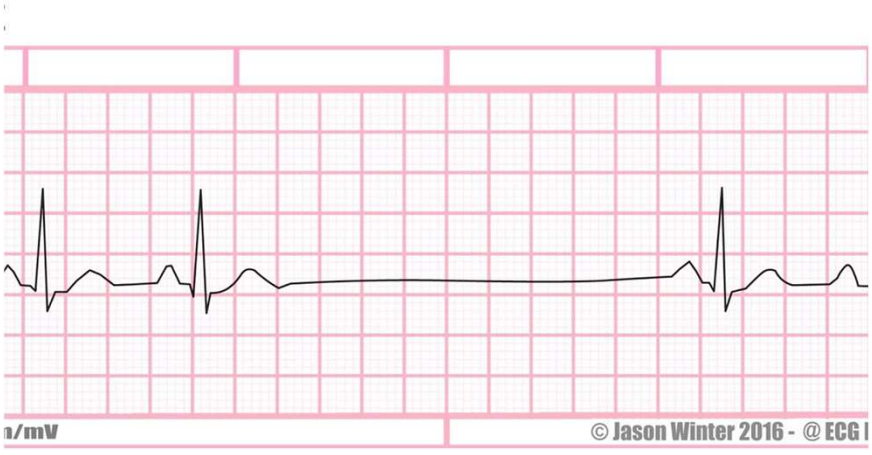
## Sinus Arrest/Pause

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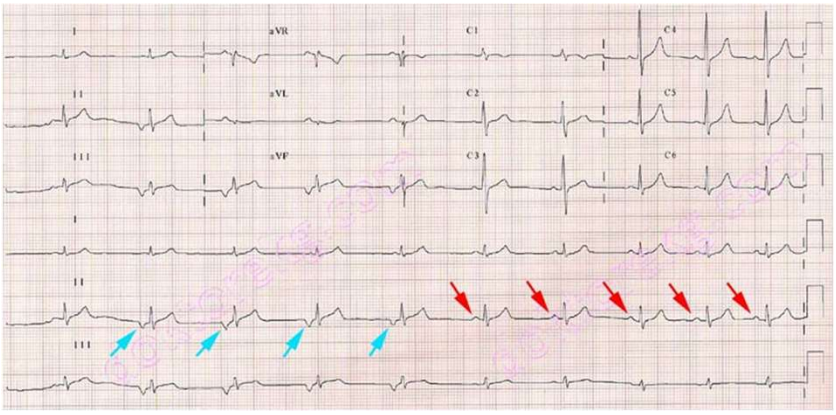
# Ectopic Atrial Rhythm



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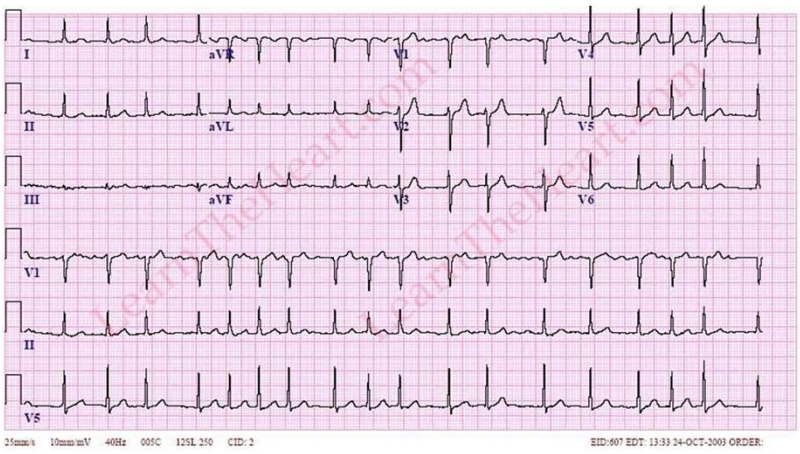
# Atrial Fibrillation

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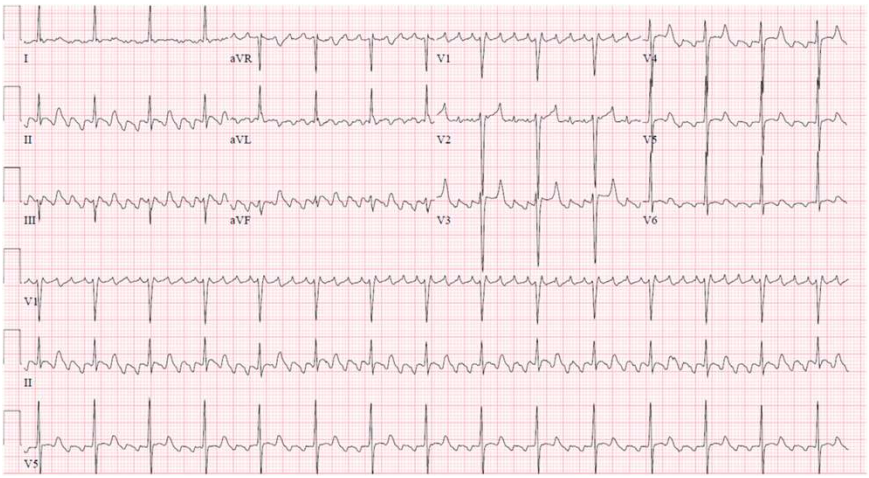
# Atrial Flutter

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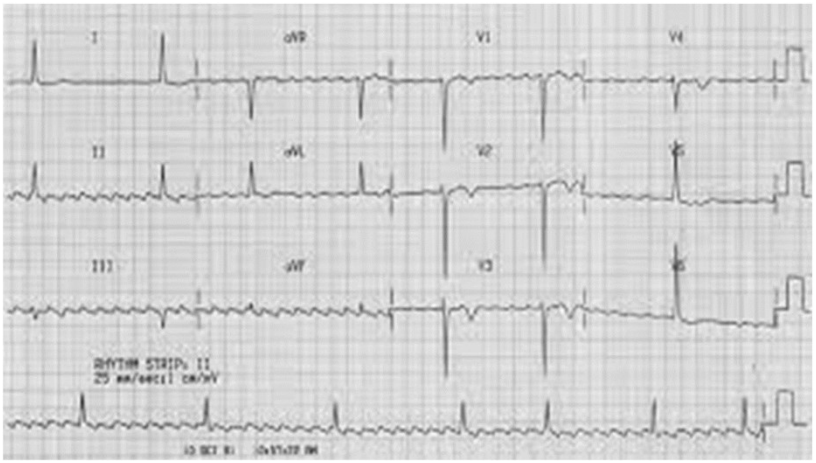
# Atypical Atrial Flutter

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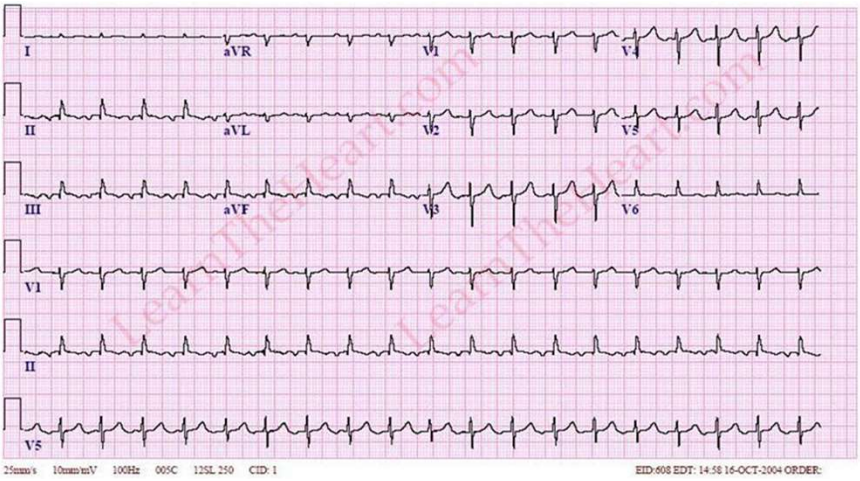
# Atrial Tachycardia

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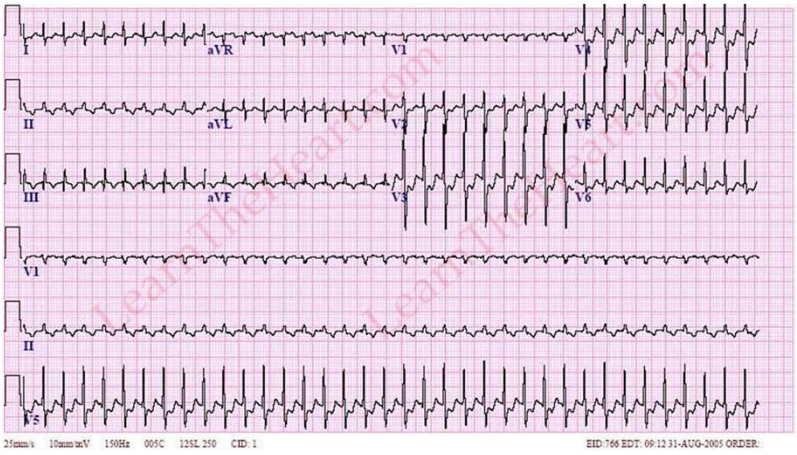
# Paroxysmal Supraventricular Tachycardia

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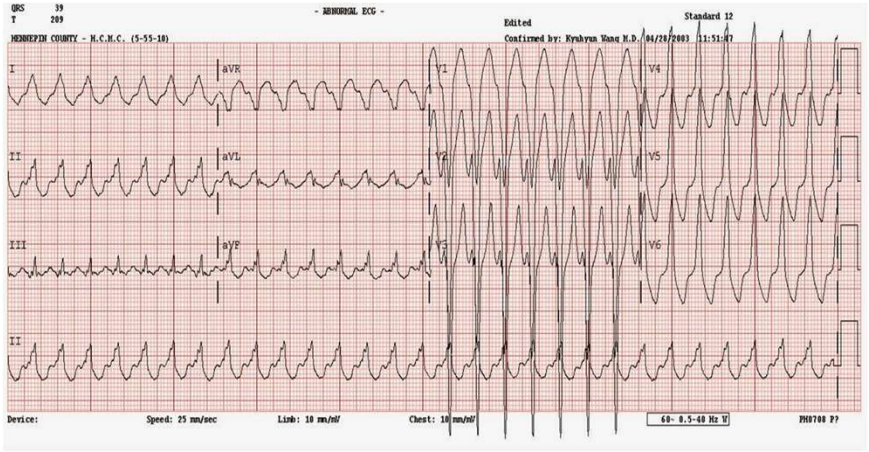
# Paroxysmal Supraventricular Tachycardia

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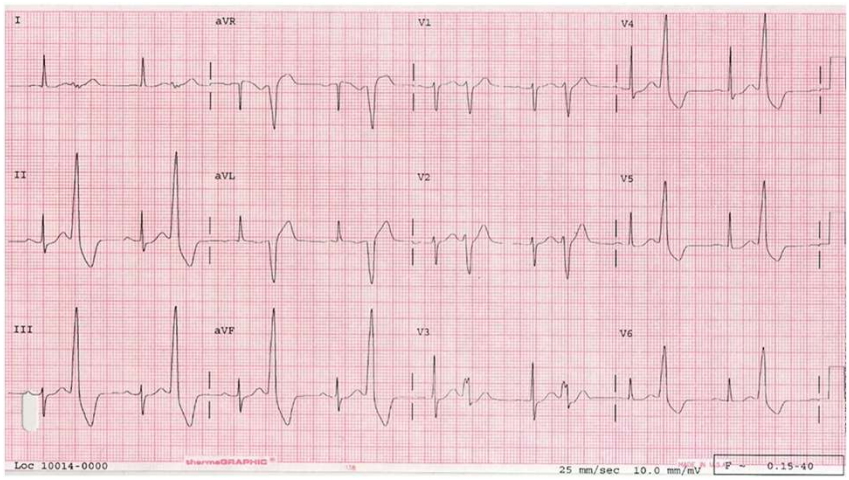
# Premature Ventricular Beats

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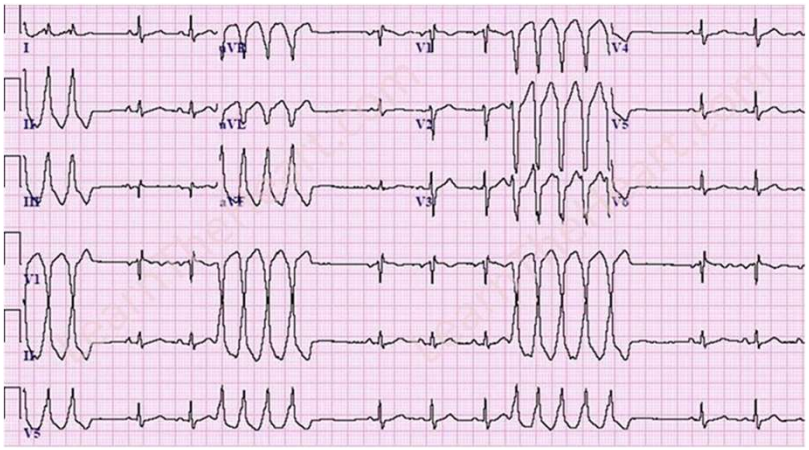
# Nonsustained Ventricular Tachycardia



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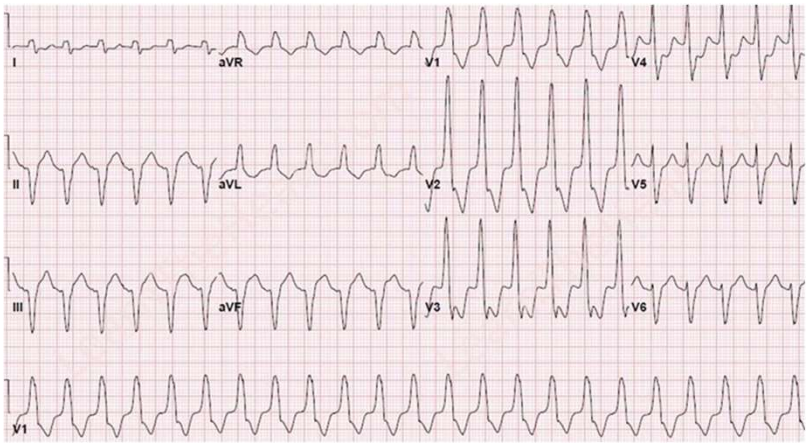
# Sustained Ventricular Tachycardia
# RBBB

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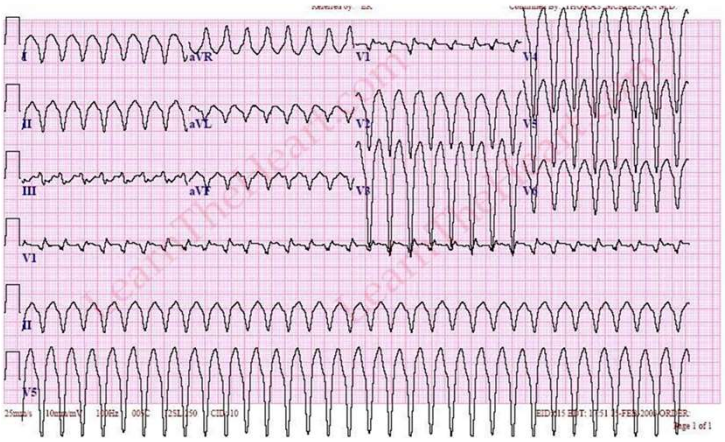
# Sustained Ventricular Tachycardia
# LBBB

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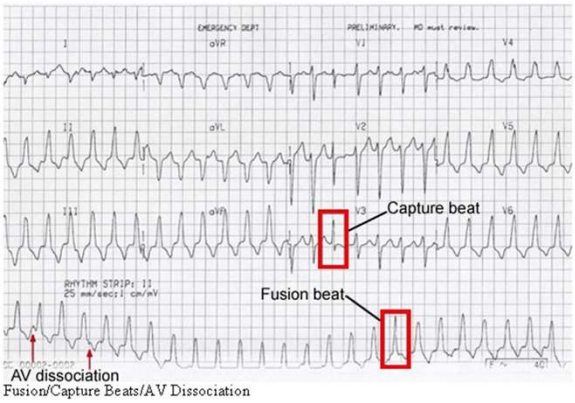
# Other Clues for VT




Fusion/Capture Beats/AV Dissociation

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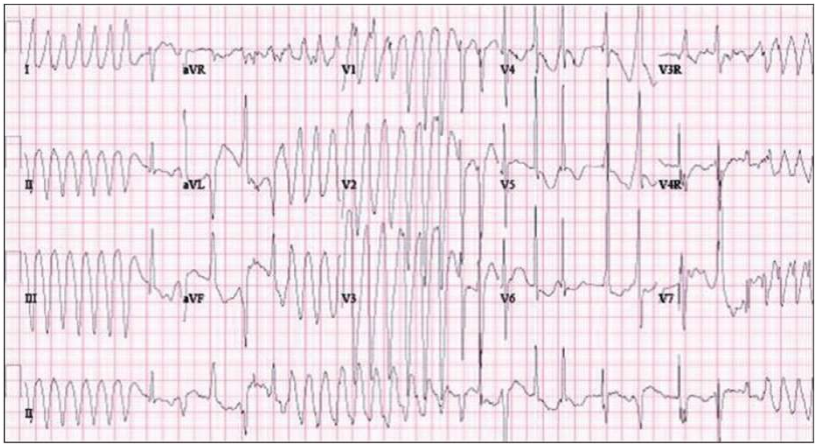
# Polymorphic Ventricular Tachycardia

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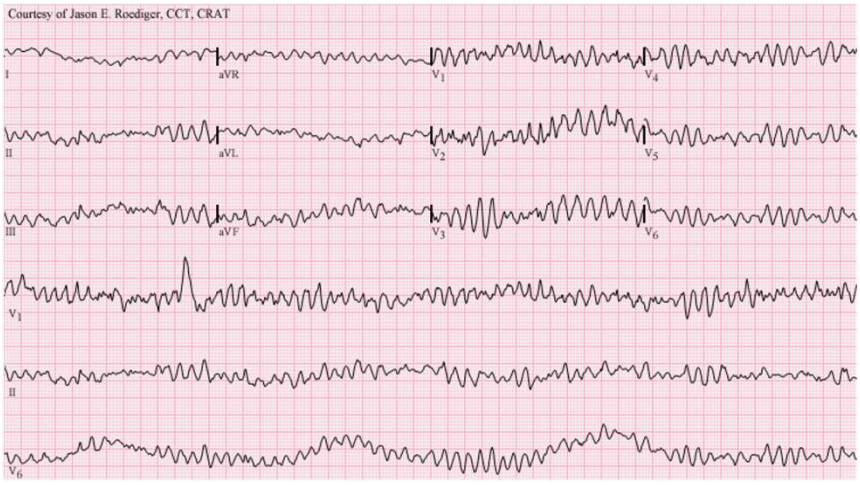
# Ventricular Fibrillation

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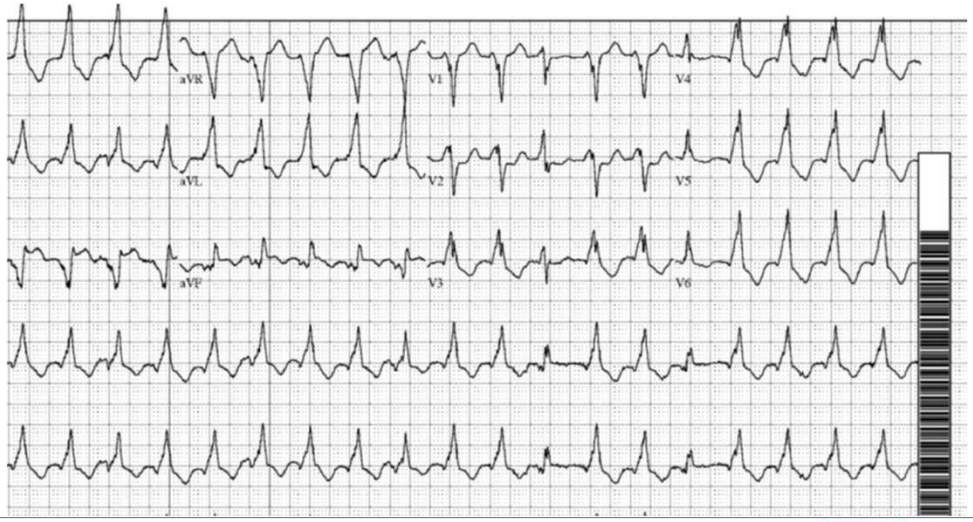
# Final Exam

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# THANK YOU

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# Cardiac Murmurs

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# Cardiac Murmurs

David Jones, MD
February 24, 2023

## Disclosures

- None

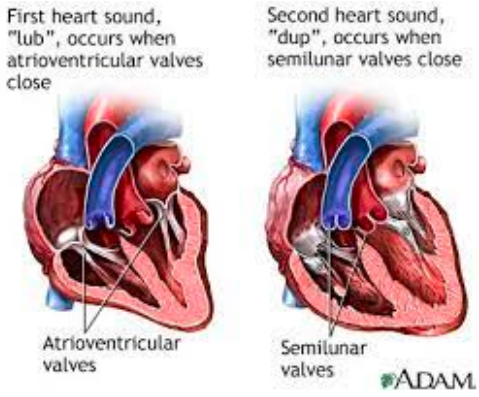
# Overview

- Basics of Murmurs and Auscultation
- Normal Heart Sounds
- Murmurs with Audio
  - Aortic Stenosis
  - Mitral Regurgitation
  - Aortic Regurgitation
  - Tricuspid Regurgitation
  - Mitral Valve Prolapse and Mitral Stenosis
  - Gallops (S3 and S4)

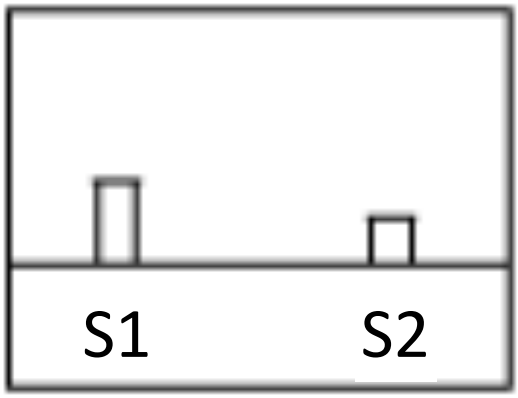


# Basics of Heart Sounds and Murmurs

- S1 = lub = beginning of systole
  - mitral/tricuspid closure
- S2 = dub = start of diastole
  - aortic/pulmonic closure
- Murmur Basics
  - Three Possibilities
    - High Flow Rate through Normal or Abnormal Orifice
    - Forward Flow through Constricted/Irregular Orifice
    - Backward Flow thru Incompetent Valve/Septal Defect/PDA



# Normal Heart Sounds

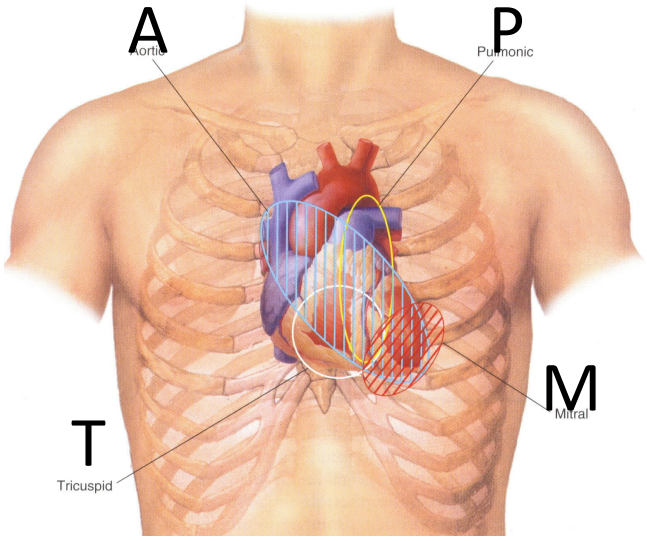





# Basics of Heart Sounds and Murmurs

- Timing (lub-dub = shorter interval, palpate carotid/radial pulse)
  - Systolic
  - Diastolic
  - Continuous
- Shape (crescendo, decrescendo, crescendo-decrescendo, plateau)
- Location of Maximal Intensity (RUSB, LUSB, LLSB, apex)
- Radiation (axilla, neck)
- Intensity (I-VI/VI)
- Pitch (high, medium, low)
- Quality (blowing, harsh, rumbling, musical)
- Maneuvers (respiration, position, Valsalva/standing)

# Auscultation Locations

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# Murmur Grading

- I/VI Very Faint
- II/VI Quiet but Heard Immediately
- III/VI Moderately Loud
- IV/VI Very Loud + Possible Thrill
- V/VI Heard with Stethoscope off Chest + Precordial Thrill
- VI/VI Audible without Stethoscope + Precordial Thrill

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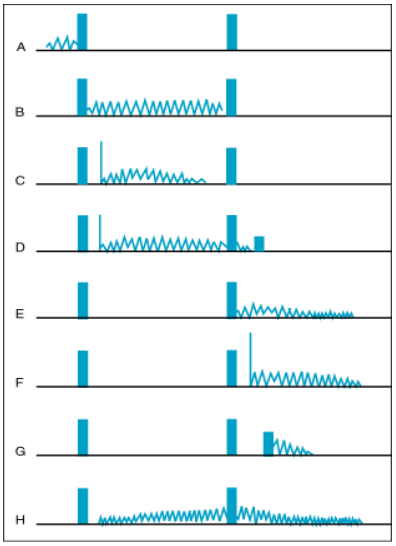
# Timing of Murmurs




S1 S2

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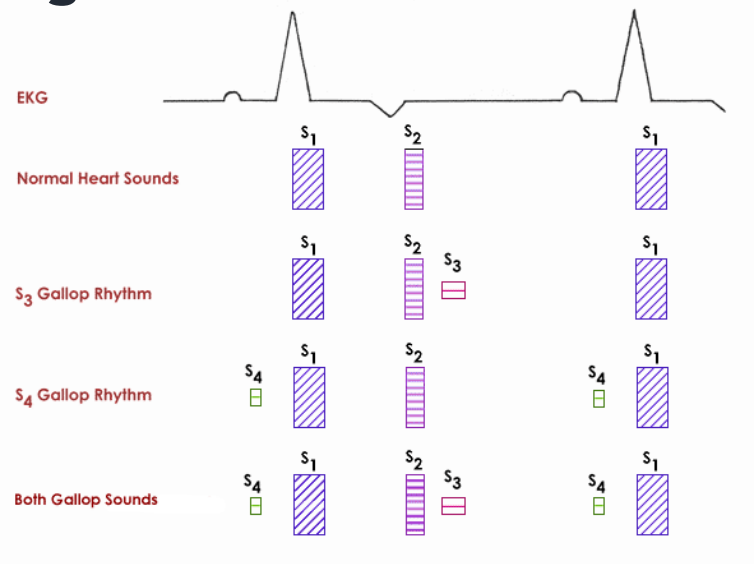
# Timing of Abnormal Heart Sounds

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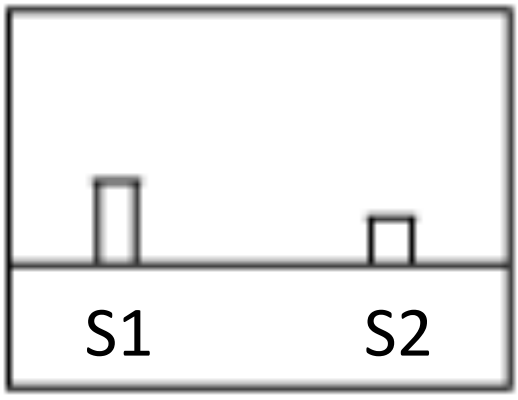
# Basics of Heart Sounds and Murmurs

- When Does It Occur - Systole or Diastole
- Where Is It Loudest - A, P, T, M
- If Systolic, Is It?
  - Ejection Type at RUSB = Aortic Stenosis
  - Holosystolic at Apex = Mitral Regurgitation
- If Diastolic, Is It?
  - Early at RUSB = Aortic Regurgitation
  - Mid to Late at Apex = Mitral Stenosis



# Normal Heart Sounds

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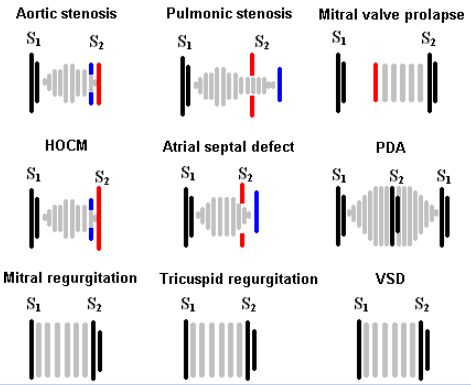
# Systolic Murmurs

- Early Systolic
  - Acute Severe Mitral Regurgitation
- Mid Systolic (Most Common Murmur, Usually Crescendo-Decrescendo)
  - Innocent/Physiologic/Flow (anemia, pregnancy, hyperthyroid)
  - Aortic Stenosis
  - Hypertrophic Cardiomyopathy
  - Pulmonic Stenosis
- Pan Systolic / Holosystolic
  - Mitral Regurgitation
  - Tricuspid Regurgitation
  - Ventricular Septal Defect

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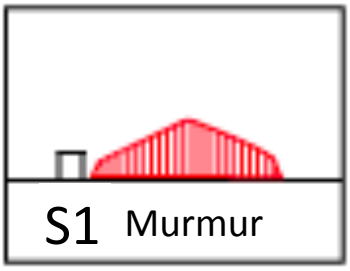
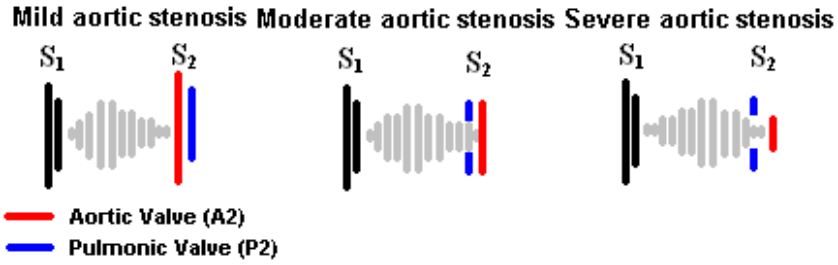
# Aortic Stenosis




- Mid Systolic Crescendo-Decrescendo Murmur
- Usually Heard Best at RUSB = Aortic Area
- Radiates to the Carotid Arteries
- A2 Decreases as Stenosis Worsens, Severity Assessed by Peak of Murmur/A2
- Associated with Gallivardin's Phenomenon = Musical Murmur at Apex
- Mimicked by: Aortic Sclerosis, Bicuspid AoV, Dilated Aorta, AV Fistula

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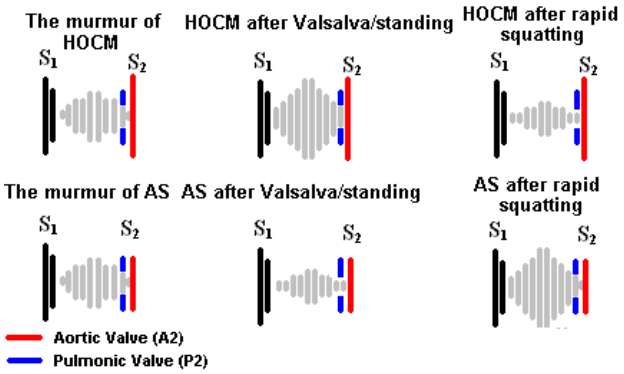
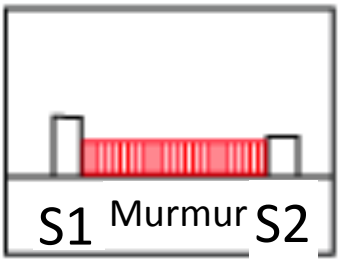
# Hypertrophic Cardiomyopathy




- Mid Systolic Crescendo-Decrescendo Murmur (can be identical to AS)
- Loudest between LSB and Apex
- Does not Radiate into Neck, no Delay in Carotid Upstroke
- Intensity Increases with Valsalva/Standing (decrease preload/LV volume)



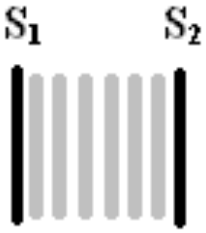
# Mitral Regurgitation





- Pan Systolic or Holosystolic Murmur
- Loudest at the LV Apex = Mitral Area
- Radiation Reflects Direction of Jet
  - toward base = anterosuperior jet = flail posterior leaflet
  - toward axilla = posterior jet = flail anterior leaflet
- Usually Associated with Systolic Thrill, Soft S3, and Diastolic Rumble

# Ventricular Septal Defect




- Pan Systolic or Holosystolic Murmur
- Heard Best at Erb's Point = LLSB at 3rd ICS
- The Smaller the VSD, the Louder the Murmur

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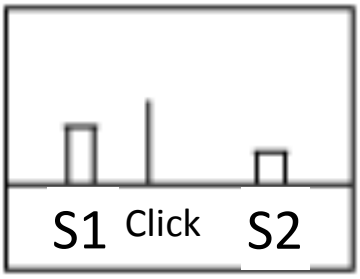
# Mitral Valve Prolapse





- Mid Systolic Click Followed by a High-Pitched Murmur
- Heard Best at the Apex = Mitral Area
- Responds to Dynamic Auscultation
  - Click is Earlier and Murmur Longer with Sudden Standing
  - Click is Later and Murmur Shorter with Sudden Squatting

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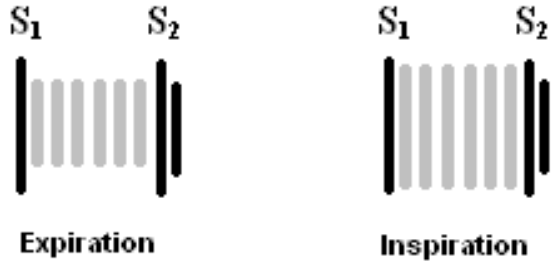
# Tricuspid Regurgitation

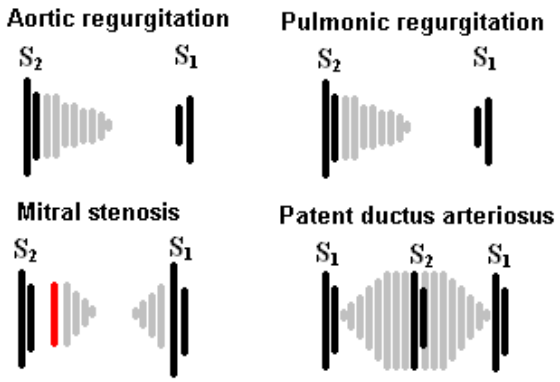



- Pan Systolic or Holosystolic Murmur
- Heard Best at LLSB = Tricuspid Area
- Radiates to the RLSB
- Louder with Inspiration

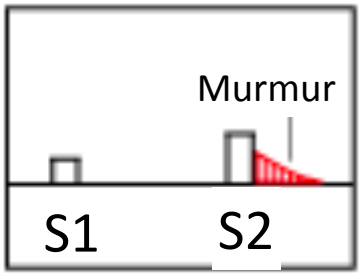


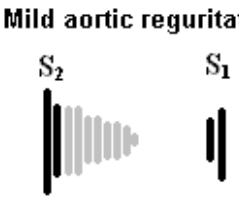
# Diastolic Murmurs

- Early Decrescendo Diastolic
  - Aortic Regurgitation
  - Pulmonic Regurgitation
    - indistinguishable from AR
- Mid- to Late- Diastolic
  - Mitral Stenosis
  - Tricuspid Stenosis - very rare



# Aortic Regurgitation





- Early Decrescendo Diastolic Murmur
- Heard Best in 2nd ICS at Left Sternal Edge
- Can be Blowing or High Pitched
- Associated with Austin Flint Murmur (early diastolic rumble at the apex due to jet striking anterior leaflet of MV)

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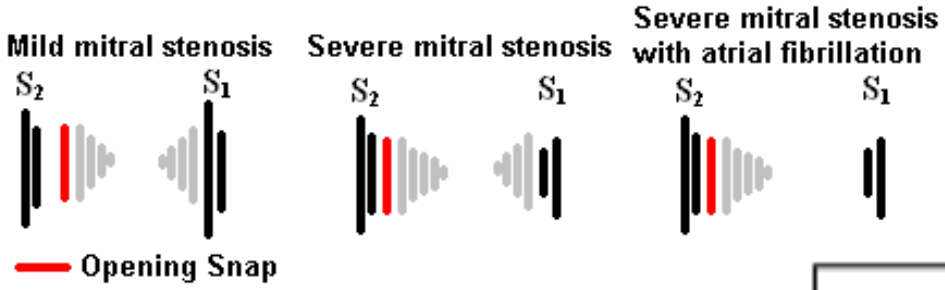
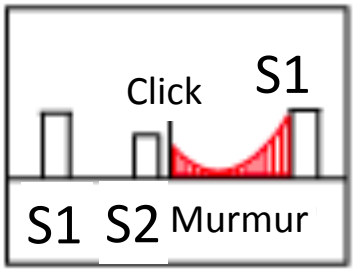
# Mitral Stenosis




- Rumbling Mid- or Late- Diastolic Murmur
- Two Components after Opening Snap -
  - Mid Diastolic (during rapid ventricular filling)
  - Pre Systolic (during atrial contraction)
- Heard Best at Apex = Mitral Area
- Little or No Radiation

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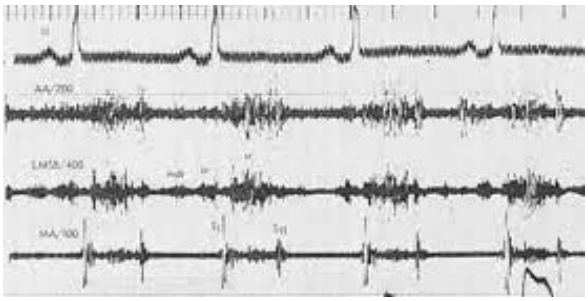
# Continuous Murmurs


- Begin with Systole, Peak near S2, and Continue into Diastole
- Examples
  - Cervical Venous Hum
  - Mammary Souffle (late 3rd trimester and lactation)
  - ***Patent Ductus Arteriosus***
  - Pericardial Friction Rub

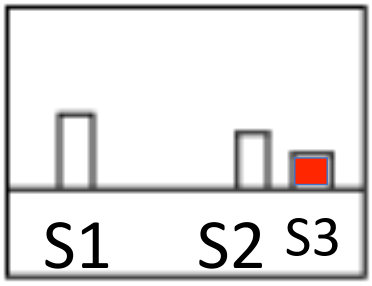


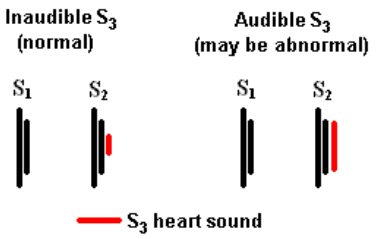
# Pericardial Friction Rub



- Heard Best at LLSB and Apex
- Should Not Truly Be Considered a Murmur
- Can Be a 2-Component or 3-Component Rub
- Can Sound Like Sandpaper

# Abnormal Heart Sounds - S3




- Known as the "Ventricular Gallop"
- S3 Produced by Large Amount of Passive Filling Blood from Left Atrium Striking Compliant LV
- Heard Best at the Apex
- S3 is Normal in Children, Pregnant Females, and Well-Trained Athletes
- Most Often Abnormal When Heard with Systolic CHF

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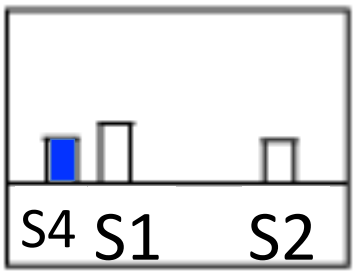
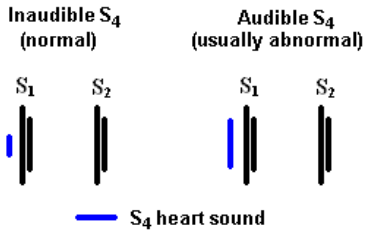
# Abnormal Heart Sounds - S4




- Known at the "Atrial Gallop"
- S4 Produced by Atrial Contraction Which Forces Blood Thru the AV Valves Striking the LV
- Most Commonly Found with Diastolic CHF or HTN
- Rarely a Normal Finding

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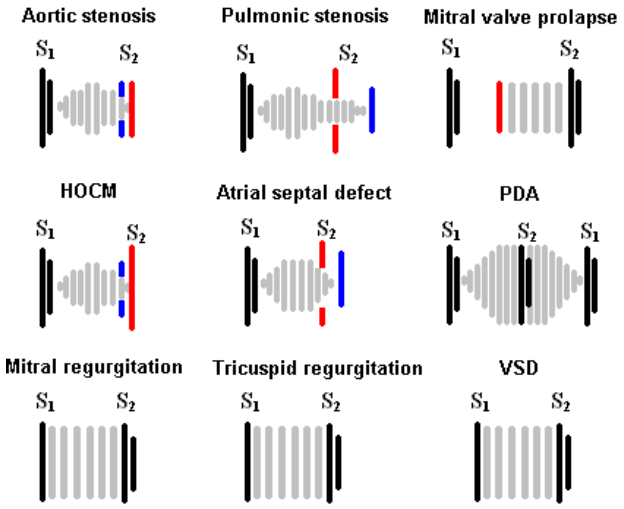
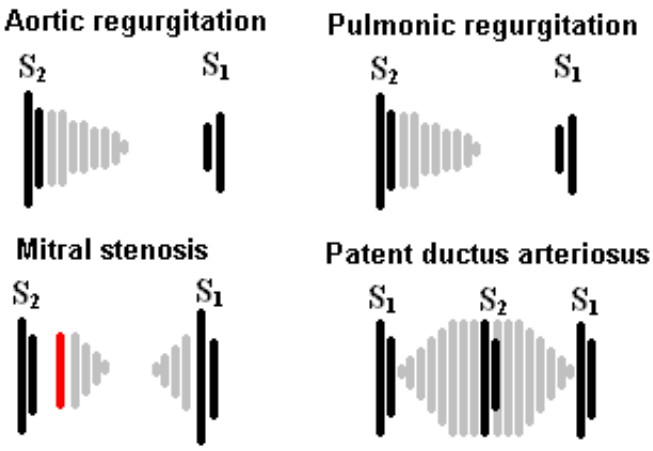
# Systolic Murmurs






# Diastolic Murmurs



# Basics of Heart Sounds and Murmurs

- When Does It Occur - Systole or Diastole
- Where Is It Loudest - A, P, T, M
- If Systolic, Is It?
  - Ejection Type at RUSB = Aortic Stenosis
  - Holosystolic at Apex = Mitral Regurgitation
- If Diastolic, Is It?
  - Early at RUSB = Aortic Regurgitation
  - Mid to Late at Apex = Mitral Stenosis

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# Murmur Referral Pearls

- Murmurs are TOUGH and TAKE A LOT OF WORK (REPETITION)
- If you are unsure about a murmur, ORDER AN ECHO and follow-up on it. REFER as needed for significant valvular abnormality
- If you are concerned about a murmur and do not have access to an echo, CONSULT your favorite cardiologist and make sure his/her scheduler knows the consult is for a "MURMUR"
- The Baptist Health Heart Institute STRUCTURAL CLINIC is staffed by a multi-disciplinary team of Structural/Interventional Cardiologists and Cardiac Surgeons as well as Echocardiography Techs

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# References


- Heart Sounds Audio
- https://www.med.umich.edu/lrc/psb_open/html/repo/primer_heartsound/primer_heartsound.html
- https://depts.washington.edu/physdx/heart/demo.html

- Good Animation on YouTube
- https://www.youtube.com/watch?v=dBwr2GZCmQM

- Nice Didactic Review
- https://www.healio.com/cardiology/learn-the-heart/cardiology-review/topic-reviews/heart-murmurs

# Pitfalls of Blood Pressure Management

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# Pitfalls of Blood Pressure Management

Aaron Strobel, MD, FACC, FSCAI

February 24, 2023

## Disclosures

- No disclosures

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# Overview

- 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure
  - Diagnosis
  - Treatment- Primary Options
  - Tailoring Treatment to the Patient
  - Resistant Hypertension
  - Future Treatments

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# Question 1a

35 year-old woman with BMI 37 presents to your office with blood pressure 138/84, What is her classification of elevated blood pressure?

A) Elevated blood pressure
B) Hypertension Stage 1
C) Hypertension Stage 2
D) Not known given one blood pressure measurement

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# Categories of BP in Adults

| BP Category | SBP | | DBP |
|---|---|---|---|
| Normal | <120 mm Hg | and | <80 mm Hg |
| Elevated | 120–129 mm Hg | and | <80 mm Hg |
| Hypertension | | | |
| Stage 1 | 130–139 mm Hg | or | 80–89 mm Hg |
| Stage 2 | ≥140 mm Hg | or | ≥90 mm Hg |

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

***Slide adapted from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults*

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# Question 1 b

What would you do next for patient?

A) Start Metoprolol
B) Encourage lifestyle changes
C) Order basic metabolic panel, sleep study and renal duplex
D) Return to clinic for repeat blood pressure check to confirm hypertension or ambulatory blood pressure monitoring

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# Diagnosis

| | Office/Clinic/Healthcare Setting | Home/Nonhealthcare/ ABPM Setting |
|---|---|---|
| Normotensive | No hypertension | No hypertension |
| Sustained hypertension | Hypertension | Hypertension |
| Masked hypertension | No hypertension | Hypertension |
| White coat hypertension | Hypertension | No hypertension |

ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

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# Question 2a

Ambulatory blood pressure measurement results:

7 AM - BP 131/79
11 AM- BP 136/83
2 PM- BP 134/88
4 PM- BP 139/86
12 AM- BP. 125/72

Now you confirmed Stage 1 Hypertension, what would you start for treatment?
A) HCTZ 25 mg
B) Losartan 100 mg
C) Lifestyle modifications
D) Amlodipine 5 mg

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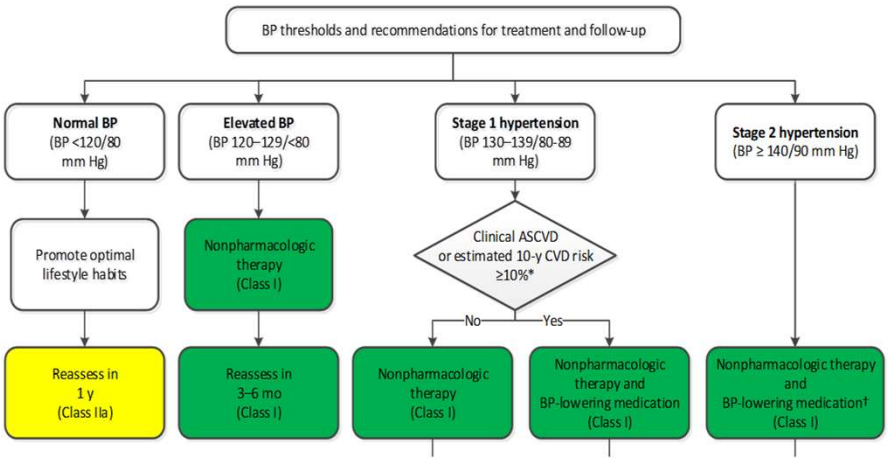
# Blood Pressure (BP) Thresholds and Recommendations for Treatment

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# What are lifestyle modifications?

- Weight loss
- DASH eating plan
- Dietary sodium reduction
- Physical activity
- Reduction in Alcohol Use
- Avoiding NSAIDS

# Nonpharmacological Interventions

| | Nonpharmacological Intervention | Dose | Approximate Impact on SBP | |
|---|---|---|---|---|
| | | | Hypertension | Normotension |
| Weight loss | Weight/body fat | Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight. | -5 mm Hg | -2/3 mm Hg |
| Healthy diet | DASH dietary pattern | Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat. | -11 mm Hg | -3 mm Hg |
| Reduced intake of dietary sodium | Dietary sodium | Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults. | -5/6 mm Hg | -2/3 mm Hg |
| Enhanced intake of dietary potassium | Dietary potassium | Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium. | -4/5 mm Hg | -2 mm Hg |

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.
DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.
Resources: Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH?
Available at: https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-how-to.
Top 10 Dash Diet Tips. Available at: http://dashdiet.org/dash_diet_tips.asp

# Nonpharmacological Interventions

| | Nonpharmacological Intervention | Dose | Approximate Impact on SBP | |
|---|---|---|---|---|
| | | | Hypertension | Normotension |
| Physical activity | Aerobic | ● 90–150 min/wk<br>● 65%–75% heart rate reserve | -5/8 mm Hg | -2/4 mm Hg |
| | Dynamic resistance | ● 90–150 min/wk<br>● 50%–80% 1 rep maximum<br>● 6 exercises, 3 sets/exercise, 10 repetitions/set | -4 mm Hg | -2 mm Hg |
| | Isometric resistance | ● 4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk<br>● 8–10 wk | -5 mm Hg | -4 mm Hg |
| Moderation in alcohol intake | Alcohol consumption | In individuals who drink alcohol, reduce alcohol† to:<br>● Men: ≤2 drinks daily<br>● Women: ≤1 drink daily | -4 mm Hg | -3 mm |

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.
†In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

# Prevalence

- In MESA, adults 45 years old without hypertension, the 40-year risk of developing hypertension (>140/90) =
  - 93% for African-Americans
  - 92% for Hispanics
  - 86% for Whites
  - 84% for Chinese

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# Question 2b

Your 37 year old patient returns 3 months later with blood pressure 144/90, what is your next step?

A) Refer back to ambulatory monitoring
B) Start propranolol 20 mg
C) Start Chlorthalidone 25 mg
D) Start Clonidine 0.1 mg PRN
E) Start Losartan/HCTZ

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# Treatment

| COR | LOE | Recommendation for Choice of Initial Medication |
|---|---|---|
| I | $A^{SR}$ | For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. |

SR indicates systematic review.

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# Monotherapy Versus Initial Combination Drug Therapy

| COR | LOE | Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy* |
|---|---|---|
| I | C-EO | Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. |
| IIa | C-EO | Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target. |

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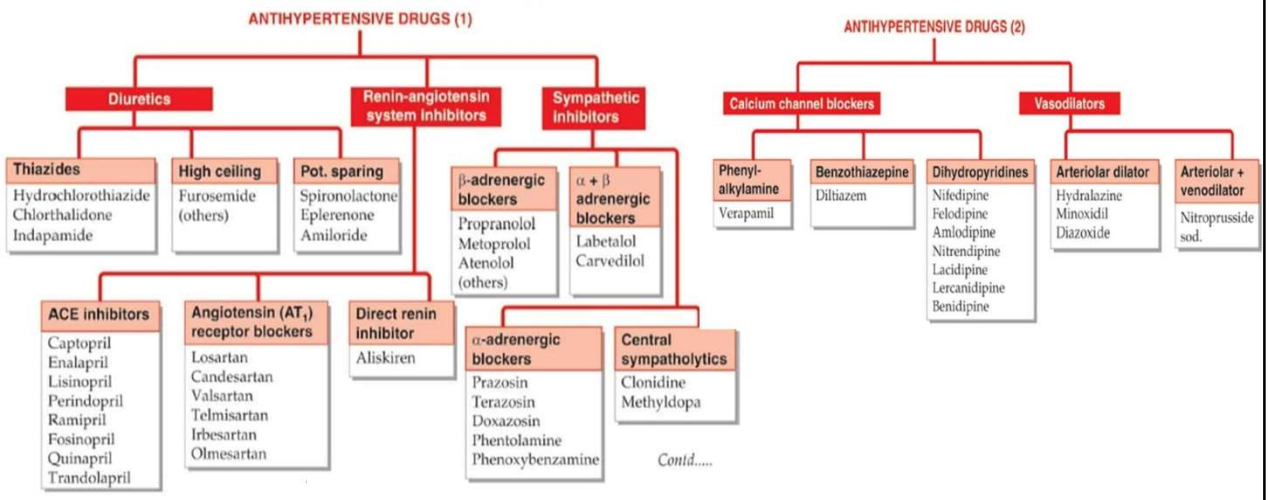
# Treatment Options




https://accesspharmacy.mhmedical.com

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# Tailoring your Treatments

# Question 3

Now your 37 year old comes back and says she is surprised but she is pregnant with her 4th child….What do you change her to for blood pressure?

A) Stop all meds, no anti-hypertensives are safe
B) Continue with chlorthalidone
C) Start lisinopril in place of chlorthalidone
D) Start nifedipine

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# Pregnancy

| COR | LOE | Recommendations for Treatment of Hypertension in Pregnancy |
|---|---|---|
| I | C-LD | Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. |
| III: Harm | C-LD | Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. |

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# Question 4

- 63 year old black man with type 2 diabetes, hyperlipidemia who presents with blood pressure 152/89, Cr 0.75 and no proteinuria, what is the recommended initial therapy per the 2017 ACC/AHA guidelines?

A) Hydrochlorothiazide
B) Valsartan
C) Atenolol
D) Lisinopril

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# Racial and Ethnic Differences in Treatment

| COR | LOE | Recommendations for Race and Ethnicity |
|---|---|---|
| I | B-R | In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. |
| I | C-LD | Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. |

# Question 5

- 75 yo male with past medical history of diabetes, hyperlipidemia, hypertension, coronary artery disease s/p PCI to LAD 6 months ago with blood pressure 159/92, current blood pressure medications include losartan 100 mg, HCTZ 25 mg, what would be your next line agent?

A) Metoprolol succinate 25 mg once a day
B) Spironolactone 25 mg once a day
C) Lisinopril 40 mg once a day
D) Clonidine 0.1 mg twice a day
E) Carvedilol 12.5 mg twice a day

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# Stable Ischemic Heart Disease

| COR | LOE | Recommendations for Treatment of Hypertension in Patients With Stable Ischemic Heart Disease (SIHD) |
|---|---|---|
| I | B-NR | In adults with SIHD with angina and persistent uncontrolled hypertension, the addition of dihydropyridine CCBs to GDMT beta blockers is recommended. |
| IIa | B-NR | In adults who have had a MI or acute coronary syndrome, it is reasonable to continue GDMT beta blockers beyond 3 years as long-term therapy for hypertension. |
| IIb | C-EO | Beta blockers and/or CCBs might be considered to control hypertension in patients with CAD (without HF*r*EF) who had an MI more than 3 years ago and have angina. |

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# Resistant Hypertension

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# Resistant Hypertension

- Uncontrolled blood pressure despite 3 drugs

OR

- BP controlled but requires at least 4 drugs

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# Resistant Hypertension

- 50% of Uncontrolled Blood Pressure is due to Pseudo-resistant HTN
  - Improper BP management
  - White Coat Affect
  - Poor medication compliance (Estimated at 30%)

- Actual prevalence or resistance hypertension is 2-8%

Resistant Hypertension. JAMA 2014; 311 (21): 2216-2244

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# Looking for Secondary Causes

- Medication Side effects (NSAIDs, estrogen pre-dominant oral contraceptives, decongestants, diet pills, stimulants, alcohol, herbal compounds) (2-4%)
- Sleep Apnea (25-50%)
- Primary hyperaldosteronism (8-20%)
- Renal artery stenosis (5-34%)
- Renal parenchymal disease (1-2%)
- Thyroid disease (<1%)
- Pheochromocytoma (< 0.1%)

AHA/ACC 2017 Hypertension Guidelines. 2018; 71: e13-e115

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# Screening Tests for Secondary HTN

- TSH
- BMP
- Duplex Ultrasound of kidneys
- Sleep Study

Primary Hyperaldosteronism
- Normal to low K → High aldo ( > 15 ng/dL) or Aldo/renin ration > 20
- Stop mineralocorticoid receptor antagonists before measurements.

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# Question 6

A 65 year old black woman with type 2 diabetes, hypertension presents to clinic with BP 160/90s mmHg….

Current Regimen:
- Chlorthalidone 50 mg qday, lisinopril 40 mg a day, amlodipine 10 mg

Labs: Cr 1.3 mg/dL. K 4.1 mEq/L

Next step for regimen change?

A) No changes, tell her to take her medications
B) NO changes until she gets a sleep study
C) Referral for renal denervation
D) Start metoprolol 12.5 mg twice a day
E) Start spironolactone 25 mg qday
F) Change lisinopril to valsartan

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# My Treatment of Resistant Hypertension

- 1st Optimize Diuretics (HCTZ or Chlorthalidone)
- 2nd ACE or ARB and CCB
- 3rd Mineralocorticoid Antagonists
- 4th Consider addition of carvedilol (preferred given alpha/beta antagonists)
- Addition of 5th agent can include vasodilator (hydralazine or minoxidil) or alpha antagonists

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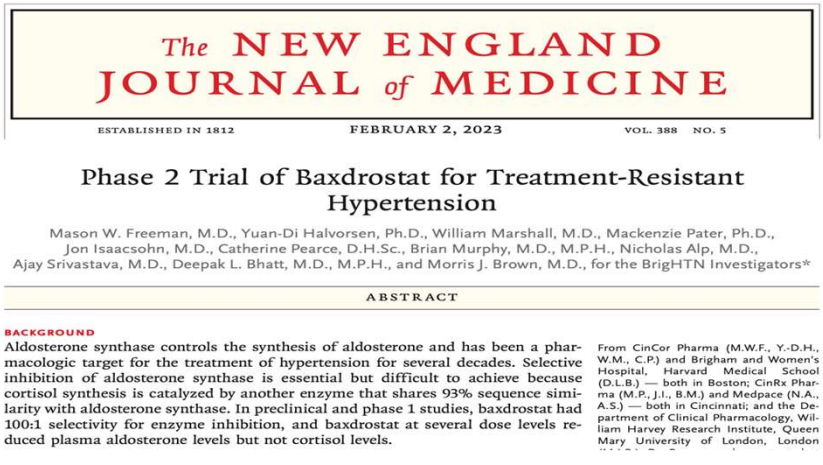
# Future ?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 2, 2023 VOL. 388 NO. 5

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators*

ABSTRACT

BACKGROUND

Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthase is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. In preclinical and phase 1 studies, baxdrostat had 100:1 selectivity for enzyme inhibition, and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels.

From CinCor Pharma (M.W.F., Y.-D.H., W.M., C.P.) and Brigham and Women's Hospital, Harvard Medical School (D.L.B.) — both in Boston; CinRx Pharma (M.P., J.I., B.M.) and Medpace (N.A., A.S.) — both in Cincinnati; and the Department of Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London

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# Questions

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# References


- 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PC Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of American College of Cardiology 2018; 71:e127-e248
- https://accesspharmacy.mhmedical.com
- Resistant Hypertension. JAMA 2014; 311 (21): 2216-2244



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# Prevention Strategies for Heart Disease

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# Cardiovascular Risk Assessment and Prevention

**Wesley Fiser MD, FACC**

**February 24, 2023**

## Disclosures

No relevant disclosures

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# Overview

- Tools for cardiovascular risk assessment
- Refining and reclassification of cardiovascular risk
- Recommendations for physical activity

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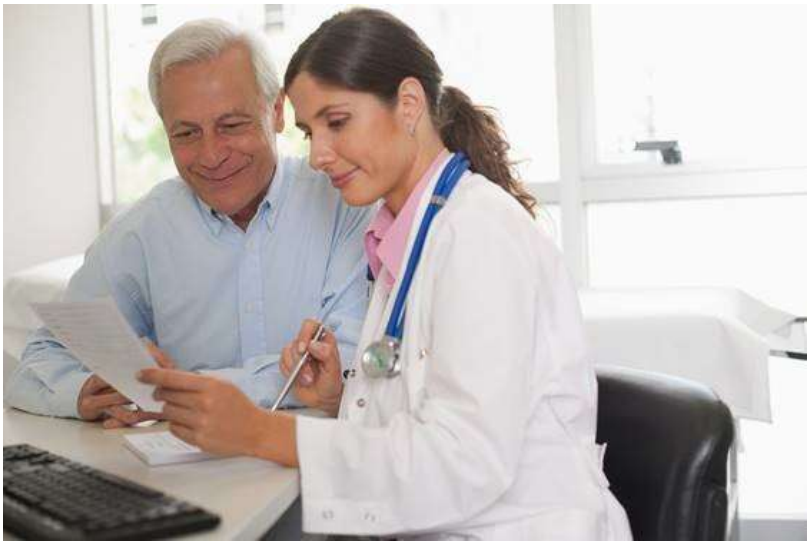

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# CPR of cardiovascular risk assessment

C calculate with pooled cohort equation (PCE)

P personalize with risk enhancers

R reclassify by coronary artery calcium score (CAC)

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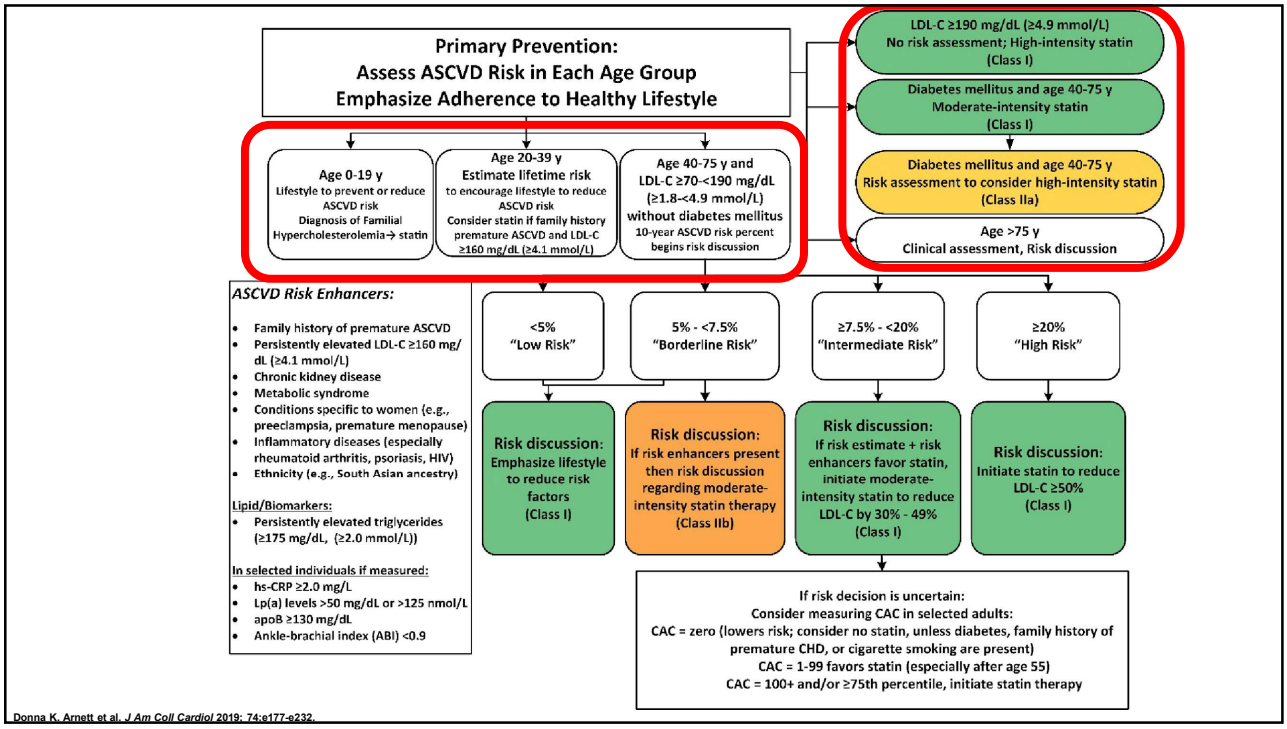
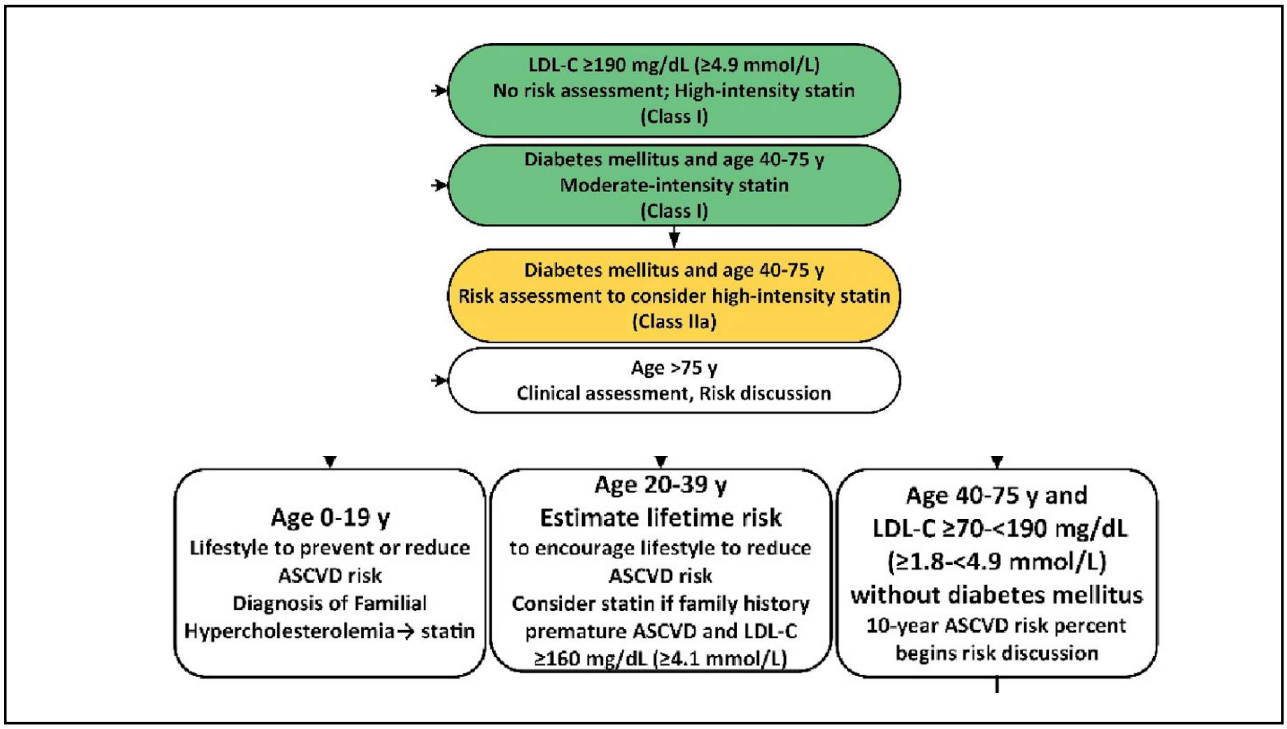
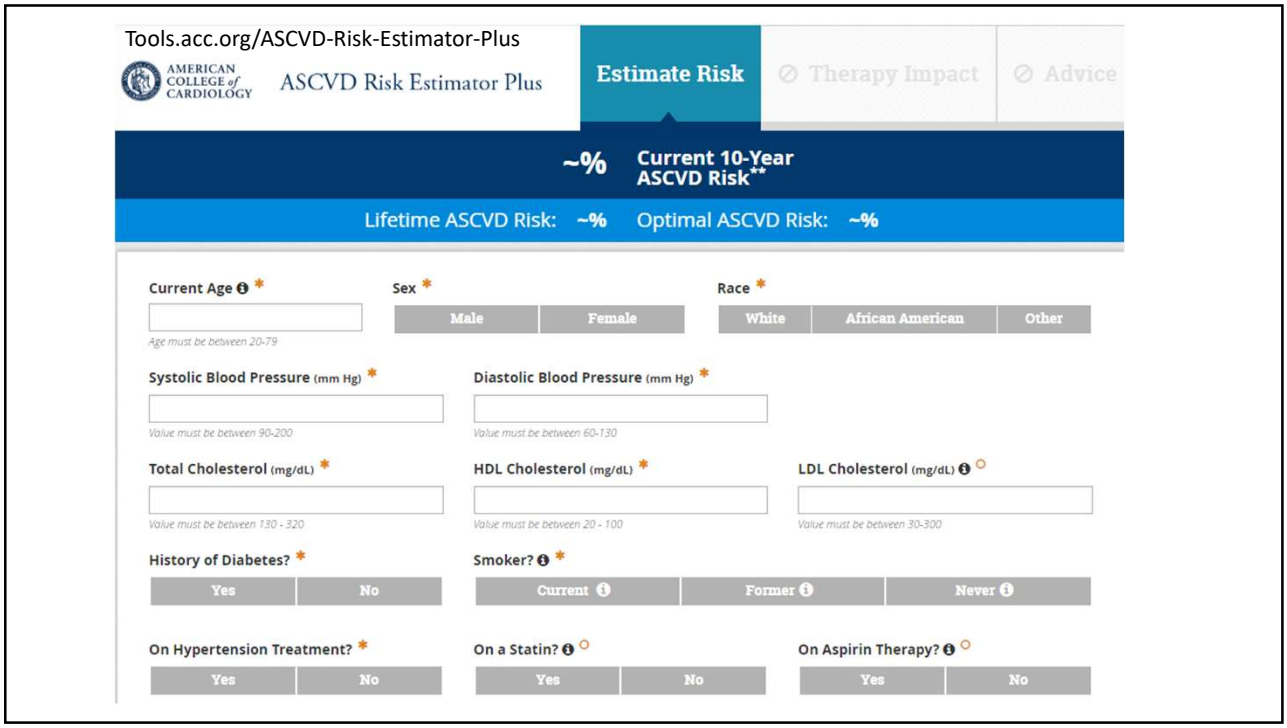
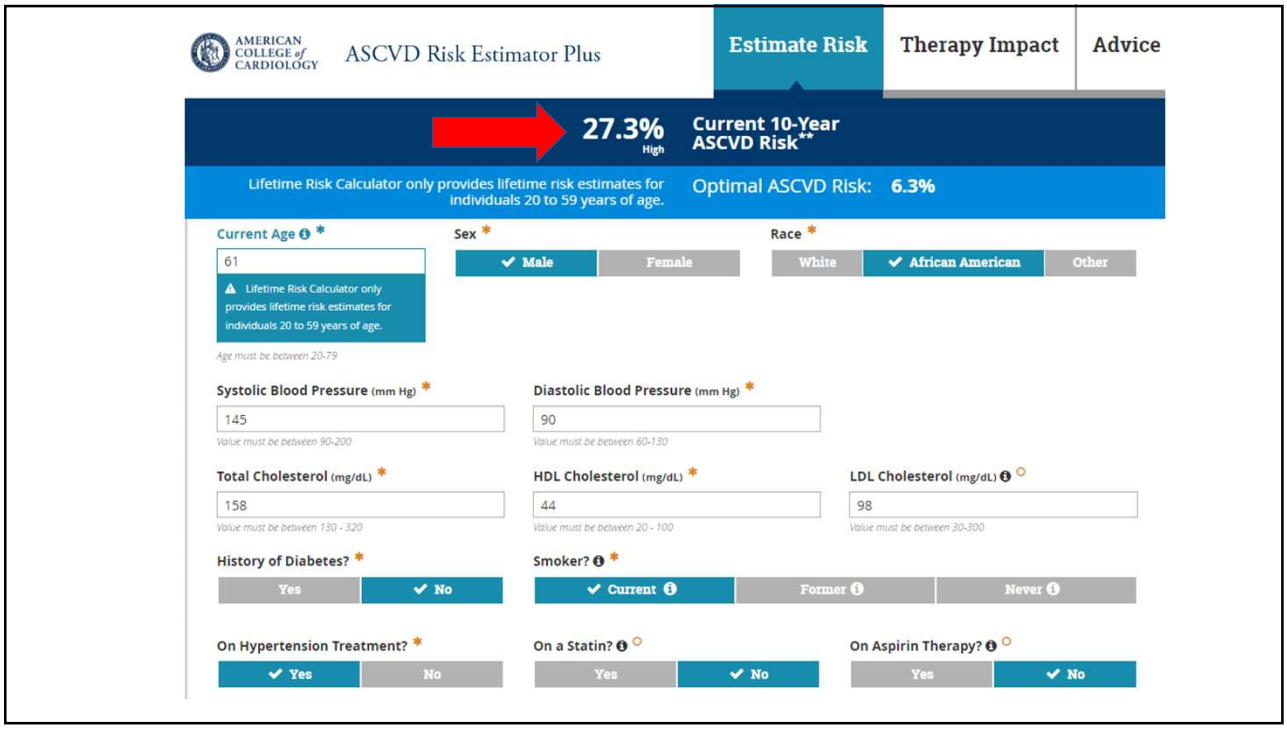
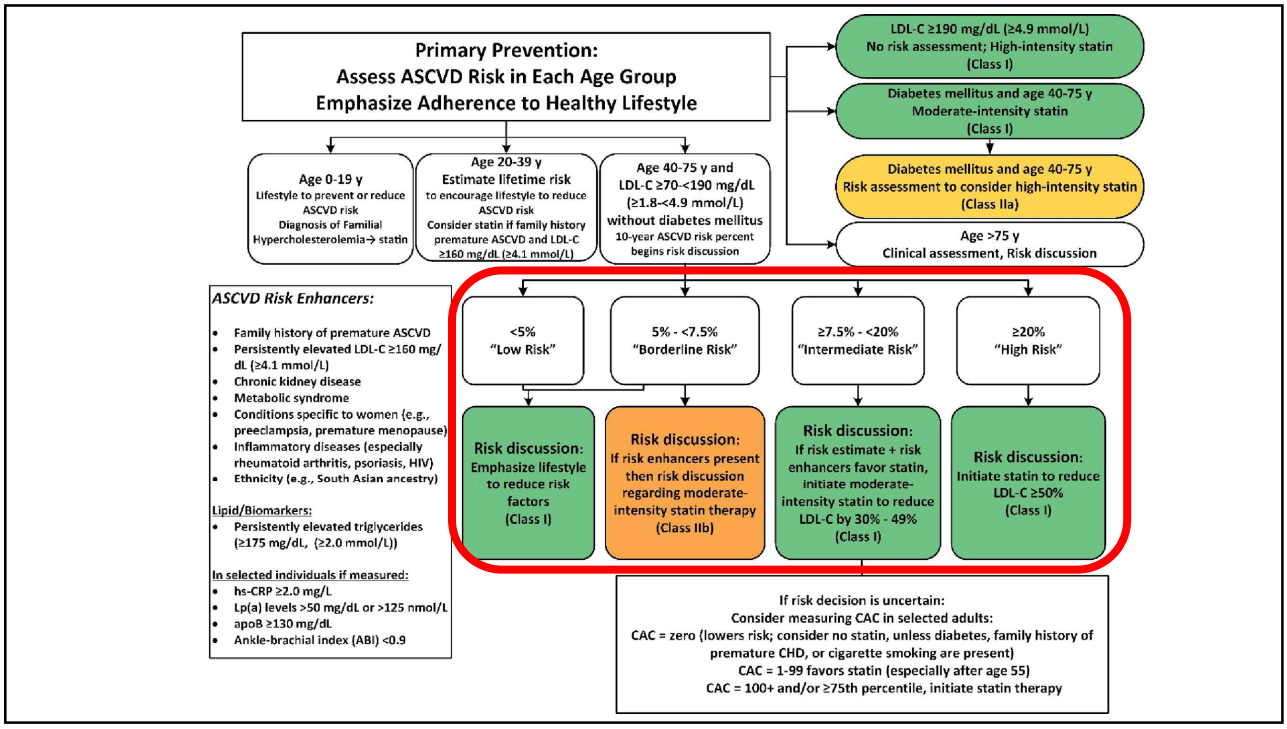


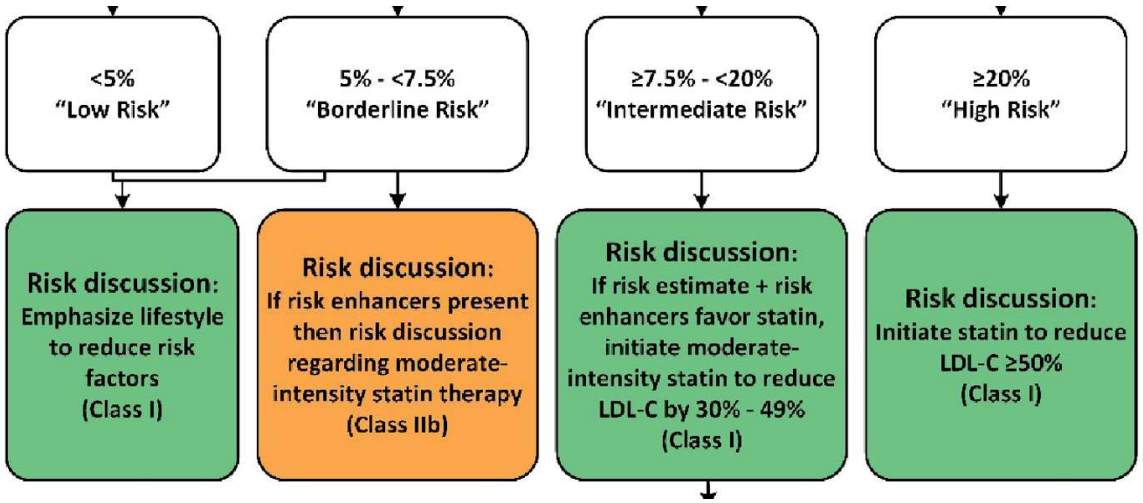

Donna K. Arnett et al. *J Am Coll Cardiol* 2019; 74:e177-e232.


LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion


Tools.acc.org/ASCVD-Risk-Estimator-Plus
AMERICAN COLLEGE of CARDIOLOGY
ASCVD Risk Estimator Plus
Estimate Risk
Therapy Impact
Advice
~%
Current 10-Year ASCVD Risk**
Lifetime ASCVD Risk: ~%
Optimal ASCVD Risk: ~%
Current Age *
Age must be between 20-79
Sex *
Male
Female
Race *
White
African American
Other
Systolic Blood Pressure (mm Hg) *
Value must be between 90-200
Diastolic Blood Pressure (mm Hg) *
Value must be between 60-130
Total Cholesterol (mg/dL) *
Value must be between 130 - 320
HDL Cholesterol (mg/dL) *
Value must be between 20 - 100
LDL Cholesterol (mg/dL)
Value must be between 30-300
History of Diabetes? *
Yes
No
Smoker? *
Current
Former
Never
On Hypertension Treatment? *
Yes
No
On a Statin?
Yes
No
On Aspirin Therapy?
Yes
No


AMERICAN COLLEGE of CARDIOLOGY
ASCVD Risk Estimator Plus
Estimate Risk
Therapy Impact
Advice
27.3%
High
Current 10-Year ASCVD Risk**
Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years of age.
Optimal ASCVD Risk: 6.3%
Current Age *
61
Lifetime Risk Calculator only provides lifetime risk estimates for individuals 20 to 59 years of age.
Age must be between 20-79
Sex *
Male
Female
Race *
White
African American
Other
Systolic Blood Pressure (mm Hg) *
145
Value must be between 90-200
Diastolic Blood Pressure (mm Hg) *
90
Value must be between 60-130
Total Cholesterol (mg/dL) *
158
Value must be between 130 - 320
HDL Cholesterol (mg/dL) *
44
Value must be between 20 - 100
LDL Cholesterol (mg/dL)
98
Value must be between 30-300
History of Diabetes? *
Yes
No
Smoker? *
Current
Former
Never
On Hypertension Treatment? *
Yes
No
On a Statin?
Yes
No
On Aspirin Therapy?
Yes
No


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy




## CPR of cardiovascular risk assessment

C calculate with pooled cohort equation (PCE)

P personalize with risk enhancers

R reclassify by coronary artery calcium score (CAC)

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# Limitations of the pooled cohort equations

| | |
|---|---|
| Risk Overestimated | • High SES<br>• Access to quality care |
| Risk Underestimated | • Hispanic and South Asian ancestry<br>• Chronic inflammatory disorders (RA, SLE)<br>• HIV<br>• Familial hypercholesterolemia<br>• Disadvantaged SES<br>• Young patients |

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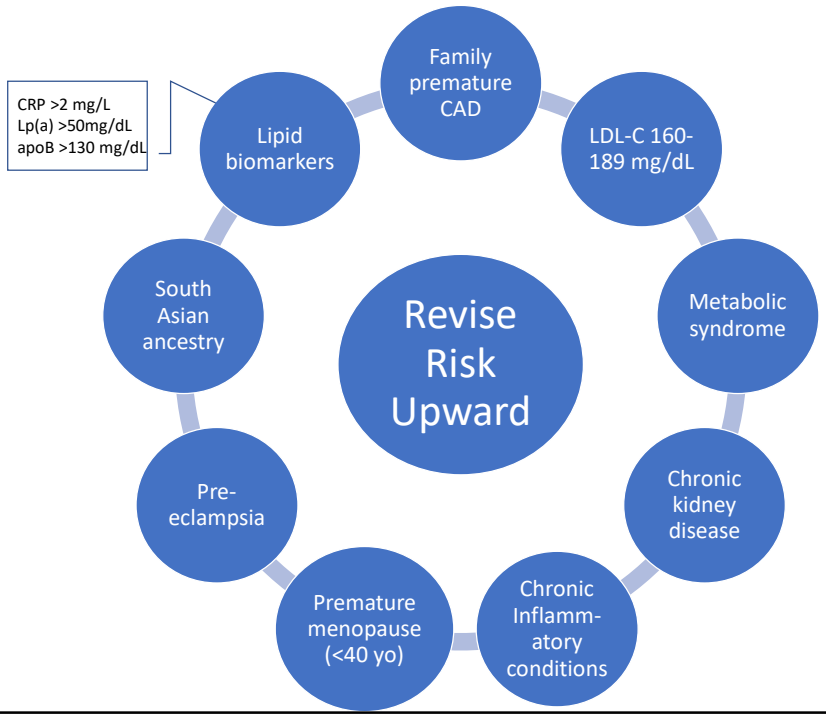

# CPR of cardiovascular risk assessment

C calculate with pooled cohort equation (PCE)

P personalize with risk enhancers

R reclassify by coronary artery calcium score (CAC)

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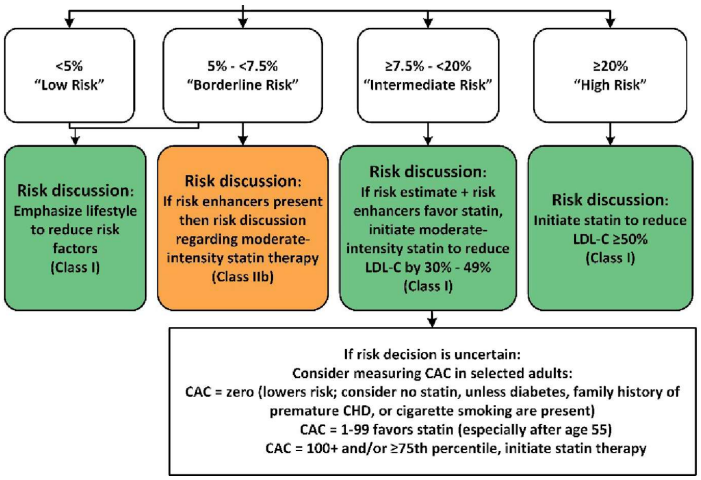
# Reclassification by coronary artery calcium score

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# Coronary artery calcium score

- Noncontrast CT of the chest
- Scan acquisition: 40 slices, 3mm thickness, prospectively gated
- Agatston score: Ca area x CT density in each coronary vessel

| Agatston score | Relative Risk |
|---|---|
| CAC 0 | LOW |
| CAC 1-300 | INTERMEDIATE |
| CAC >300 | HIGH |

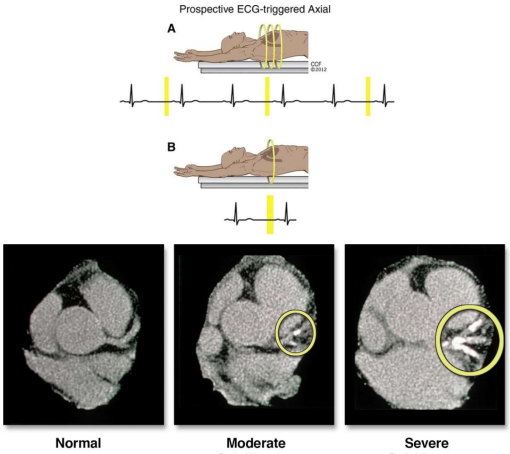


Image: Dey et al Circulation 2014

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# MESA-adjusted ASCVD risk score


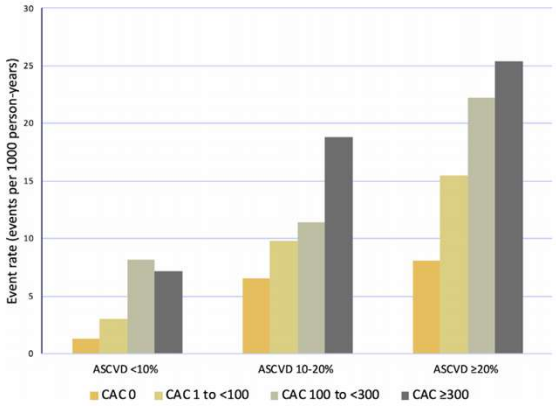


Image: https://www.ajconline.org/article/S0002-9149(19)30813-6/pdf
Arpa et al AJC 2019

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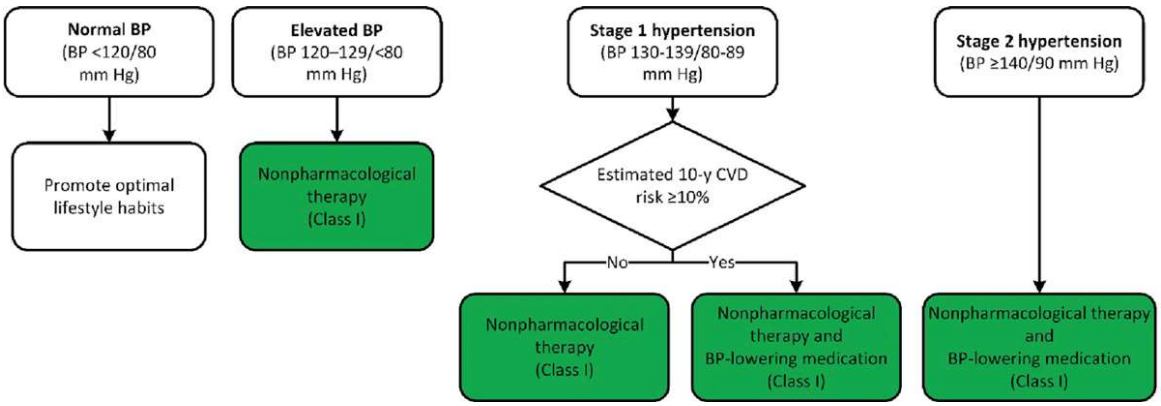
# ASCVD risk and hypertension




Arnett et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

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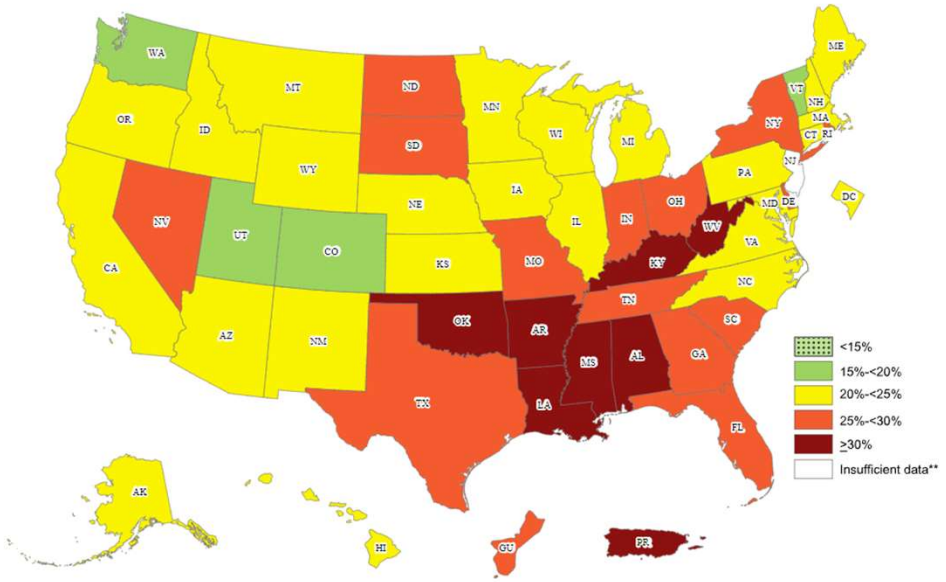
## Map: Overall Physical Inactivity

Prevalence of Self-Reported Physical Inactivity* Among US Adults by State and Territory, BRFSS, 2017–2020




CDC Jan 2022

# WHO weekly exercise recommendations

- Age 18-64
- At least 150-300 min of moderate intensity aerobic exercise (3-6 MET, 64-76% max HR, 5-6/10 scale)
- At least 75-150min vigorous intensity exercise (6-9 MET, 77-93% max HR, 7-8/10 scale)
- Resistance training 2 days per week
- Age >65 emphasize functional balance and strength training moderate intensity 3d/week
- High intensity interval training produces large improvements in cardiorespiratory fitness compared with continuous moderate intensity exercise

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# Exercise intensity

**Examples of Moderate- and Vigorous-Intensity Aerobic Activities**

| 2020 WHO Physical Activity Guidelines for Aerobic Exercise | Activity[a] | Duration (min/wk) |
|---|---|---|
| 150-300 min moderate-intensity aerobic exercise per week | Walking (2.5 miles/h, moderate pace) | 150-300 |
| | Ballroom dancing (slow pace) | 150-300 |
| | Gardening and yardwork | 113-225 |
| | Bicycling (light, <10 mph) | 113-225 |
| | Brisk walking (3.5 miles/h, fast pace) | 105-209 |
| 75-150 min vigorous-intensity aerobic exercise per week | Jogging (4.0 miles/h) | 75-150 |
| | Swimming (leisure) | 75-150 |
| | Hiking | 75-150 |
| | Bicycling (moderate, 12-14 miles/h) | 56-113 |
| | Running (6 miles/h) | 46-92 |

Tucker W, Fegers-Wustrow I, Halle M, et al. Exercise for Primary and Secondary Prevention of Cardiovascular Disease. *J Am Coll Cardiol.* 2022 Sep, 80 (11) 1091–1106

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## Cardiovascular benefits of exercise

- 23-40% reduction in CVD
- 27-31% reduction in all cause mortality
- The most significant relative benefit is changing from inactivity to 30min walking per day.
- An increase in 1000 steps/day decreases risk of death by 12%
- The highest risk patient benefits the most
- Consider written exercise prescription

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## THANK YOU

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# Cardiac Pharmacology:
# Novel Agents and Emerging Trends

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# Cardiac Pharmacology: Novel Agents and Emerging Trends

Thomas D. Conley, MD FACC FSCAI

February 24, 2023

## Disclosures

- None

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# Overview

- Novel Drug Approvals
  - Brief review of results of RCTs
- Emerging Trends
  - Novel therapies on the horizon
- Paxlovid Drug Interactions with Cardiovascular Drugs

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# Recent Novel Drug Approvals

- **2019**
  - Tafamidis – we discussed in 2019, now approved
- **2020**
  - Bempedoic acid
- **2021**
  - Inclisiran – also discussed in 2019, now approved
  - Vericiguat
- **2022**
  - Mavacamten

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# Tafamidis for TTR Amyloid Cardiomyopathy

- Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.
- Prevalence uncertain
  - 13% pts with HFpEF
  - 16% pts undergoing TAVR
  - 5% pts with presumed HCM
- Median Survival 2.5-3.6 yrs after diagnosis

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# ATTR-ACT Study

- Multicenter, DBPC, Phase 3 trial
- Tafamidis 80 mg vs. 20 mg vs. Placebo (30 months)
- Endpoints
  - Mortality 29.5% vs. 42.9% (HR 0.70)
  - CV-related hospitalizations (RR 0.68)
  - Functional Capacity/QOL
    - both better ($p<0.001$)

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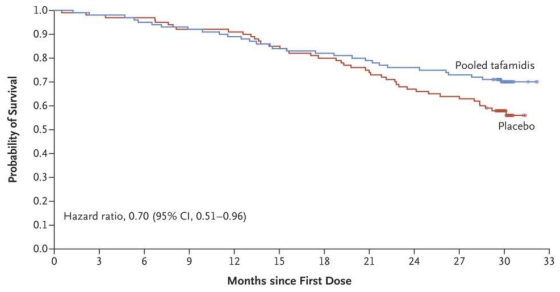
**A Primary Analysis, with Finkelstein–Schoenfeld Method**

| | No. of Patients | P Value from Finkelstein–Schoenfeld Method | Win Ratio (95% CI) | Patients Alive at Mo 30 | Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 |
|---|---|---|---|---|---|
| | | | | *no. (%)* | *per patient per yr* |
| Pooled Tafamidis | 264 | <0.001 | 1.70 (1.26–2.29) | 186 (70.5) | 0.30 |
| Placebo | 177 | | | 101 (57.1) | 0.46 |

**B Analysis of All-Cause Mortality**




**No. at Risk (cumulative no. of events)**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pooled tafamidis | 264 (0) | 259 (5) | 252 (12) | 244 (20) | 235 (29) | 222 (42) | 216 (48) | 209 (55) | 200 (64) | 193 (71) | 99 (78) | 0 (78) |
| Placebo | 177 (0) | 173 (4) | 171 (6) | 163 (14) | 161 (16) | 150 (27) | 141 (36) | 131 (46) | 118 (59) | 113 (64) | 51 (75) | 0 (76) |

**C Frequency of Cardiovascular-Related Hospitalizations**

| | No. of Patients | No. of Patients with Cardiovascular- Related Hospitalizations | Cardiovascular- Related Hospitalizations | Pooled Tafamidis vs. Placebo Treatment Difference |
|---|---|---|---|---|
| | | *total no. (%)* | *no. per yr* | *relative risk ratio (95% CI)* |
| Pooled Tafamidis | 264 | 138 (52.3) | 0.48 | 0.68 (0.56–0.81) |
| Placebo | 177 | 107 (60.5) | 0.70 | |

MS Maurer et al. N Engl J Med 2018;379:1007-1016.

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Original Article

# Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., Christie M. Ballantyne, M.D., for the **CLEAR Harmony Trial**

Bempedoic acid, an inhibitor of ATP citrate lyase, reduces levels of low-density lipoprotein (LDL) cholesterol.

DBPC, Parallel, RCT in patients with ASCVD, HeFH or both with LDL >70 mg/dl on "maximally tolerated statin therapy", +/- other Rx
The primary end point was safety, and the principal secondary end point (principal efficacy end point) was the percentage change in the LDL cholesterol level at week 12 of 52 weeks

N Engl J Med Volume 380(11):1022-1032March 14,2019

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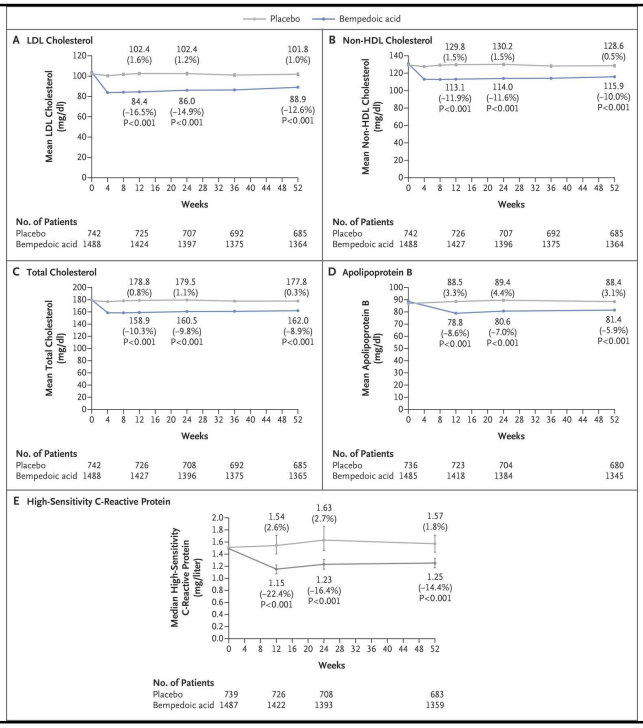
## CLEAR Harmony Trial Results




## Inclisiran - Novel Treatment of Hyperlipidemia: Small Interfering RNA (siRNA)

- Background
  - PCSK9 degrades LDL receptors
  - Inhibition of PCSK9 increases LDL receptor expression and hence LDL clearance
- RNA Interference provides a mechanism to regulate gene expression
- siRNAs selectively prevent the Translation of their target mRNAs
- **Inclisiran** is a synthetic siRNA now approved for treatment of HLD
- **Orion 1** - dose finding trial. We discussed this in 2019
- **Orion 10 & 11** – Phase III, DBPC RCTs

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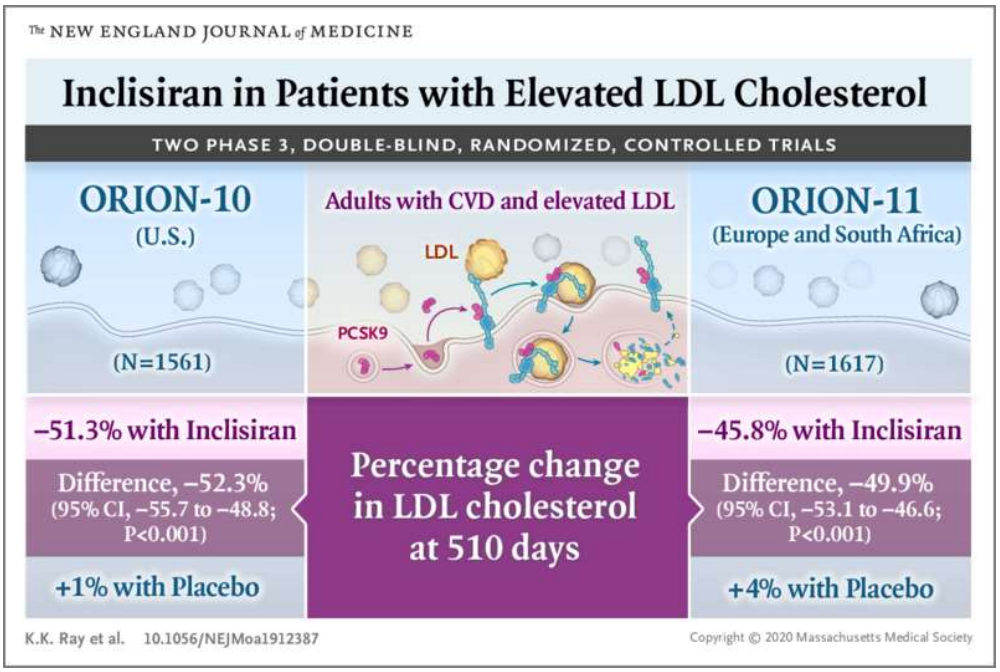
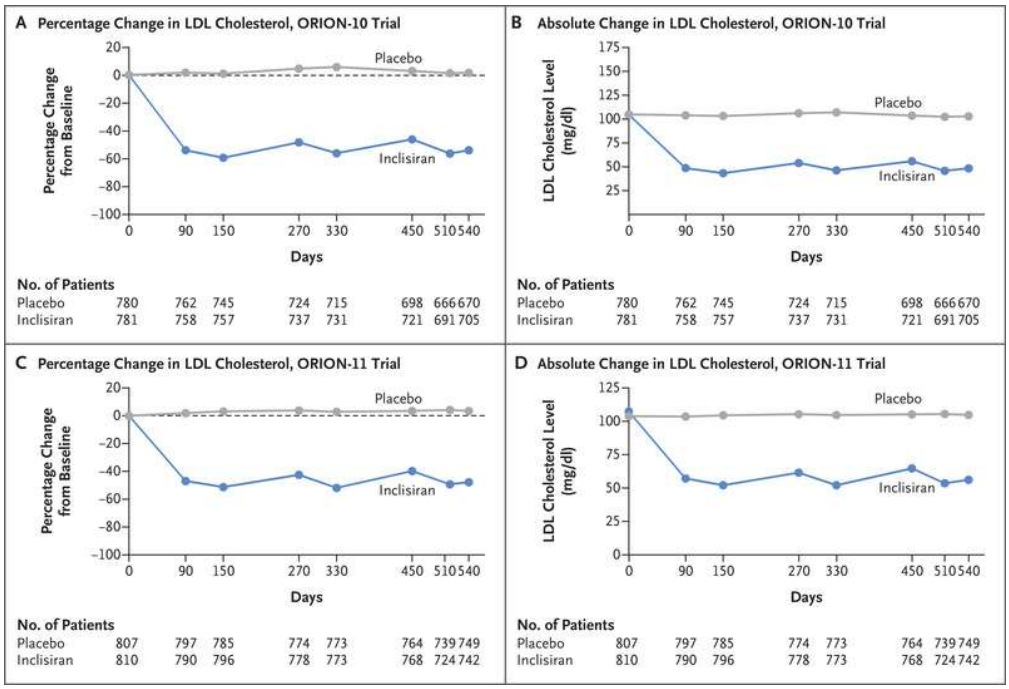

The NEW ENGLAND JOURNAL of MEDICINE
Inclisiran in Patients with Elevated LDL Cholesterol
TWO PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS
ORION-10
(U.S.)
(N=1561)
Adults with CVD and elevated LDL
LDL
PCSK9
ORION-11
(Europe and South Africa)
(N=1617)
–51.3% with Inclisiran
Difference, –52.3%
(95% CI, –55.7 to –48.8; P<0.001)
+1% with Placebo
Percentage change in LDL cholesterol at 510 days
–45.8% with Inclisiran
Difference, –49.9%
(95% CI, –53.1 to –46.6; P<0.001)
+4% with Placebo
K.K. Ray et al. 10.1056/NEJMoa1912387
Copyright © 2020 Massachusetts Medical Society


A Percentage Change in LDL Cholesterol, ORION-10 Trial
Percentage Change from Baseline
Placebo
Inclisiran
Days
No. of Patients
Placebo 780 762 745 724 715 698 666 670
Inclisiran 781 758 757 737 731 721 691 705
B Absolute Change in LDL Cholesterol, ORION-10 Trial
LDL Cholesterol Level (mg/dl)
Placebo
Inclisiran
Days
No. of Patients
Placebo 780 762 745 724 715 698 666 670
Inclisiran 781 758 757 737 731 721 691 705
C Percentage Change in LDL Cholesterol, ORION-11 Trial
Percentage Change from Baseline
Placebo
Inclisiran
Days
No. of Patients
Placebo 807 797 785 774 773 764 739 749
Inclisiran 810 790 796 778 773 768 724 742
D Absolute Change in LDL Cholesterol, ORION-11 Trial
LDL Cholesterol Level (mg/dl)
Placebo
Inclisiran
Days
No. of Patients
Placebo 807 797 785 774 773 764 739 749
Inclisiran 810 790 796 778 773 768 724 742

# Vericiguat

- Vericiguat enhances production of cyclic guanosine monophosphate (cGMP) by directly stimulating soluble guanylate cyclase (sGC) independent of nitric oxide (NO) and enhances sGC sensitivity to endogenous NO, thereby increasing cGMP production.
- Increased levels of cGMP lead to smooth muscle relaxation and vasodilation.
- An increase in cardiac output and cardiac index and a decrease in systemic vascular resistance has been noted with vericiguat

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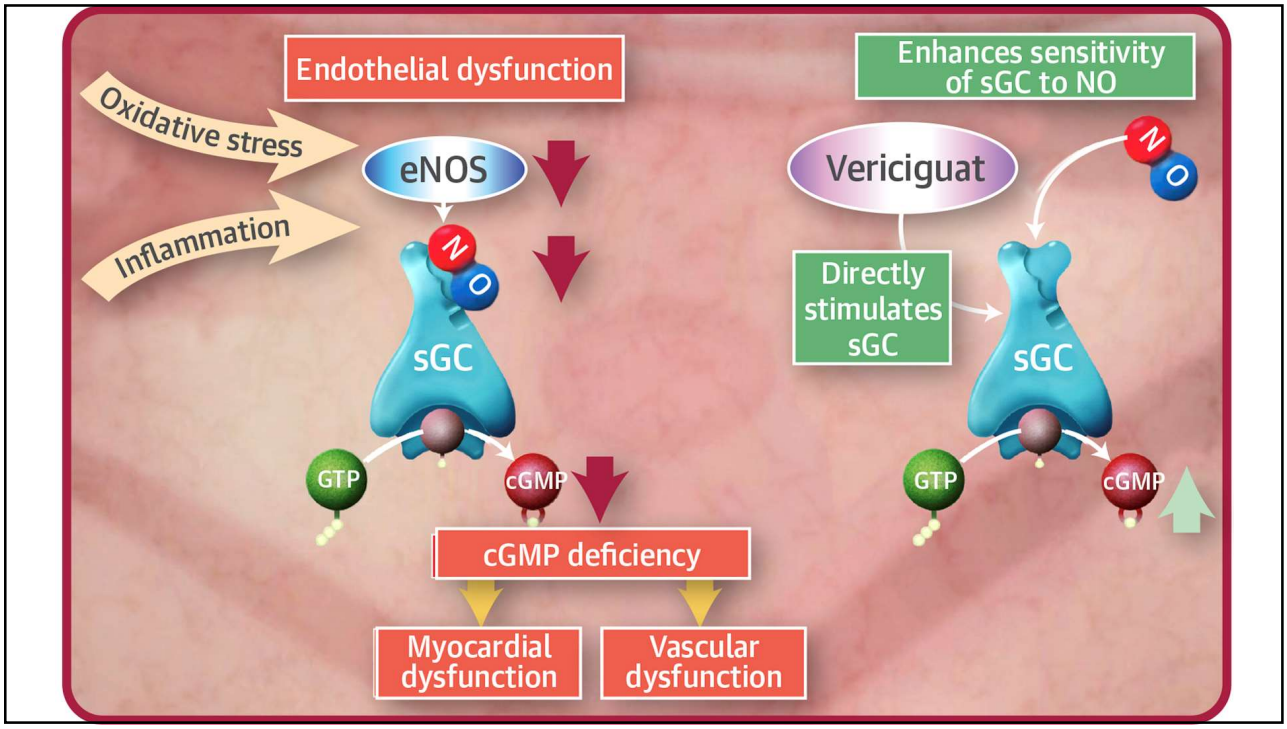

Original Article

# Vericiguat in Patients with Heart Failure and Reduced Ejection

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., Christopher M. O'Connor, M.D., for the **VICTORIA Study Group**

Randomized, double-blind, placebo-controlled trial of 5050 patients with chronic heart failure (New York Heart Association class II, III, or IV) and an ejection fraction of less than 45% to receive vericiguat (target dose, 10 mg once daily) or placebo, in addition to guideline-based medical therapy. The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure.

N Engl J Med Volume 382(20):1883-1893 May 14, 2020

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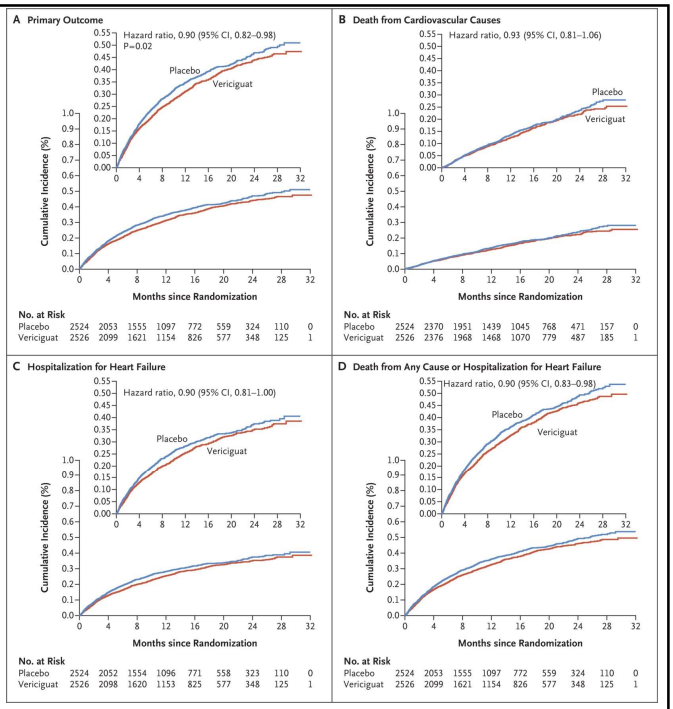
## VICTORIA Study Results

Among patients with high-risk heart failure, the incidence of death from cardiovascular causes or hospitalization for heart failure was lower among those who received vericiguat than among those who received placebo.



# Mavacamten in HOCM

- Hypertrophic obstructive cardiomyopathy (HOCM) is characterized by unexplained left ventricular (LV) hypertrophy associated with dynamic LV outflow tract obstruction.
- Mavacamten is a first-in-class targeted inhibitor of cardiac myosin, which has been shown to reduce LV outflow tract obstruction, improve exercise capacity, and relieve symptoms of HOCM
- Mavacamten MOA:
  - Reversible inhibitor selective for cardiac myosin.
  - Modulates the number of myosin heads that can enter "on actin" (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation.
  - Excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state are mechanistic hallmarks of HCM.
  - Shifts the overall myosin population towards an energy-sparing, recruitable, super-relaxed state.
  - Reduces dynamic LVOT obstruction and improves cardiac filling pressures.

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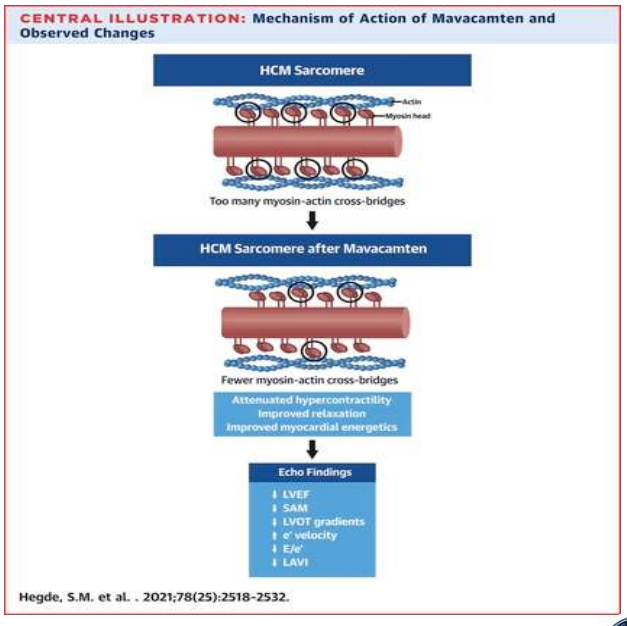


Sheila M. Hegde et al. *J Am Coll Cardiol* 2021; 78:2518-2532.



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

# Mavacamten RCT's

**DBPC, parallel, RCT's** comparing mavacamten vs placebo in patients with HOCM with:

- LVOT gradient ≥50 mm Hg)
- LVEF ≥55%
- NYHA class II-III symptoms

- **EXPLORER-HCM** "Efficacy and Safety of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy"
  - Evaluated effect of mavacamten on clinical parameters (subjective and objective)
- **VALOR-HCM** "Myosin Inhibition to Defer Surgical Myectomy or Alcohol Septal Ablation in Obstructive Hypertrophic Cardiomyopathy".
  - Evaluated effect of mavacamten on avoidance of Septal Reduction Therapy (SRT – Myectomy)

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# EXPLORER-HCM - RESULTS

- Primary outcome: ≥1.5 ml/kg/min increase in $pVO_2$ with ≥1 NYHA class improvement or ≥3.0 ml/kg/min increase in $pVO_2$ with no worsening of NYHA class at 30 weeks
  - 37% of the mavacamten group vs. 17% of the placebo group (p = 0.0005).
- Secondary outcomes:
  - Post-exercise LVOT gradient change from baseline to week 30
    - -47 mm Hg in the mavacamten group vs. -10 mm Hg in the placebo group (p < 0.0001)
  - Peak O2 Consumption ($pVO_2$) change from baseline to week 30
    - 1.4 ml/kg/min in the mavacamten group vs. -0.1 ml/kg/min in the placebo group (p = 0.0006)
- Long-term extension study (n = 231, median 62 weeks):

  Change in resting LVOT gradient from baseline: -32.8 mm Hg

  Change in Valsalva LVOT gradient from baseline: -46.4 mm Hg

  Change in LVEF from baseline: -9%

  Change in N-terminal pro–B-type natriuretic peptide from baseline: -488 ng/L

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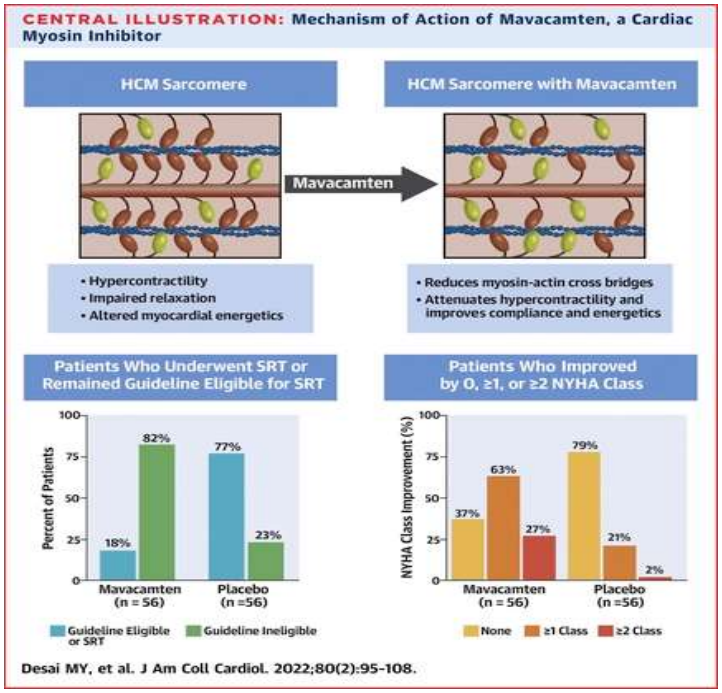
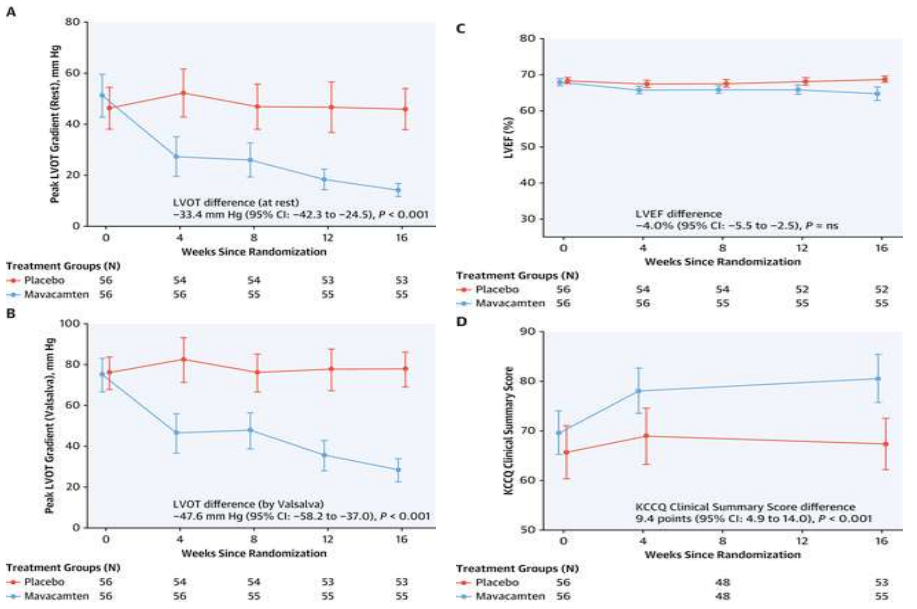
# VALOR-HCM RESULTS




Milind Y. Desai et al. *J Am Coll Cardiol* 2022; 80:95-108.

JACC




Milind Y. Desai et al. *J Am Coll Cardiol* 2022; 80:95-108.



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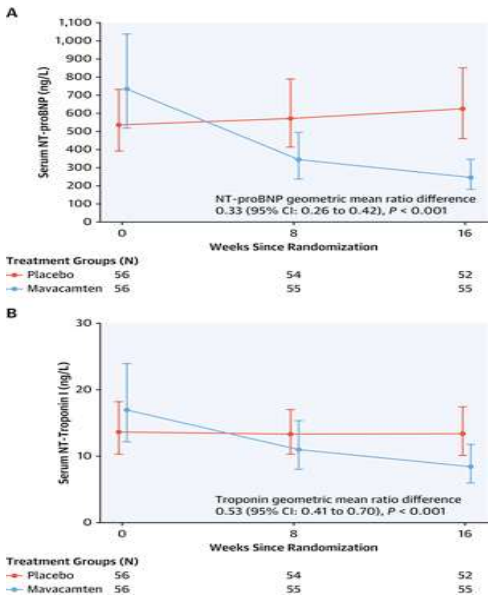


Milind Y. Desai et al. *J Am Coll Cardiol* 2022; 80:95-108.

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# Emerging Trends: Targeted Therapy

- Current Therapy consists of Pharmacotherapy and Surgery
  - Variable efficacy
  - Side effects
  - Surgical complications
- Targeted therapy
  - Exploits Specific Therapeutic drugs against pathogenic molecules (proteins or genes) or cells
  - Specific binding to disease-causing molecules or cells, sparing normal tissue
  - Widely used in Oncology, New Frontier for Cardiology

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# Emerging Trends: Categories of Targeted Therapy

- Protein Therapies
  - Monoclonal Abs
  - Bispecific Abs
  - Peptides
  - Cytokines
- Gene Editing
  - CRISPR/Cas9
  - Base Editing
  - CRISPR Interference/Activation
- Nucleic Acid Drugs
  - DNA
  - miRNA
  - siRNA
  - ASO (antisense oligonucleotides)
  - mRNA
- Immunotherapy
  - CAR-T

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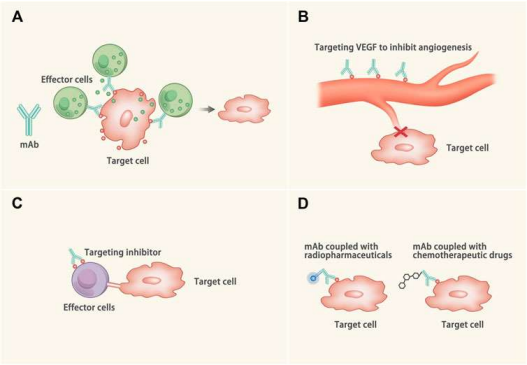
# Emerging Trends: Protein Therapies

- Monoclonal Abs
  - Activate immune response
  - Inhibit survival of pathologic tissue
  - Block inhibitory signals, or
  - Couple with therapeutic drugs
  - Examples:
    - Abciximab – GP IIb/IIIa inhibitor – ACS antiplatelet
    - Evolocumab/Alirocumab - PCSK9-I - Hyperlipidemia
    - Canakinumab – anti-inflammatory IL-1 inhibitor
      - **CANTOS** Trial – (ACS Trial we discussed in 2019)
      - Covid Myocarditis Trial (ongoing)
    - Tocilizumab – anti-inflammatory IL-6 inhibitor – ACS
- Bispecific Abs
  - Bridge cells or receptors, stimulate cofactors or piggyback active agents
  - Animal models

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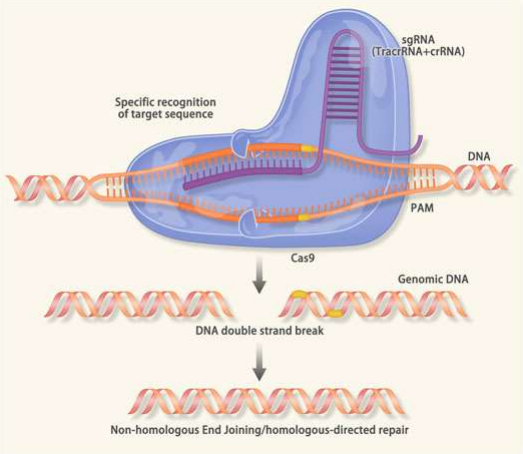
# Emerging Trends: Gene Editing

- **CRISPR/Cas9** (Clustered Regularly Interspaced Short Palindromic Repeats, CRISPR Associated Protein 9)
  - DSB (Double Stranded Break) of DNA leads to gene repair thus modifying DNA
  - Examples (animal models)
    - HCM, NIDC, PCSK9-I, TTR Amyloid
- **Base Editing**
  - Substitue cytosine for thymine without causing DSB (Animal models)
- **CRISPR Interference/Activation**
  - Inhibits/Enhances transcription of target gene

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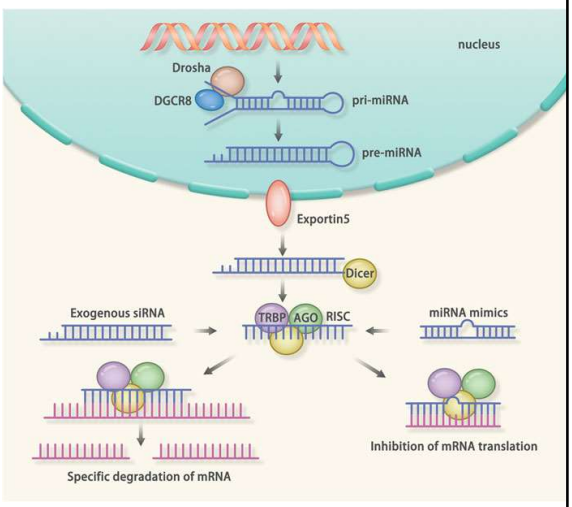
# Emerging Trends: Nucleic Acid and Immunotherapy

- **Nucleic Acid (Adeno-Associated Viral Vector)**
  - **DNA** (direct transcription - animal models)
  - **miRNA** (micro RNA, interfere or activate expression – animal models)
  - **siRNA** (small interfering RNA - inclisiran)
  - **ASO** (anti-sense oligonucleotides, inhibit gene expression – Phase III trials underway for HLD)
  - **mRNA** ( direct translation – animal models)
- **CAR-T**
  - Chimeric Antigen Receptor-Modified T cells
  - Antigen-specific binding T Cell Activation
  - Specifically kills Target Cells

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# Emerging Trends: Categories of Targeted Therapy

| Category | Advantages | Disadvantages |
|---|---|---|
| mAb | High specificity; mature clinical application; no off-target events | High price; immune response (except whole human antibody); complex preparation procedures |
| bAb | High specificity; synergistic effect of different antigen binding domains; no off-target events | Complex preparation procedures; no clinical products; high price |
| CRISPR/cas9 | Specific gene editing | Off-target events; gene rearrangement; oncogenes activation; immune response of the host |
| BE | Specific gene editing; no gene rearrangement | Low efficiency of gene editing (40%); immune response of the host; off-target events |
| Nucleic acid drugs | Easy to prepare | Off-target events (miRNA and siRNA); gene insertion (DNA); oncogenes activation |
| CAR-T | High specificity; no off-target events | Ineffective for intracellular lesions; cytokine release syndrome; complex preparation procedures |

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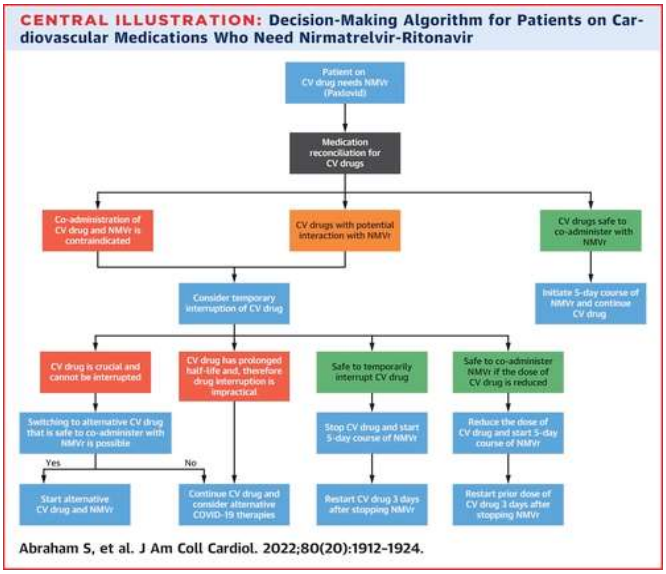
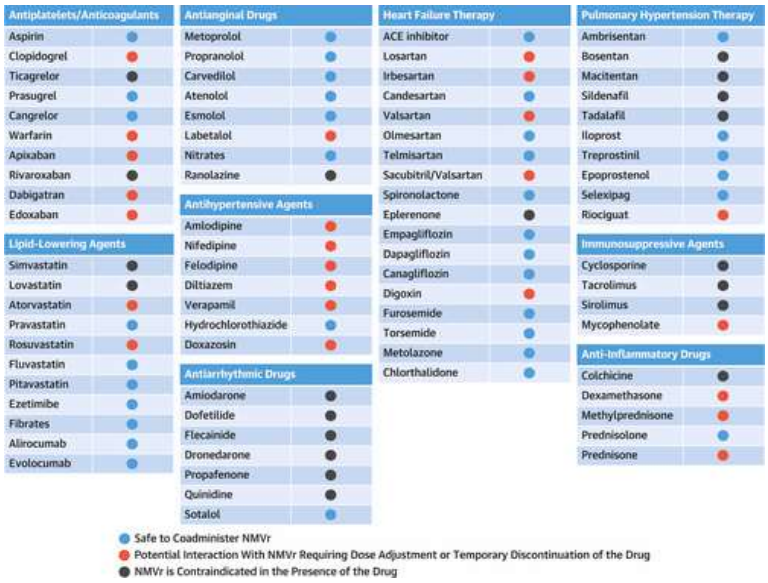



**Sonu Abraham et al. *J Am Coll Cardiol* 2022; 80:1912-1924.**



JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY




**Sonu Abraham et al. *J Am Coll Cardiol* 2022; 80:1912-1924.**



JACC

# Thank you!

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# Non-Statin Lipid Management

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# Non-Statin Lipid Management

Faheem Beg, MD

February 24, 2023

## Disclosures

- None

# Overview

- **What is the rationale for prescribing LDL-C lowering therapy?**
- **Who should be prescribed LDL-C lowering therapies?**
- **What LDL-C lowering drugs are currently available?**
- **What is statin intolerance?**
- **What other medications can be considered?**

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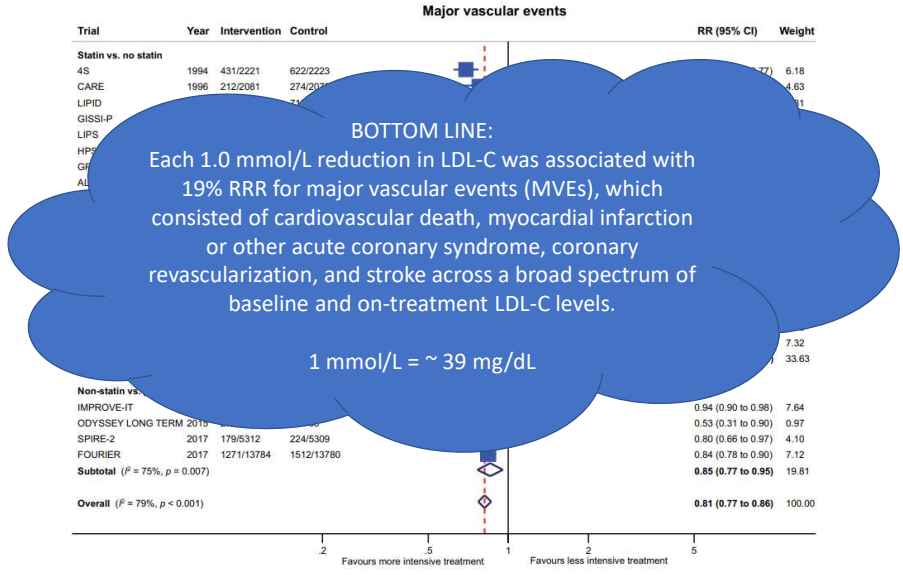
# RATIONALE FOR LIPID LOWERING THERAPY




BOTTOM LINE:
Each 1.0 mmol/L reduction in LDL-C was associated with 19% RRR for major vascular events (MVEs), which consisted of cardiovascular death, myocardial infarction or other acute coronary syndrome, coronary revascularization, and stroke across a broad spectrum of baseline and on-treatment LDL-C levels.

1 mmol/L = ~ 39 mg/dL

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# WHO SHOULD BE PRESCRIBED LIPID LOWERING THERAPIES

FIGURE 1 Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider

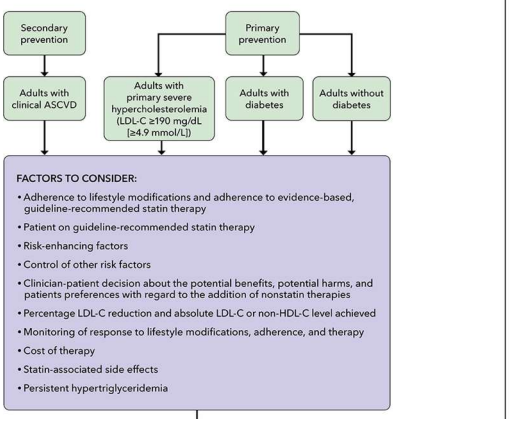


**TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events**

| |
|---|
| **Major ASCVD Events** |
| Recent ACS (within the past 12 months) |
| History of MI (other than recent ACS event listed above) |
| History of ischemic stroke |
| Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation) |
| **High-Risk Conditions** |
| Age ≥65 years |
| Heterozygous familial hypercholesterolemia |
| History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) |
| Diabetes |
| Hypertension |
| CKD (eGFR 15-59 mL/min/1.73 $m^2$) |
| Current smoking |
| Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe |
| History of congestive HF |

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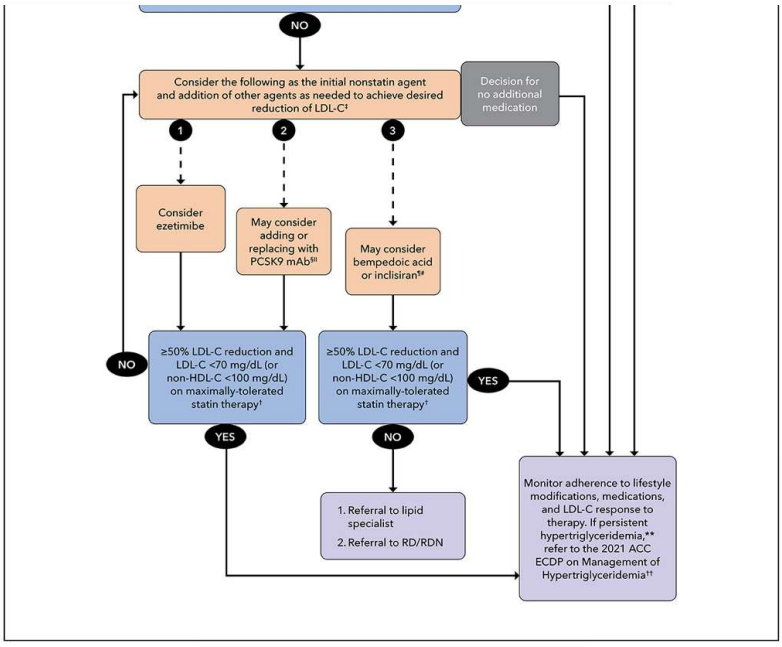
# GOAL LDL-C LEVEL WITH THERAPY

FIGURE 2B Adults With Clinic

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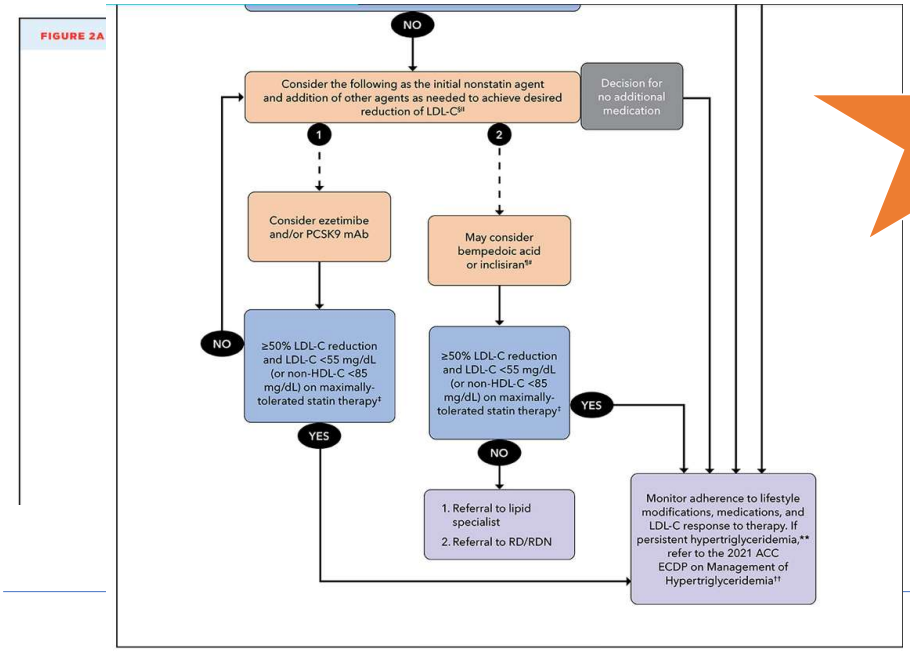
# GOAL LDL-C LEVEL WITH THERAPY





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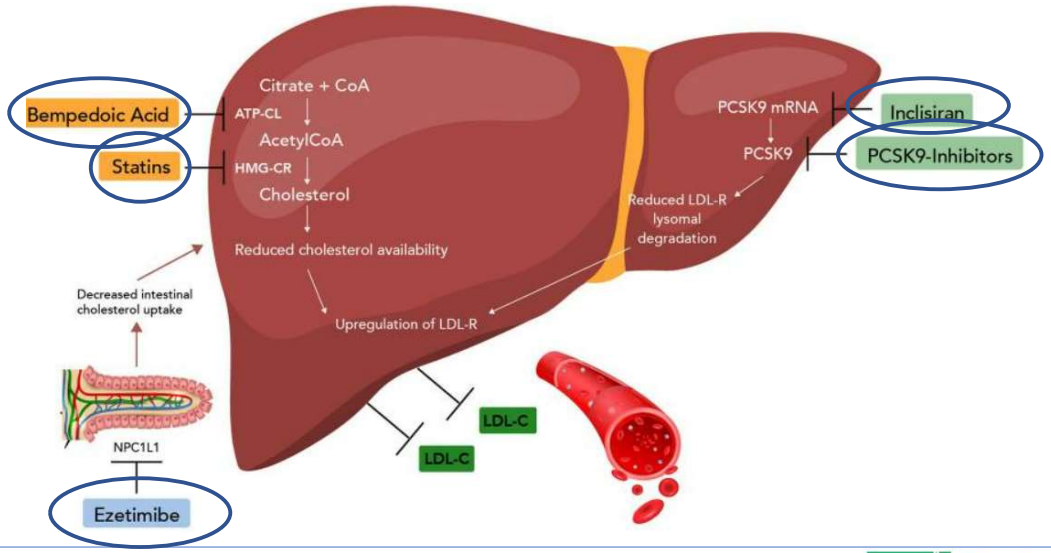
# CURRENT LDL-C LOWERING DRUGS

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# CURRENT LDL-C LOWERING DRUGS

**Table I** **Efficacy, event reduction, and approval status of lipid-lowering therapies**

| Class of agent | LDL reduction efficacy (%) | Event reduction | Approval status |
|---|---|---|---|
| Statins | 30–50 | + | + |
| Ezetimibe | 15–20 | + Combined with statin | + |
| PCSK9 inhibitors | 50–60 | + For MoAb combined with statin | + |
| Bempedoic acid | 17–25 | Outcome trial in progress | + |

This table summarizes the efficacy and approval status for different therapies that target LDL.
LDL, low-density lipoprotein.

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# CURRENT LDL-C LOWERING DRUGS

**Table 1. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)***

| *High intensity* | *Moderate intensity* | *Low intensity* |
|---|---|---|
| Daily dosage lowers LDL-C by approximately ≥ 50% on average | Daily dosage lowers LDL-C by approximately 30% to 50% on average | Daily dosage lowers LDL-C by < 30% average |
| **Atorvastatin (Lipitor), 40† to 80 mg** | **Atorvastatin, 10** *(20)* **mg** | *Simvastatin, 10 mg* |
| **Rosuvastatin (Crestor), 20** *(40)* **mg** | **Rosuvastatin,** *(5)* **10 mg** | **Pravastatin, 10 to 20 mg** |
| | **Simvastatin (Zocor), 20 to 40 mg‡** | **Lovastatin, 20 mg** |
| | **Pravastatin (Pravachol), 40** *(80)* **mg** | *Fluvastatin, 20 to 40 mg* |
| | **Lovastatin (Mevacor), 40 mg** | *Pitavastatin, 1 mg* |
| | *Fluvastatin XL (Lescol XL), 80 mg* | |
| | **Fluvastatin, 40 mg twice daily** | |
| | *Pitavastatin (Livalo), 2 to 4 mg* | |

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# WHAT IS STATIN INTOLERANCE

**Table 2** Clinical definition of statin intolerance.

| Definition | Characteristics |
|---|---|
| Statin intolerance is defined as one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin, or partial intolerance, with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage. | |
| Complete | Inability to tolerate any dose or regimen of a statin |
| Partial | Ability to tolerate a lower dose of statin than is required to achieve the desired therapeutic objective |

**Table 3** Modifiable factors associated with statin intolerance[27,77,78].

- Hypothyroidism
- Other therapies with potential drug to drug interactions (e.g., gemfibrozil, protease inhibitors, amiodarone, calcium channel blockers, azole antifungals, macrolides, immunosuppressants, colchicine)
- Alcohol use
- Strenuous exercise
- Vitamin D deficiency
- Obesity
- Diabetes

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# WHAT IS STATIN INTOLERANCE

**Keep Trying Statins**

Once a patient starts one or more non-statin lipid lowering medications, the effort to identify a tolerable statin treatment regimen should not be abandoned as most patients with reported statin intolerance can tolerate some degree of statin therapy (agent, dose, and/or dosing regimen).

**Identifying a Tolerable Statin Regimen**

To identify a tolerable statin regimen, clinicians should consider using several different strategies. Finding an acceptable regimen may require modification of the statin, statin dose, and/or dosing regimen.

**"Nocebo" Effect:**

It is reasonable to attribute some proportion of statin-associated symptoms to the nocebo effect. For patients with statin intolerance, it is reasonable to consider the nocebo effect as a possible cause; however, this does not make such symptoms less clinically relevant and ASCVD risk related to elevated atherogenic lipoproteins should be addressed.

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# CURRENTLY AVAILABLE NON-STATIN DRUGS

| Drug name | Mechanism of action | Dosage | Frequency | Route of administration | LDL-C lowering (%) | Adverse drug effects |
|---|---|---|---|---|---|---|

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# EZETIMIBE

**Mechanism of action:**
Inhibits NPC1L1 protein; reduces cholesterol absorption in small intestine.

**Dose:**
10 mg orally daily, with or without food. Take either 2h before or 4h after Bile Acid Sequestrants, if used in combination

**Mean Percent reduction in LDL-C:**
Monotherapy—18%; combination therapy with statin therapy (incremental reduction)—25%

**Precautions:**
- Not recommended in patients with moderate/severe hepatic impairment.
- Persistent elevations in hepatic transaminases may occur with concomitant statin therapy.
- Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy.

**Adverse effects:**
Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities.

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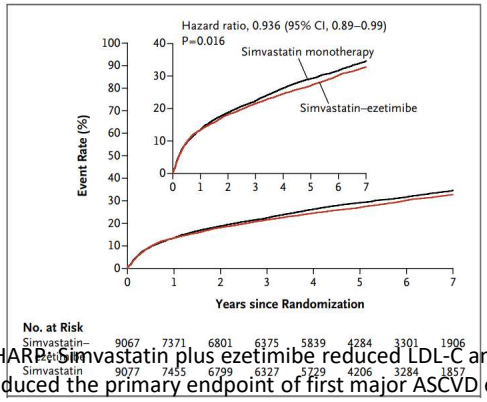
# EZETIMIBE




SHARP: Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years

IMPROVE-IT (The addition of ezetimibe to moderate-intensity statin th
lowering
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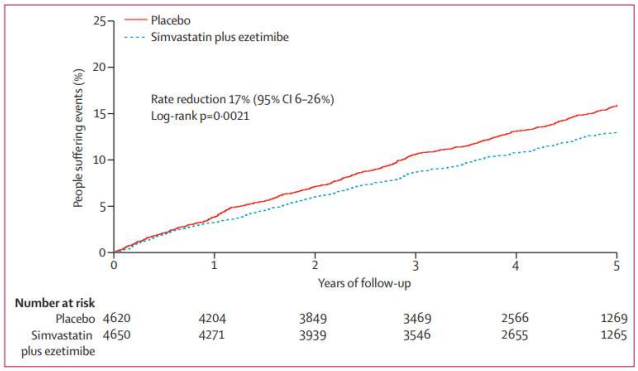


*Figure 2*: **Life-table plot of effects of allocation to simvastatin plus ezetimibe versus placebo on major atherosclerotic events**
Numbers remaining at risk of a first major atherosclerotic event at the beginning of each year are shown for both treatment groups.

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# ALIROCUMAB

**Mechanism of action:**
Human monoclonal Antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C

**Dose and route of administration:**
Administer SC in the thigh, abdomen, or upper arm. In adults with ASCVD or primary hyperlipidemia: initiate75 mg SC every 2 weeks. If more LDL-C reduction needed, may increase dose to 150 mg every 2 weeks.
Alternative starting dose is 300 mg SC every 4 weeks. For the 300-mg dose, administer 2 (150-mg) injections consecutively at 2 different injection sites.

**Mean Percent reduction in LDL-C:**
Alirocumab 75 mg and 150 mg SC every 2 weeks decrease LDL-C by an additional 45% and 58%, respectively, when added to maximally tolerated statin therapy.

**Adverse effects:**
In patients with primary hyperlipidemia: nasopharyngitis, injection site reactions, influenza; in patients with ASCVD: noncardiac chest pain, nasopharyngitis, myalgia. No evidence of increase in cognitive adverse effects observed in ODYSSEY Outcomes or CANTAB.

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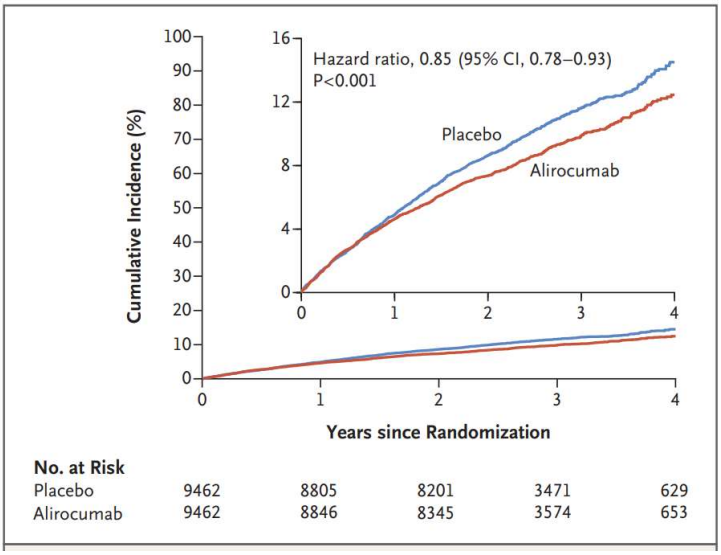
# ALIROCUMAB

**ODYSSEY Outcomes: 18,600 post-ACS (4-52 weeks) patients on evidence-based statin therapy; addition of alirocumab reduced the primary endpoint of CHD death, MI, ischemic stroke, or hospitalization for UA.**

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# EVOLOCUMAB

**Mechanism of action:**
Human monoclonal Antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL-C

**Dose and route of administration:**
Evolocumab: In adults with ASCVD, adults with primary hypercholesterolemia, including with established clinical ASCVD administer 140 mg SC every 2 weeks or 420 mg SC once monthly in abdomen, thigh, or upper arm. To administer 420-mg dose, either use the prefilled single-dose on-bodyinfuser or give 3 (140-mg) injections consecutively within 30 min.

**Mean Percent reduction in LDL-C:**
140 mg every 2 weeks and 420 mg SC every 4 weeks, decrease LDL-C by an additional 64% and 58%, respectively, when added to maximally tolerated statin therapy.

**Adverse effects:**
In patients with primary hyperlipidemia: nasopharyngitis, upper respiratory tract infection, influenza, backpain, and injection site reactions; in patients with ASCVD: diabetes, nasopharyngitis, upper respiratory tract infection. No evidence of an increase in cognitive adverse effects observed in FOURIER or EBBINGHAUS.

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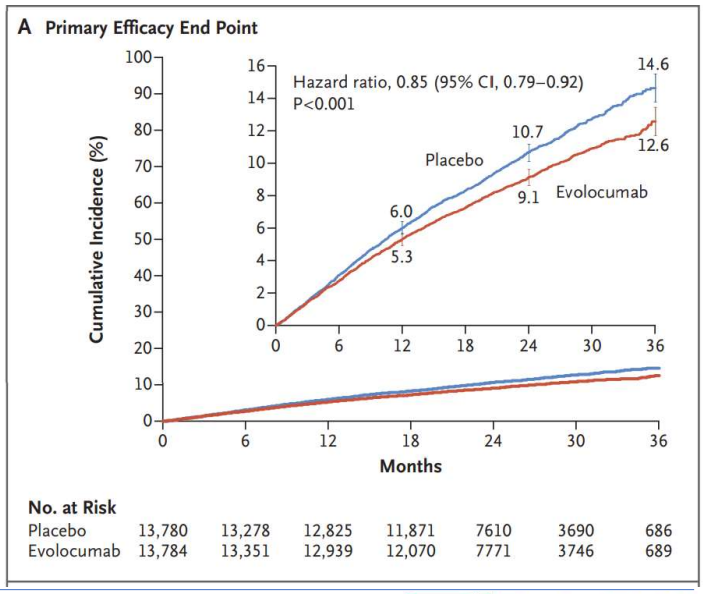
# EVOLOCUMAB

**FOURIER: 27,564 patients with prior MI, stroke, or PAD on atorvastatin 20 mg or equivalent; addition of evolocumab reduced the primary endpoint of CV death, MI, stroke, revascularization, or hospitalization for unstable angina.**

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# BEMPEDOIC ACID

**Mechanism of action:**
ACL (adenosine triphosphate-citrate lyase) inhibitor; inhibits cholesterol synthesis in the liver; increases LDL receptor density. Bempedoic acid and its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver.

**Dose:**
180 mg orally once daily, with or without food

**Mean Percent reduction in LDL-C:**
Combination therapy with statin therapy (placebo-corrected incremental reduction)—17%-18%.

**Precautions:**
Can cause hyperuricemia. Consider alternative therapy with a history of tendon disorders or tendon rupture. Avoid concomitant simvastatin>20 mg daily or pravastatin>40 mg daily

**Adverse effects:**
Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes

**CLEAR Outcomes trial completion expected later in 2022**

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# INCLISIRAN

**Mechanism of action:**
Small interfering RNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors.

**Dose:**
Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician

**Mean Percent reduction in LDL-C:**
48%-52%

**Precautions:**
None

**Adverse effects:**
Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea

**ORION-4 & VICTORION-2P ongoing trials with estimated completion in 2027**

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# CONCLUSION

- Each 1.0 mmol/L reduction in LDL-C was associated with 19% RRR for major vascular events
- Therapy is indicated in primary prevention and secondary prevention. “Very High Risk” requires additional consideration.
- Statins, Ezetimibe, PCSK9 inhibitors (Alirocumab and Evolocumab), Bempedoic Acid and Inclisiran
- Spectrum ranging from partial to complete. Try to identify modifiable risk factors and the statin that works.
- Percent reduction in LDL-C, Cost, and route of administration important in determining therapy.

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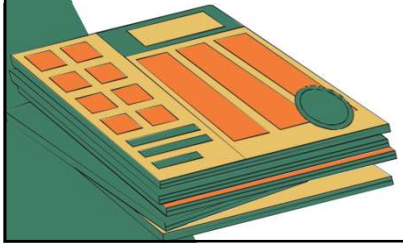
# HF Update: 2022 Heart Failure Classifications

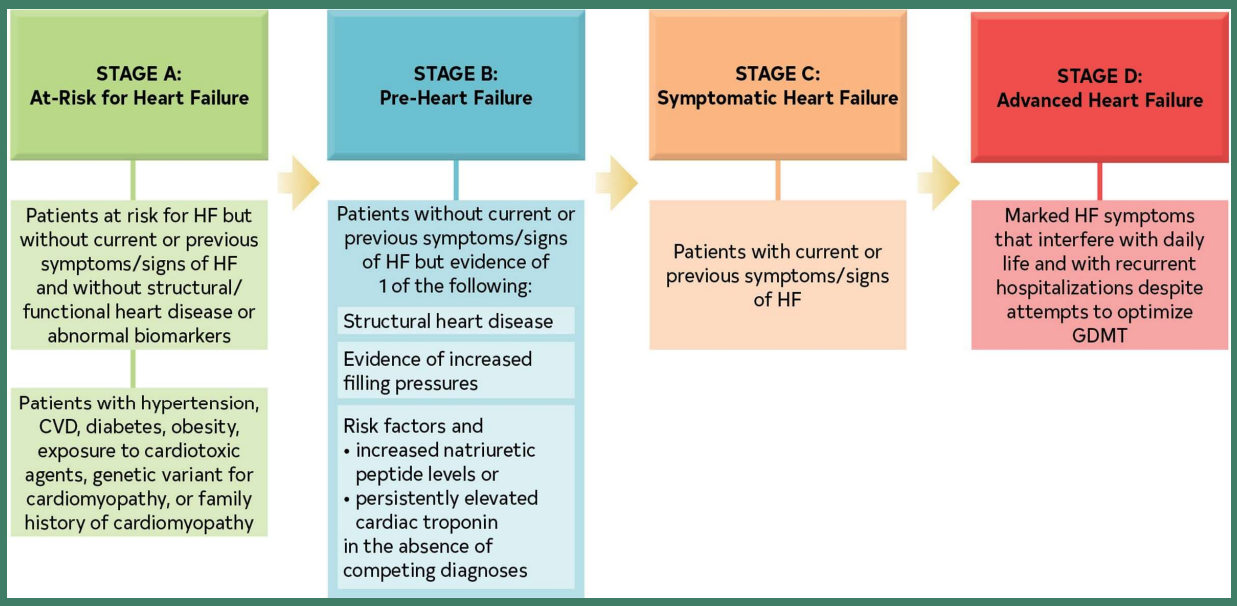
# Heart Failure for Primary Care

Anusha Sunkara MD
Advanced Heart Failure and Transplant Cardiology, Baptist Health, Little Rock, AR

## Classification of heart failure by EF

- **HFrEF**- LVEF </=40%
- **HFpEF**- LVEF >50% with evidence of spontaneous or provokable increased LV filling pressures.
- **HFmrEF** LVEF 41-49% with evidence of spontaneous or provokable increased LV filling pressures.





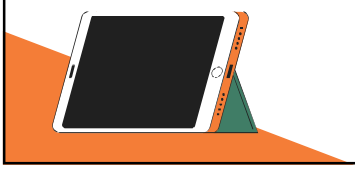

## Classification of heart failure by stages

# Causes of heart failure

Ischemic

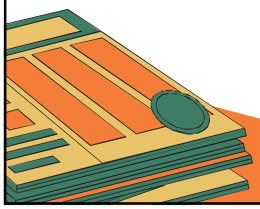
Non ischemic

- Idiopathic
- Familial
- HTN
- Substance abuse
- Chemotherapy or medication related
- Infiltrative ( Amyloid, sarcoid, hemochromatosis)
- Myocarditis
- Peripartum cardiomyopathy
- Stress/Takosubo cardiomyopathy



## Initial evaluation of patient with heart failure

- Physical examination- JVD is the most reliable indicator of volume overload.
- Labs- BNP is a prognostic marker however serial BNP measurement has no significant clinical benefit.
- EKG and Echocardiogram.



# What is GDMT for heart failure

ACEI/ARNI

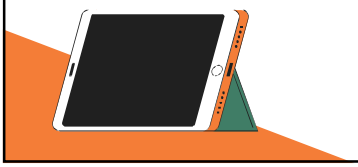
Beta Blockers

SGLT2i

MRA

Diuretics as needed

## My patient does not have DM, can I still add SGLT2i



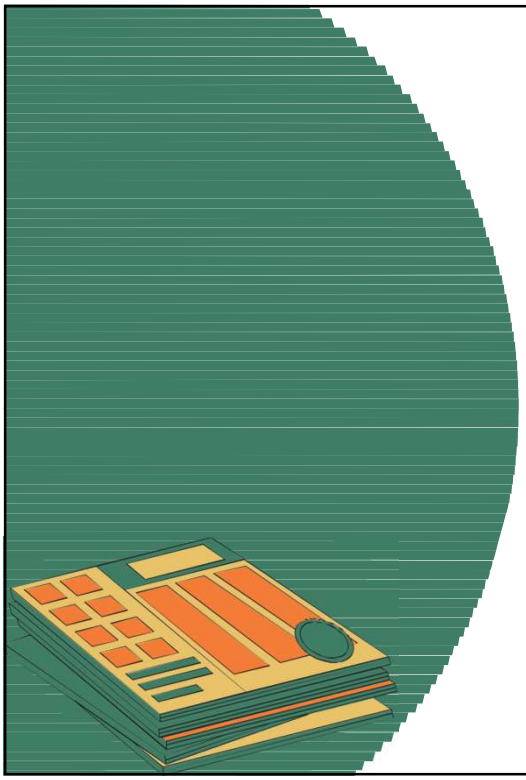
SGLT2i have been studied and proven in patients with heart failure WITHOUT DM II.

Contraindications for SGLT2i

- Dialysis
- eGFR<30 ml/min/1.73m2
- ESRD

Adverse effects

- Genital fungal infections
- UTIs
- Euglycemic Diabetic Ketoacidosis
- Lower limb ulcerations and soft tissue infections



## I started my patient on sacubitril/valsartan and now has worsening creatine, should I stop it?

- An initial fall in GFR is expected with addition of ARNI.
- >0.5mg increase in Cr /25% drop in GFR noted in 13.6% in PIONEER-HF.

## When should I refer a patient for advanced heart failure therapies

I- Inotropes Previous or ongoing

N- NYHA class or Natriuretic peptides

E- End-organ dysfunction  Worsening renal or liver function

E- Ejection fraction  LVEF<20%

D- Defibrillator shocks

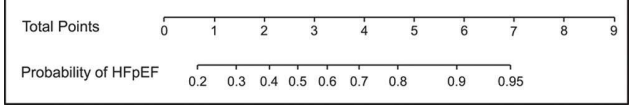
H- hospitalizations

E- Edema or escalating diuretics

L- Low Blood pressure

P- prognostic medication

| | Clinical Variable | Values | Points |
|---|---|---|---|
| $H_2$ | **H**eavy | Body mass index > 30 kg/m$^2$ | 2 |
| | **H**ypertensive | 2 or more antihypertensive medicines | 1 |
| F | Atrial **F**ibrillation | Paroxysmal or Persistent | 3 |
| P | **P**ulmonary Hypertension | Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg | 1 |
| E | **E**lder | Age > 60 years | 1 |
| F | **F**illing Pressure | Doppler Echocardiographic E/e' > 9 | 1 |
| $H_2$FPEF score | | | Sum (0-9) |




# What is HFpEF

Patients with classic signs of heart failure syndrome with LVEF more than or equal to 50%, evidence of diastolic dysfunction or other relevant structural changes on echo.

H2FPEF score helps in identification of patients with HFpEF.

# Causes of HFpEF

Pathophysiology not completely understood- related to coronary microvascular disease, endothelial dysfunction.

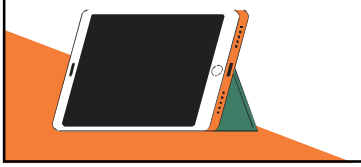
Infiltrative cardiomyopathies such as amyloid should be excluded.

# Treatment for HFpEF patients

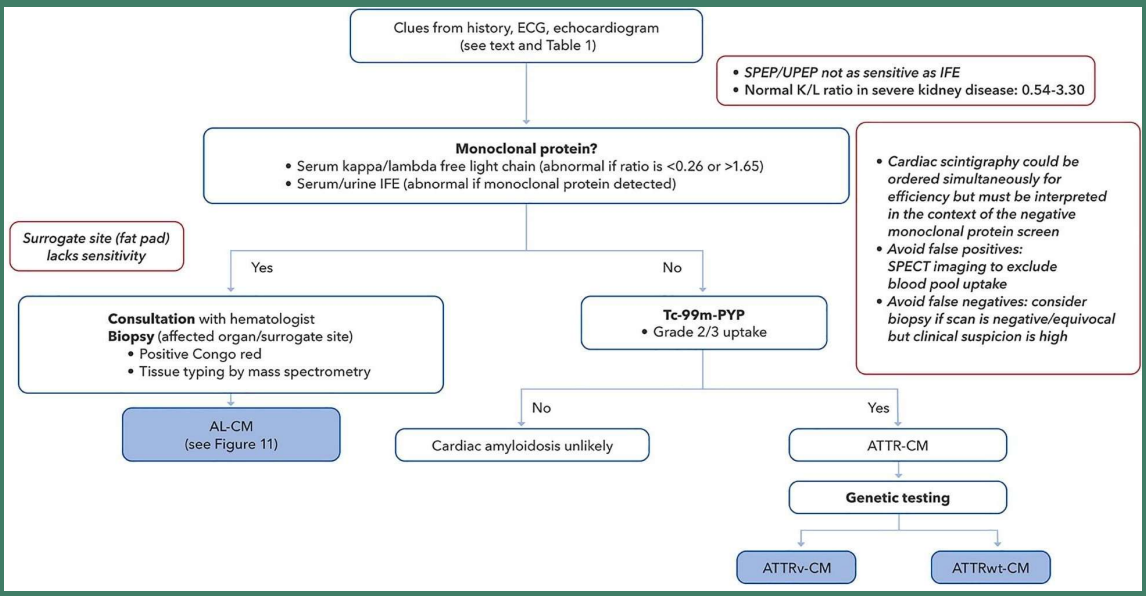
| Risk factor optimization | Newer therapeutic options | Future therapies |
|---|---|---|
| Bp control | Entresto- Largest benefit in women and patients with mildly reduced LVEF (45-52%) | Inter-atrial shunt devices- (investigational) |
| Glycemic control | SGLT2i- currently a class IIa recommendation. Have shown benefit in terms of improvement in symptoms and HF hospitalizations. | |
| Treatment of Atrial Fibrillation | | |
| Weight loss | | |
| Treatment of volume overload with diuretics | | |

# What is amyloidosis

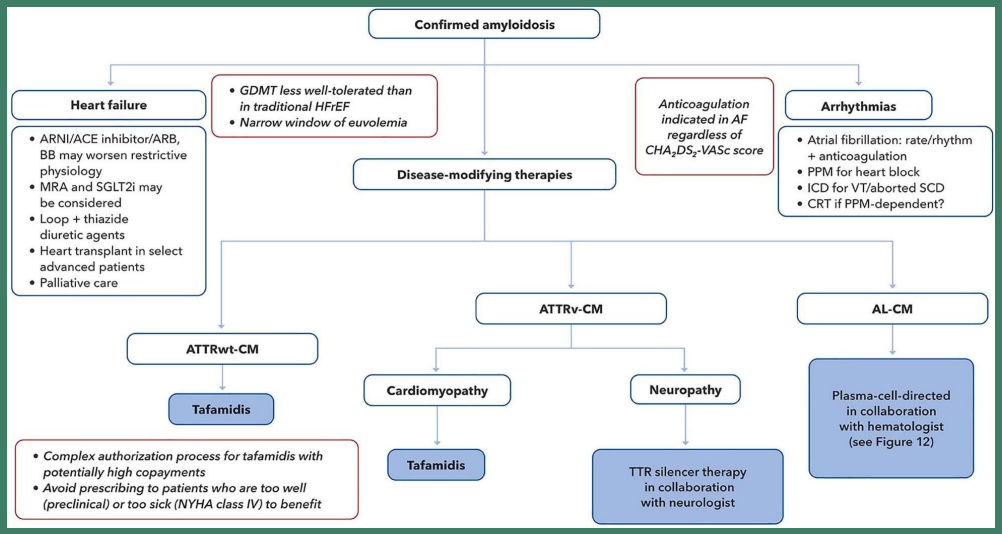
- Spectrum of diseases that result from misfolding of proteins that aggregate as amyloid fibrils in various organ systems.
- In cardiac amyloidosis, amyloid fibrils accumulate in the interstitial space between cardiac myocytes resulting in cellular injury, loss of compliance. Physiologically it presents as HFpEF/restrictive cardiomyopathy.
- Many precursor proteins are identified than can result in systemic amyloidoses.
- 2 major categories of cardiac amyloidosis are AL and ATTR amyloid.




## What are the clinical clues for amyloidosis?




# Diagnostic pathway of cardiac amyloidosis



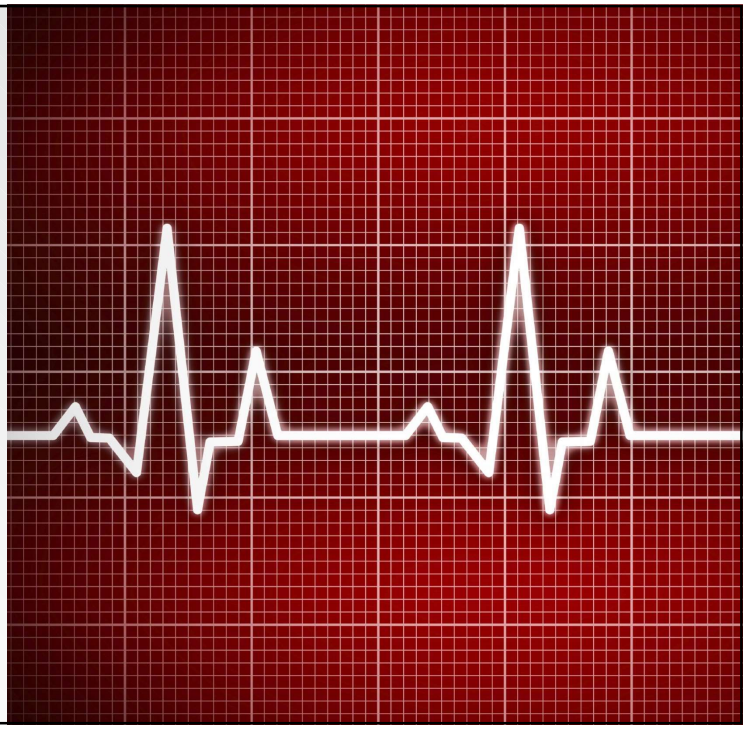

# Treatment of cardiac amyloidosis

# Non-Surgical Structural Options

# Non-Surgical Structural Options

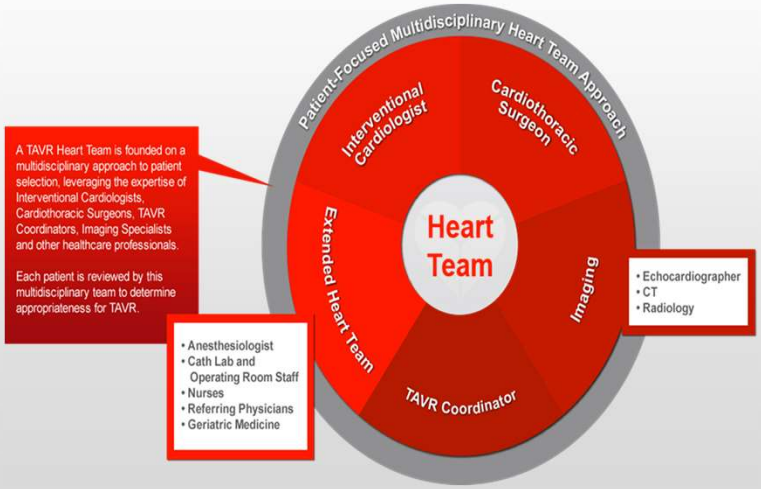
ERNESTO

RUIZ-RODRIGUEZ, M.D.



## Structural Heart Disease: The Revolution

- Most exciting and fastest growing field in cardiovascular medicine
- Incredible advancements in technology have allowed previously unthinkable procedures to become the norm
- For many patients with structural heart disease, previously high-risk open-heart surgeries have been replaced by non-surgical minimally invasive procedures with lower risk, less trauma, and faster recovery
- Procedures such as heart valve repairs and replacements can now be performed through catheters
- Originally designed for high-risk populations, structural heart procedures are being performed on lower risk populations




## Transcatheter Aortic Valve Replacement

- TAVR has completely transformed the way we managed patients
- Approved for use in intermediate to high surgical risk or inoperable patients and likely to be utilized in progressively lower-risk patients
- Structural Heart Team involved with all aspects of the decision-making and delivery of this complex technology
- Management of patients is best achieved by a multidisciplinary, collaborative team (cardiologists with expertise in heart valve disease, structural interventional cardiologists, imaging specialists, cardiovascular surgeons, cardiovascular anesthesiologists, and cardiovascular nursing professionals)
- Minimalist approach (conscious sedation, expedited discharge)

## Transcatheter Valve-in-Valve Implantations

- Failing surgical valves can be managed without the need for repeating open heart surgery

## MitraClip

- Percutaneous Mitral Valve Edge-to-Edge Repair
- Novel method of treatment that is targeted for patients who are not good candidates for surgical therapy for mitral regurgitation

## Cryptogenic Stroke and Patent Foramen Ovale (PFO)

- New data from the CLOSE, REDUCE and RESPECT trials demonstrated a lower rate of recurrent ischemic stroke after patent foramen ovale closure compared with antiplatelet therapy alone in patients with a patent foramen ovale and recent cryptogenic stroke

## High Risk Complex Coronary Artery Disease

- High risk patients with complex disease who are not good candidates for open heart surgery can no be revascularized with specialized techniques using “best practices” guidelines
- This may include hemodynamic “protection” with mechanical circulatory support

## Extracorporeal Membrane Oxygenation (ECMO)

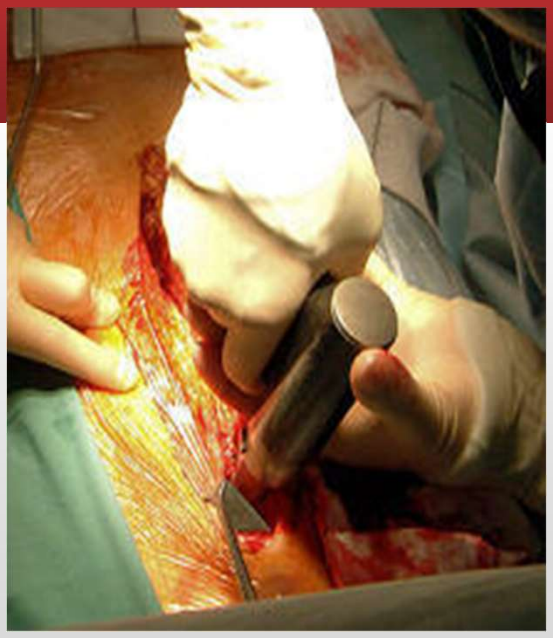
- Form of life support for people with life-threatening illness or injury that affects the function of their heart or lungs

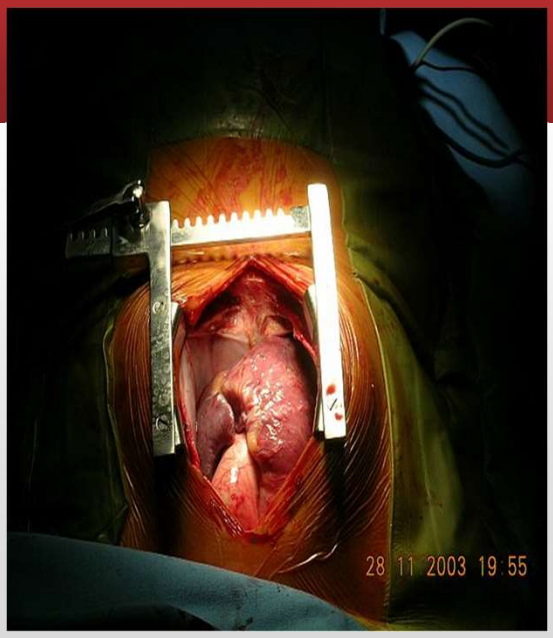
## AngioVac

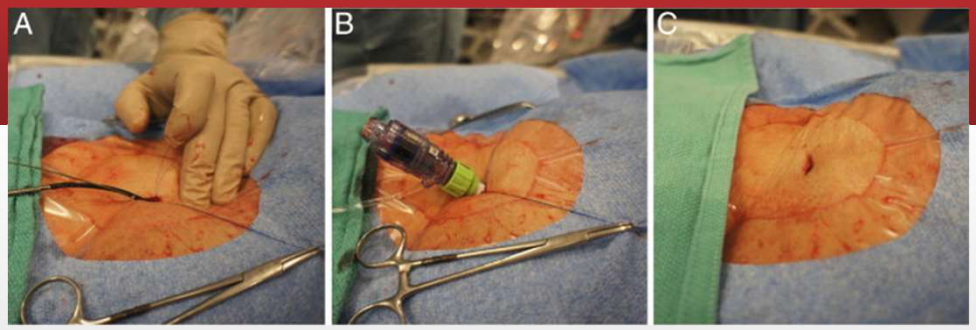
- Percutaneous removal of right-sided heart masses including thrombus and vegetations

## What's New?

- Transcatheter Mitral Valve Replacement



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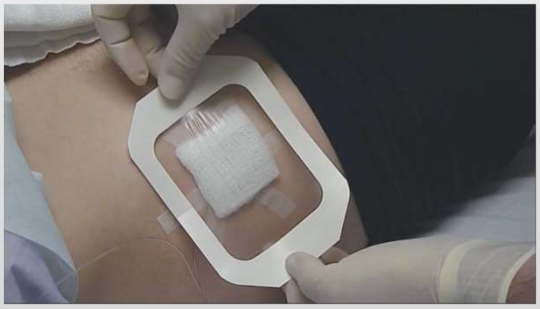

## The World of Medicine is Changing

## Structural Heart Coordinator

- Erika Jaco
- Office: (501) 202-1521
- Fax: (501) 202-6302

# Emerging roles for Cardiac CT/MR

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# Emerging roles for Cardiac CT/MR

RAMEY MARSHELL, MD

February 24, 2023

## Disclosures

- None

# Overview

- **Review contemporary uses & diagnostic effectiveness of cardiac CTA.**
- **Discuss paradigm shift in work-up of acute (stable) chest pain.**
- **Clinical application of cardiac MRI.**

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# BACKGROUND

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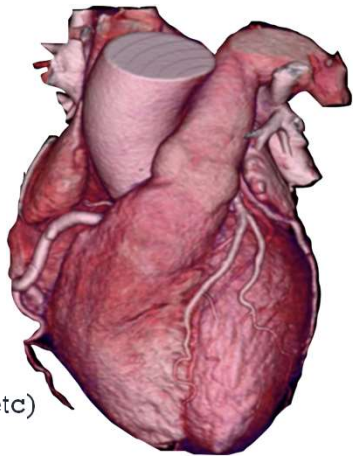
# Cardiac Computed Tomography (CCT)

- **CT Heart WITHOUT Contrast**
  - Coronary Artery Calcium Score (CACS)
- **CT Heart WITH Contrast (Cardiac CTA)**
  - Anatomic CAD detection / plaque assessment
  - Functional assessment of CAD (FFRct / CT perfusion)
  - Stents
  - Bypass grafts
  - Anomalous coronary arteries
  - Heart defects (congenital & acquired)
  - Pre-procedure planning (TAVR, Watchman, AF ablation, etc)



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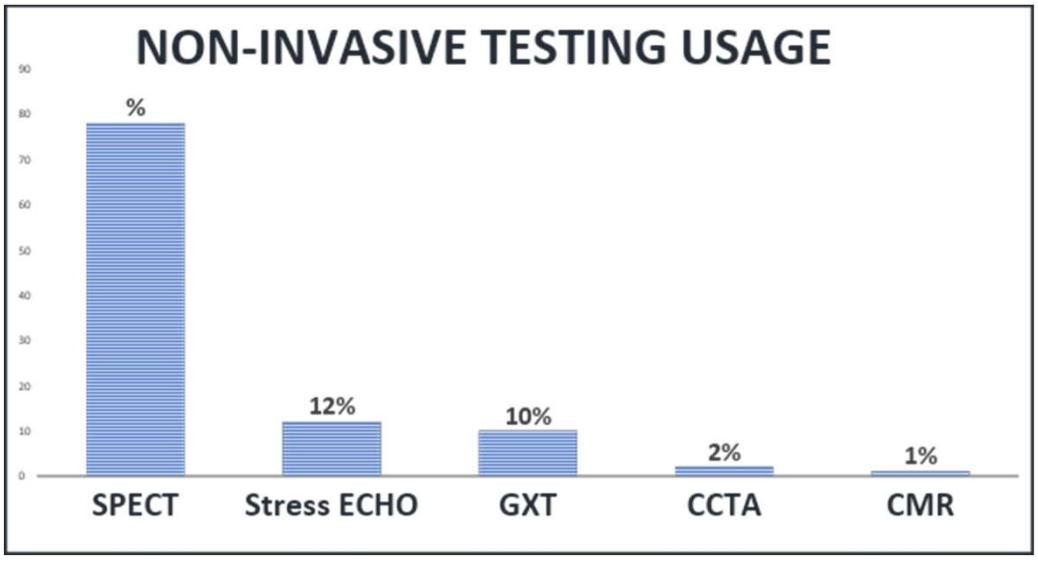


Patel, *et al. American Heart Journal*. 2014.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D., Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

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N = 397,954

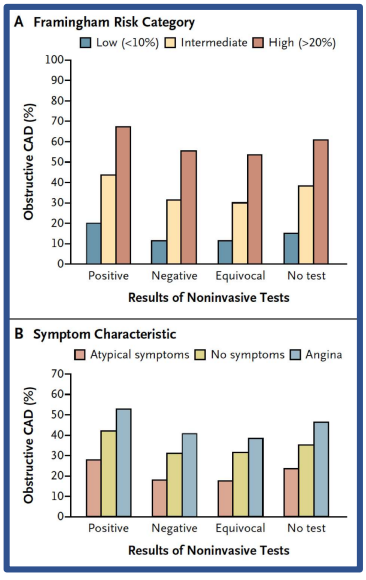
↓

LHC

↓

38% Obstructive CAD

***** Having a Positive Stress Test increased that number to only 41%**

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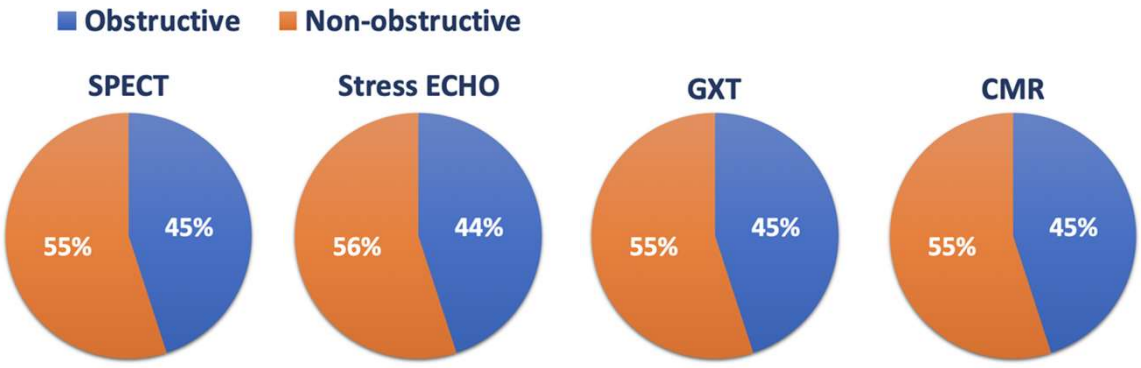
# Diagnostic Yield of Non-Invasive Functional Testing




**58% overall with non-obstructive CAD**

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# Coronary CT Angiography (CCTA)

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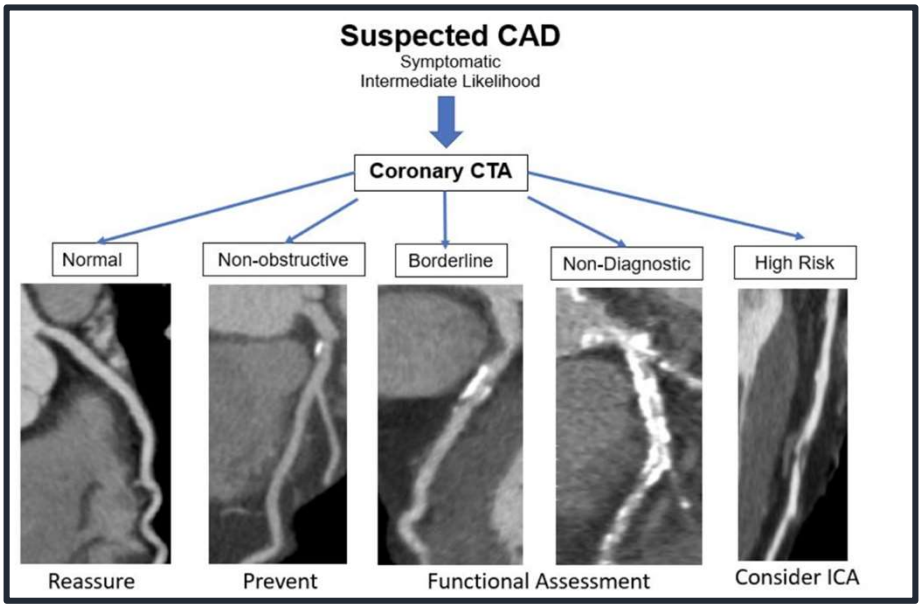


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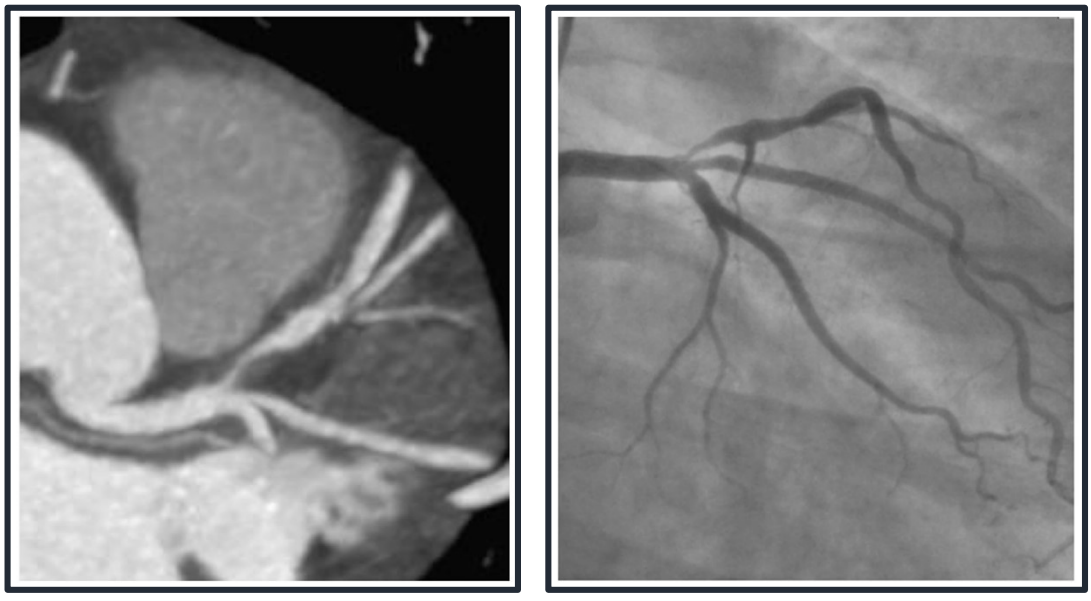

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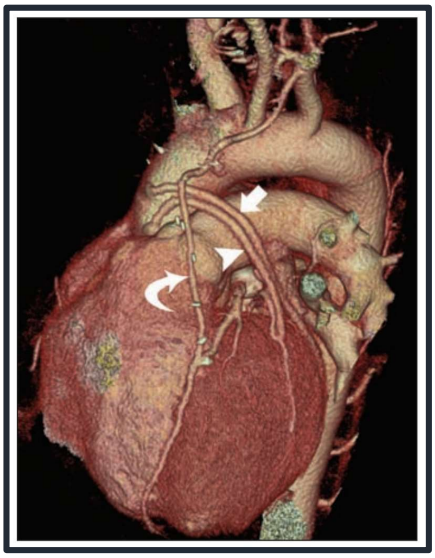

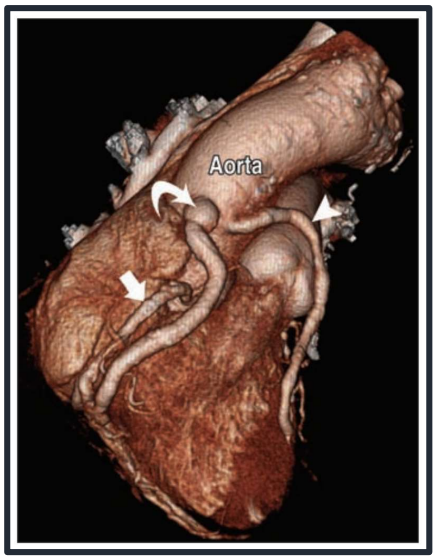


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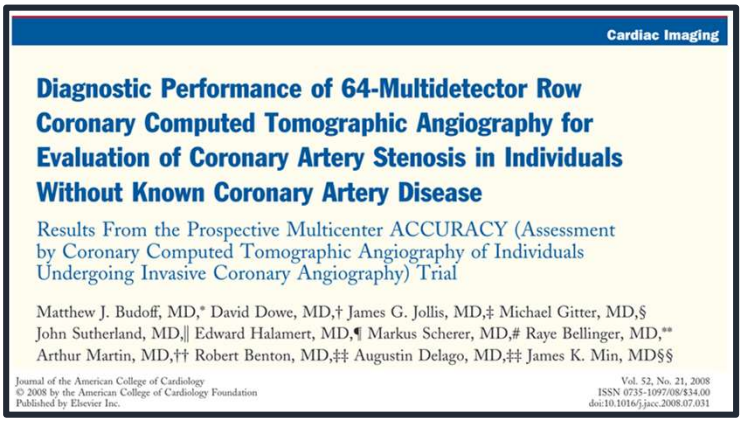

Cardiac Imaging

**Diagnostic Performance of 64-Multidetector Row Coronary Computed Tomographic Angiography for Evaluation of Coronary Artery Stenosis in Individuals Without Known Coronary Artery Disease**

Results From the Prospective Multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) Trial

Matthew J. Budoff, MD,* David Dowe, MD,† James G. Jollis, MD,‡ Michael Gitter, MD,§ John Sutherland, MD,‖ Edward Halamert, MD,¶ Markus Scherer, MD,# Raye Bellinger, MD,** Arthur Martin, MD,†† Robert Benton, MD,‡‡ Augustin Delago, MD,‡‡ James K. Min, MD§§

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doi:10.1016/j.jacc.2008.07.031

**<u>99% NPV</u>** for ruling out obstructive CAD

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2012 VOL. 367 NO. 4

# Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain

Udo Hoffmann, M.D., M.P.H., Quynh A. Truong, M.D., M.P.H., David A. Schoenfeld, Ph.D., Eric T. Chou, M.D., Pamela K. Woodard, M.D., John T. Nagurney, M.D., M.P.H., J. Hector Pope, M.D., Thomas H. Hauser, M.D., M.P.H., Charles S. White, M.D., Scott G. Weiner, M.D., M.P.H., Shant Kalanjian, M.D., Michael E. Mullins, M.D., Issam Mikati, M.D., W. Frank Peacock, M.D., Pearl Zakroysky, B.A., Douglas Hayden, Ph.D., Alexander Goehler, M.D., Ph.D., Hang Lee, Ph.D., G. Scott Gazelle, M.D., M.P.H., Ph.D., Stephen D. Wiviott, M.D., Jerome L. Fleg, M.D., and James E. Udelson, M.D., for the ROMICAT-II Investigators

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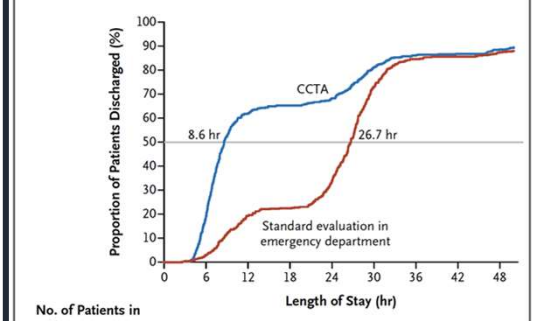


| No. of Patients in Emergency Department or Hospital | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| CCTA | 501 | 404 | 191 | 174 | 159 | 95 | 70 | 66 | 57 |
| Standard evaluation | 499 | 484 | 403 | 387 | 331 | 135 | 77 | 72 | 63 |

Figure 2. **Length of Stay in the Hospital and Proportion of Patients Discharged.**

The cumulative frequency of discharge from the index visit according to the length of stay is shown. The horizontal line indicates the median length of stay in the two study groups, which was significantly different (8.6 hours in the CCTA group vs. 26.7 hours in the standard-evaluation group, P<0.001).

- **Reduced LOS** (23 v. 31 h, p = .001)
- **3-fold higher rate of direct ED discharge** (47 v. 12%, p = .001)
- **Significant reduction in time-to-diagnosis** (10 v. 19 h, p = .0001)
- **18% reduction in ED costs**
- **No difference in MACE at 28d**

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Coronary CT Angiography and 5-Year Risk of Myocardial Infarction

The SCOT-HEART Investigators*

N ENGL J MED 379;10 NEJM.ORG SEPTEMBER 6, 2018

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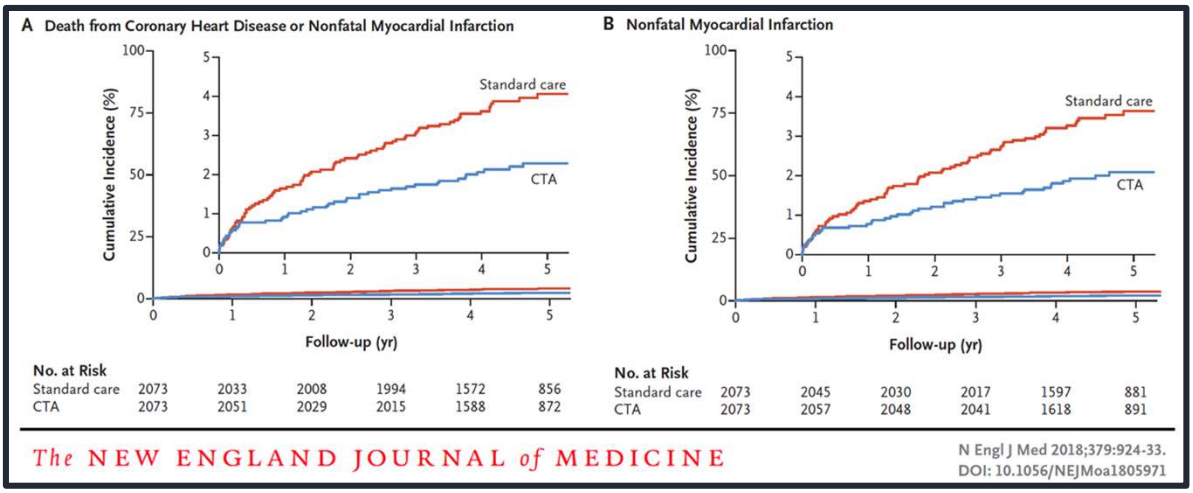


**<u>41% reduction</u>** in the primary 5yr event rate in favor of CCTA (N = 48, 2.3%) v. standard care (N = 81, 3.9%) [HR .59, p = .004]

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# Anatomic + Functional Assessment

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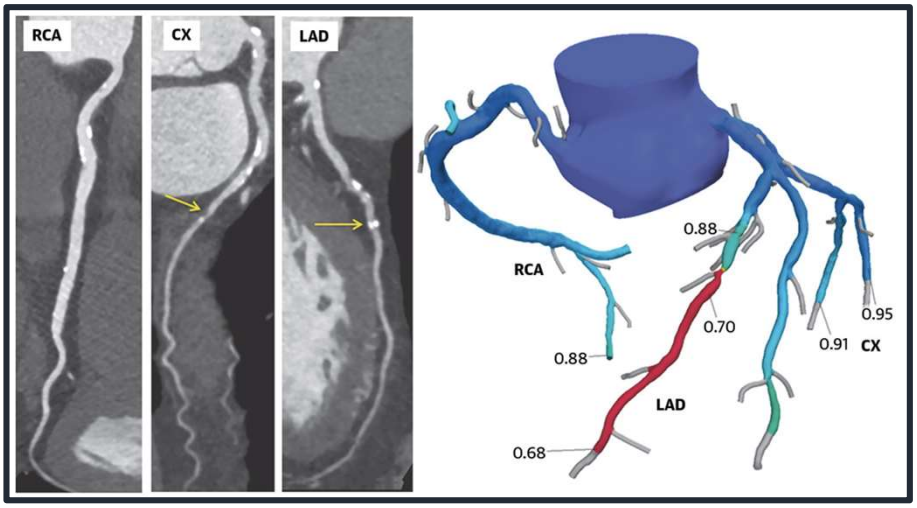
# Fractional Flow Reserve (FFRCT)

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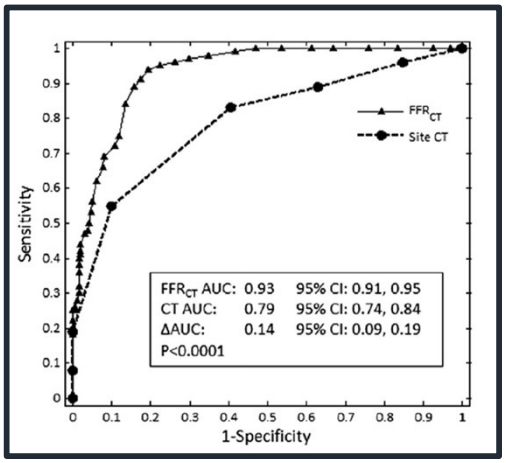


- **Diagnostic Performance:**
  - AUC for ≥ 50% stenosis = .79
  - AUC for **FFR$_{CT}$ ≤ .80 = .93**
- FFR$_{CT}$ correctly **re-classified 68%** with CCTA > 50% stenosis as functionally **NOT** significant

**NXT Trial introduced potential for FFR$_{CT}$ as a reliable gatekeeper to ICA**

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# 2021 ACC/AHA CHEST PAIN GUIDELINES

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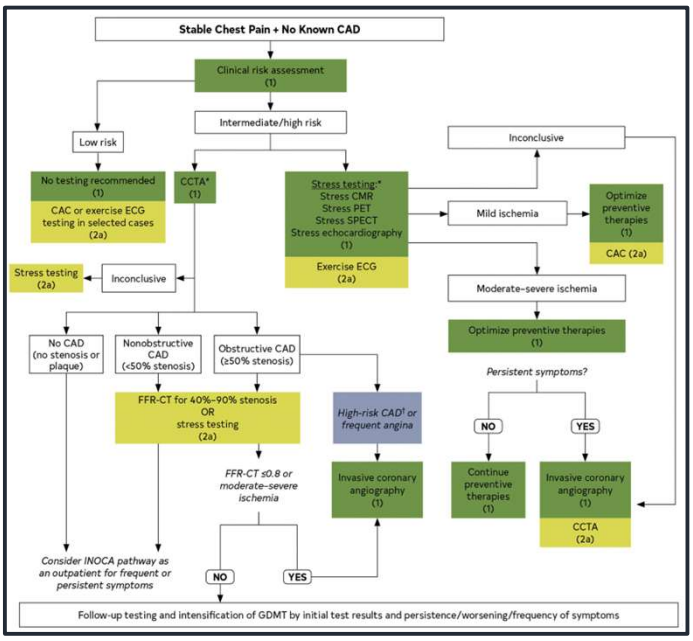


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# Cardiac Magnetic Resonance Imaging

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# Cardiac MRI Uses (not comprehensive)

- General - - chamber volumes (class I) | precise EF (class I) | Qp:Qs (class I)
- Myocarditis (I)
- Dilated Cardiomyopathy (I)
- Hypertrophic Cardiomyopathy (I)
- Arrhythmogenic Cardiomyopathy (I)
- LV Non-Compaction Cardiomyopathy (I)
- Myocardial Iron Overload (I)
- Cardiac Sarcoidosis (I)
- Cardiac Amyloidosis (I)
- Ischemic Heart Disease - - Viability (I) | Ischemic Cardiomyopathy (I)
- MINOCA (I)
- Valvular Heart Disease - - AS / AI (II) | MR (II) | TR (II) | PI (I) | Prosthetic Valves (II)
- Cardiac Masses (class I)
- Pericardial Disease - - Pericarditis (I) | Constriction (I) | Congenital Anomalies (I)
- Congenital Heart Disease - - Shunts (I) | Complex CHD (I)

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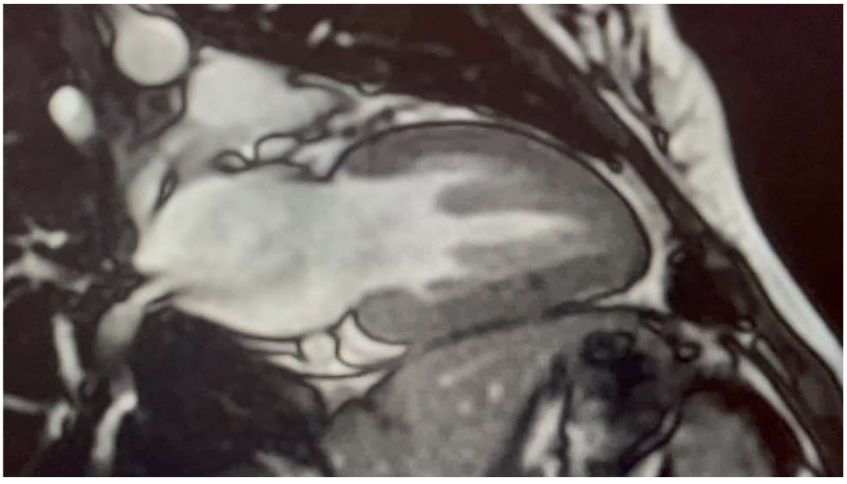
# Normal 2 Chamber CMR



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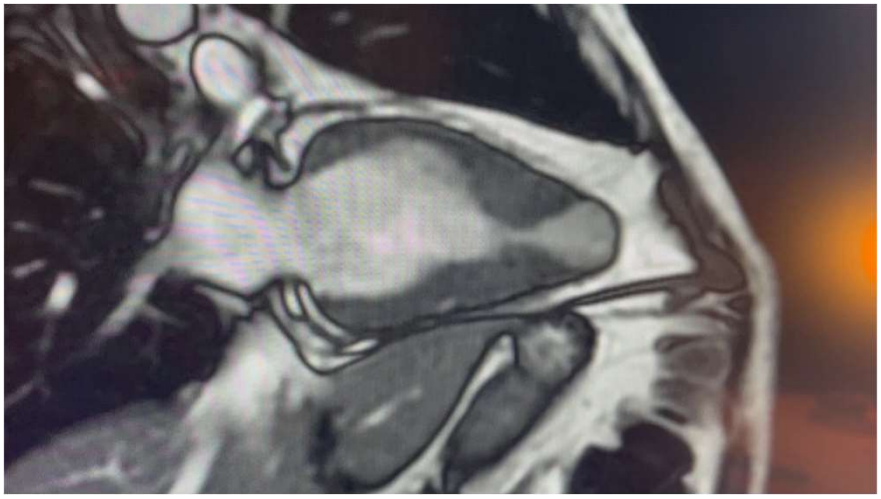
# Apical Hypertrophic Cardiomyopathy



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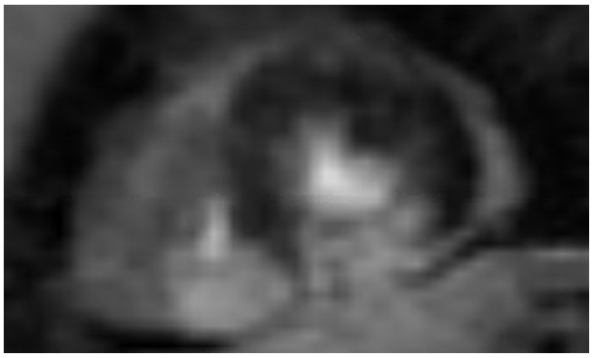
# Sub-acute RCA Infarct



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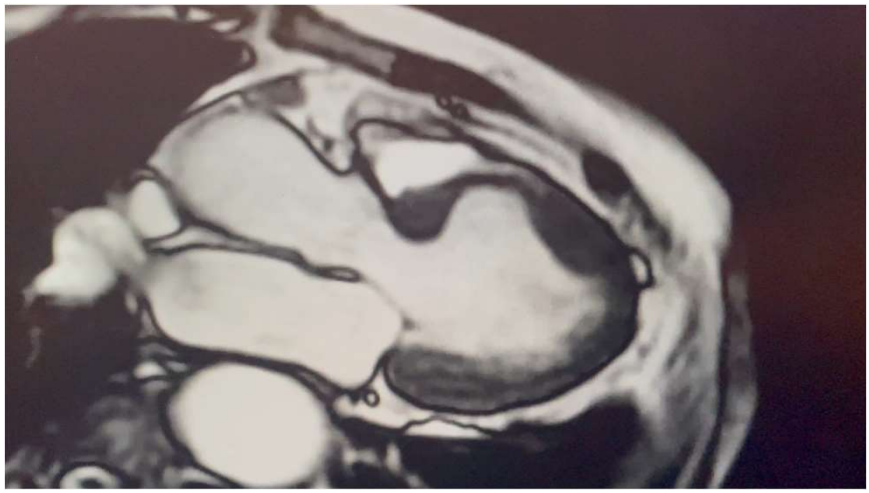
# Cardiac Sarcoidosis



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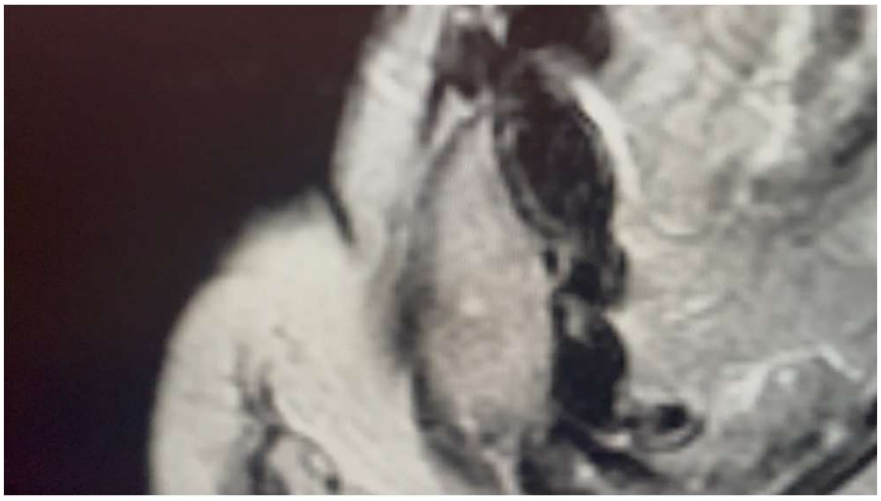
# Cardiac Sarcoidosis



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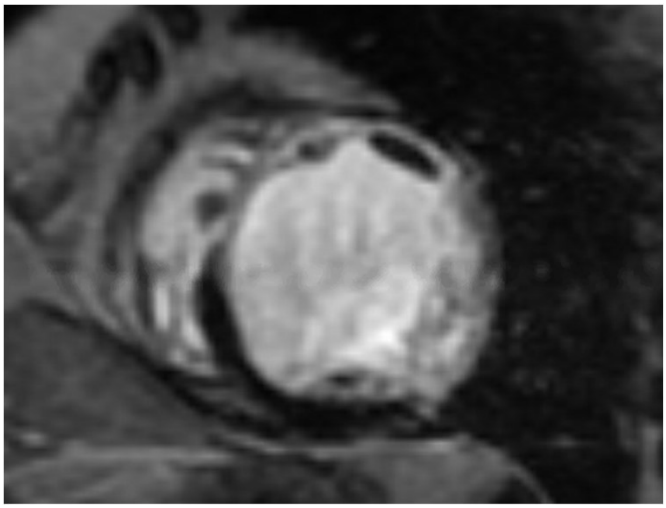
# Ischemic Cardiomyopathy



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# Not All Edema is HF

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# Not All Edema Is Heart Failure

F. Dwight Chrisman MD FACC
Interventional Cardiology/Peripheral Interventions/Vein Center Director
February 24, 2023

## Disclosures

- None to disclose

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# Overview

- - Review major causes of Edema
  - Etiology
  - Pathophysiology
- - Discuss how venous disorders can impact quality of life
- - Treatment options for superficial venous disease

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# Major Causes of Edema

- Lifestyle – sedentary
- Lymphedema
- Sodium
- HTN therapy
- NSAIDS
- Steroids
- Estrogens
- Thiazolidinediones
- Gabapentin
- Thyroid Function
- Liver damage
- Kidney Disease
- Malnutrition
- Obstruction/Cancer
- Pregnancy
- DVT
- Venous Insufficiency

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# Lifestyle – Sedentary

- Lack of movement
  - Leads to lymphatic system pressure gradient shift in wrong direction
  - Increased risk of thromboembolism
    - Stagnant flow

  - Lymph system propels against a hydraulic pressure gradient
    - From interstitial space to central veins
      - Via
        - Extrinsic forces (Lifestyle affects)
        - Intrinsic rhythmic contractility of lymphatic muscle cells (Lymphedema)

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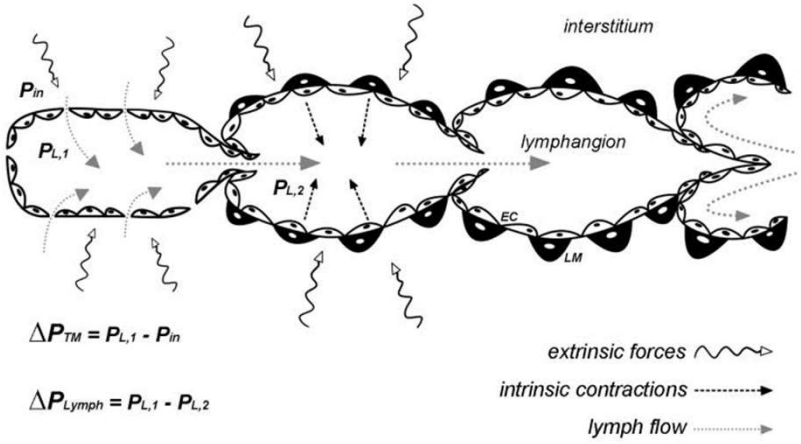
# Lymphatic Gradient Forces (1)

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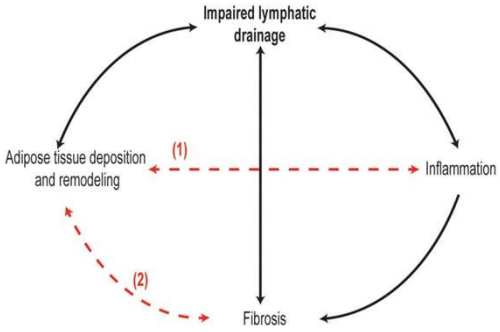
# Lymphedema

- Pathophysiological events (2)
  - Lymph stasis
  - Lymphatic vessel remodeling and dysfunction
  - Inflammation
  - Adipose tissue deposition
  - Fibrosis

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# Sodium (Na)

- Increased pressure in venous circulation favors movement of fluid interstitial

- Alteration of Starling forces
  - Affecting all capillary beds
    - Afferent mechanisms – signals kidneys receive for Na and water retention
    - Efferent mechanisms – kidney response to signals (3)

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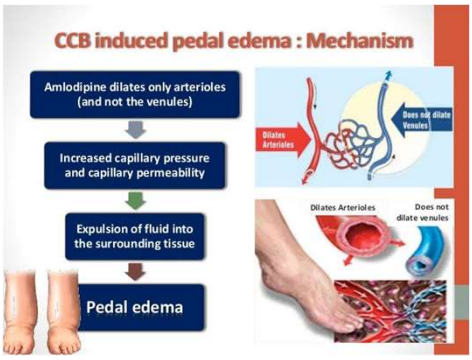
# Amlodipine (DHP)

- Dilates blood vessels improving flow
- Puts pressure on smaller vessels leading to leaking to tissues
  - Increased capillary permeability (4)
  - Preferential arteriolar or pre-capillary dilation without commensurate dilation in the venous or post-capillary circulation.




  - How to help the edema
    - Reduce dose
    - Add ACE or ARB
    - Switch to non-dihydropyridine
      - Verapamil or diltiazem
      - Addition of diuretics is of little help

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# NSAID Therapy

- NSAIDS – inhibit the metabolism of aldosterone
  - Aldosterone can induce myocardial fibrosis and vascular stiffening
- NSAIDS – promote Na and water retention
  - Inhibit synthesis of prostaglandins
  - Reduction in prostaglandin-induced inhibition of:
    - Renal chloride reabsorption
    - Action of antidiuretic hormone (5)
    - Can elevate the BP about 5mmHg

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# Steroids

- Cortisone (mineralcorticoids/glucocorticoids)
  - Involved in regulating balance of water, sodium and electrolytes
  - Regulate electrolyte excretion in the kidney
  - Aldosterone results in increased Na reabsorption
  - Results are positive Na balance, increased extracellular fluid volume

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# Estrogen

- Estrodiol
  - Lowers operating point for osmoregulation of arginine vasopressin
    - Hormone that helps blood vessel constriction
    - Hormone that helps kidneys control total water and salt in body
  - This increases plasma volume some
  - Overall volume is similar but more shifted to the extracellular space (6)

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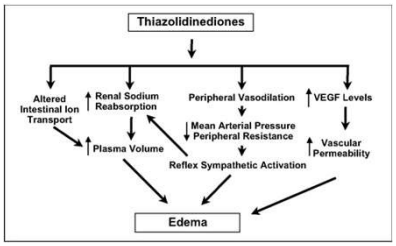
# Thiazolidinediones




- Pioglitazone and Rosiglitazone
  - Class affect
  - Up to 7.5% incidence
  - Multifactoral and no fully understood
    - Reduction in renal excretion of Na
    - Increased Na and free water retention
    - May synergistically act with insulin leading to vasodilation
      - Leads to Na reabsorption and increased extracellular volume (7)

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# Gabapentin

- Incidence of 2-8%
- Typically dose related
- Mechanism
  - Largely unknown
  - Theorized to be similar to CCB mechanism
    - Effect on presynaptic calcium channels

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# Thyroid Function

- Myxedema - extreme manifestation of hypothyroidism
  - Mucopolysaccharide deposition in dermis
  - Resultant swelling from connective tissues deposition
    - Protein-mucopolysaccharide complex binds water
    - Edema results

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# Liver Damage

- Cirrhosis
  - Slows the flow of blood through the liver
  - Subsequently increasing venous portal pressure
  - Occurs in 50% within 10 years of diagnosis of cirrhosis
    - Peripheral arterial vasodilation
    - Under filling circulatory volume
    - Activation of renin-angiotensin-aldosterone system
    - Avid Na and water retention (8)

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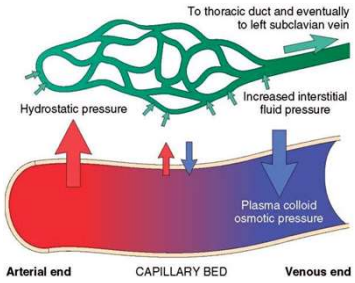
# Kidney Disease




- Nephrotic syndrome
  - Abnormal renal Na retention
  - Increased capillary wall permeability
  - Urinary protein loss
    - Leads to decrease plasma albumin concentration
    - Lowers plasma oncotic pressure
    - Fluid shifts from intravascular to interstitial space
    - Arterial blood volume is decreased and then becomes a loop
      - Hormonal stimulation to try to correct the situation

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# Malnutrition

- Kwashiorkor
  - Loss of fluid balance between hydrostatic and oncotic pressure at vessel walls
  - Albumin helps keep fluid intravascular
  - With this low intravascular volume feedback mechanism continues
    - ADH increases with more edema
    - Plasma renin increases leading to more Na retention
- Marasmus
  - Severe dietary malnutrition with calorie deficiency
  - Resultant hypoalbuminemia
- Anorexia
  - Protein loss/hypoalbuminemia
    - Low levels lead to inability to draw water into blood vessels

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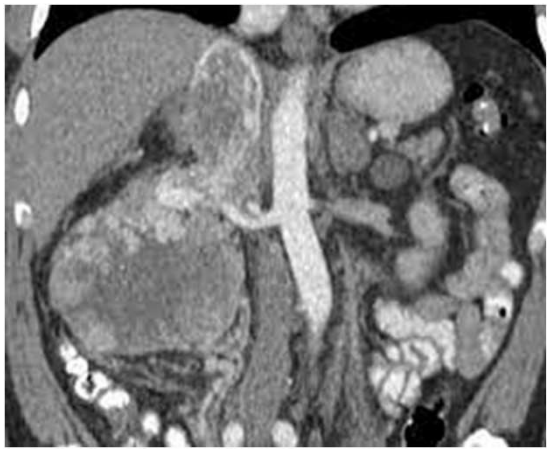
# Cancer

- Multiple Etiologies
  - Obstruction
  - Chemotherapy side affect
  - Hormone therapy
  - Radiation therapy
  - Steroids
  - Poor nutrition



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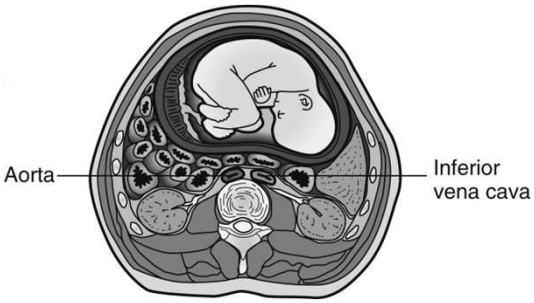
# Pregnancy Edema

- Adrenal glands produce more aldosterone and cortisol
  - Subsequent retaining of fluid
- Obstruction
  enlarging uterus interfering with blood flow

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# Deep Vein Thrombosis

- Thrombus
  - Outflow obstruction – pain and swelling
  - Partial outflow obstruction
    - Edema but possibly no pain
    - Leg pain typically 50% of time
    - The higher the obstruction could be bilateral edema

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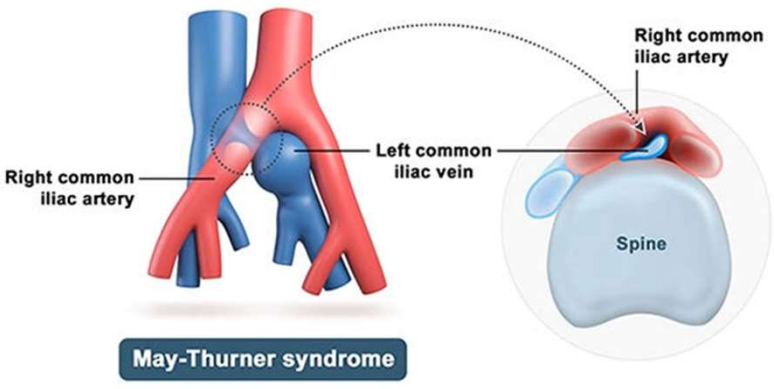
# May-Thurner Syndrome

- Unilateral
  - Left lower extremity

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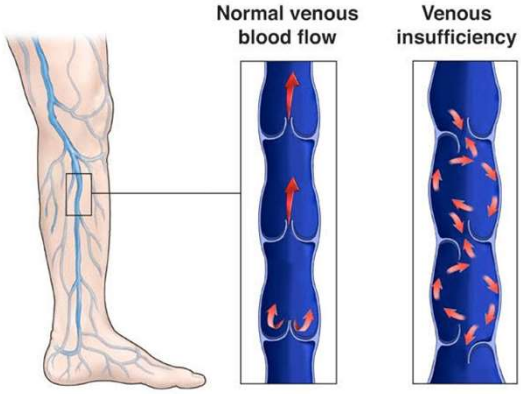
# Venous Insufficiency

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# Superficial Venous Insufficiency Treatment

- **Arkansas Cardiology Vein Center**
  - 501-202-4920 – phone
  - 501-202-4925 – fax

  - Venous US lower extremity superficial reflux study
  - Foam sclerotherapy
  - Phlebectomy
  - Superficial venous ablation

  - Dwight Chrisman MD FACC
  - Jacques Smith APN

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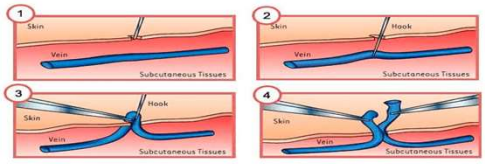
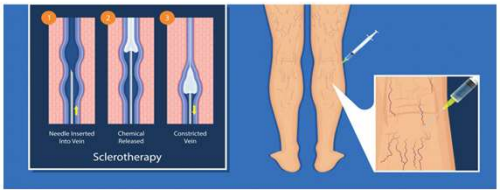
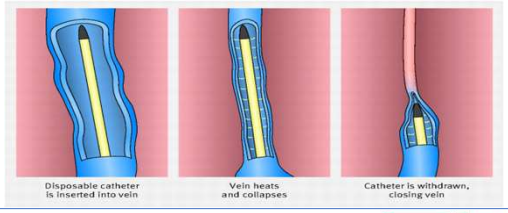
- Stab Phlebectomy




- Foam Sclerotherapy




- Superficial Venous Ablation

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## Quality of Life Impact with Superficial Venous Treatment

- **Mobility improvement**
  - Affects other heath status – ie cardiac status
- **Improved healing**
  - Less chance of deterioration to sepsis
- **Psychological affect**
  - Become more active
  - Become more engaged in health care
- **Discomfort improvement**
  - Less pain medication use
  - Less addition of meds to try to improve edema – ie more diuretics
- **Compliance improvement**
  - Positive feedback to other aspects of their health

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# Thank You

- **F. Dwight Chrisman MD FACC**
  - Interventional Cardiology
  - Peripheral Intervention
  - Vein Center Director

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# Common Therapies that Increase CV Risk

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# Common Therapies that Increase CV Risk

Kapil Yadav, MD, FACC, RPVI
Interventional, Endovascular, & Structural Cardiology
February 24, 2023

## Disclosures

- None

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# Overview

- NSAIDs & Cardiovascular Risk
- QTc Prolonging Medications
- Amphetamine derivatives & stimulants
- Phentermine & anorectics
- Drug-Induced PAH – Aminorex, Fenfluramine, Dexfenfluramine, SSRIs
- Cardiotoxic Chemotherapy
- Testosterone Supplements

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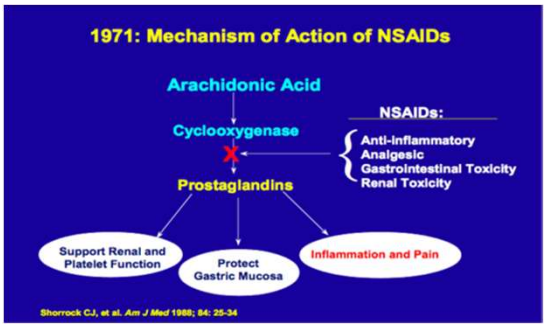
# NSAIDs & CV Risk

- NSAIDs – Most used OTCs
- 54 million elderly patients with arthritis
- NSAIDs Indications – Gout, OA, RA, & MSK pain

Ibuprofen
Naproxen
Naproxen sodium
Indomethacin
Ketorolac (only parenteral NSAID)

Does not include acetaminophen.

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# NSAIDs & CV Risk

- Increased Adverse Cardiovascular Events (MI, CVA)
- Increased Blood Pressure
- Increased CHF Risk
- Increased Bleeding Risk
- Increased Arrythmia Risk

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# NSAIDs & CV Risk

- 24,000 patients in PRECISION trial showed a 5% risk of adverse CV event
- Higher Risk with Higher Dose & Pre-existing CV disease
- NSAIDs have higher CHF Risk
- NSAIDs block protective effect of ARB & ACE-1
- In a Meta analysis – rofecoxib was associated with higher Afib risk

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# NSAIDs – Trials that raised concerns

| STUDY | Participants | RESULT |
|---|---|---|
| VIGOR, 2000 | 8076 | COX-2 -Increased CV risk, no difference in mortality |
| CLASS, 2000 | 8095 | COX-2 -No increase in CV risk |
| Metaanalysis, 2001 | 18000 | COX-2 Increased CV risk |
| TARGET, 2004 | 18325 | COX-2 No difference in CV risk, increase in blood pressure |
| APPROVE, 2005 | 2586 | COX-2 Increased CV risk (thrombotic events, CHF, HTN ) |
| APC+PreSAP | 3800 | COX-2 Increased CV risk |
| Metaanalysis, 2006 | 145343 | Increased CV risk for both COX-2 and tNSAIDs, not naproxen |
| MEDAL, 2009 | 34701 | COX-2 No difference in CV risk |
| Metaanalysis, 2013 | 124513 | Increased CV risk for both COX-2 and tNSAIDs, not naproxen |
| Danish, 2014 | 83677 | Increased CV risk for COX2 and Diclofenac |

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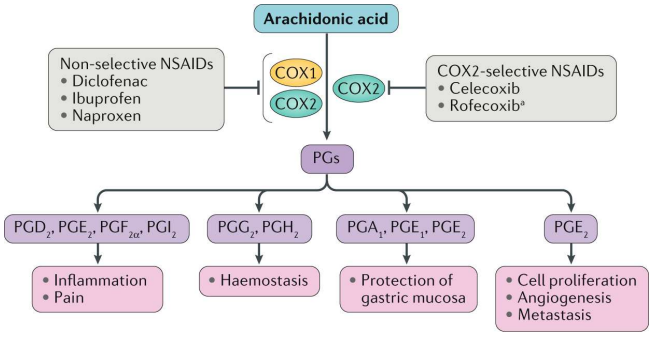
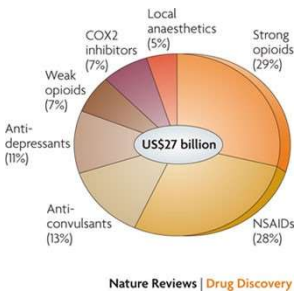
# NSAIDs – Mechanism of Action




Nature Reviews | Drug Discovery

- Most trials are retrospective & non-randomized
- CV risks of MI & death is similar
- (PRECISION Trial)

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| COX 2 inhibitor versus: | No of trials | Events/person years: Allocated COX 2 inhibitor | Events/person years: Allocated NSAID | Rate ratio: COX 2 inhibitor: NSAID |
|---|---|---|---|---|
| **Vascular events** | | | | |
| (a) Naproxen | 42 | 185/16 360 (1.1%/year) | 81/10 978 (0.7%/year) | 1.57 (1.21 to 2.03) P=0.0006 |
| Ibuprofen | 24 | 46/5848 | 47/5160 | |
| Diclofenac | 26 | 101/10 886 | 79/6913 | |
| Other non-naproxen | 7 | 8/166 | 4/274 | |
| (b) Any non-naproxen | 51 | 155/16 900 (0.9%/year) | 130/12 347 (1.1%/year) | 0.88 (0.69 to 1.12) P=0.3 |
| Any NSAID | 91 | 340/33 260 (1.0%/year) | 211/23 325 (0.9%/year) | 1.16 (0.97 to 1.38) P=0.1 |
| Heterogeneity between (a) and (b): $\chi^2$=10.2, df=1, P=0.001 | | | | |
| Between non-naproxen NSAIDs: $\chi^2$=2.6, df=2, P=0.3 | | | | |
| **Myocardial infarction** | | | | |
| (a) Naproxen | 42 | 99/16 360 (0.6%/year) | 30/10 978 (0.3%/year) | 2.04 (1.41 to 2.96) P=0.0002 |
| Ibuprofen | 24 | 21/5848 | 21/5160 | |
| Diclofenac | 26 | 61/10 886 | 32/6913 | |
| Other non-naproxen | 7 | 5/166 | 2/274 | |
| (b) Any non-naproxen | 51 | 87/16 900 (0.5%/year) | 55/12 347 (0.4%/year) | 1.20 (0.85 to 1.68) P=0.3 |
| Any NSAID | 91 | 186/33 260 (0.6%/year) | 85/23 325 (0.4%/year) | 1.53 (1.19 to 1.97) P=0.0009 |
| Heterogeneity between (a) and (b): $\chi^2$=4.3, df=1, P=0.04 | | | | |

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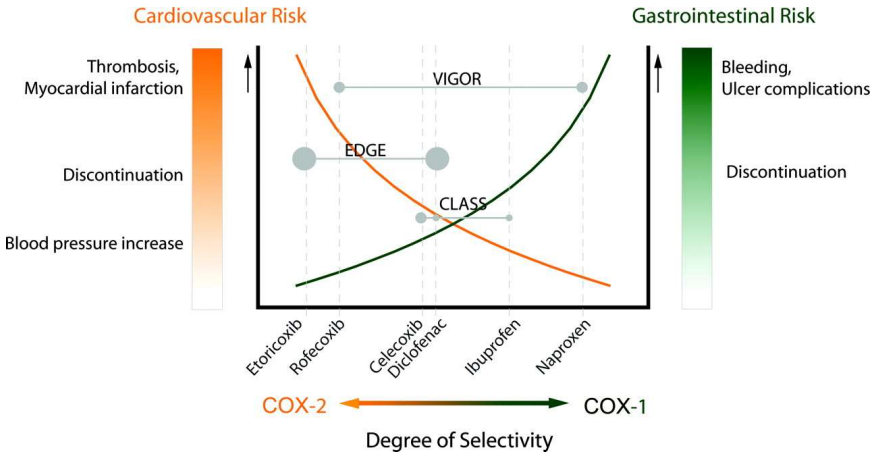


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# VIGOR study – Incidental finding

The New England Journal of Medicine

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

Claire Bombardier, M.D., Loren Laine, M.D., Alise Reicin, M.D., Deborah Shapiro, Dr.P.H., Ruben Burgos-Vargas, M.D., Barry Davis, M.D., Ph.D., Richard Day, M.D., Marcos Bosi Ferraz, M.D., Ph.D., Christopher J. Hawkey, M.D., Marc C. Hochberg, M.D., Tore K. Kvien, M.D., and Thomas J. Schnitzer, M.D., Ph.D., for the VIGOR Study Group

**Patients with Events (Rates per 100 Patient-Years)**

| Event Category | Rofecoxib N=4047 | Naproxen N=4029 | Relative Risk (95% CI) |
|---|---|---|---|
| **Confirmed CV events** | **45 (1.7)** | **19 (0.7)** | **0.42 (0.25, 0.72)** |
| Cardiac events | 28 (1.0) | 10 (0.4) | 0.36 (0.17, 0.74) |
| Cerebrovascular events | 11 (0.4) | 8 (0.3) | 0.73 (0.29, 1.80) |
| Peripheral vascular events | 6 (0.2) | 1 (0.04) | 0.17 (0.00, 1.37) |

*NEJM 2000; 343:1520-8*

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## Gastrointestinal Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis

The CLASS Study: A Randomized Controlled Trial

JAMA® The Journal of the American Medical Association

| | All Patients | | Patients Not Taking Aspirin | |
|---|---|---|---|---|
| Adverse Effects | Celecoxib Group (n = 3987) | NSAID Group (n = 3981) | Celecoxib Group (n = 3154) | NSAID Group (n = 3169) |
| Cardiovascular | | | | |
| Cerebrovascular accident | 5 (0.1) | 10 (0.3) | 3 (<0.1) | 5 (0.2) |
| Myocardial infarction | 10 (0.3) | 11 (0.3) | 3 (<0.1) | 4 (0.1) |
| Angina | 24 (0.6) | 22 (0.6) | 10 (0.3) | 7 (0.2) |
| **Total** | **37** (0.9) | **39** (1.0) | **16** (0.5) | **14** (0.4) |
| Withdrawals | 12 (0.3) | 13 (0.3) | 9 (0.3) | 5 (0.2) |

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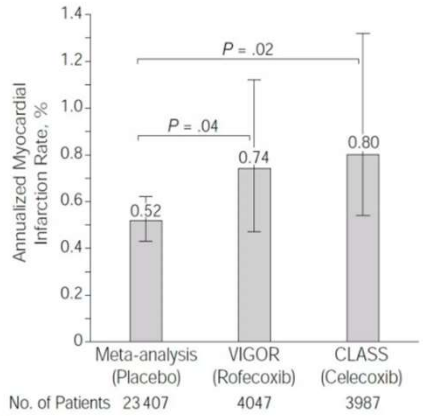


- MI= myocardial infarction

*Mukherjee D , Topol E. Risk of CV events associated with COX2 inhibitors JAMA 2001, 286 954-959*

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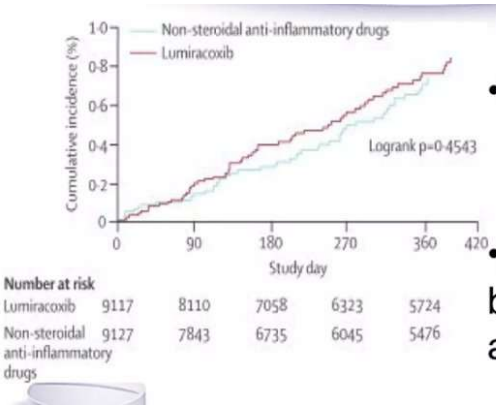
# TARGET Study – LANCET 2004




- Primary endpoints
  - Nonfatal and silent MI, stroke and CV death
- No difference between tNSAIDs and Cox-2

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# 2004 FDA Warning for all NSAIDs

- Public Health Advisory concerning the use of NSAIDs, including COX-2 selective agents
- COX-2 selective agents (rofecoxib, celecoxib, & valdecoxib) may be associated with an increased risk of serious CV events (heart attack and stroke)
- Long-term use of a non-selective NSAID, naproxen may be associated with an increased cardiovascular risk compared to placebo.
- December 23, 2004

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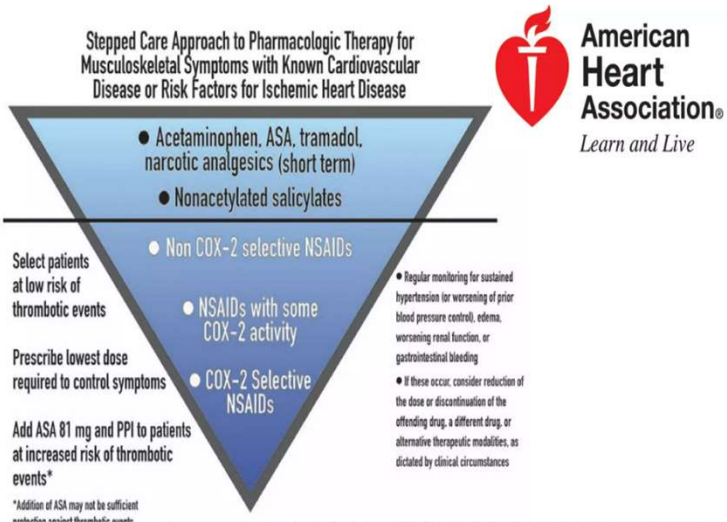


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# ADHD Meds

## Amphetamine Derivatives & Stimulants

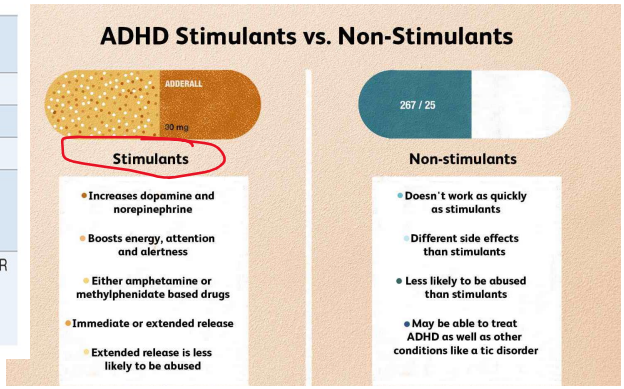
Table 3

FDA-approved medications for ADHD in adults

| Medication | Brand names |
|---|---|
| Amphetamine mixed salts | Adderall XR |
| Atomoxetine | Strattera |
| Dexmethylphenidate | Focalin XR |
| Lisdexamfetamine | Vyvanse |
| Methylphenidate | Aptensio, Concerta, Metadate, Metadate ER, Ritalin |

Amphetamine mixed salts IR and dextroamphetamine ER frequently are used off-label to treat adult ADHD

ADHD: attention-deficit/hyperactivity disorder; ER: extended release; IR: immediate release




- 5% of adults & 10% of children have ADHD
- Adults are more likely to use Rx

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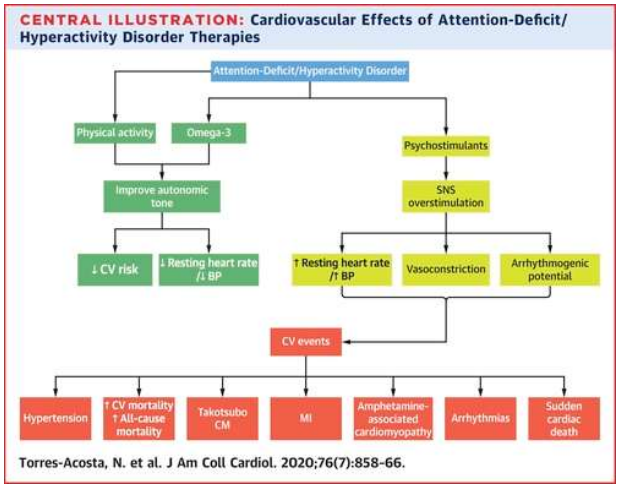
# ADHD Meds & CV Effects




- Increases SBP
- Increases HR
- Increases Arrhythmias
- Increases CHF/TICM
- ?? Increases Death (NHS)

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# ADHD Meds & CV Effects

- A small study showed ADHD Rx was a/w Increase Mean change in BP & HR (+5.3 mmHg SBP)
- Package insert includes caution regarding BP & HR
- Schelleman et al showed a 1.8 fold increase in sudden death
- NHS & FDA has a "black-box" warning describing the cardiovascular risks of stimulant drugs

**Cases of Sudden Death Reported to the FDA Advisory Committee from the AERS Database.***

| Patients | Amphetamines | | Methylphenidate | |
|---|---|---|---|---|
| | Unadjudicated Sudden Deaths | Cases Meeting WHO Criteria for Sudden Death | Unadjudicated Sudden Deaths | Cases Meeting WHO Criteria for Sudden Death |
| | *number* | | | |
| Age, 1–18 yr | | 12 | | 7 |
| Age, >18 yr | | 5 | | 1 |
| Total | 28 | 17 | 16 | 8 |

* Data are from the Adverse Event Reporting System (AERS) of the Food and Drug Administration (FDA).[1] Amphetamines include mixed amphetamine salts (Adderall), amphetamine, biphetamine, and dextroamphetamine. WHO denotes World Health Organization.

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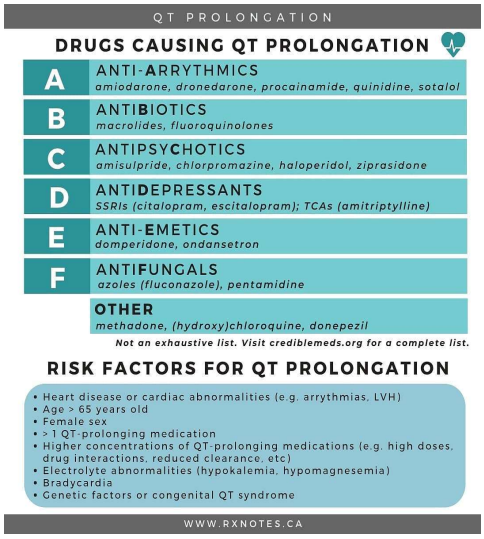
# QTc Prolonging Medications




- QTc – 350 to 450 ms
- Half of RR interval
- Do an EKG prior to prescribing QTc prolonging meds
- Identify high risk patients – CAD, CHF, elderly, electrolyte abnormalities, LQTS

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# Weight Loss Medications & CV Effects

- Phentermine & Anorectics
- IFU Cardiovascular adverse effects – palpitations, tachycardia, and elevated blood pressure.
- Contraindications – PMHx of coronary artery disease, stroke, arrythmias, congestive heart failure and uncontrolled hypertension.

- Increases HR
- Increases Arrythmias
- Increases BP

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# Drug Induced PAH

- PAH – an enigma
- Genetic Predisposition – GADD45a, GALNT13
- Vasoconstrictor meds

| Definite | Likely | Possible |
|---|---|---|
| • Aminorex<br>• Fenfluramine<br>• Dexfenfluramine<br>• Toxic rapeseed oil<br>• Benfluorex<br>• Selective serotonin reuptake inhibitors[a] | • Amphetamines<br>• Dasatinib<br>• L-tryptophan<br>• Methamphetamines | • Cocaine<br>• Phenylpropanolamine<br>• St John's Wort<br>• Amphetamine-like drugs<br>• Interferon α and β<br>• Some chemotherapeutic agents such as alkylating agents (mitomycine C, cyclophosphamide)[b] |

[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors; [b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

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## Cardiotoxic Chemotherapy

- Anthracyclines
- Oxidative stress
- Cardiomyopathy
- VEGF inhibitors
- CV events
- Immunotherapy like pembrolizumab

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## Testosterone Replacement Therapy (TRT)

- FDA label for TRT – Primary & Secondary Hypogonadism. 3 million patients use TRT for these indications
- FDA has a warning label of increased MI & CV risks for TRT
- Widely used off label to improve fatigue, mood, sexual function, etc.
- Labs needed for TRT – FT, LH & FSH

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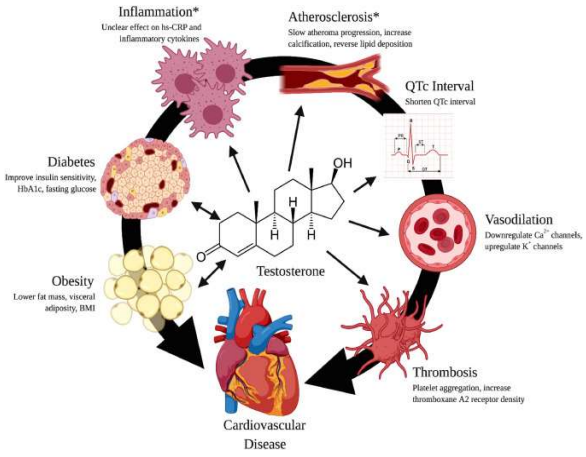
# Testosterone – Positive Effects




- Lowers visceral adiposity
- Improves insulin sensitivity
- Improves Hgba1C
- Shortens QTc
- Improves vasodilation

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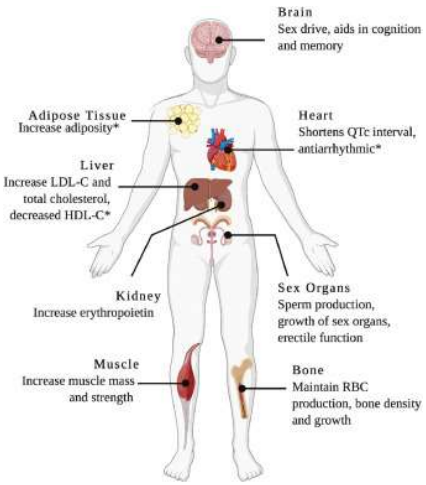
# Testosterone & Cardiac Effects

- Elevated LDL
- Decreased HDL
- Worsens OSA (afib risk)
- Worsens Erythrocytosis (Smokers, Polycythemia, clotting disorders)
- Increased Thrombolic risk & VTE

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## Testosterone & Cardiac Effects - Evidence

- DBRCT was stopped due to high CV deaths in older men (avg age 74).
- Meta Analysis of 51 small studies didn't show increase CV risk.
- Retrospective cohort study shows increase MI within 90 days.
- Despite conflicting data, FDA has a warning label of increased MI & CV risks for TRT.

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## Conclusion

- NSAIDs increase CV risk – MI, CHF and arrythmias.
- Multiple trials and MAs confirmed the adverse CV effects.
- CV risk was dose dependent – use lowest effective dose @ lowest frequency.
- Using AHA stepped care approach for NSAIDs use in all elderly patients.
- TRT is appropriate in patients with hypogonadism.
- TRT has a risk of MI and other CV events in high-risk patients.
- ADHD med reduction if clinically significant HTN & tachycardia noted.
- SSRIs, Macrolides, fluoroquinolones & antifungals can increase QTc interval and cause Torsade de Pointes.
- OTC supplements especially stimulants like ginseng can increase BP.
- Weight loss medications like phentermine
- Pseudoephedrine can cause hypertension with use.

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# Sports Cardiology

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# Sports Cardiology

Jay D. Geoghagan, MD FACC

February 24, 2023

## Disclosures

- None

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# Overview

- Most sports-related deaths are cardiovascular in nature.
- Etiologies encompass the entire spectrum of cardiovascular disease.
- Most events are in individuals without previous CV diagnoses.
- Besides young athletes, we must consider:
  - Increased numbers of those who are physically active both with and without prior CV disease
  - Tactical athletes
  - "Masters" athletes
  - Post Covid

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# A Definition

- **Sports Cardiology** is a new and rapidly evolving cardiological sub-specialty, whose **main objectives** are the **assessment of sports-related cardiovascular risks**, with particular reference to **concealed diseases** that may **predispose athletes to SCD**, and the differential diagnosis between the **physiologic changes** induced by regular exercise on the heart (athlete's heart) and **pathological changes** of cardiomyopathies. Sports Cardiology has the task of designing and implementing **preventive strategies**, mostly relying on pre-participation cardiovascular **screening** aimed to identify at-risk athletes and **implementation of resuscitation programs** for management of unpredictable cardiac arrest occurring in the athletic field.

International Journal of Cardiology, 2023-01-01, Volume 370, Pages 472-475

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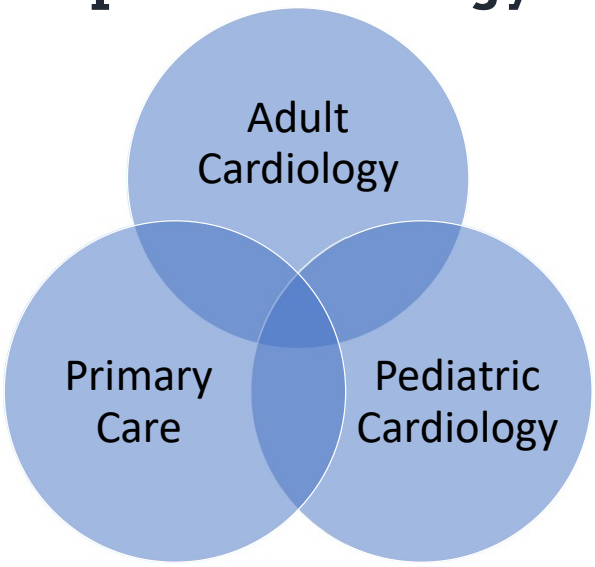
# Sports Cardiology

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# Sports Cardiology

- Because this topic is so broad, the American College of Cardiology has a three-day symposium on this topic every year.
- Therefore, we will restrict the focus:
  - Preparticipation
  - Masters athletes
  - Tactical athletes
  - Post-Covid

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# Preparticipation Screening

- What is the risk of sudden death in athletes?
- Is screening effective?
- Who should we screen?
- Are there any guidelines?

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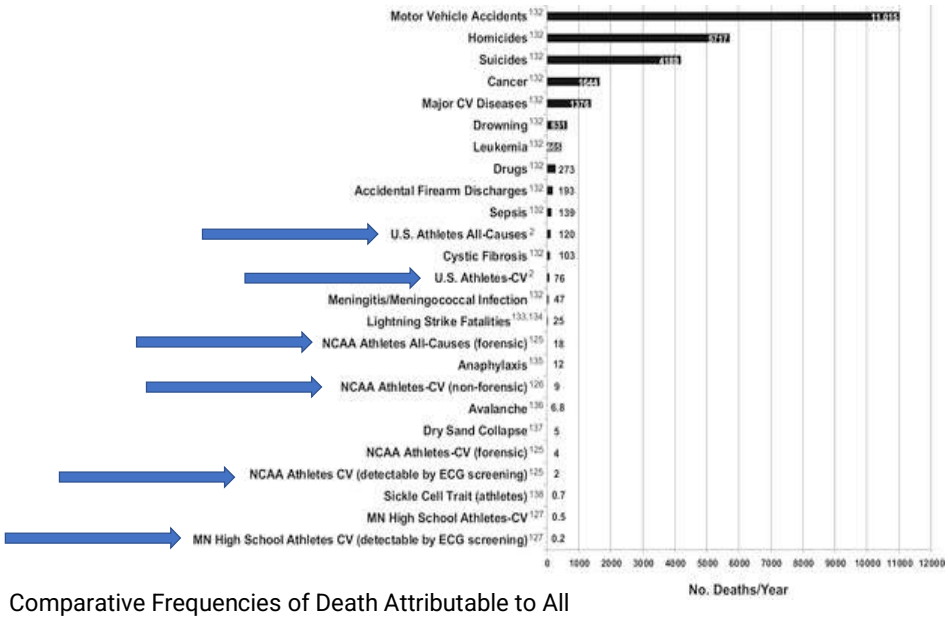


Comparative Frequencies of Death Attributable to All Causes in Young Individuals Aged <25 Years

**Barry J. Maron et al. *J Am Coll Cardiol* 2014; 64:1479-1514.**

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

# Sports Cardiology

- The incidence of SCD in athletes increases with age and is greater in men.
- In apparently healthy adults (>35 years) the estimated rate of SCD ranges from 1:15,000 to 1:50,000.
- In young (≤35 years) competitive athletes the incidence of fatal events is significantly lower, 0.4–3:100,000 participants per year.
- Adolescent and young adults involved in sports activity have a ~3 times greater risk of SCD than their non-athletic counterparts.
- However, sports is not *itself* the cause of the enhanced mortality; rather, it acts as a trigger of cardiac arrest in susceptible athletes

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# Sports Cardiology

- Most common mechanism of cardiac arrest during sports activity is abrupt, adrenergic-dependent ventricular fibrillation because of an underlying cardiovascular disorder.
- The cause of SCD reflects the age of participants:
  - In middle-aged/senior athletes --->atherosclerotic coronary artery disease

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## Sports Cardiology

- In young competitive athletes (age ≤ 35 years)
  - Hypertrophic cardiomyopathy
  - Arrhythmogenic cardiomyopathy
  - Congenital anomalies of coronary arteries
  - Aortic rupture in Marfan's syndrome
  - Myocarditis (either acute myocardial inflammation or post-inflammatory myocardial scar)
  - Valvular diseases.

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## Sports Cardiology

- Many athletes experiencing SCD have no evidence of structural heart disease

- The cause of arrhythmic death is a primary electrical cardiac condition.
  - Inherited cardiac ion channel defects (channelopathies)
    - Long QT syndrome
    - Catecholaminergic polymorphic ventricular tachycardia
    - Brugada syndrome, or idiopathic ventricular fibrillation

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# Sports Cardiology

- In young athletes, screening beyond a History and Physical is controversial.
- A screening ECG is the main point of controversy.
  - Strongly endorsed by many experts in the international community.
  - Evidence has varied but most of the favorable evidence has come from select populations in smaller countries, e.g., Italy and Israel.
- Main concerns involve:
  - Accurate interpretation of ECGs in athletes
  - Cost
- In older athletes, ECGs would generally be appropriate.
- Symptomatic athletes are evaluated as usual.

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# Sports Cardiology

- The American Academy of Pediatrics has a 5th edition monograph (that they will sell you) on preparticipation evaluation.
- The American Heart Association (AHA) has a 14-element screening recommendation.

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# Sports Cardiology

**TABLE 1** The 14-Element AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes

| |
|---|
| Medical history* |
| Personal history |
| 1. Chest pain/discomfort/tightness/pressure related to exertion |
| 2. Unexplained syncope/near-syncope† |
| 3. Excessive and unexplained dyspnea/fatigue or palpitations, associated with exercise |
| 4. Prior recognition of a heart murmur |
| 5. Elevated systemic blood pressure |
| 6. Prior restriction from participation in sports |
| 7. Prior testing for the heart, ordered by a physician |
| Family history |
| 8. Premature death (sudden and unexpected, or otherwise) before 50 y of age attributable to heart disease in ≥1 relative |
| 9. Disability from heart disease in close relative <50 y of age |
| 10. Hypertrophic or dilated cardiomyopathy, long-QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac conditions in family members |
| Physical examination |
| 11. Heart murmur‡ |
| 12. Femoral pulses to exclude aortic coarctation |
| 13. Physical stigmata of Marfan syndrome |
| 14. Brachial artery blood pressure (sitting position)§ |

AHA indicates American Heart Association. *Parental verification is recommended for high school and middle school athletes. †Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion. ‡Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction. §Preferably taken in both arms. Modified with permission from Maron et al. (3). Copyright © 2007, American Heart Association, Inc.

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# Sports Cardiology

- Masters Athletes
  - Recreational and competitive athletes over 35 yo
  - Exercise > 5 hours weekly with emphasis on "goals"
  - Many have risk factors or known CV disease
  - 4 main questions about endurance sports and CV disease
    - Arrhythmias?
    - Cardiomyopathy?
    - Aortopathy?
    - Coronary disease?

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# Sports Cardiology

- Masters Athletes
  - Arrhythmias?
    - Strongest association with endurance sports is atrial fibrillation
    - Cardiac remodeling, inflammation, genetics, lifestyle
  - Cardiomyopathy?
    - Ventricular remodeling, alterations in function and relaxation
  - Aortopathy?
    - Ongoing longitudinal studies about athlete's aorta

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# Sports Cardiology

- Masters Athletes
  - Coronary disease?
    - Increased coronary calcium seen in marathon runners
    - Underappreciated traditional risk factors
      - Unhealthy diet
      - Genetics
      - Lifestyle choices in younger life (roaring 20s)
      - Viral infections

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# Sports Cardiology

- Tactical Athletes
  - Military, Law Enforcement, Firefighters, Emergency Response Providers
  - High demand for physical fitness
  - Mentally and physically demanding occupational tasks often in extreme conditions
  - Increased CV risk on duty rather than off duty
  - Focus is on service and not competition
  - Testing, treatment, and return to duty may be governed by regulations in addition to medical guidelines

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# Sports Cardiology

- **COVID-19**
- Young athletes have a low incidence of cardiac involvement and risk of clinic events with COVID-19 infection .
- CMR is a valuable tool in diagnosing myocarditis but should not be used in screening asymptomatic athletes or those with low pre-test clinical probability of myocarditis.
- Return to play after COVID-19 infection should be guided by symptoms. Those with cardiopulmonary symptoms or more severe illness warrant cardiac evaluation.
- The risk of COVID-19 vaccine associated myocarditis is low but present in young males and highest after the second mRNA vaccine dose. Most patients (~90%) have a benign clinical course.
- There appears to be a clear benefit to vaccination in avoiding hospitalization and intensive care unit stay among young individuals.

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# Sports Cardiology - Summary

- SCD is tragic, especially in a young athlete.
- Screening beyond a history and physical is controversial.
- Return to play decisions are often complex.
- Masters athletes need to focus on traditional risk factors.
- Tactical athletes have different stressors than other athletes.
- Return to play after viral infections should be guided by symptoms.
- Bystander CPR, AEDs, and emergency action plans are vitally important.

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# Sports Cardiology - References


- Maron B, Friedman R, Kligfield P, et al. Assessment of the 12-Lead Electrocardiogram as a Screening Test for Detection of Cardiovascular Disease in Healthy General Populations of Young People (12–25 Years of Age). *J Am Coll Cardiol.* 2014 Oct, 64 (14) 1479–1514.
- Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 15: Legal Aspects of Medical Eligibility and Disqualification Recommendations Matthew J. Mitten, JD, Chair, Douglas P. Zipes, MD, FAHA, MACC, Barry J. Maron, MD, FACC, and William J. Bryant, JDand on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and the American College of Cardiologyand on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and the American College of Cardiology
- International Journal of Cardiology, 2023-01-01, Volume 370, Pages 472-475,
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