HOCM My Heart Is So Thick?

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Hypertrophic Cardiomyopathy

Disclosures

- None

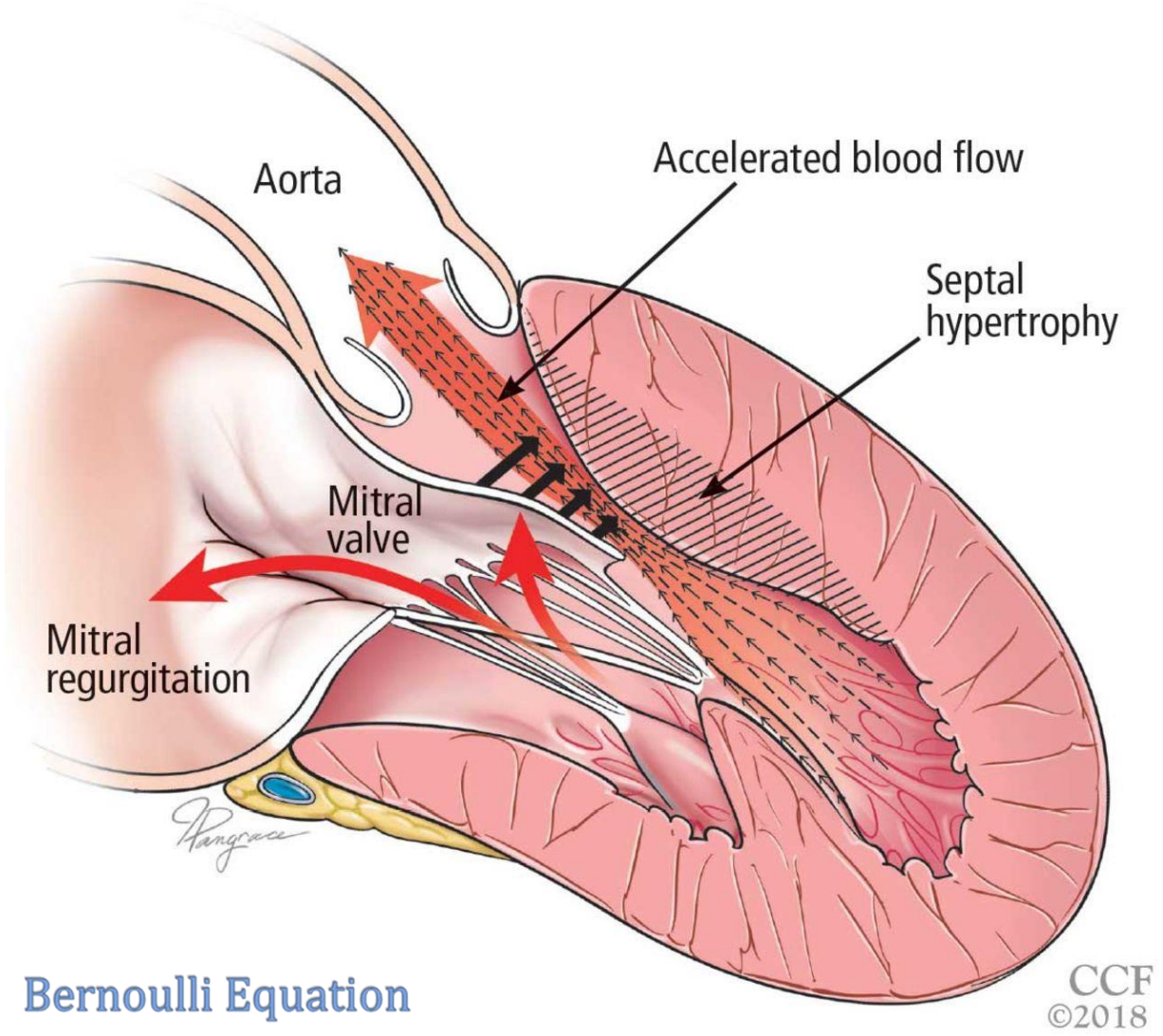
Definitions

- Left Ventricular Hypertrophy (LVH)
  - Left Ventricular Wall Thickening most commonly due to systemic process (HTN, Athletes Heart)
- Hypertrophic Cardiomyopathy (HCM)
  - Left Ventricular Wall thickening (>15mm) in absence of other identifiable cause
- Hypertrophic Obstructive Cardiomyopathy (HOCM)
  - Cardiac thickening with Septal hypertrophy and abnormal mitral valve function
  - Resulting in Left Ventricular Outflow Tract (LVOT) obstruction (>30mmHg)
  - Occurs in up to 70% of patients with HCM

LVOT Obstruction

- Septal hypertrophy
- Systolic Anterior Motion (SAM) of Mitral Valve
  - Venturi effect "sucks" anterior leaflet/chordae into outflow tract
  - Worsens obstruction and Mitral Regurgitation (late systole)

- Increases with:
  - Decreased Preload
    - Dehydration, Valsalva, Exercise
  - Decreased afterload
  - Increased Contractility



Bernoulli Equation

Conservation of Energy Principle

Relationship between Velocity and Pressure

$$\Delta P = \tfrac{1}{2}\rho(V_2^2 - V_1^2) + \int_1^2 \frac{dv}{dt} \times ds + R(v)$$

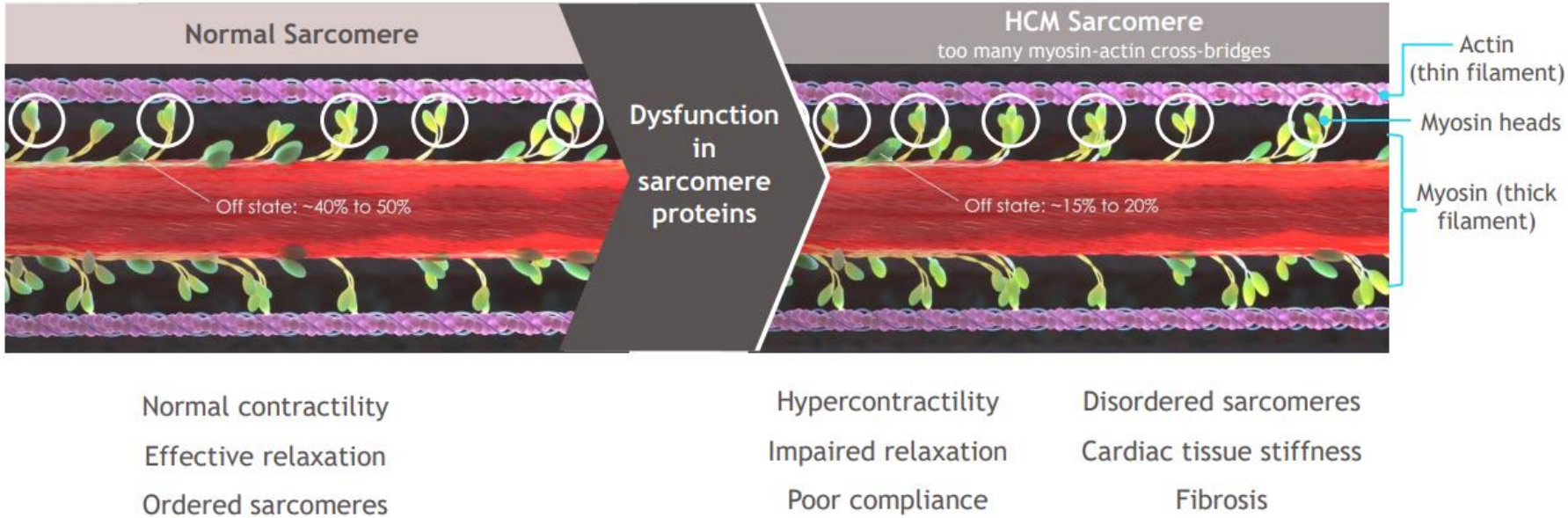
convective acceleration | flow acceleration | viscous friction

Modified Bernoulli's Equation $\Delta P = 4 (v_2^2 - v_1^2)$

Simplified Bernoulli's Equation $\Delta P = 4 v^2$

Pathophysiology

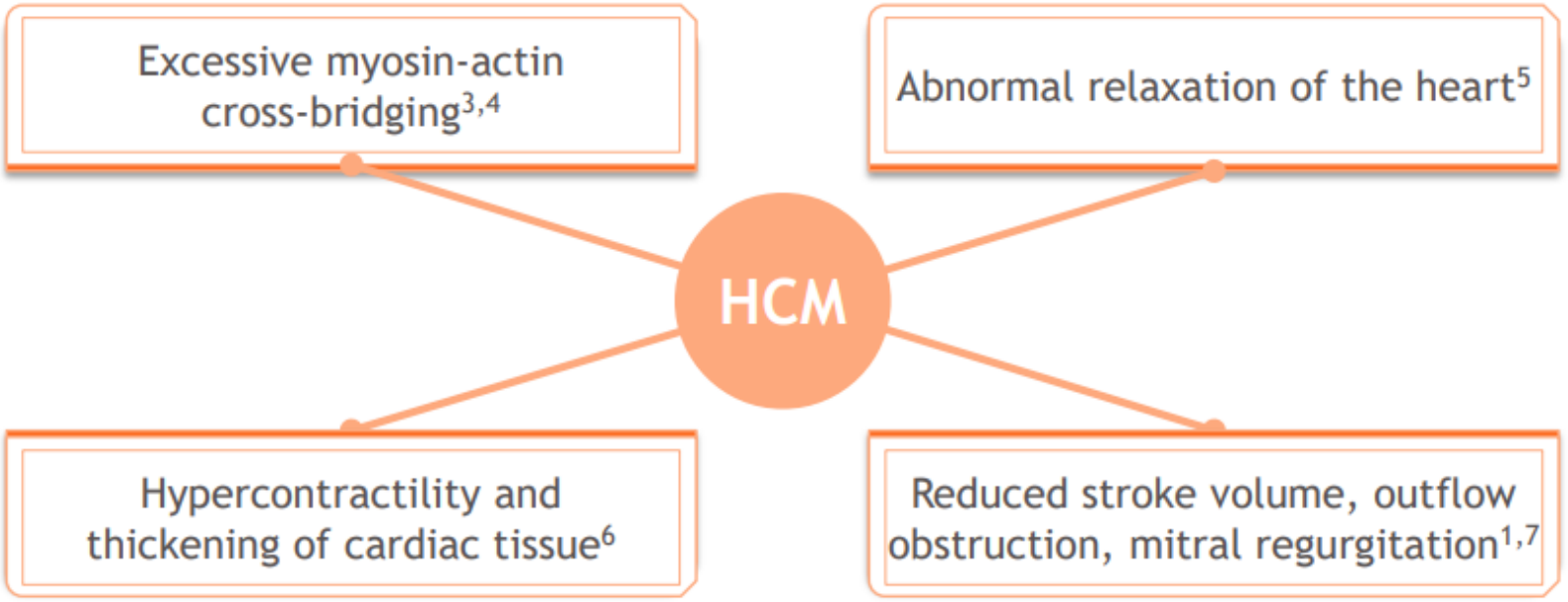
- Primarily a Disorder of the Sarcomere caused by abnormal intracellular calcium metabolism and increased actin-myosin cross-bridges
- Genetic Causes
  - Autosomal Dominant
  - Beta-Myosin heavy chain gene on Cr14
  - Mutations of genes for sarcomeric proteins



HCM, hypertrophic cardiomyopathy.

1. Spudich JA et al. *Pflugers Arch* 2019;471:701-717. 2. Trivedi DV et al. *Biophys Rev* 2018;10:27-48. 3. Nag S et al. *Nat Struct Mol Biol* 2017;24:525-533. 4. Alamo L et al. *eLife* 2017;6:e24634. 5. Sequeira V et al. *FEBS Lett* 2019;593:1616-1626.

Pathophysiology and Symptoms



HCM symptoms[8,9]

- Dyspnea
- Fatigue
- Chest pain
- Palpitations
- Syncope

HCM complications[1,2]

- Heart failure
- Arrhythmias
- Stroke
- Sudden cardiac death

In the early stages of cardiac remodeling or even in the presence of cardiomyopathy, patients with HCM can be asymptomatic or minimally symptomatic[10,11]

HCM, hypertrophic cardiomyopathy.

1. Mayo Clinic. Accessed April 22, 2021. https://www.mayoclinic.org/diseases-conditions/hypertrophic-cardiomyopathy/symptoms-causes/syc-20350198. 2. Maron BJ et al. *Lancet* 2013;381:242-255. 3. Nag S et al. *Nat Struct Mol Biol* 2017;24:525-533. 4. Kronert WA et al. *eLife* 2018;7:e38064. 5. Ommen SR et al. *J Am Coll Cardiol* 2020;76:e159-e240. 6. Cohn R et al. *Stem Cell Reports* 2019;12:71-83. 7. Nagueh SF et al. *J Am Soc Echocardiogr* 2011;24:473-498. 8. Wexler RK et al. *Am Fam Physician* 2009;79:778-784. 9. Marian AJ, Braunwald E. *Circ Res* 2017;121:749-770. 10. Elliott PM et al. *Eur Heart J* 2014;35:2733-2779. 11. Marian AJ et al. *Circ Res* 2017;121:749-770.

Clinical Presentation

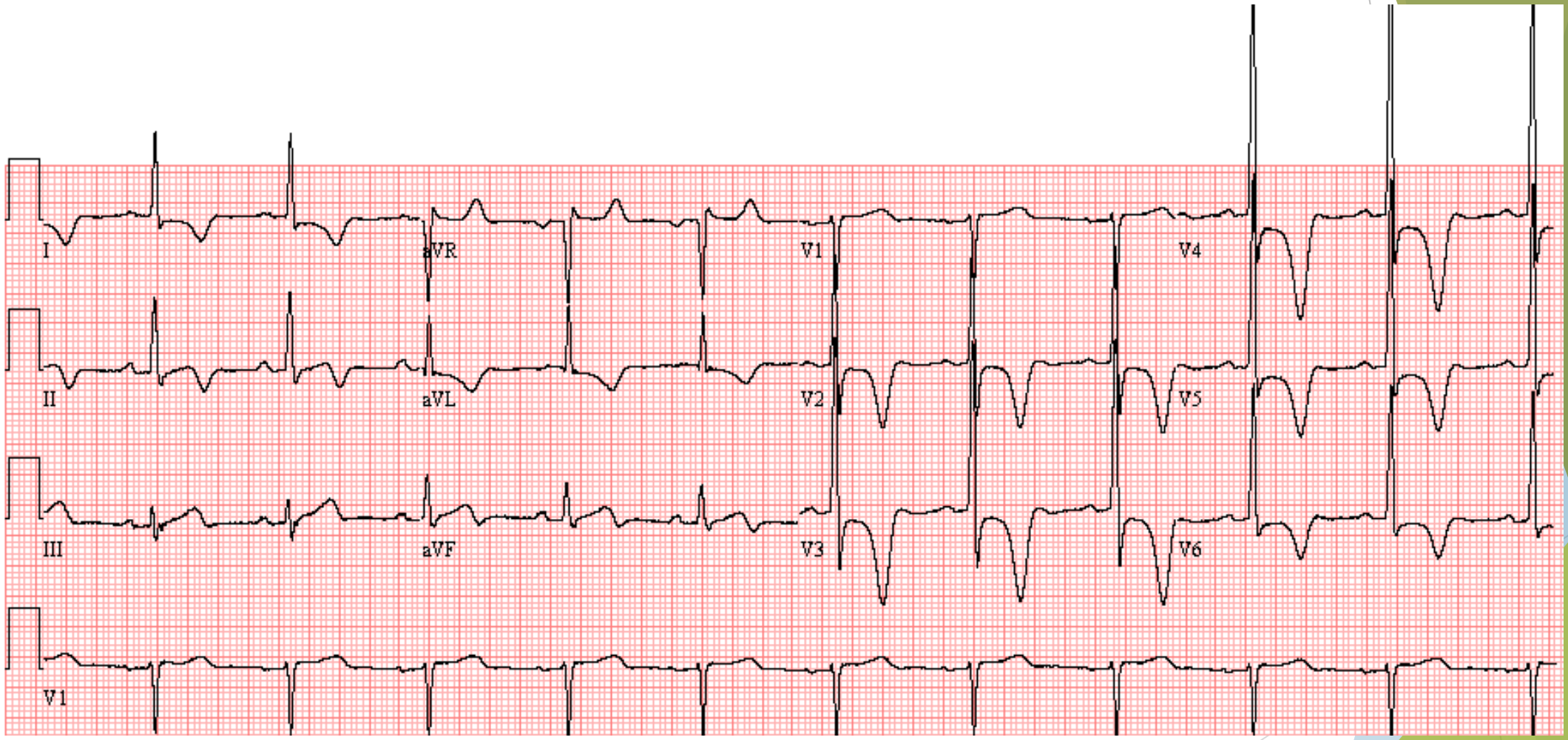
- Symptoms
  - DOE / CHF
  - Angina
  - Presyncope/Syncope
  - Palpitations
- Any age
- Sudden Cardiac Death
- Leading cause of death in competitive athletes
- Can be asymptomatic and found incidentally on echo/exam

Diagnosis

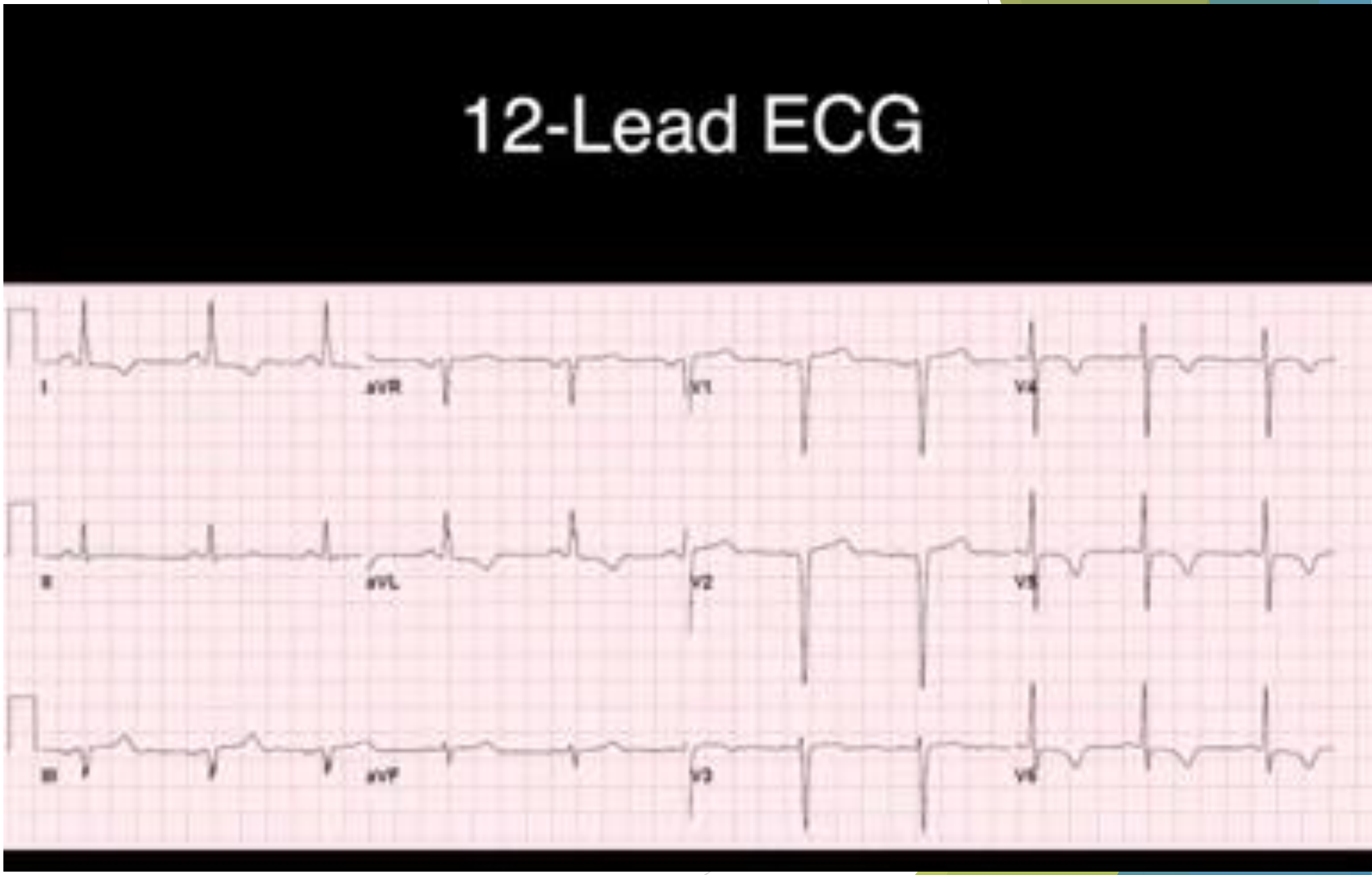
- Clinical exam
  - Crescendo-Decrescendo Systolic Murmur, lower left sternal border +- S4
  - Increases with Valsalva (reduces preload), Decreases with Squatting/Hand grip (increases LV volume)
- EKG
- ECHO
- Cardiac MRI

- Angiography
- Exercise Stress ECHO
- Genetic Testing/Family Screening

EKG



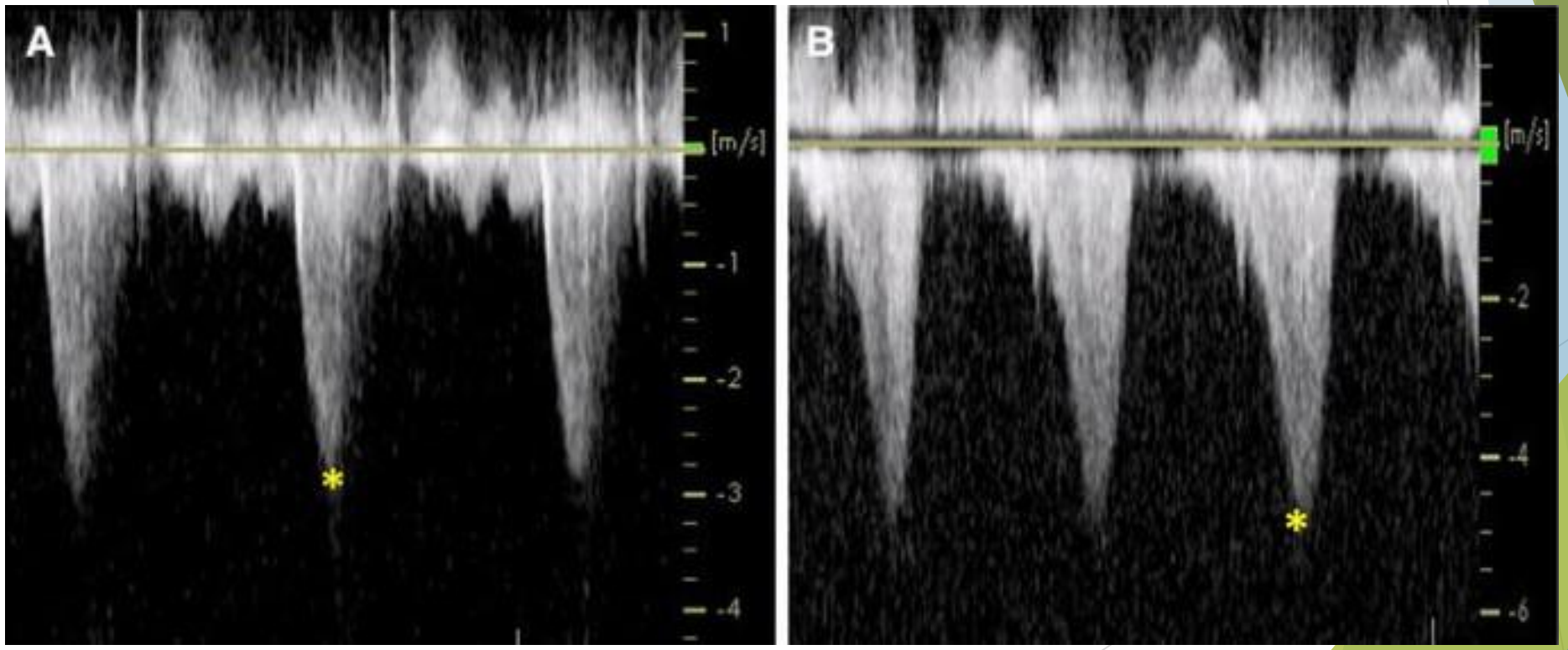
ECHO



- https://www.youtube.com/watch?v=VgSNwupg6nM
- Joseph Menardi

Doppler

- Valsalva decreased LV filling/preload -> small LV -> worsening the obstruction



Other Considerations

- Uncontrolled Hypertension
- Athletes Heart
  - No abnormal diastolic parameters
  - Improves with discontinuing exercise
- Amyloidosis
  - Can cause LVH
  - Low voltage on EKG

Prognosis

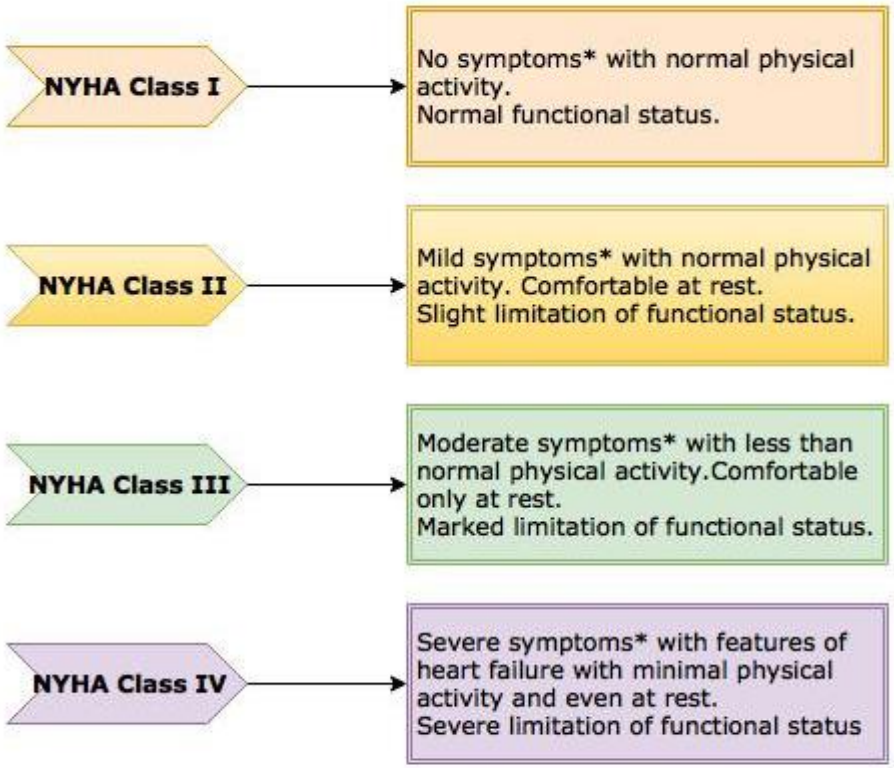
- Mortality 3% per year
- 6-8% with history of arrhythmia/NSVT
- Progressive heart failure

Management

- Screening of 1st degree relatives
  - ECHO and genetic counselling
- Avoid Competitive Sports
- Education regarding dehydration, medications, exercise

- Monitoring
  - Office visits
  - Yearly Holter
  - ECHO

NYHA Classifications



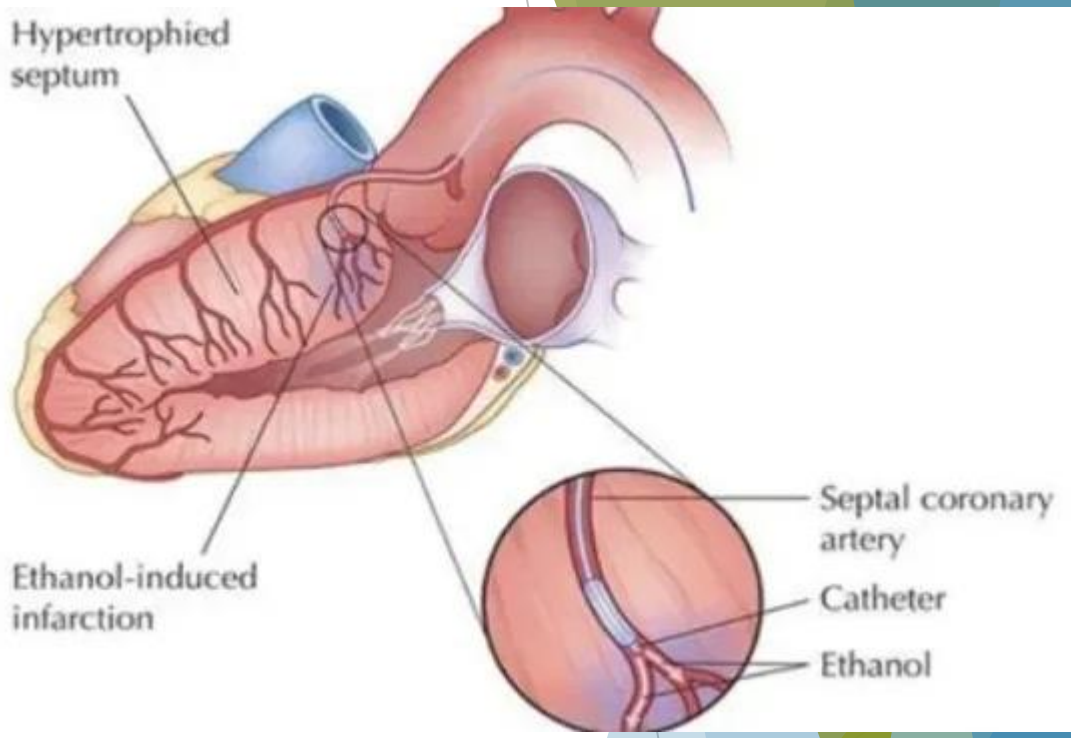
Symptoms - Fatigue, palpitations, chest pain, dyspnea, syncope

Medications

- Beta-Blockers and Calcium Channel Blockers
  - Slow HR -> longer diastolic filling time -> reduced myocardial consumption -> reduced ischemia and LVOT obstruction
- Disopyramide
  - Class 1 antiarrhythmic + strong negative inotrope
- NEW - Mavacamten (Camzyos)
  - Cardiac Myosin modulator

Non-responders

- Surgery
  - Myomectomy/myectomy
  - +- Mitral Valve Surgery
  - Class 1 evidence if persistent NYHA Class III-IV or need for other surgery
- Alcohol Septal Ablation
  - Controlled MI in 1st septal artery to reduce basal ventricular septum size and gradient
- DDD pacemaker
  - RV apical pacing/AV synchrony -> abnormal septal contraction affecting LVOT parameters
- Advanced Heart Failure / Heart Transplant



https://www.heartplace.com/service/alcohol-septal-ablation

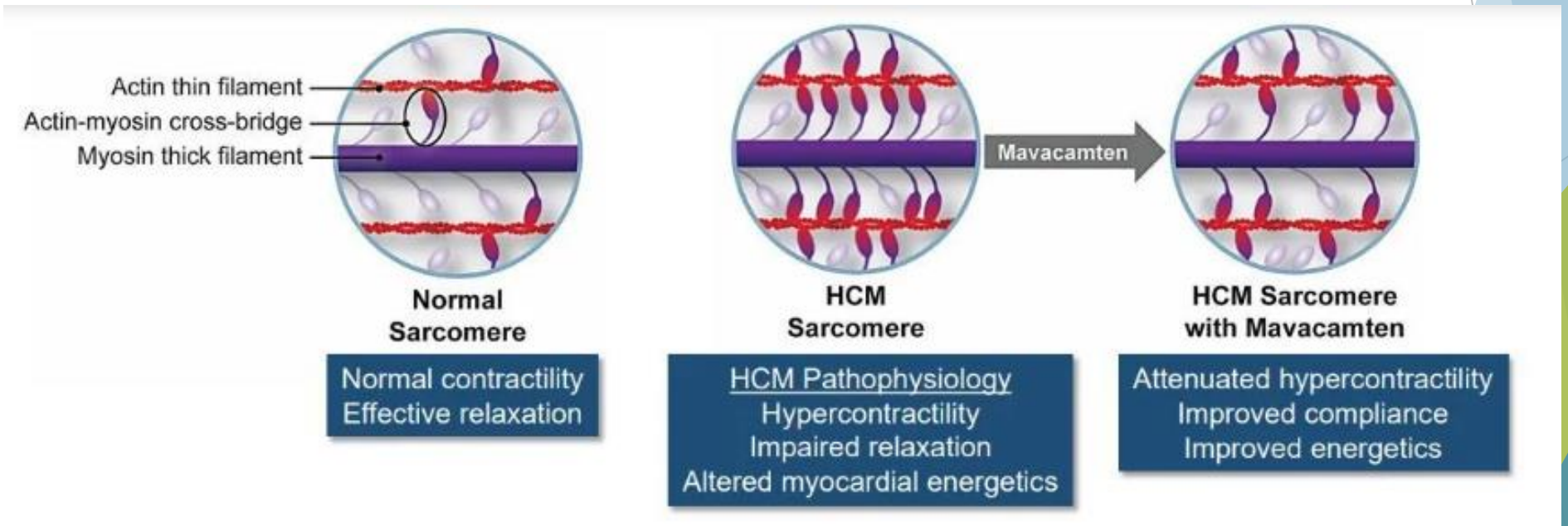
Arrhythmias and Risk of SCD

- Sustained Ventricular Tachycardia/Fibrillation
- Increased risk of atrial fibrillation
  - Patients are dependent on atrial kick for ventricular filling and atrial fibrillation can reduce cardiac output by up to 40% - symptomatic

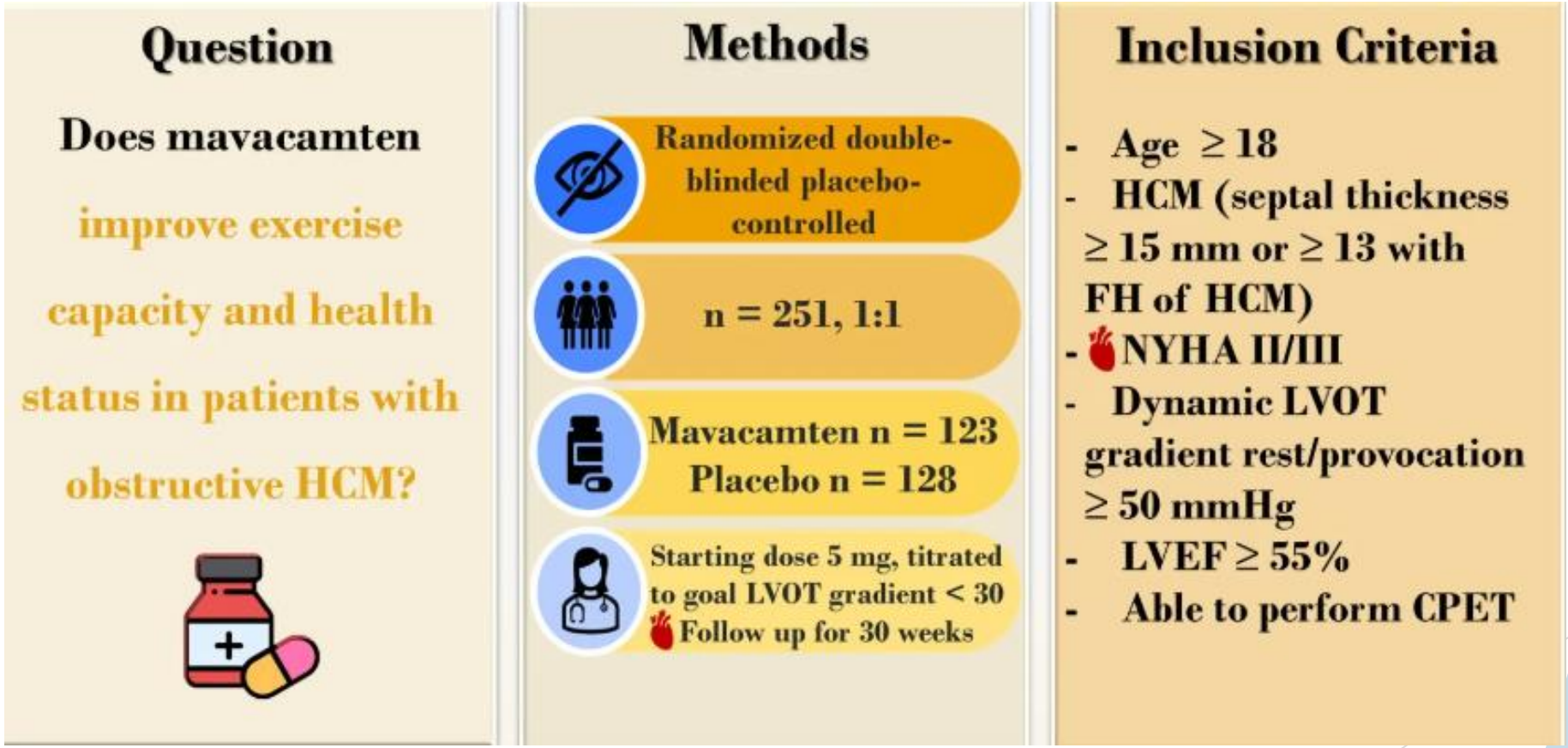
- AICD - Class 1
  - HCM with documented cardiac arrest/sustained VT
- AICD - Class 2a
  - SCD in 1 or more first degree relative with HCM
  - LVH >30mm in any LV segment
  - Hx of Syncope thought to be related to arrhythmia
  - LV apical aneurysm with scar/LGE on cMRI
  - LV dysfunction <50%

Mavacamten (Camzyos)

- Mechanism of Action
  - Cardiac Myosin Inhibitor
  - Stabilizes relaxed state reducing cross-bridge formation
  - Inhibits ATPase activity in myosin reducing contractility



Explorer-HCM (2020)

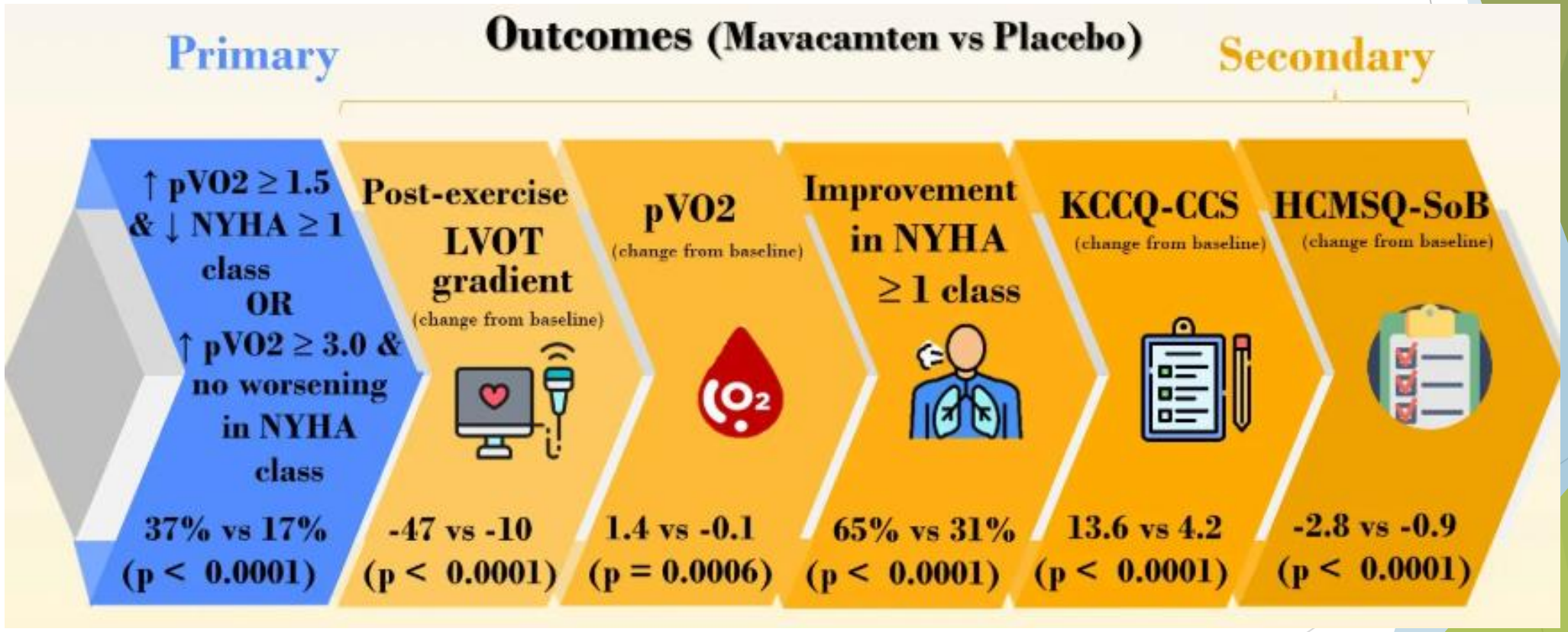


Credit: Rawan Amir – Cardionerds.com

Select baseline patient characteristics in EXPLORER-HCM[1,2]

Select baseline patient characteristics		
Values in the table are mean ± SD, n (%)	**CAMZYOS** (n=123)	**Placebo** (n=128)
Age, mean (SD), years	59 (12.2)	59 (11.8)
Women, n (%)	57 (46)	45 (35)
Race, n (%)		
White	115 (94)	114 (89)
Black or African American	1 (1)	5 (4)
American Indian or Alaska Native	0	1 (1)
Asian	4 (3)	2 (2)
Unknown	3 (2)	6 (5)
Background HCM treatment, n (%)		
Beta blocker Calcium channel blocker[†]	94 (76) 25 (20)	95 (74) 17 (13)
NYHA class, n (%)		
Class II Class III	88 (72) 35 (28)	95 (74) 33 (26)
pVO_2 mean (SD), mL/kg/min	18.9 (4.9)	19.9 (4.9)
LVOT gradient at baseline, mean (SD), mmHg		
Valsalva Postexercise[‡]	72 (32) 86 (34)	74 (32) 84 (36)
LVEF, mean (SD), (%)	74 (6)	74 (6)
Critical cardiac history		
Atrial fibrillation, n (%)	12 (10)	23 (18)
Implantable cardioverter-defibrillator, n (%)	27 (22)	29 (23)
Prior invasive SRT, n (%)	11 (9)	8 (6)

Explorer-HCM



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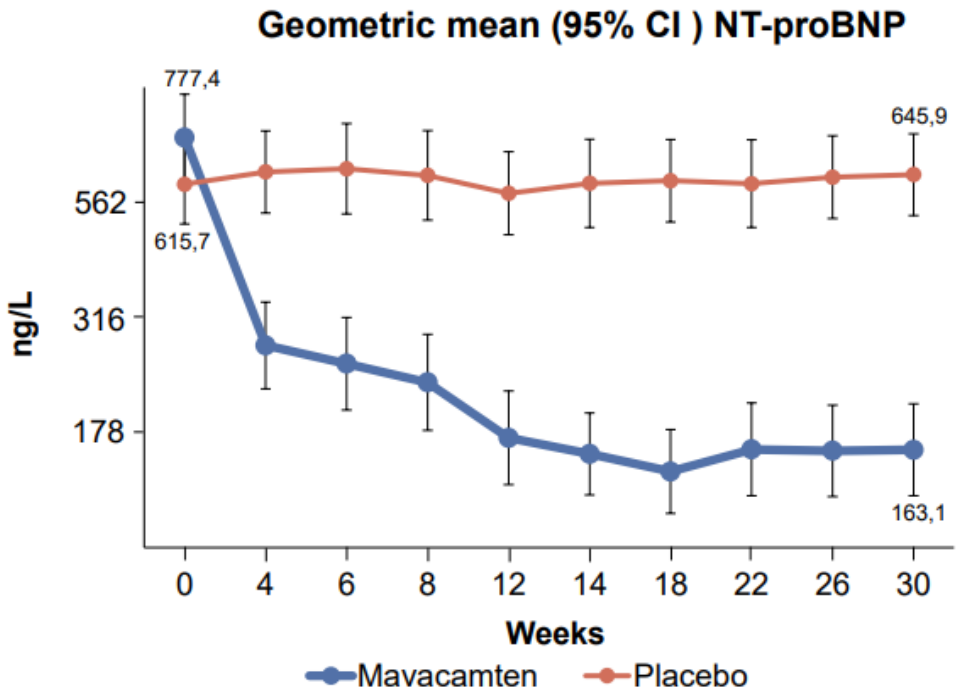
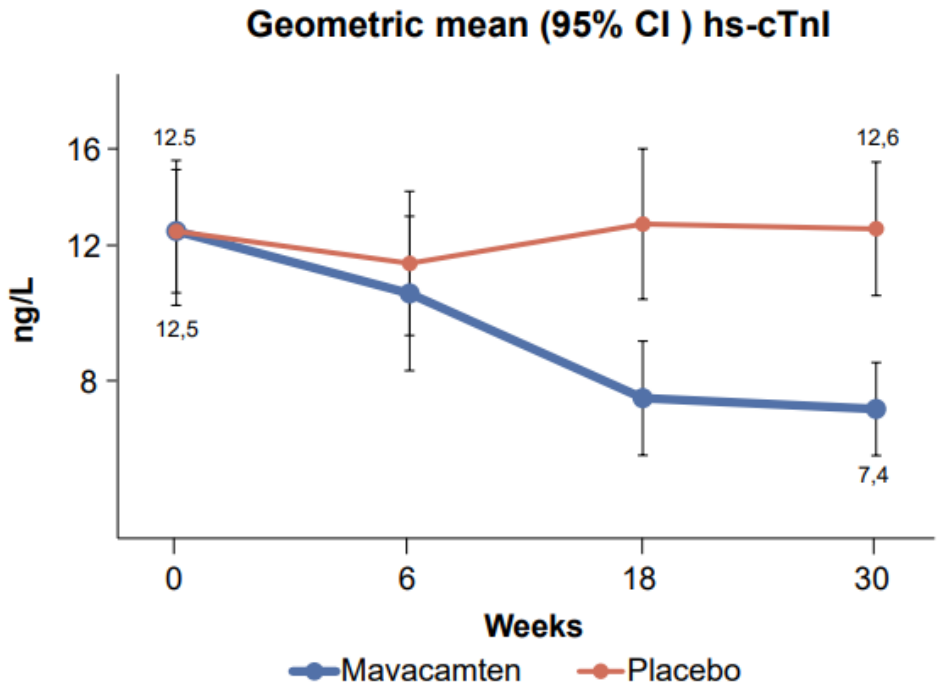
Outcomes

EXPLORER-HCM

Exploratory Endpoints: Cardiac Biomarkers





Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial
Olivotto, IacopoBartunek, Jozef et al.
The Lancet, Volume 396, Issue 10253, 759 - 769

Safety

Adverse events Preferred term	Mavacamten (N = 123)	Placebo (N = 128)
Patients with ≥1 TEAEs, n (%)	108 (87.8)	101 (78.9)
Total number of SAEs	11	20
Patients with ≥1 SAE, n (%)	10 (8.1)	11 (8.6)
Atrial fibrillation	2 (1.6)	4 (3.1)
Syncope	2 (1.6)	1 (0.8)
Stress cardiomyopathy	2 (1.6)	0
Cardiac failure congestive	0	1 (0.8)
Sudden death	0	1 (0.8)

- There was a 97% completion rate through 30 weeks of treatment
- 3 patients discontinued due to AEs: 2 on mavacamten, 1 on placebo
  - No patients withdrew due to reduced LVEF or symptoms of heart failure

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Valor-HCM (2024)

Question

Would adding mavacamten to maximally-tolerated medical therapy allow severely symptomatic oHCM patients to improve so that they no longer qualify for or choose not to undergo septal reduction therapy (SRT)?

Methods

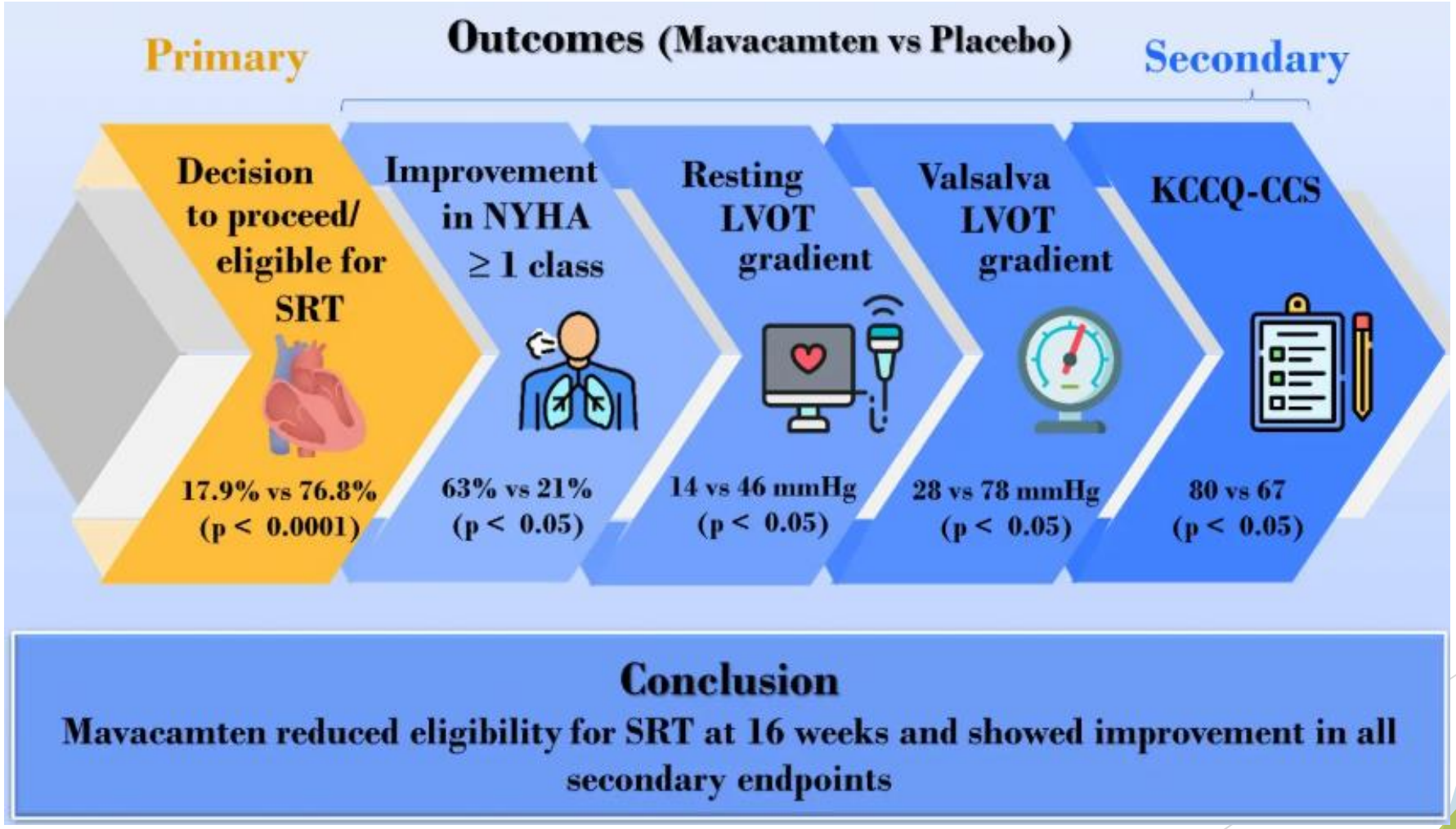
- Randomized double-blinded placebo-controlled
- n = 112, 1:1
- Mavacamten n = 56
  Placebo n = 56
- Starting dose 5 mg, titrated based on LVEF and LVOT
  Follow up for 16 weeks

Inclusion Criteria

- Age ≥ 18 years
- HCM (septal thickness ≥ 15 mm or ≥ 13 with FH of HCM), LVEF ≥ 60%
- Severe symptoms despite medical therapy (including disopyramide)
- NYHA III/IV or II with syncope
- Dynamic LVOT gradient rest/provocation ≥ 50 mmHg
- Referred for SRT within 12 months

Credit: Rawan Amir – Cardionerds.com

Valor-HCM



Credit: Rawan Amir – Cardionerds.com

So Now What?

- 59M
- HOCM with NYHA Class III symptoms
  - DOE, dizziness with exercise
- Septal LV thickness 1.8cm with peak Gradient 84mmHg
- No arrhythmias
- Maxed on Metoprolol Succinate 100mg PO OD
- BP 134/92, HR 52bpm
- Negative Genetic Testing

- Would you like to go for major cardiac surgery…….?
  - …….or try a new once a day oral capsule medication?

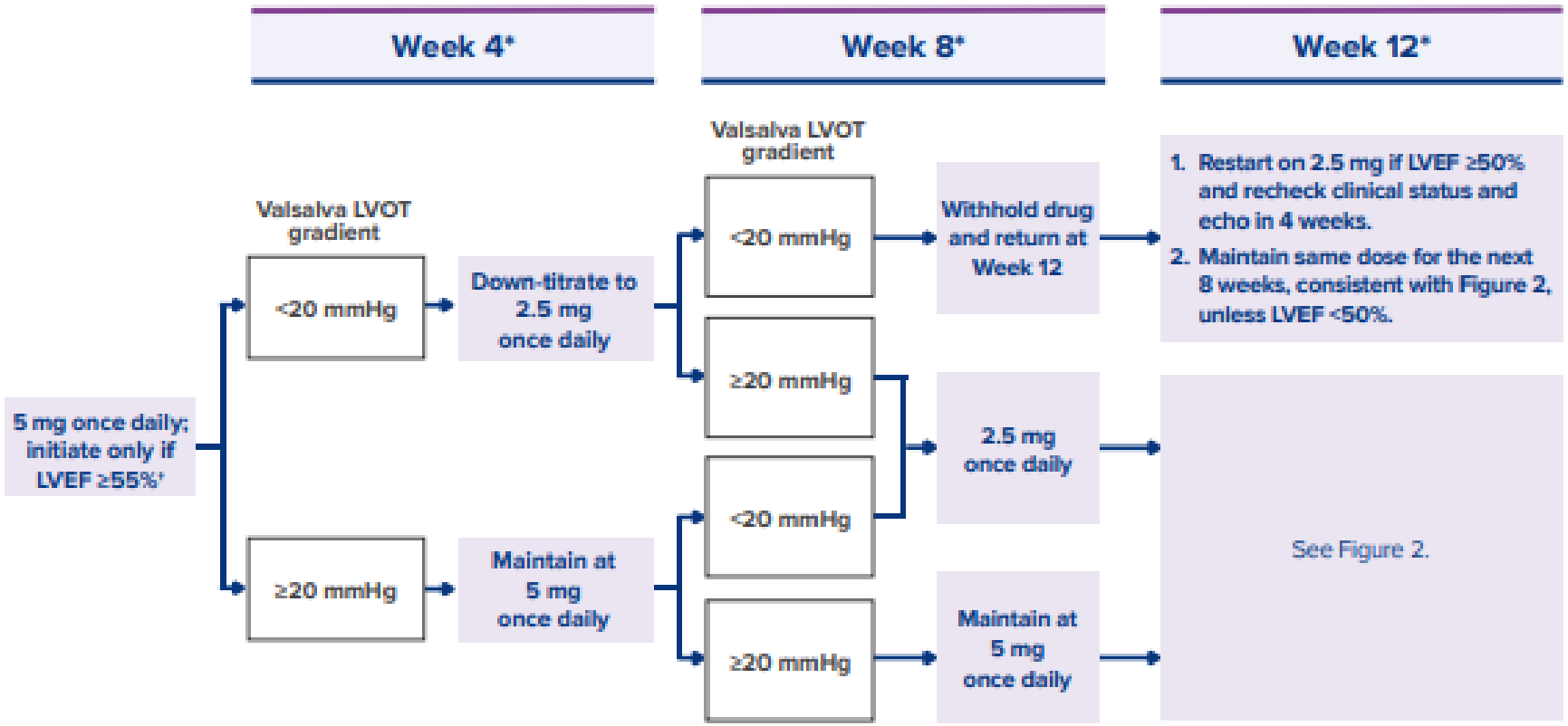
Indications for Mavacamten

- Indications
  - Baseline LVEF >55% at rest
  - LV Wall thickness >15mm (or >13mm with FHx)
  - LVOT peak gradient >50mmHg at rest or with valsalva
  - Class II-III symptoms despite use of BB/CCB

- Target Gradient – 20-30mmHg
- Contraindications or Discontinuing
  - Drop in EF <50% or clinically worsening status
  - Certain CYP450 inhibitors/inducers (Restricted prescribing program REMS which monitors all of this) – is currently being relaxed due to long term safety data
    - Strong - Fluconazole, Fluoxetine, Esomeprazole
    - Moderate – Carbamazepine, Phenytoin, Rifampin, St. johns Wort

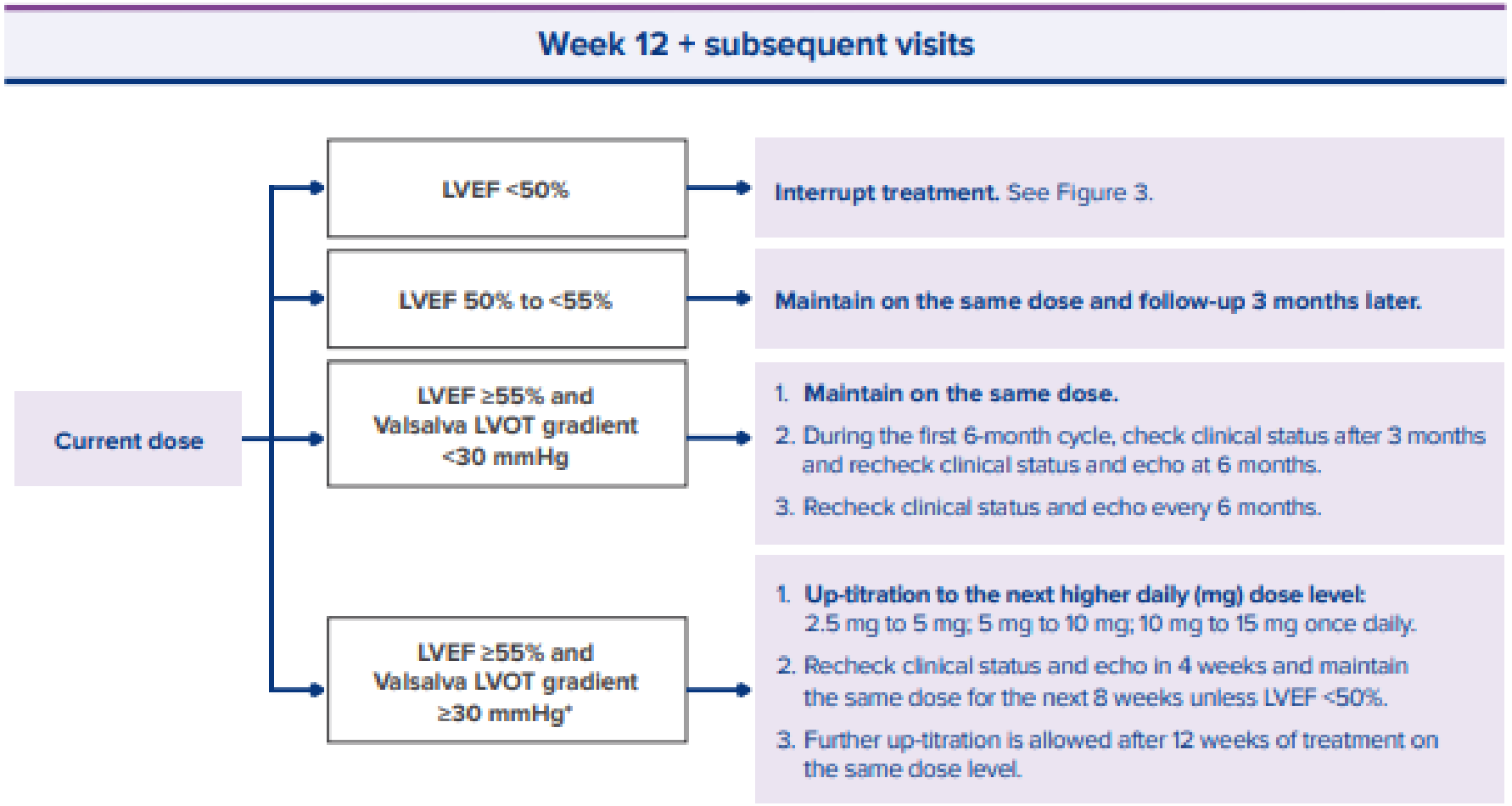
Dosing and Titration

Figure 1: Initiation Phase



*Interrupt treatment if LVEF is <50% at any clinic visit; restart treatment after 4 weeks if LVEF is ≥50%. See Figure 3.

Figure 2: Maintenance Phase



My Experience

- 3x Patients
  - 2 reached goal at 5mg
  - 1 trialed 10mg but felt unwell and chose to stay at 5mg as this had made her feel better (starting gradient 74mmHg, down to 34mmHg – now 24mmHg)

Questions?