Hypertrophic Cardiomyopathy in 2024

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Disclosure

- No financial conflicts of interest

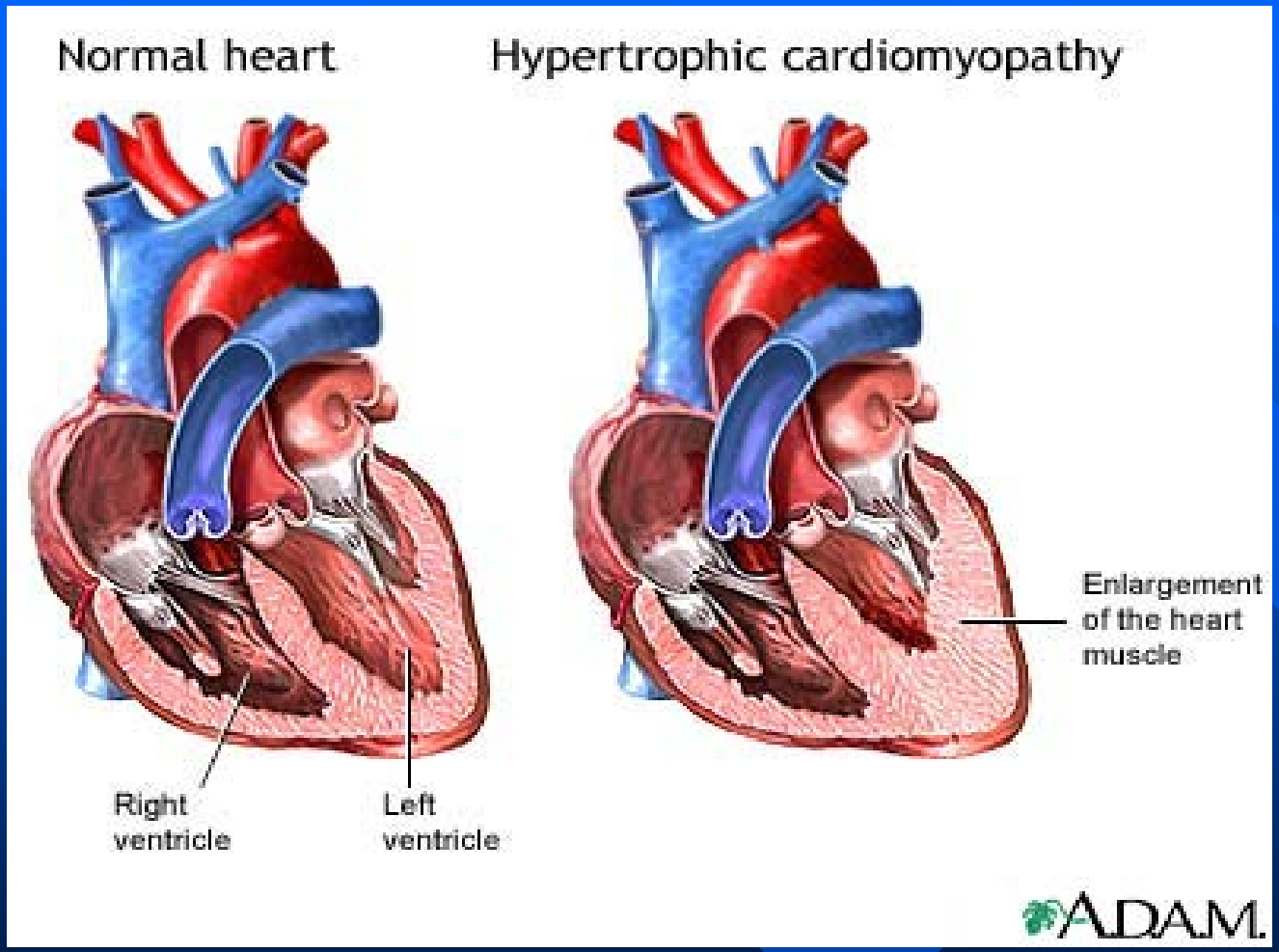
Objectives

- Describe the pathophysiology, clinical manifestations, diagnostic methods, and treatment options for hypertrophic cardiomyopathy in 2024.

Description

- *Inappropriate myocardial hypertrophy that occurs in the absence of an obvious cause for the hypertrophy(e.g., aortic stenosis or systemic hypertension), often predominantly involving the interventricular septum of the nondilated LV that shows hyperdynamic systolic function.*
- In ¼ of patients a *dynamic pressure gradient in the subaortic area that divided the LV into a high pressure apical region and a lower pressure subaortic region.*

Braunwald, 2005


Normal heart
Hypertrophic cardiomyopathy
Enlargement of the heart muscle
Right ventricle
Left ventricle
A.D.A.M.

History

- First described in mid 19th century by a French pathologist – Henri Liouville.
- Reports by Brock and Teare in England brought this subject to modern attention in the 1950's.
- Several names have been used to describe this condition – IHSS, muscular subaortic stenosis.

Genetics of HCM

- Autosomal Dominant inheritance.
- 2/3 of patients have a family history.
- Initially thought to be ideopathic, but recently it has been shown to be due to mutations in the genes encoding proteins in the contractile apparatus.
- More than 100 different mutations in 10 genes encoding contractile sarcomeric proteins. 2 genes coding for non-sarcomeric proteins.

Genetics of HCM

- Mutations in B-MyHC (Chromosome 14q1)
  - Most common cause of HCM(35-50%)
  - Patients manifest at younger age and there is more extensive hypertrophy and higher incidence of SCD.
- Myosin binding protein C (MyBP-C)
  - Second most common (20-25%)

Genetics of HCM

- Mutations associated with high incidence of SCD and premature death have high penetrance and present with early onset.
- Those with low penetrance present later with milder LVH.
- (Exception is cTnT gene in which patients have high incidence of SCD, but less hypertrophy).

Genetics of HCM

- Great variability in the expression of genotypes due to modifier genes.
- Modifier genes effect the severity of the disease.

Prevalence

- Estimated to be 1 in 500. Making it one of the most prevalent genetically transmitted cardiac disorder.
- Identified most in adults in the 4th and 5th decades of life.
- Detectable cardiovascular abnormalities develop during times of rapid growth.
- Has been described in infants and young children but data is lacking.

Pathogenesis

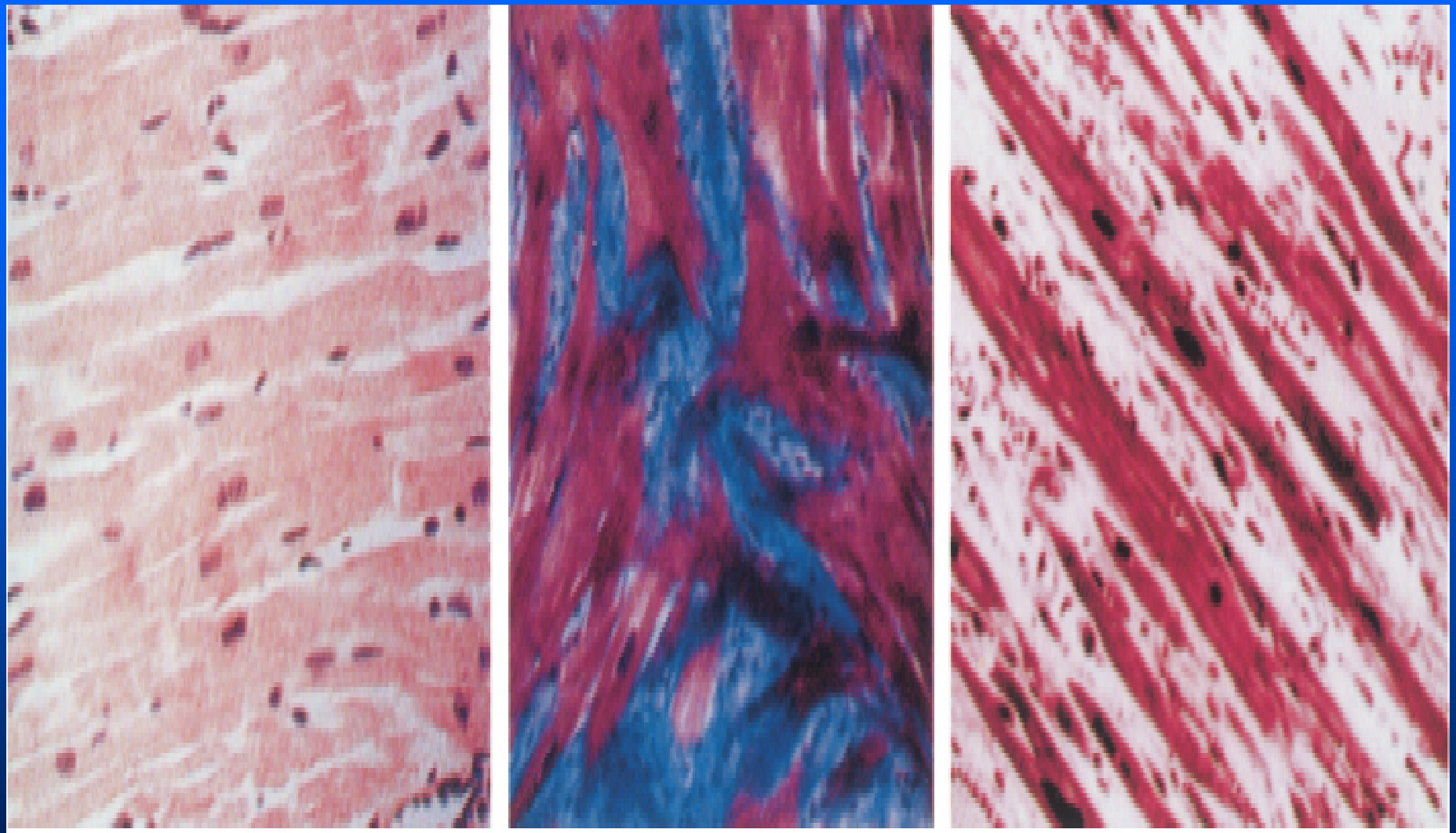
- Mutations lead to impaired cardiac myocyte contractile function.
- This leads to sarcomeric disarray, hypertrophy, and increased fibrosis.
- Also leads to stress responsive growth factors to be released. These stimulate myocyte hypertrophy and fibroblast proliferation.

Pathogenesis

- It is possible that mutations in sarcomere proteins could affect the Ca +2 sensitivity causing abnormal acto-myosin interaction during cardiac cycles.
- It has also been postulated that these mutations may reduce binding affinity for the actin filaments and/or impair the ability of the mutant myosin to displace actin filaments.

Pathology

- Marked increase in myocardial mass and small ventricular cavities. Atria are dilated and often hypertrophied due to high resistance to of the ventricles caused by diastolic dysfunction and the effects of AV valve regurgitation.
- Myofiber disarray.
- Interstitial and replacement fibrosis.
- Extensive myocyte hypertrophy.



A B C

HCM types

- Left Ventricular
  - Symmetrical - 5%
  - Asymmetrical - 95%
    - » Septal hypertrophy – 80%
    - » Apical hypertrophy - 9%
    - » Midventricular hypertrophy – 4%
    - » Rare types – 2%

Classification

- Obstructive
  - Subaortic obstruction
  - Midventricular obstruction
- Non-obstructive
  - Normal systolic function
  - Impaired systolic function

Hypertrophic Obstructive Cardiomyopathy

- Subaortic vs. midventricular
- Subaortic is most common
- Mitral valve - contributes to obstruction. It is pulled against the septum by abnormally located papillary muscles and elongated leaflets. 20% of patients have intrinsic mitral valve abnormalities.

Symptoms

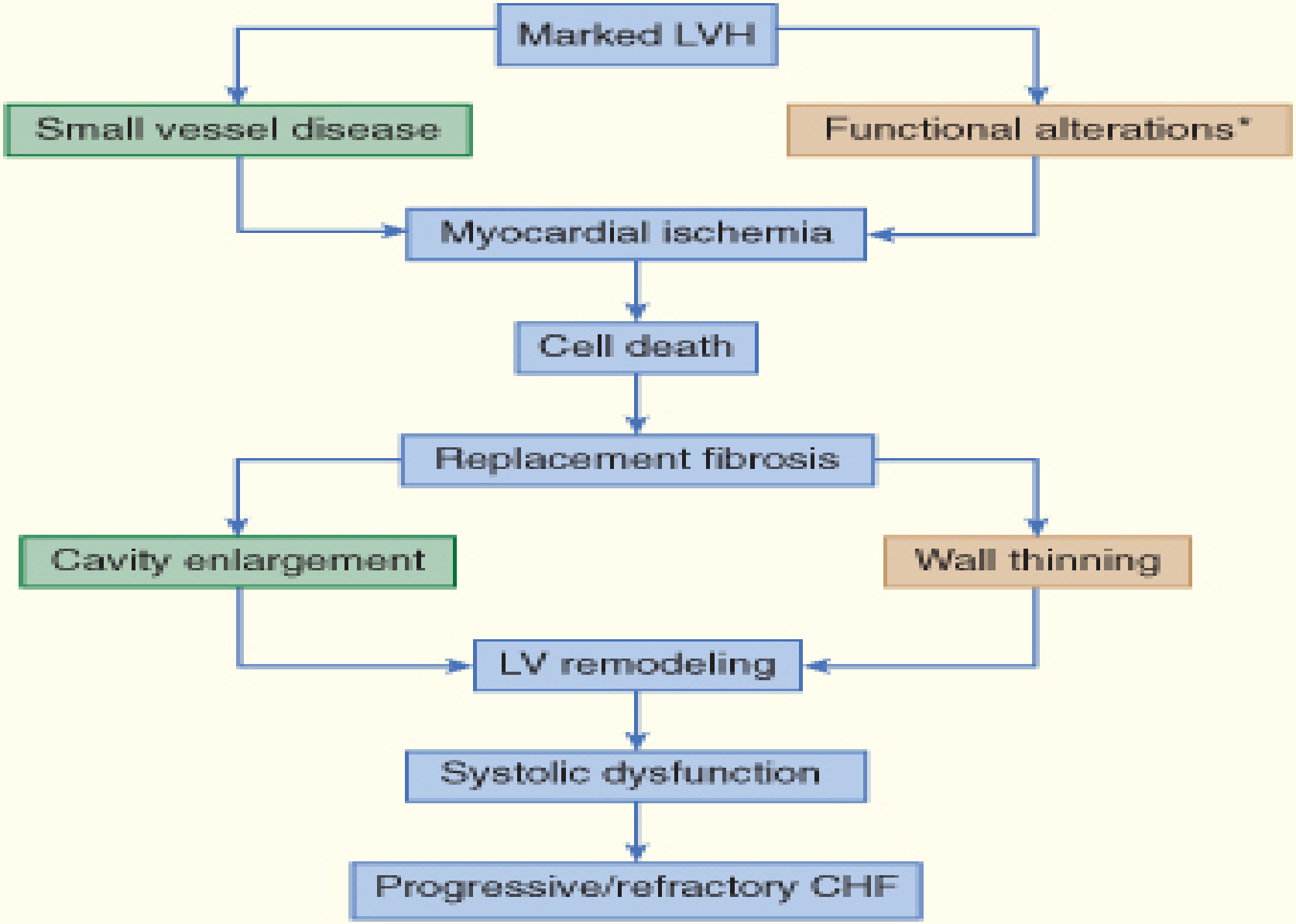
- Dyspnea
- Syncope
- SCD
- Presyncope
- Angina
- Asymptomatic – identified during family screening.

Symptoms

- Exertional symptoms like chest pain and dyspnea can be caused by ischemia, diastolic dysfunction, and CHF.
- Symptoms of syncope, presyncope, chest pain, and dyspnea can be caused by LVOT obstruction in asymmetric septal hypertrophy.

Ischemia

- Increased demand for oxygen
  - Myocardial hypertrophy
  - Diastolic dysfunction
  - Myocyte disarray
  - Lvot obstruction
  - Arrythmia
- Reduced perfusion
  - Small vessel disease
  - Abnormal vascular responses
  - Myocardial bridges
  - Increased coronary vascular resistance



Cardiac Arrest

- Several mechanisms for generation of ventricular arrhythmias.
  - PAF, VT, rapid AV conduction via accessory path, AV block, ST with abnormal vascular responses/ischemia.

Physical Exam

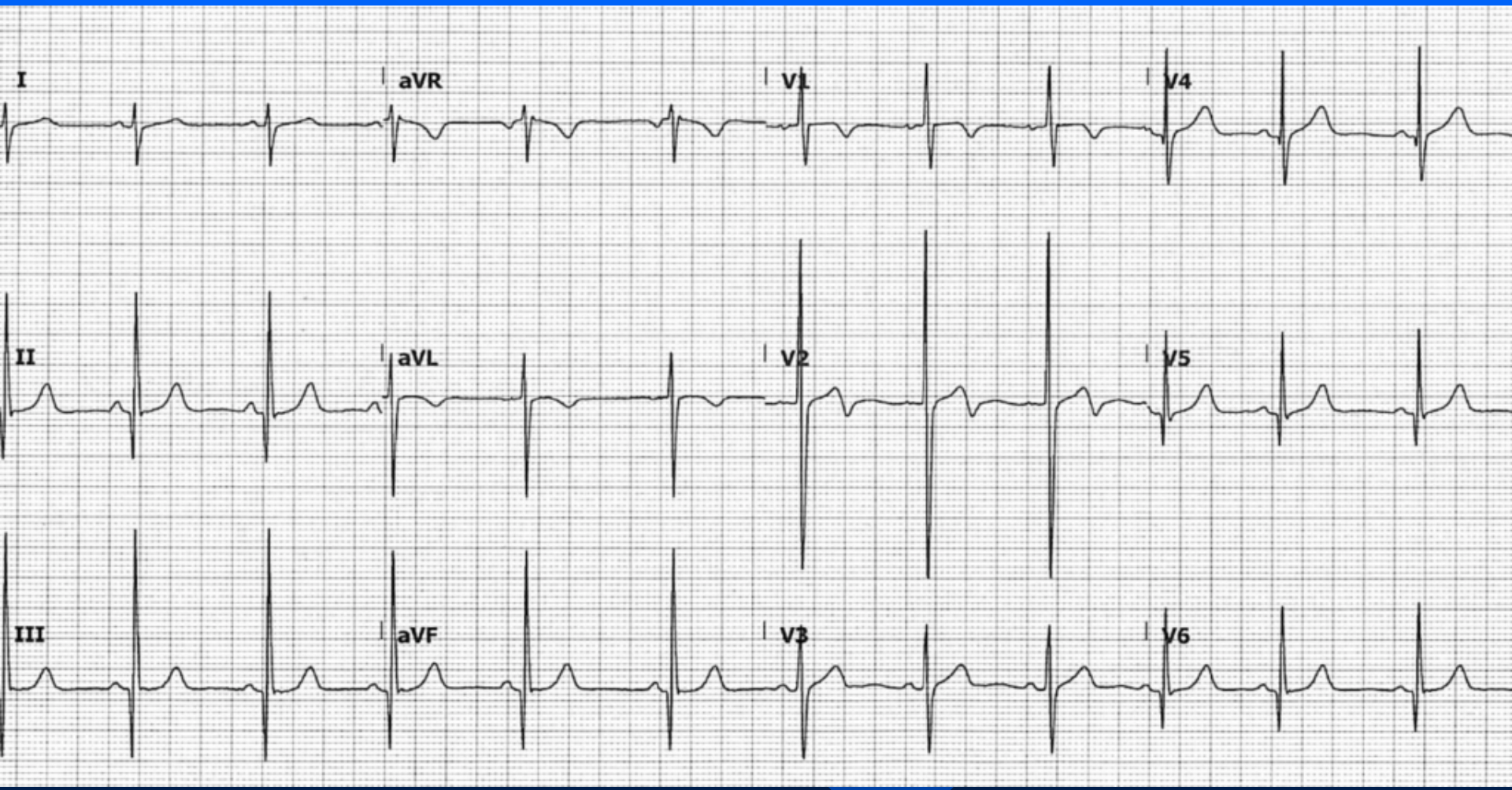
- PMI- lateral displacement and abnormally forceful and diffuse.
- Gallops
- Murmur – systolic, harsh, crescendo-decrescendo
- Bifid arterial pulse- rises briskly and then declines in midsystole as a the gradient develops, followed by a secondary rise.
- Paradoxical split of S2 + an S4

Murmur

- Increase by – valsalva, standing, isoproterenol, digitalis, amyl nitrite, exercise, ntg, tachycardia, hypovolemia.
- Decrease by – squatting, phenylephrine, isometric grip, beta blockade.

Diagnostic Tests

- ECG – LVH strain pattern. Abnormal Q waves representing septal hypertrophy. TWI in V3-V5 in apical HCM.
- Echo
- Chest Xray
- MRI
- Radionuclide scanning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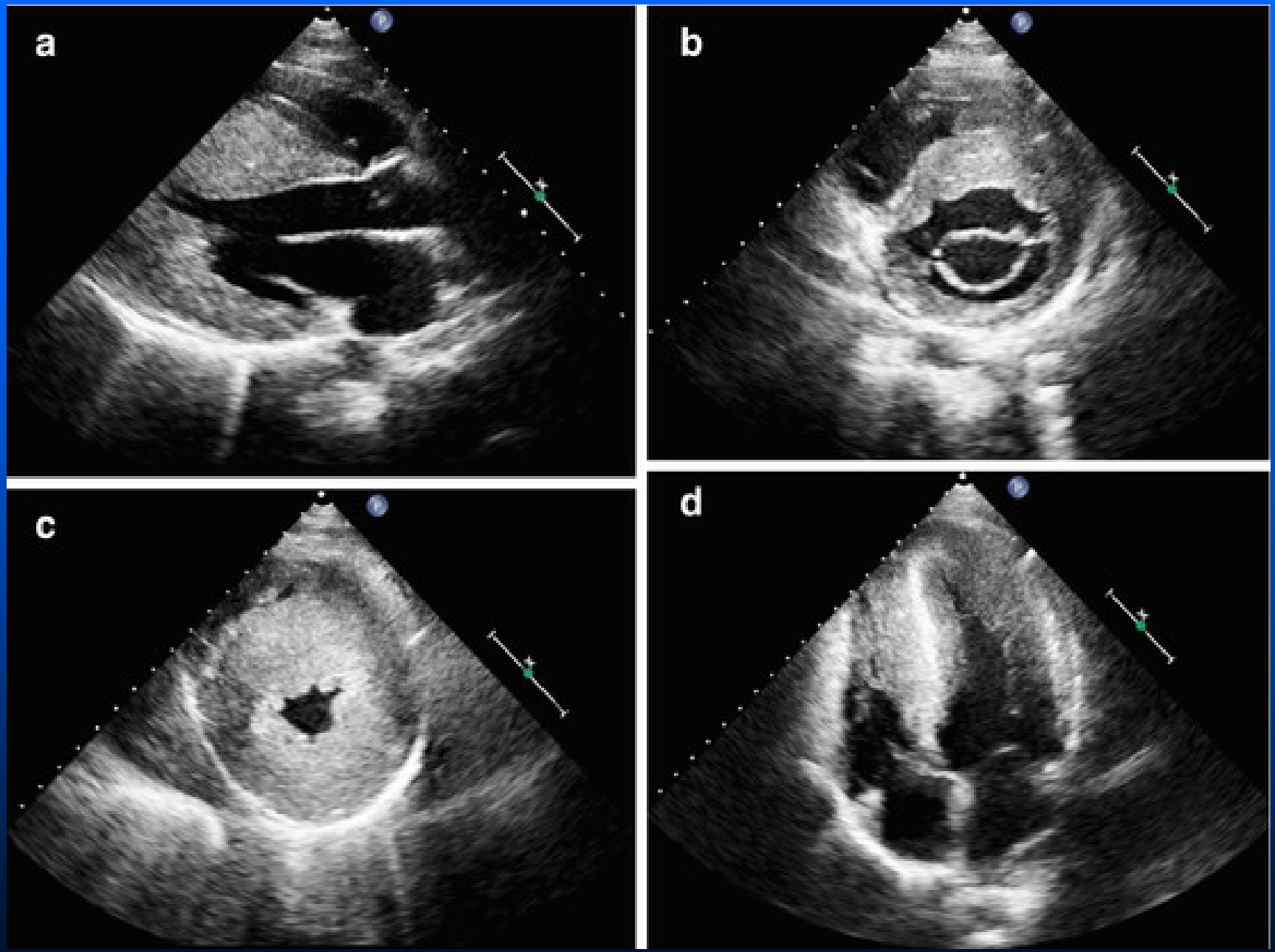
V4
II
aVL
V2
V5
III
aVF
V3
V6


a
b
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d

Assessing Risk

- Non-invasive testing including cardiac monitor, maximal exercise testing and thorough history.

Risk factors

- Syncope
- Prior cardiac arrest – 1/3 of those who survive initial arrest die within 7 yrs.
- FH – 25% of HCM patients have some family history of sudden death.
- Echo – 30mm of hypertrophy has been suggested as a risk factor.
- Cardiac monitoring – 20% of adult HCM patients present with NSVT. Most sensitive marker for increased risk of SCD in adult.

Risk Factors

- Blood pressure response to exercise – fall or failure of bp to rise with exercise. Detected in 25% of patients with HCM.

Summary of risk factors

- Prior cardiac arrest or sustained VT
- Multiple, repetitive burst of NSVT
- FHx of premature HCM death
- Syncope, presyncope
- Hypotensive response of BP to exercise
- LVH > 30mm

EP Study?

- Inducible VT is associated with a higher risk of future SCD. However, having aggressive protocols will generate polymorphic VT in at least 1/3 of patients w/out sustained arrythmia or structural heart disease. Furthermore 1/3 of patients with HCM with previous cardiac arrest are non inducible.

Role of EP Study

- WPW
- Atrial Flutter
- Investigate and guide treatment of sustained monomorphic VT in HCM.

Prognosis

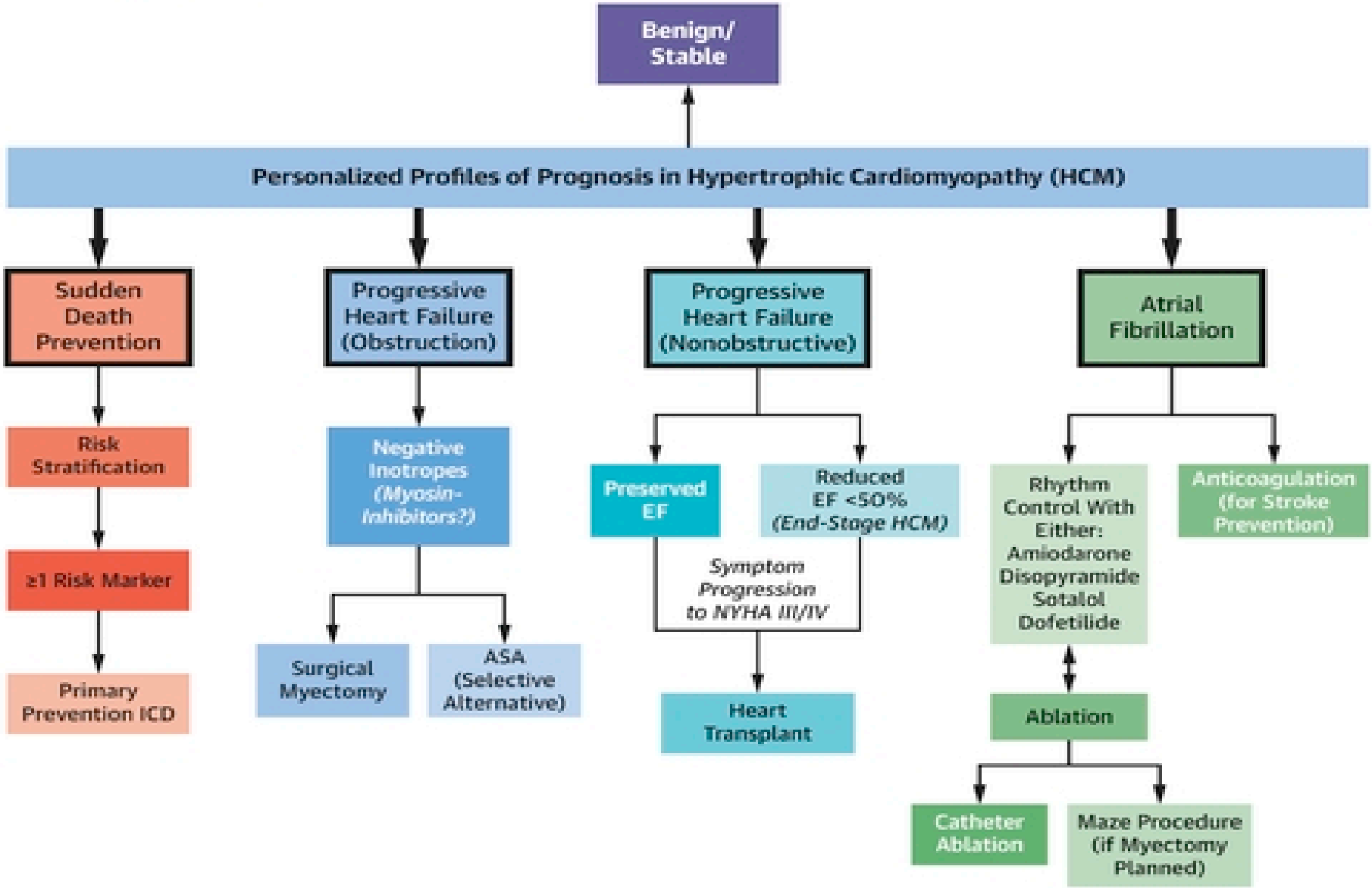
- Most patients remain asymptomatic
- Mortality 1-4%
- SCD
- End stage heart failure only in less than 5%

Pregnancy

- Most tolerate pregnancy well.
- Major progression of symptoms, a-fib, syncope are uncommon and related to condition prior to pregnancy.
- Study by Thamen R et al. in 2003 looked at 271 pregnancies of patients with HCM. 28.3% had cardiac symptoms during pregnancy (90% of these patients were symptomatic before pregnancy). Symptoms deteriorated in less than 10% of patients during pregnancy.

Thaman R, Varnava A, Hamid MS, et al. Pregnancy related complications in women with hyprtrophic cardiomyopathy. Heart. 2003;89:752–756. doi: 10.1136/heart.89.7.752.

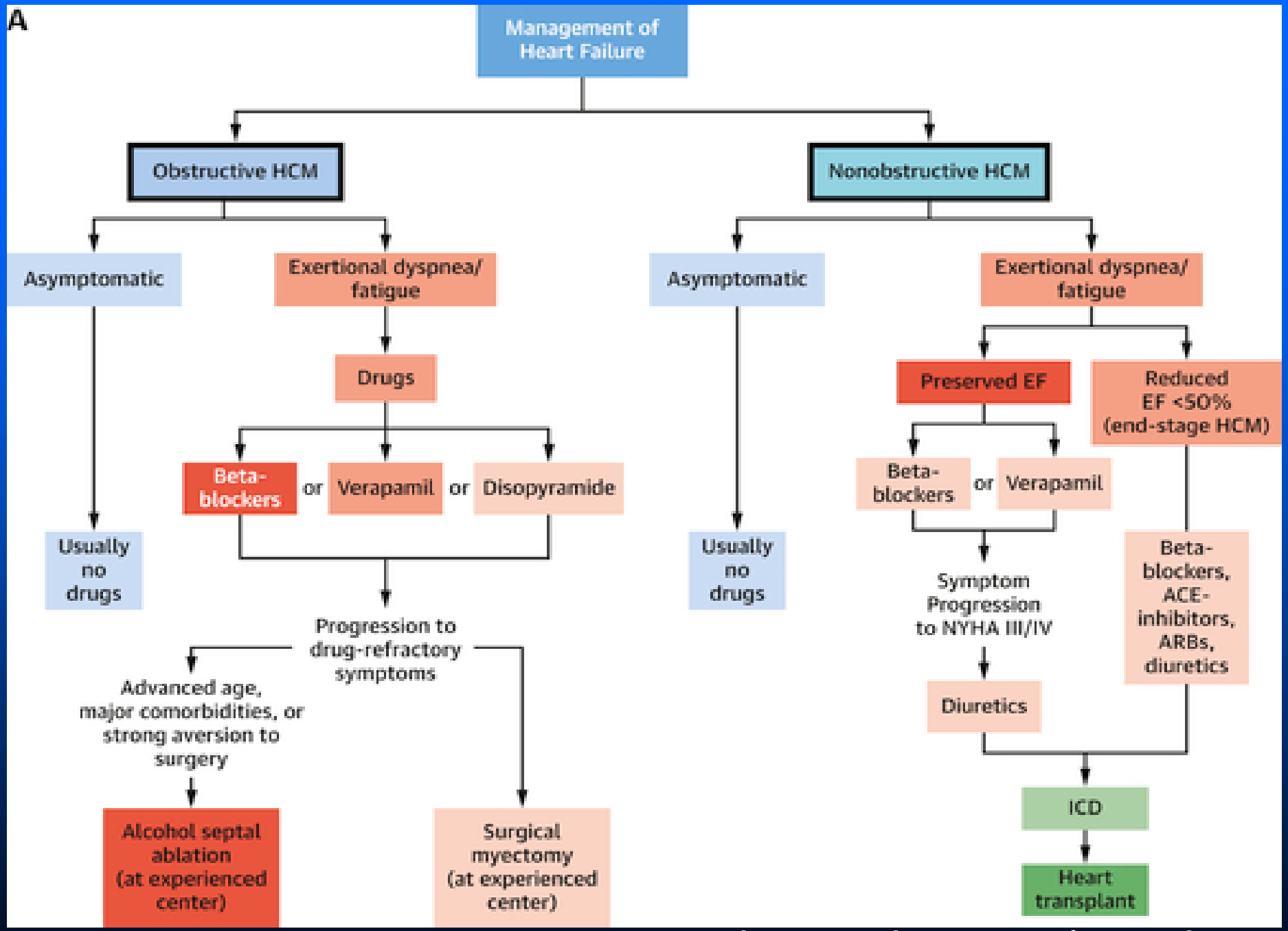
CENTRAL ILLUSTRATION: Management Guidelines for Hypertrophic Cardiomyopathy



Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.

Medical Therapy for Hypertrophic Obstructive CM

- Beta blocker
- Calcium channel blocker
- Disopyramide
- If LV Dysfunction – diuretics, vasodilators, digitalis.
- Mavacamten



Maron, B, Desai, M, Nishimura, R. et al. Management of Hypertrophic Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022

Mavacamten

- Selective and reversible inhibitor of the cardiac myosin ATPase

EXPLORER-HCM

- Randomized placebo controlled double blind study.
- 251 enrollees followed for 30 weeks.
- Inclusion criteria: HOCM with gradient >= 50 mmHg, LVEF>=55%, NYHA 2-3 symptoms.
- Exclusion criteria: Syncope, sustained ventricular tachycardia with exercise within past 6 months.

Lancet 2020;396:759-69.

EXPLORER-HCM

- Principal Findings:
- The primary outcome, ≥1.5 ml/kg/min increase in pVO2 with ≥1 NYHA class improvement or ≥3.0 ml/kg/min increase in pVO2 with no worsening of NYHA class at 30 weeks, occurred in 37% of the mavacamten group compared with 17% of the placebo group ($p = 0.0005$).

EXPLORER-HCM

- 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 ($p < 0.0001$)

pVO2 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 ($p = 0.0006$)

EXPLORER-HCM

- Cardiac magnetic resonance (CMR) substudy analysis:

Change in LV mass index: -17.4 g/m2 in the mavacamten group vs. -1.6 g/m2 in the placebo group ($p < 0.0001$)

Change in LVEF: -6.6% in the mavacamten group vs. -0.3% in the placebo group ($p = 0.0025$)

EXPLORER-HCM

- Long-term extension study (n = 231, median 62 weeks):

Treatment-emergent adverse events: 4.3%

Change in resting LVOT gradient from baseline to 84 weeks: -32.8 mm Hg

Change in Valsalva LVOT gradient from baseline to 84 weeks: -46.4 mm Hg

Change in LVEF from baseline to 84 weeks: -9%

Change in N-terminal pro–B-type natriuretic peptide from baseline to 84 weeks: -488 ng/L

Non-obstructive therapy

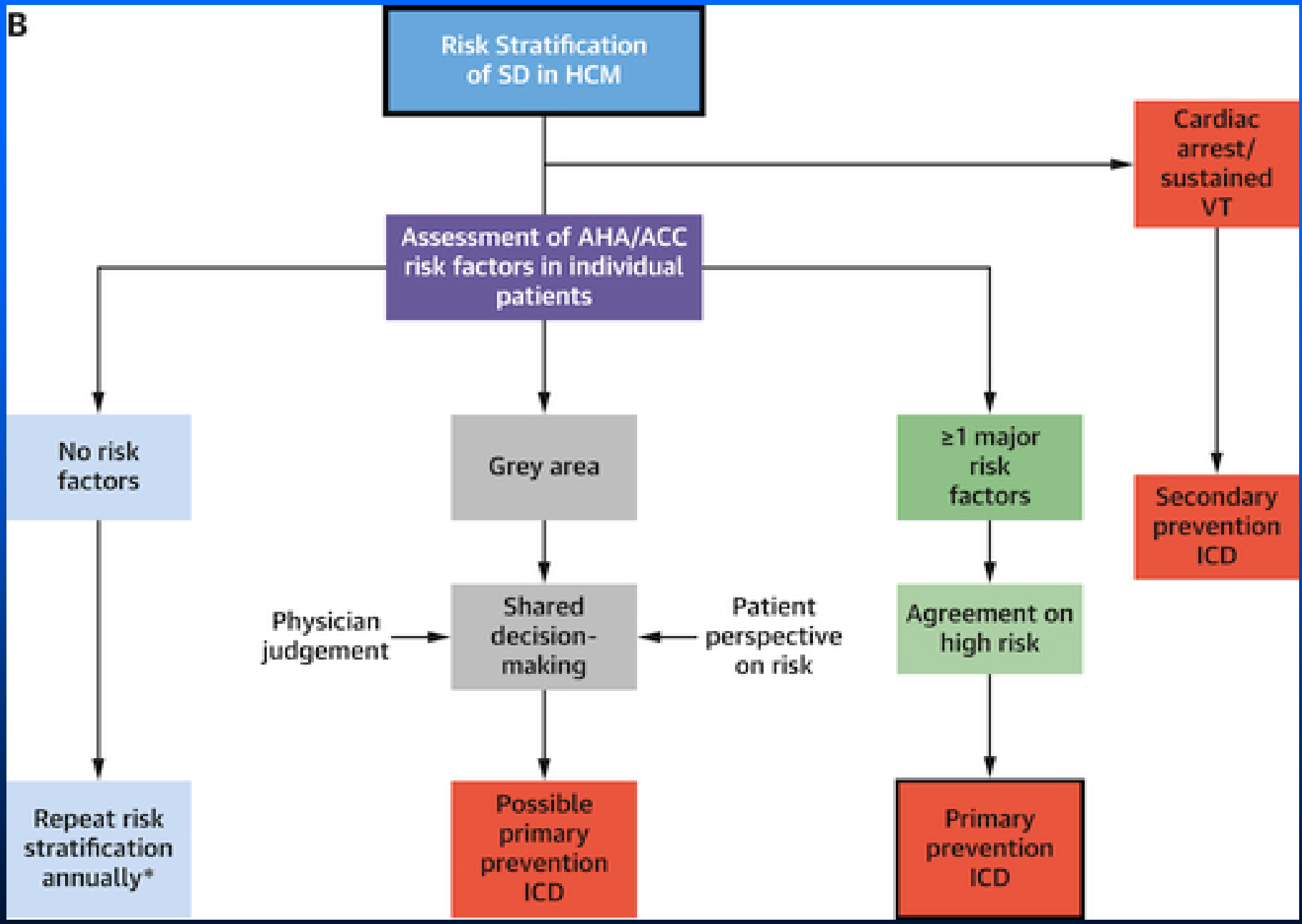
- Beta blockers
- Calcium channel blockers (verapamil, diltiazem)
- Diuretics only in Pulmonary Congestion
- If LV Dysfunction – conventional CHF treatment.

Management of HCM

- Lifestyle modifications – avoid strenuous exercise or competitive sports. Half of deaths in HCM occur during or just after physical activity.

SCD

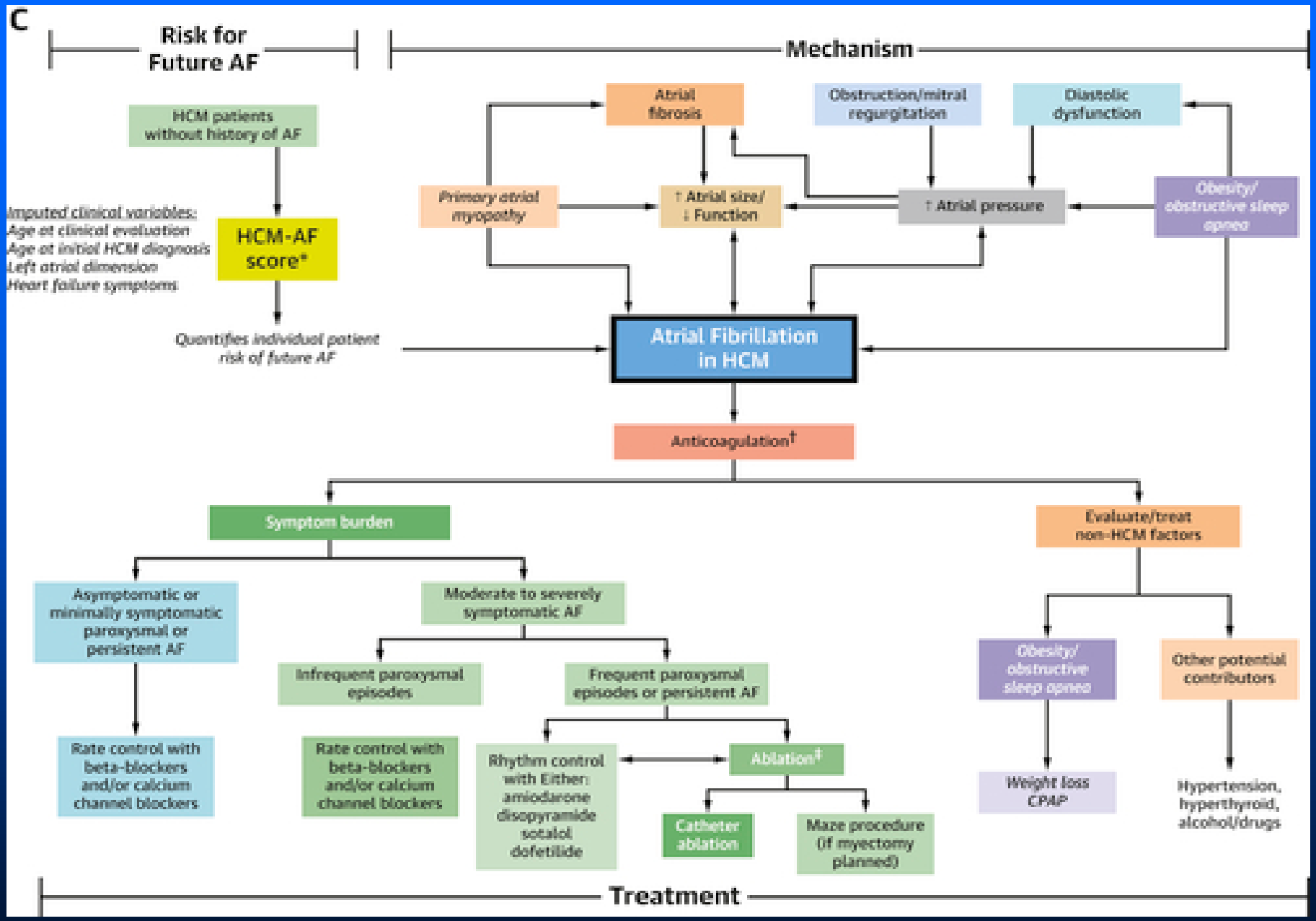
- ICD – most effective treatment modality for the high risk patient and should be considered for patients with prior cardiac arrest or ventricular arrhythmias.
- Little evidence that pharmacological strategies reduce risk of Sudden Cardiac Death.
- DDD pacing has shown some symptomatic improvement.



Barry J. Maron et al. J Am Coll Cardiol 2022; 79:390-414.

Atrial Fibrillation Treatment

- Cardioversion
- Amiodarone effective for reducing AF recurrences.
- Beta blocker, verapamil for rate control
- A-V node ablation and pacemaker placement.
- Anticoagulation



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Surgical Indications

- Heart Failure and outflow gradient of 50mm or more. HF symptoms that do not respond to medical therapy.
- Patients with provocable obstruction are sometimes referred for surgery.

Therapies

- Myomectomy of septum
  - 2% mortality at experienced centers.
  - 70% improvement in symptoms and exercise capacity.
  - MVR – decreases obstruction
- Alcohol Septal Ablation
  - 2% mortality
  - BBB in up to 60%
  - Complete AV block in 0-40%

Therapies

- Advantages of ethanol ablation – avoidance of CP bypass, shorter hospital stay, shorter recovery time, less expense.
- Advantages of myectomy – more immediate and complete relief, smaller incidence of complete heart block, excellent long term results, no risk of coronary dissection or unwanted myocardial infarction, ability to deal with concomitant problems.

Therapies conclusion

- Both therapies reduce LVOT obstruction and significantly improve NYHA functional class in these patients.
- Careful consideration of benefits and drawbacks should be looked into for each individual patient.

Thank you!