Hypertrophic Cardiomyopathy (HCM)

Nandini Nair MD, PhD, MHL, CPE, FSVM, FACC, FACP, FHFSA, FAHA
Professor, Dept of Medicine,
Division of Cardiology,
TTUHSC, Lubbock ,TX

Learning Objectives

- **Define current concepts in hypertrophic cardiomyopathy**
- **Apply current algorithms to triage patients**
- **Discuss current diagnostic and treatment modalities for hypertrophic cardiomyopathy**

History of disease recognition

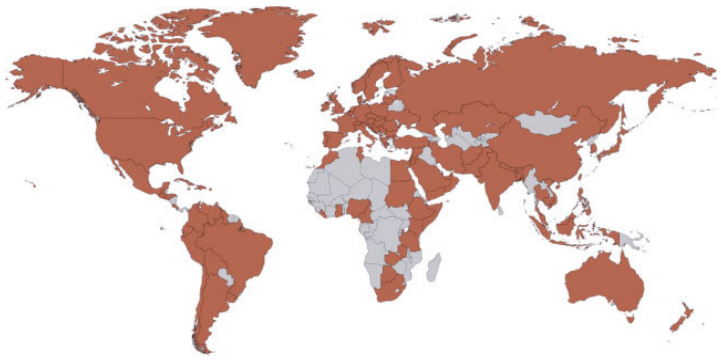
1868	First pathological description by Vulpian who called it idiopathic hypertrophic subaortic stenosis (IHSS).
1957-1958	Brock reported 3 cases /attributed it to systemic hypertension.
1958	Teare published a case series of 8 autopsy cases who had asymmetrical hypertrophy of the heart, 7 of whom died suddenly. Bercu et al. called it 'pseudoaortic stenosis'.
1961	Brockenbrough] described the famous Brockenbrough–Braunwald–Morrow sign.
1963	Nonobstructive form of HCM identified
1964	Morrow et al. [19] performed the first surgical myectomy for HCM.
1965	Bjork postulated that SAM caused LVOTO.
1969	Moreyra et al.pioneered the use of M-Mode echocardiography in HCM diagnosis. Shah et al described Systolic Anterior Motion of the MV using echocardiography
1972	Introduction of cross-section/2D echocardiography
1980	First ICD implanted in a patient with HCM to prevent sudden cardiac death (SCD)
1990	First pathogenic mutation iudentified in HCM
1995	Use of alcohol septal ablation (ASA) as an alternative to surgical myectomy by Sigwart.
2000	First efficacy study on ICD in the prevention of SCD in the HCM population
2002	ACC/AHA/NASPE guidelines recommended (class IIb) the use of ICD in primary prevention of SCD in HCM.

Journal of Clinical Medicine 2017, *6*(12), 118;

Epidemiology

- (HCM) is the most common inherited cardiovascular disorder, affecting **1 in 500 individuals worldwide**
- Clinical manifestations :
- **diastolic dysfunction,**
- **left ventricular outflow tract obstruction, ischemia,**
- **atrial fibrillation, abnormal vascular responses**
- **In 5% of patients, progression to a 'burnt-out' phase characterized by systolic impairment.**
- Disease-related mortality :
- **sudden cardiac death,**
- **Heart Failure,**
- **Embolic stroke**
- The majority of individuals with HCM, however, **have normal or near-normal life expectancy,** owing in part to contemporary management strategies including **family screening, risk stratification, thromboembolic prophylaxis, and implantation of ICD**

Global burden of HCM



125 Countries involving 90% of world population

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Prevalence
1:200-1:500

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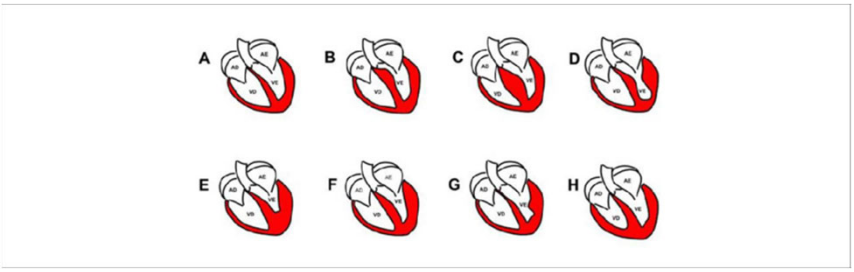
Estimated ~15-20 million
affected worldwide

Maron BJ et al JACC 2022

Types of HCM

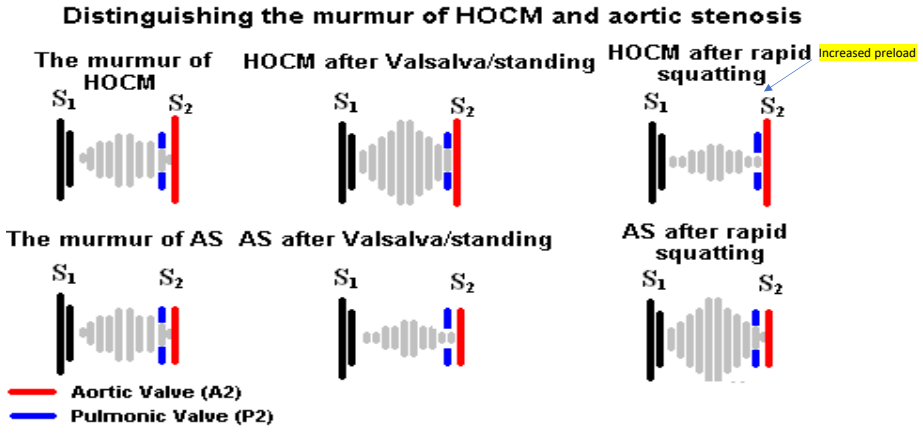


(A) Normal heart.
(B) Sigmoid septum
(C) Reverse septal curvature
(D) Mid-ventricular obstruction without apical aneurysm.
(E) Apical.
(F) Symmetric
(G) Asymmetric hypertrophy in the lateral wall
(H) Hypertrophic cardiomyopathy in right ventricle.

Oliveira, et al. "Cardiac magnetic resonance and computed tomography in hypertrophic cardiomyopathy: an update." *Arquivos brasileiros de cardiologia* 107 (2016): 163-172.

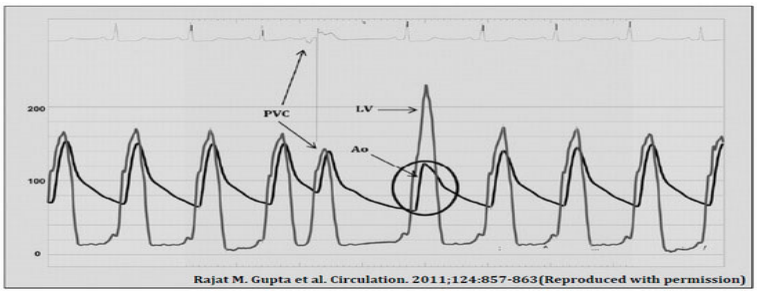
Pathogenic mutations of HCM.		
Gene	Protein	Frequency (%)
Cardiac myosin-binding protein C	MYBPC3	30–40%
β cardiac myosin heavy chain	MYH7	20–30%
Cardiac troponin T	TNNT2	5–10%
Cardiac troponin I	TNNI3	4–8%
Regulatory myosin light chain	MYL2	2–4%
Essential myosin light chain	MYL3	1–2%
α tropomyosin	TPM1	<1%
α cardiac actin	ACTC1	<1%
Muscle LIM protein	CSRP3	<1%

Physical Examination



Diagnostic Evaluation

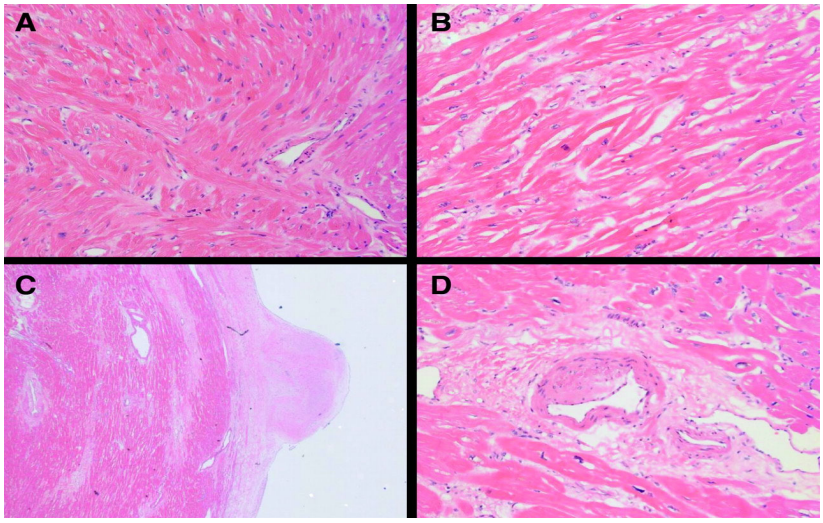
Brockenbrough sign after a premature ventricular contraction (PVC) in HCM (Hypertrophic cardiomyopathy).



Pulse pressure, as recorded in the femoral artery, decreases in the post-extrasystolic beat (circled) while intracavity pressure in the LV (Left ventricle) increases due to greater obstruction in the LVOT (Left ventricular outflow tract)

- After a PVC, there is a compensatory pause that causes an increase in diastolic filling time and therefore an increase in diastolic volume.
- The normal physiologic response to increased stretch according to Frank Starling's Law is to increase stroke volume by an increase in contractility, causing the arterial pulse pressure to rise.
- In patients with HOCM, the increase in contractility after a PVC worsens the LVOT obstruction, causing a decrease in the arterial pulse pressure

Histopathology of the myocardium obtained during myectomy.

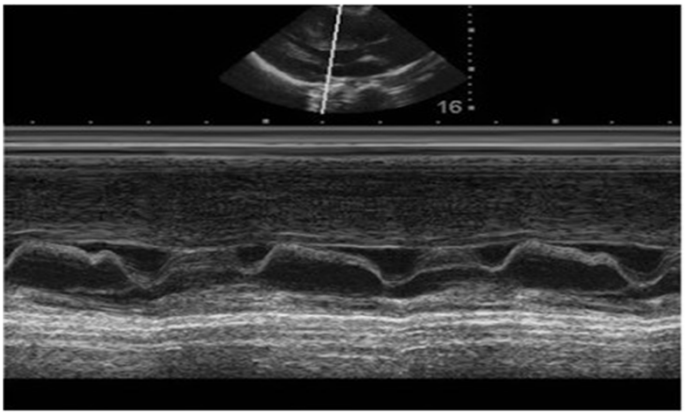


Rajat M. Gupta et al. Circulation. 2011;124:857-863

American Heart Association

Figure 8. Histopathology of the myocardium obtained during myectomy. **A** and **B**, Myocyte disarray; **C**, endocardial fibrosis; and **D**, arteriolar hyperplasia. All of these findings are consistent with, although not specific for, hypertrophic cardiomyopathy.

Systolic Anterior Motion of the mitral leaflet in HCM



Parato et al Cardiovascular Ultrasound 2016 14(1):30 DOI: 10.1186/s12947-016-0072-5

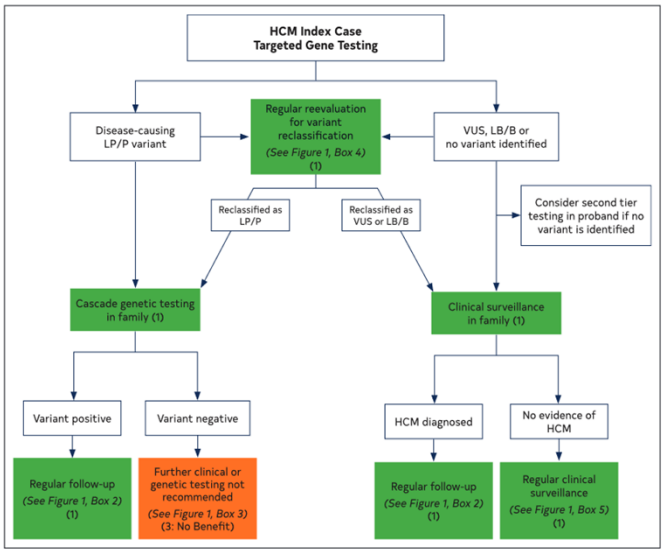
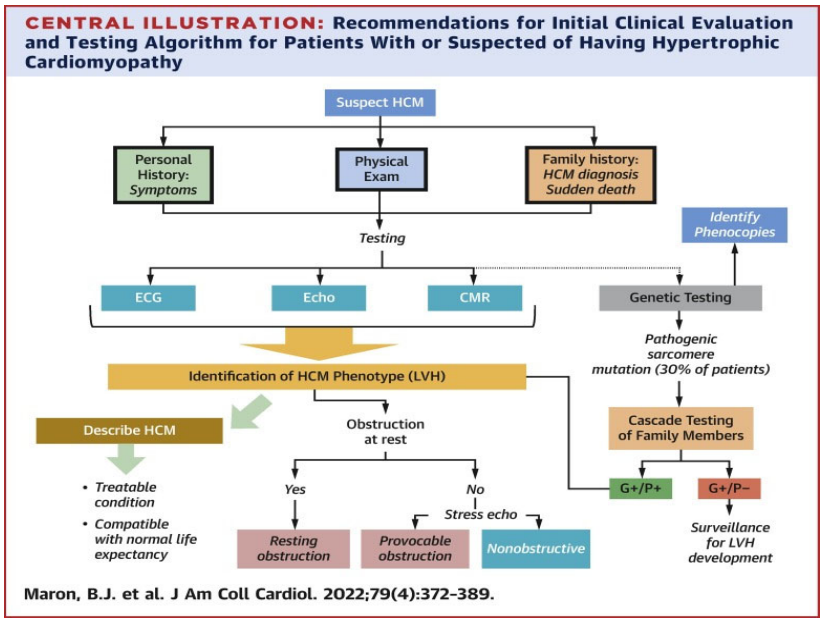


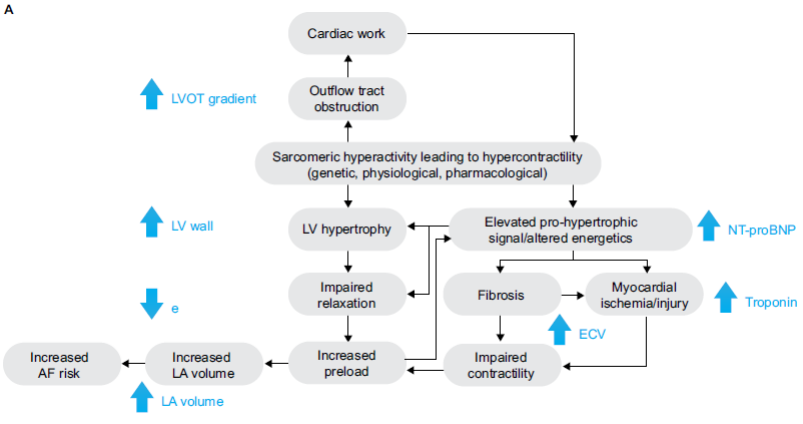
Figure 2. Genetic testing process in HCM.
Colors correspond to the Class of Recommendation in Table 2. HCM indicates hypertrophic cardiomyopathy; LB/B, likely benign/benign; LP/P, likely pathogenic or pathogenic; and VUS, variant of unknown significance.

Steve R. Ommen et al Circulation. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: 142, 25, Pages: e533-e557, DOI: (10.1161/CIR.0000000000000938)



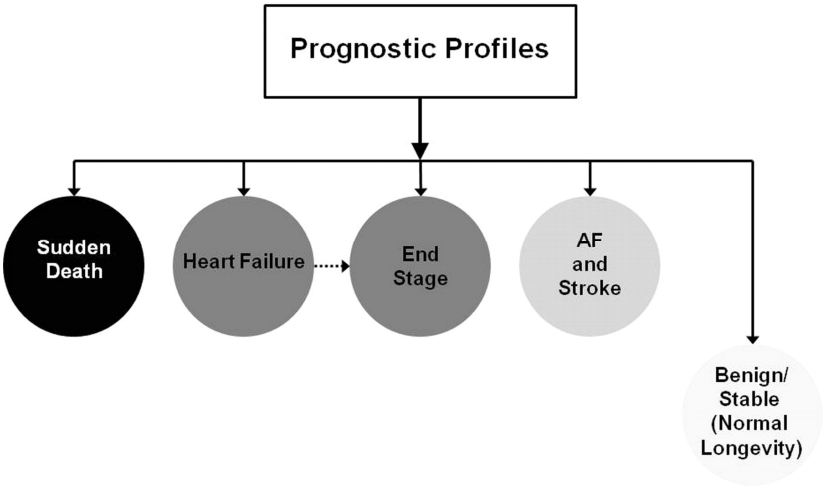
Pathophysiology

A



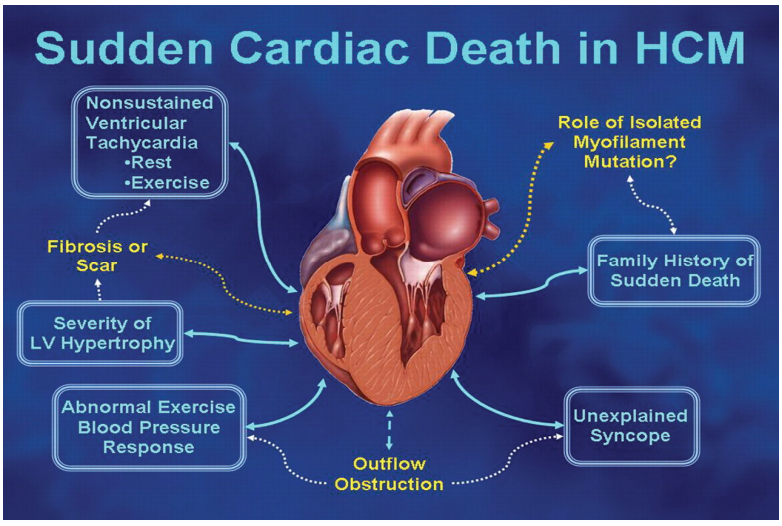
Edelberg et al American Journal of Cardiovascular Drugs 2022 https://doi.org/10.1007/s40256-022-00532-x

Prognosis profiles for HCM and targets for therapy.

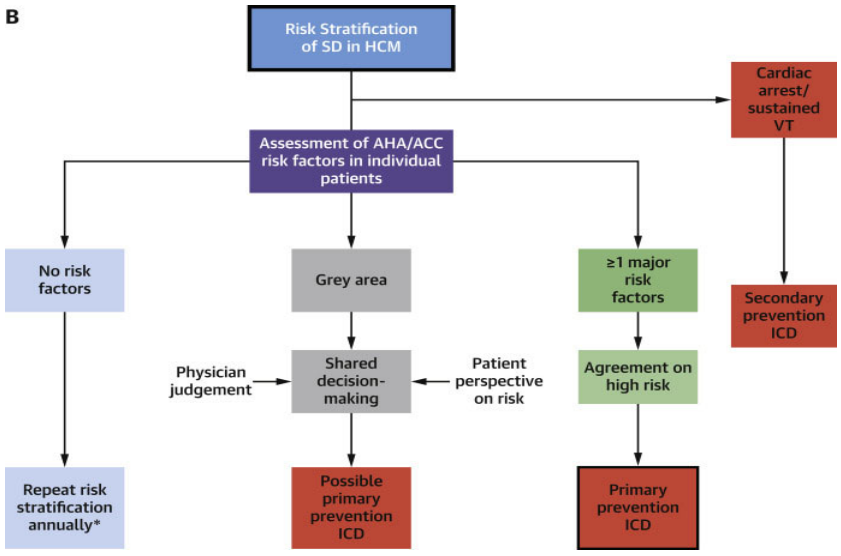


Writing Committee Members et al. Circulation. 2011;124:2761-2796

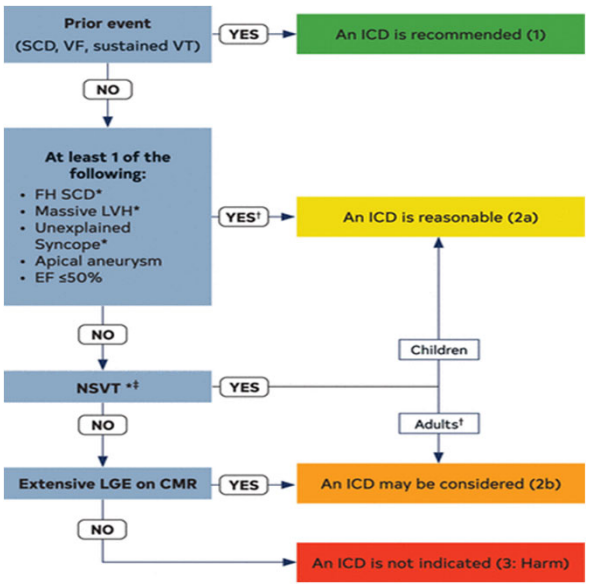
Sudden cardiac death (SCD) in hypertrophic cardiomyopathy.



Steve R. Ommen, and Bernard J. Gersh Eur Heart J 2009;30:2558-2559



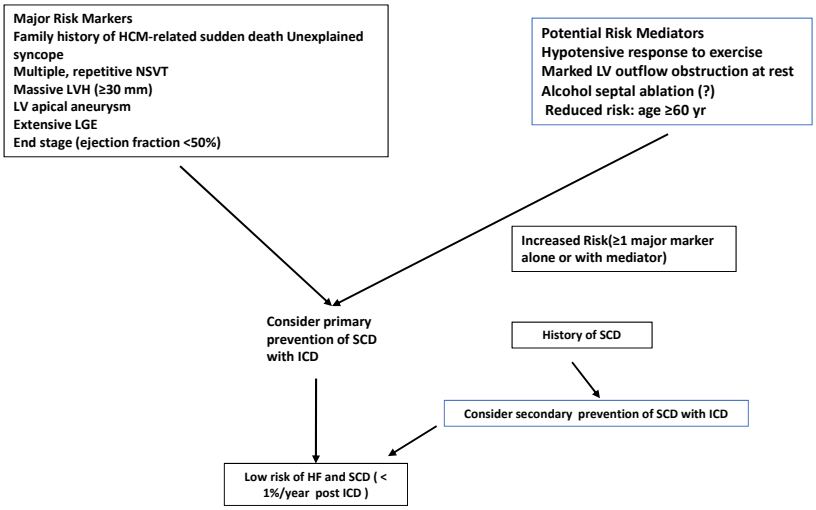
Maron et al Annu. Rev.Med. 2022. 73:363–75



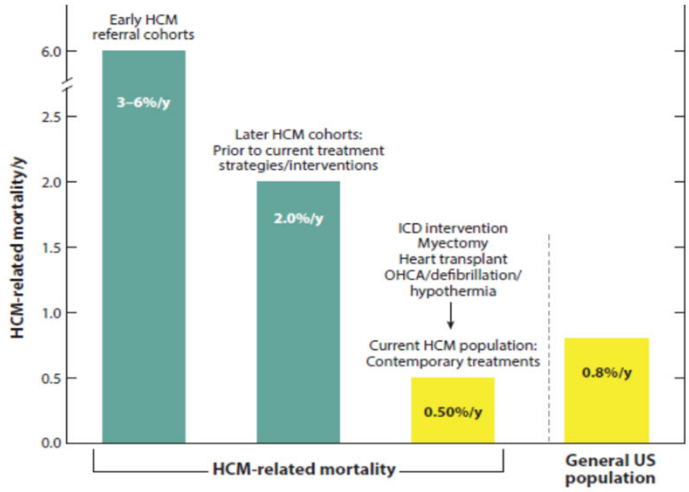
Steve R. Ommen. Circulation. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary, Volume: 142, Issue: 25, Pages: e533-e557, DOI: (10.1161/CIR.0000000000000938)

Therapeutics/Disease Management

Algorithm for prevention of SCD

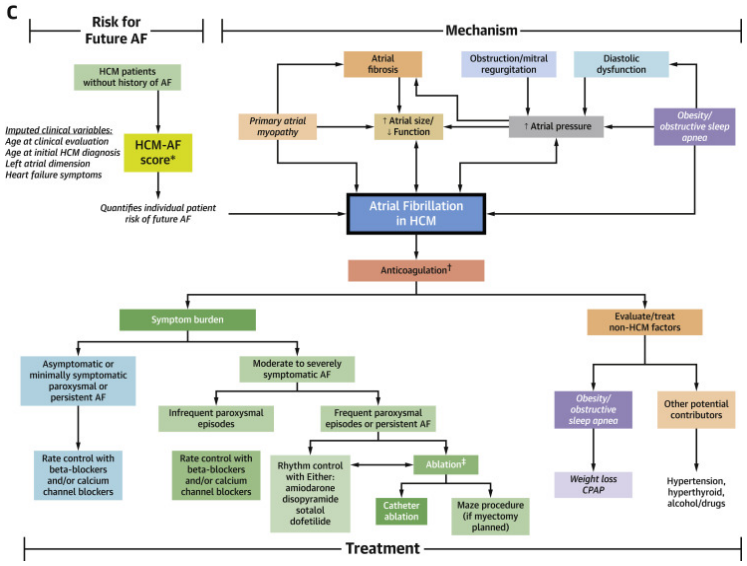


Effect of therapies on HCM –related mortality



Maron et al Annu. Rev.Med. 2022. 73:363–75

Management of Atrial Fibrillation in HCM



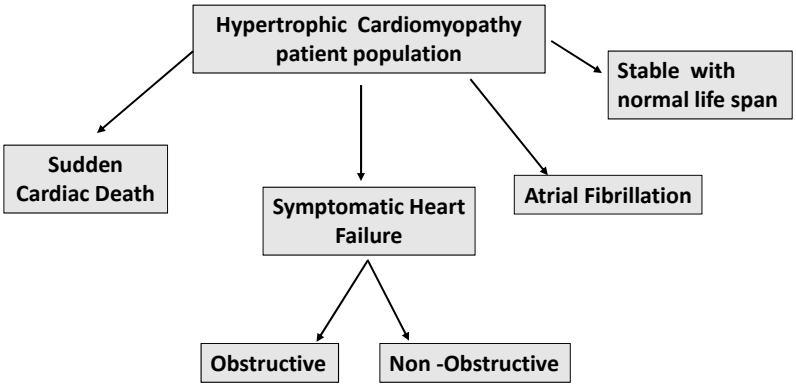
Maron et al Annu. Rev.Med. 2022. 73:363–75

Importance of distinguishing HCM from Athlete's Heart

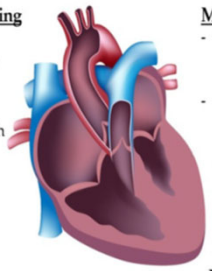
Athlete's Heart

- LV cavity >55mm
- No pathological findings
- Vo2> 110%
- **LV wall 13-15 mm of thickness If present in female athletes it is suggestive of HCM as the max wall thickness is rarely >11mm**

Disease manifestations



Medical Management of HCM



Antifibrotic and anti-cardiac remodeling

- **Spironolactone:** No effect on collagen synthesis/ degradation markers, cardiac MRI, clinical or functional parameters
- **ARBs**:
  - **Losartan**: no significant difference in LV hypertrophy, myocardial performance or exercise capacity
  - **Valsartan**: unpublished results

Myocardial metabolism modulators

- **Perhexilline**: prematurely terminated clinical trial due to lack of efficacy and high rate of adverse effects
- **Trimetazidine:** No significant difference in pVO2, 6-minute walk distance, quality of life, diastolic function, cardiac stress and injury biomarkers

Late sodium current inhibitors

- **Ranolazine:** No significant difference in exercise performance, diastolic function, quality of life
- **Eclelazine**: prematurely suspended trial due to lack of efficiency

Ca2+ desensitizers

- **ECGs**: no in vivo studies
- **Nebivolol**: no in vivo studies
- **NAC**: no significant effect on hypertrophy or fibrosis

?

Myosin inhibitors

- **Blebbistatin**: no in vivo studies due to lack of cardiac myosin II selectivity
- **Mavacamten:** Significant reduction in LVOT gradient, symptoms, cardiac MRI parameters and cardiac biomarkers
- **CK 274**: ongoing clinical trial
- **MYK 581**: ongoing pre-clinical trials

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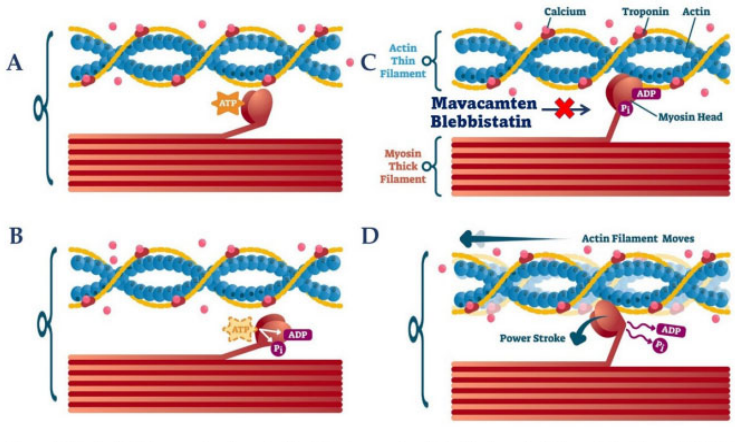
(Panel A): Binding of ATP to myosin head domain produces a decrease in actin affinity thus leading to actin dissociation (relaxed state).

(Panel C): Myosin-to actin filaments.



(Panel B): ATP hydrolysis leads to formation of ADP and Pi.

(Panel D): Conformational changes prompted by Pi release determine the power stroke, with ADP being released at the end of this phase and with a start of a new cycle.

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New drugs – Mechanism of action

- **Mavacamten**: (1) inhibits the release of Pi, (2) decreases the number of myosin heads that bind to actin.
- **Blebbistatin**: inhibits Pi release after ATP hydrolysis.

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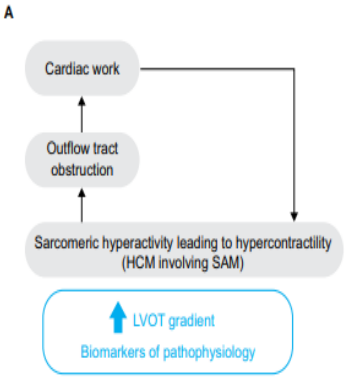
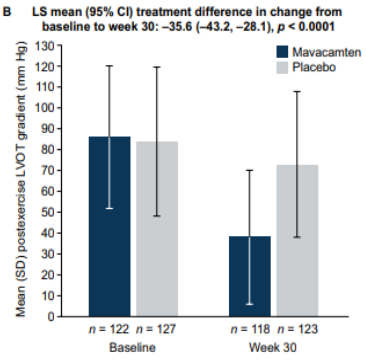
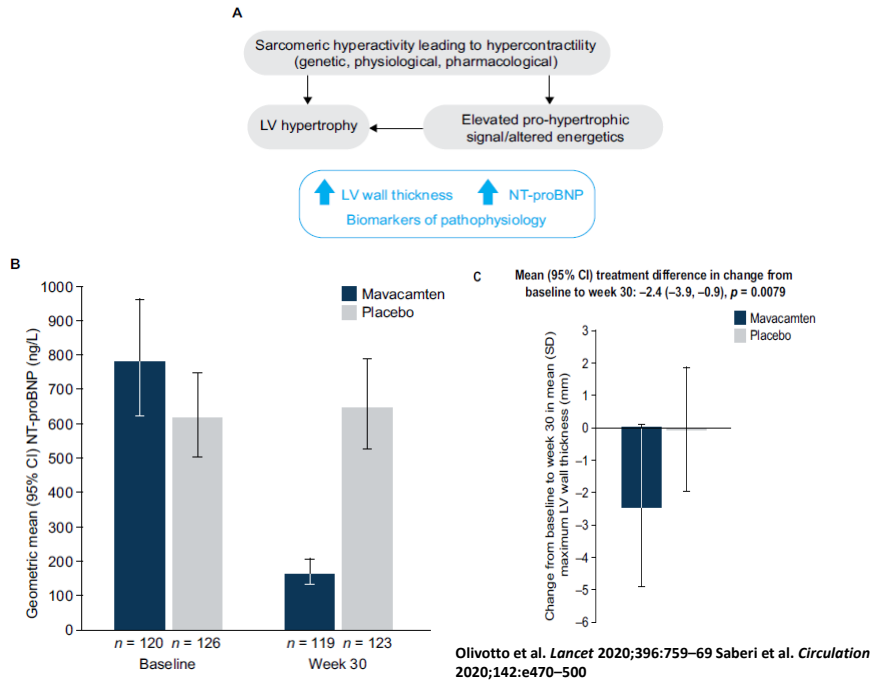


Fig. 1 A The relationship between hypercontractility of the heart, LVOT obstruction, and cardiac work.

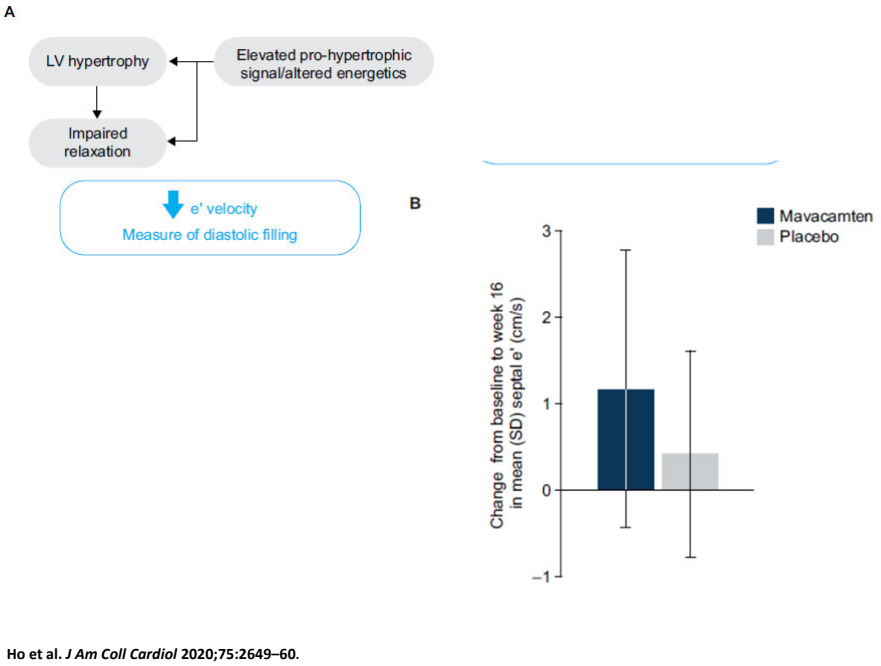


B The effect of mavacamten on post-exercise LVOT peak gradient.

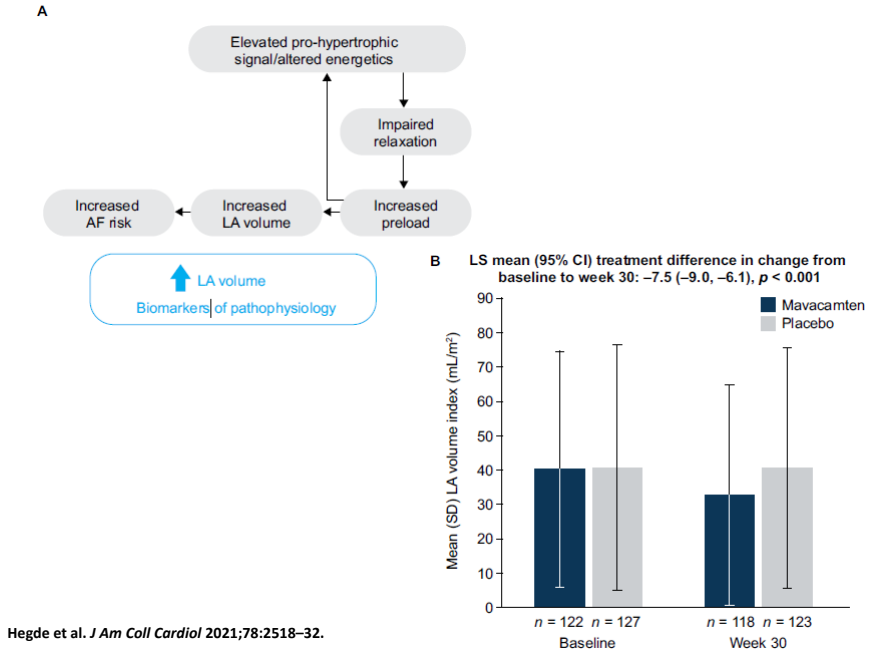
(EXPLORER-HCM). Olivotto et al. Lancet 2020;396:759–69



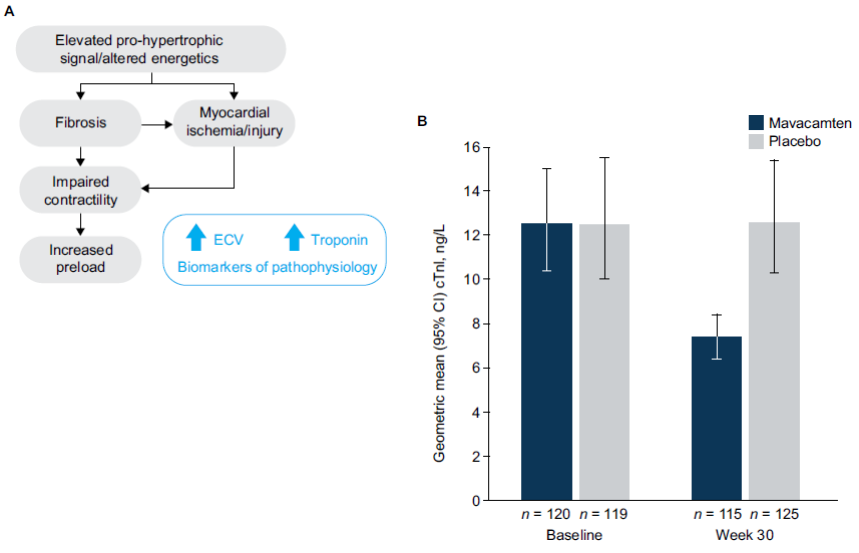
Olivotto et al. *Lancet* 2020;396:759–69 Saberi et al. *Circulation* 2020;142:e470–500



Ho et al. *J Am Coll Cardiol* 2020;75:2649–60.



Hegde et al. *J Am Coll Cardiol* 2021;78:2518–32.



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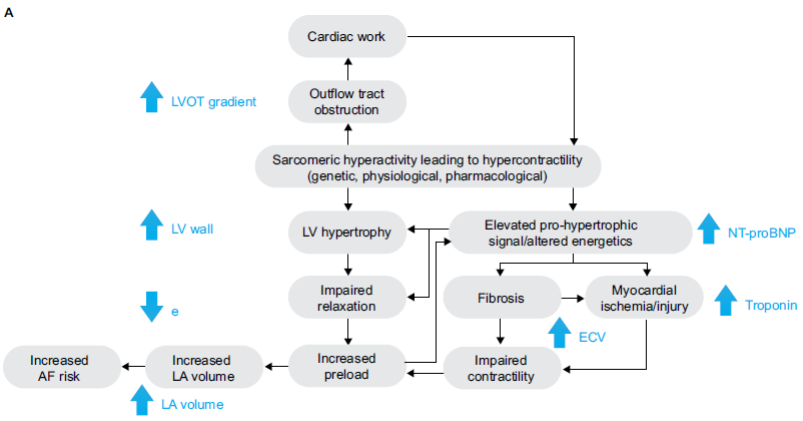
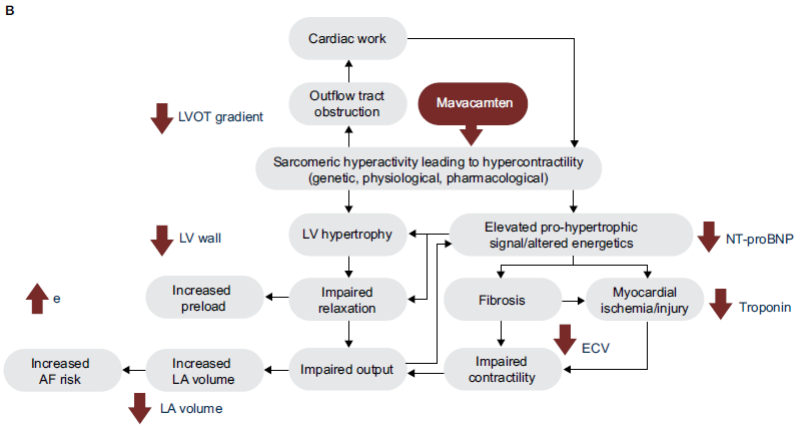


Edelberg et al American Journal of Cardiovascular Drugs 2022 https://doi.org/10.1007/s40256-022-00532-x



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Summary of clinical trials involving myosin inhibitors

Study	Type of Study	Population/ Intervention	Primary Endpoint	Key Findings
PIONEER-HCM [53]	Phase II open-label study	21 symptomatic oHCM: Cohort A: 10–20 mg Mavacamten Cohort B: 2–5 mg Mavacamten	Post-exercise LVOT gradient	Significant decrease of LVOT gradient (−89.5 mmHg in Cohort A and −25.0 mmHg in Cohort B) Secondary outcomes: - increase in pVO2 - well tolerated
EXPLORER-HCM [55]	Phase III RCT	251 symptomatic oHCM patients: Mavacamten vs. Placebo	- Increase in pVO_2 with >1.5 mL/kg/min and at least one NYHA class reduction Or - Increase in pVO_2 of >3 mL/kg/min without NYHA class worsening	Primary outcome: 37% vs. 17% of patients (Mavacamten, respectively placebo) Secondary outcomes: - greater reductions in post-exercise LVOT gradient - greater increase in pVO2 - improved symptom scores
MAVERICK-HCM [62]	Phase II RCT	59 symptomatic non-oHCM Mavacamten vs. Placebo	Frequency and severity of adverse events	No significant difference in the rate of serious adverse events Secondary outcomes: - important reduction of NT-proBNP and cTnI
PIONEER-OLE [65]	Phase II open label extension study	20 (estimated enrollment) Mavacamten as in PIONEER- HCM	Frequency and severity of adverse events up to 260 weeks	Intermediate results at 1 year: - Persistent decrease in LVOT gradient, NT-proBNP, IVS and LAVI - well tolerated
MAVA-LTE (NCT03723655)	Phase II and III open label extension study	310 (estimated enrollment) Mavacamten as in EXPLORER-HCM and MAVERICK-HCM	Frequency and severity of adverse events up to 252 weeks	Ongoing study
VALOR-HCM (NCT04349072)	Phase III RCT	100 (estimated enrollment): Mavacamten vs. Placebo	No of subjects who remain guideline eligible for SRT at Week 16	Ongoing study
REDWOOD-HCM (NCT04219826)	Phase II RCT	60 (estimated enrollment) CK-3773274	Incidence of reported adverse events	Ongoing study

IVS = interventricular septum thickness; LAVI = indexed left atrial volume; LVOT = left ventricle outflow tract; oHCM = obstructive hypertrophic cardiomyopathy; pVO2 = peak oxygen consumption; RCT = randomized controlled trial; SRT = septal reduction therapy.

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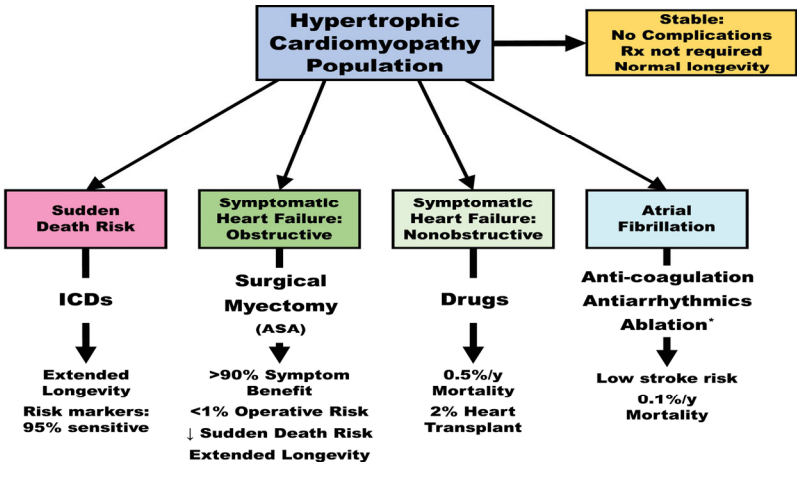
Current Treatments available for HCM



The American Journal of Medicine 2020 133886-888DOI:(10.1016/j.amjmed.2020.03.015)

Summary

- **Shared decision-making**
- **Referral to multidisciplinary HCM centers** with graduated levels of expertise can be important to optimizing care
- **Counseling patients** with HCM regarding the potential for genetic transmission of HCM
- **Optimal care for patients with HCM requires cardiac imaging to confirm the diagnosis**, characterize the pathophysiology for the individual, and identify risk factors/markers
- Assessment of an **individual patient's risk for SCD** continues to evolve
- **Septal reduction therapies** (**surgical septal myectomy and alcohol septal ablation**), have better outcomes.
- **Patients with HCM** and persistent or paroxysmal atrial fibrillation have increased risk of stroke such that oral anticoagulation should be considered independent of the CHADS2-VASC score
- **Heart failure in patients with HCM:** an ejection fraction <50% connotes significantly impaired systolic function and identifies individuals with poor prognosis and who are at increased risk for SCD.
- **The beneficial effects of exercise** can be extended to patients with HCM.

A 25-year-old man presents for evaluation of hypertrophic cardiomyopathy (HCM). He has no exertional symptoms. His father died suddenly at the age of 40 years. A Holter monitor shows occasional premature ventricular complexes (PVCs), but no nonsustained ventricular tachycardia (NSVT). On a Bruce protocol stress test, he has ST depressions with exercise and a hypotensive response to exercise. The aortic outflow velocity is 4 msec; the septal wall thickness is 30 mm.

What is the most appropriate therapy?

A. Metoprolol
B. Diisopyramide
C. Implantable ICD
D. Alcohol ablation of septum
E. Surgical myectomy

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Patient has 3 of the 5 traditional risk factors family history of sudden cardiac death, septal hypertrophy of 30mm, hypotensive response to exercise, nonsustained V. tach, syncope

A 30-year-old man comes to our clinic with a one-year history of exertional chest pain, dyspnea, palpitations. He has had a known heart murmur for several years. Does not take any medications and supplements and denies any recreational substance abuse. A grade 3/6 diamond shaped systolic murmur is appreciated over the lower left sternal border; it is louder during strain phase of Valsalva maneuver and softer with squatting.
what is the diagnosis?
A Hypertrophic Cardiomyopthy
B Sarcoidosis
C Amyloidosis
D Hemochromatosis
E Mitral valve prolapse

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The murmur was louder on Valsalva maneuver and softer with squatting characteristic of hypertrophic cardiomyopathy because of changes in the preload