HCM Changing Trends

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- References to sudden cardiac death - 2400-year old Aphorisms of Hippocrates.
- Seventeenth and eighteenth century- Theophile Bonet, John Baptiste Morgagni, William Harvey, and Giovanni Maria Lancisi variously reported enlarged hearts with increased muscle bulk
- Two French pathologists,Hallopeau and Liouville, described the classic appearance of ASH of IVS in 1869

1957

- Dr. Paul Wood - functional muscular subvalvar aortic stenosis due to gross hypertrophy of the outflow tract.
- Paul Wood had neither the benefit of echo/ surgical view/ PM specimen
- He deduced the nature based solely on his findings : a jerky pulse, double apex beat, and ejection systolic murmur.
- He continued:"*for reasons still difficult though, we do not understand how the muscle gets so thick that it tends to obstruct and cause the outflow tract murmur and thrill… To elucidate the nature of this obstruction I would hesitate to use sympathiometric agents; they may well be dangerous and any manoeuvre which alters afterload or preload however may be instructive*."
- In our current era of declining examination skills, it seems nothing short of miraculous

1958

- First contemporary account of hypertrophic cardiomyopathy by Dr Robert Donald Teare, a pathologist working at St George's hospital in London.

- reported asymmetric hypertrophy of the interventricular septum in 8 patients between the ages of 14 and 44
- Seven of these caused sudden death in young adults

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Clinical Course and Management of Hypertrophic Cardiomyopathy

Barry J. Maron, M.D.

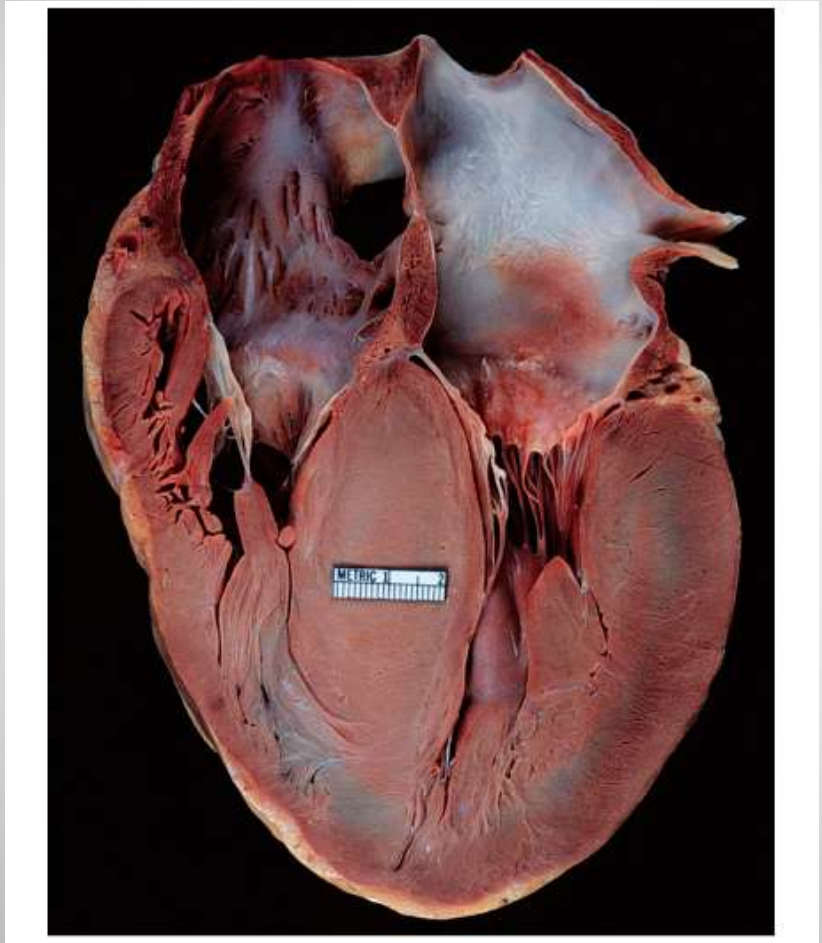
Introduction

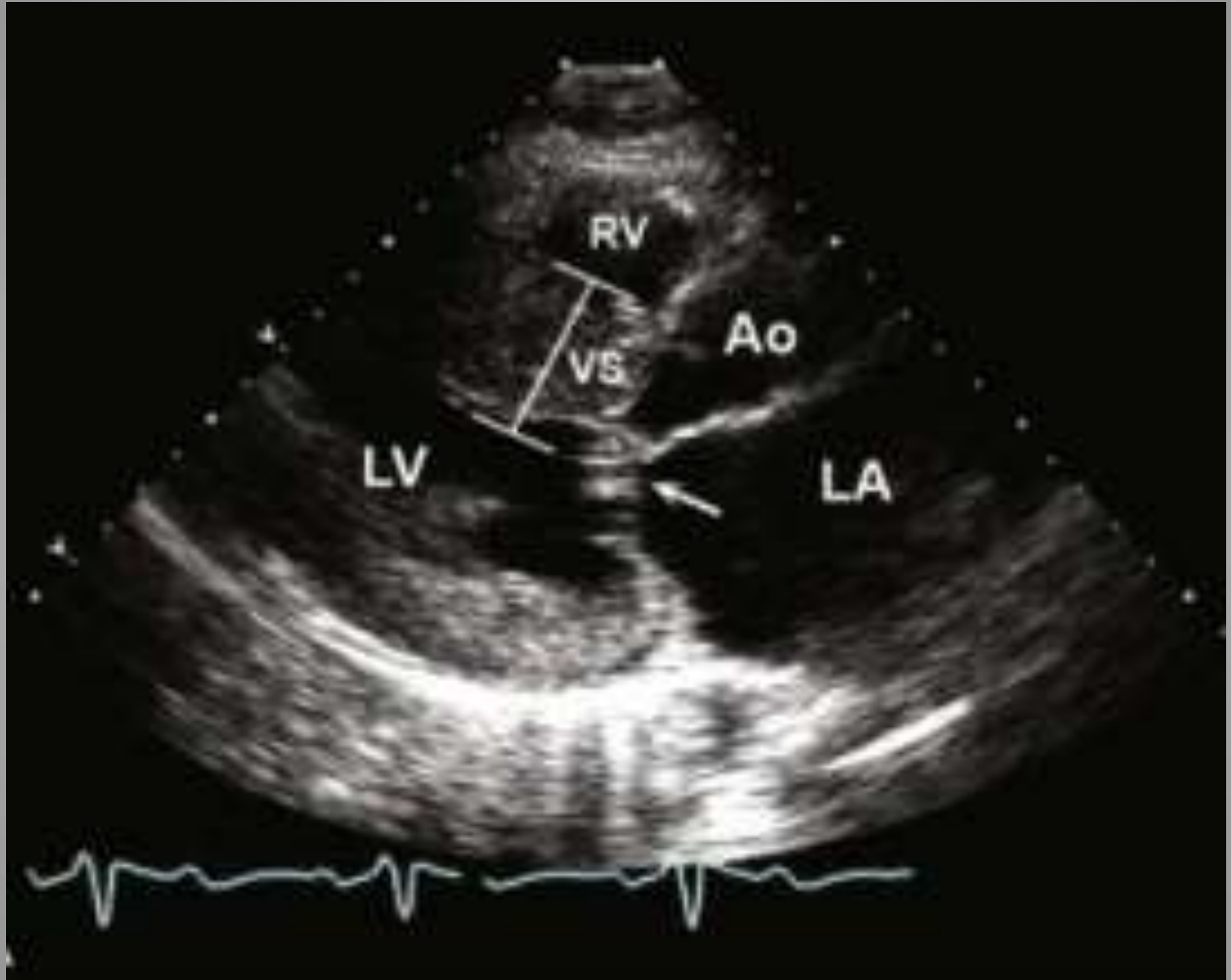
- The most common monogenic cardiovascular disorder
- Is diverse in presentation and natural history
- Frequently misunderstood
- Often under recognized in clinical practice.

- First clinical description - 55 years ago by Braunwald group at the NIH
- was called idiopathic hypertrophic subaortic stenosis
- More than 18,000 reports
- HCM differs markedly from the disease of previous eras.

Definition

- Hypertrophied, nondilated left ventricle
- Identified by means of echocardiography or magnetic resonance imaging
- In the absence of another cardiac, systemic, metabolic, or syndromic disease.




RV
VS
Ao
LV
LA

M-mode or 2D cut-off value of left ventricular wall thickness to make a diagnosis of HCM is:

- ≥15 mm in adults;
- >12–15 mm in relatives;
- ≥2 SD in pediatric patients
- septal-to-posterior diastolic wall thickness ratio ≥ 1.3 (or ≥1.5 in hypertensive patients)

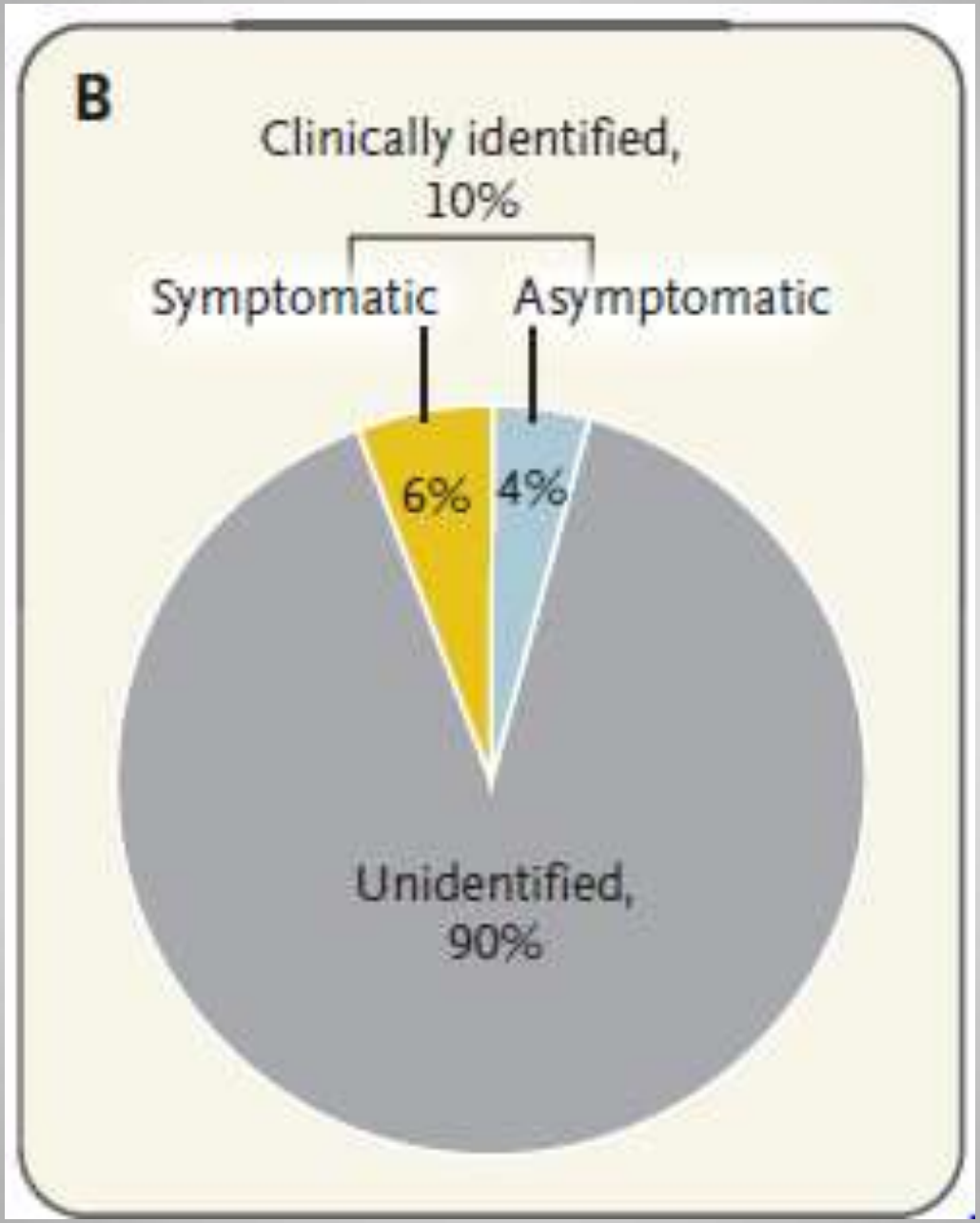
Epidemiology

- prevalence of 1 case per 500 persons in the general population (by echo)
- prevalence (1 case per 200) when both clinical and genetic diagnoses, including those in family members
- 750,000 persons in the United States may be affected by HCM.
- However, the disease has been diagnosed in only 100,000
- Under recognition - women and blacks

- Identified in 122 countries
- Spontaneous mutations probably accounting for majority
- 20 million people globally affected.
- Affects both sexes equally
- Clinical, phenotypic expression and genetic substrate do not vary according to demographic characteristics.

A

Distribution (in red), 122 countries, accounting for 88% of world population
Prevalence, 1 case per 200–500 persons
Estimated 20 million people affected worldwide


B
Clinically identified,
10%
Symptomatic
Asymptomatic
6%
4%
Unidentified,
90%

Genetic factors

- Inherited in an autosomal dominant pattern
- Associated with mutations in 11 or more genes encoding proteins of contractile components of the cardiac sarcomere
- Beta-myosin heavy chain and myosin-binding protein C genes most commonly involved.
- More than 2000 sarcomere mutations identified.
- Genotype–phenotype correlations have been inconsistent
- single (or multiple) sarcomere variants are unreliable in predicting prognosis

- gene carriers - no cardiac events or symptoms, and many will never have HCM but can transmit

- can also identify metabolic and storage phenocopies (e.g., lysosome-associated membrane protein 2 [LAMP2] cardiomyopathy, Fabry's disease, PRKAG2, and amyloidosis) that mimic HCM

Morphology

- Borderline thickness (13 to 14 mm) - hypertension or physiologic athlete's heart
- However, any LV thickness is consistent with the spectrum of HCM, including normal dimensions in gene carriers.
- Greater LV thickness is associated with an increased risk of sudden death but not of progression to heart failure.

Phenotype expression

- includes a myriad of asymmetric patterns of hypertrophy that are highly variable even among first-degree relatives.
- These patterns can be
  - diffuse
  - segmental (including apical)
  - Focal
  - noncontiguous
  - extension into the right ventricle
  - elongated mitral leaflets
  - blood-filled crypts

ECHOCARDIOGRAPHY

- Diffuse hypertrophy of the ventricular septum and anterolateral free wall (70% to 75%)
- Basal septal hypertrophy (10% to 15%)
- Concentric hypertrophy (5%)
- Apical hypertrophy (<5%)
- Hypertrophy of the lateral wall (1% to 2%).
- Mitral annulus velocity, Ea - status of myocardial relaxation - reduced in most patients with HCM


2D/CD/Dop
Delete Set
Lock Set
UNIVERSITY OF MICHIGAN HEALTH SYSTEM
CW Focus= 83mm
CW Gain= 12dB
3V2c
H3.5MHz 180mm
ECHO
General
Pwr= 0dB
MI2d=1.6 TIS=0.8
Store in progress
1:57:15
CW:2MHz
2.0
m/s
B

Family screening

- diagnostic imaging every 12 to 18 months from the ages of 12 to 21 years
- LVH commonly develops during periods of accelerated growth
- Possibility of delayed penetrance of the phenotype into midlife
- extended imaging surveillance at 5-year intervals.

Outflow obstruction

- 70% have mechanical impedance to left ventricular outflow (gradients ≥30 mm Hg) at rest or with physiological provocation
- Subaortic gradients are characteristically dynamic and subject to change with physiological loading conditions
- these changes are often responsible for daily fluctuations in symptoms.

- Outflow obstruction is usually produced by
  - mitral-valve systolic anterior motion and septal contact due to flow drag
  - Congenital, anomalous insertion of the papillary muscle directly into the mitral valve

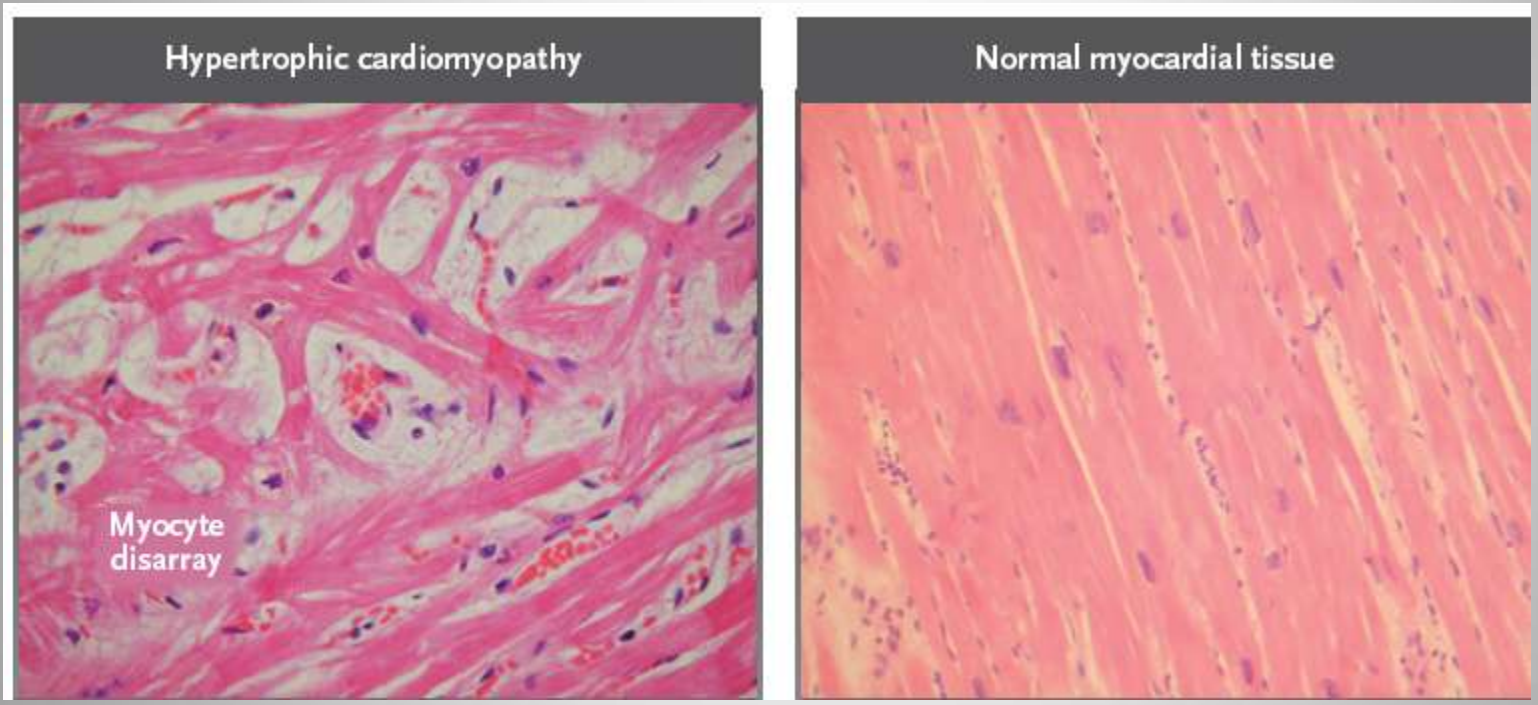
Clinical course

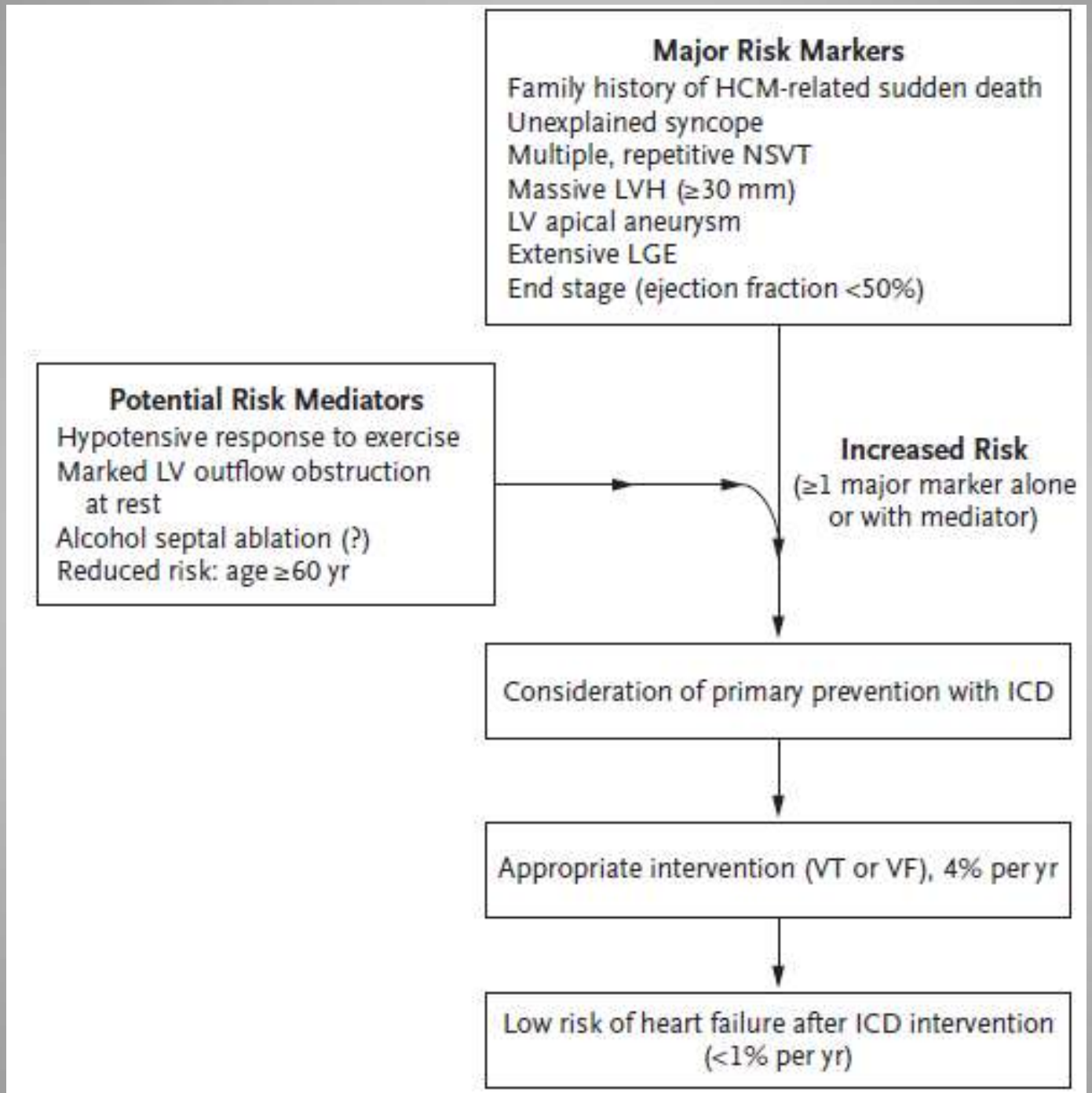
- Diverse in nature
- Most patients
  - remain free of clinically significant symptoms and adverse events
  - do not require major treatment interventions
  - have normal or extended longevity
- Few have adverse effects

Sudden death

- HCM initially described - SCD
- The most visible complication
- Media coverage of cardiac arrests in competitive athletes
- Unpredictable arrhythmogenic substrate - disorganized myocardial architecture, interstitial collagen deposition, and replacement scarring as a consequence of coronary microvascular mediated flow dysfunction and ischemia

HISTOPATHOLOGY




Major Risk Markers
Family history of HCM-related sudden death
Unexplained syncope
Multiple, repetitive NSVT
Massive LVH (≥30 mm)
LV apical aneurysm
Extensive LGE
End stage (ejection fraction <50%)
Potential Risk Mediators
Hypotensive response to exercise
Marked LV outflow obstruction at rest
Alcohol septal ablation (?)
Reduced risk: age ≥60 yr
Increased Risk
(≥1 major marker alone or with mediator)
Consideration of primary prevention with ICD
Appropriate intervention (VT or VF), 4% per yr
Low risk of heart failure after ICD intervention (<1% per yr)

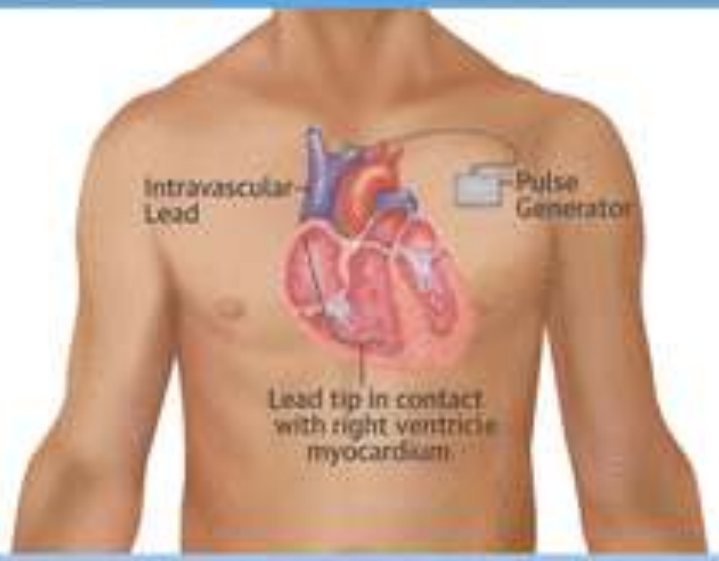
- Paradoxically, patients with HCM who survive into the 7th decade and beyond, even those with risk markers, are largely protected from sudden death
- SCD rate 0.2% per year, which is similar to the rate in the general population
- Minority – fatal arrhythmias without risk factors

- Intense competitive sports not recommended
- moderate level of noncompetitive exercise is acceptable
- genetically affected persons without LVH - no restriction on activity
- abnormal ECG patterns (present in 90%) do not predict the clinical course
- may represent diagnostic markers for the subsequent development of HCM

- Defibrillator interventions 4% per year for primary prevention
- 10% per year for secondary prevention after cardiac arrest
- intervals of 10 to 15 years - between implantation and intervention
- rate of device complications (3 to 5% per year) —
  - Inappropriate shocks due to supraventricular or sinus tachycardia
  - lead fractures.
- Subcutaneous defibrillators have potential advantages
  - protection of the venous system in younger
  - avoidance of long-term lead complications,
- efficacy of such defibrillators remains unclear

S-ICD

Transvenous ICD



S-ICD Advantages

- Eliminate need for vascular access
- Possible to implant without fluoroscopy
- Reduced mid-term risk of lead malfunction
- Eliminate certain procedural risks (e.g. pneumothorax, tamponade)
- Improved arrhythmia discrimination
- Relative ease of extraction
- Hardware infections not associated with endocarditis

Transvenous ICD Advantages

- Pacemaker and ATP functionality
- Smaller pulse generator
- Better battery longevity
- Shorter charge time-faster shock delivery
- Able to deliver CRT
- No pre-implant ECG screening required
- Long-term follow-up data available

Lewis, G.F. et al. J Am Coll Cardiol. 2016; 67(4):445-54.

Atrial Fibrillation

- Atrial fibrillation is the most common sustained arrhythmia in patients with HCM,
- usual age at onset 50 to 55 years
- Predisposing factors
  - Hemodynamic loading conditions with LAE
  - primary atrial myopathy
- Adverse consequences - to loss of the atrial kick in diastolic dysfunction.

- Repetitive episodes of AF impair the quality of life
- but do not increase the risk of SCD or progression of HF
- The frequenc y can be reduced with
  - amiodarone/ sotalol/ disopyramide/ dofetilide
  - catheter ablation
  - maze procedure combined with myectomy
- Transition from paroxysmal to permanent AF 25%

Heart failure

- Exertional dyspnea and fatigue
- With or without chest pain
- Women have more severe symptoms, with greater impairment in cardiopulmonary exercise performance
- No difference in mortality including SCD

Heart Failure and Outflow Obstruction

- primary cause is LVOTO → elevated LV pressure and secondary MR
- often accompanied by PAH,DD and absence of an increase in stroke volume with exercise
- heart failure is about 5% per year

- Beta blockers and CCB’s have inconsistent effects on the resting gradient
- Although exercise provoked obstruction can be blunted by inhibiting sympathetic stimuli with beta-blockers.
- The negative inotropic properties of disopyramide with a beta-blocker can reduce resting gradients
- drug therapy alone doesn’t alter the natural history of HCM

Table 2. Medical Therapy in Patients with Hypertrophic Cardiomyopathy.*

Drug	Drug Actions*			Dose			Side Effects
	Decrease Resting Gradient	Decrease Exercise Gradient	Improve Diastolic Function	Initial	Maximal	End Point of Adjustment	
Beta-blockers (e.g., atenolol, propranolol, and metoprolol)	+	+++	+	25 mg twice daily	600 mg daily	Resting heart rate <60–70 beats/min	Bradycardia, hypotension, fatigue, bronchospasm
Calcium blockers (e.g., verapamil)	+	+++	++	240 mg daily (long-acting formulation)	480 mg daily	Resting heart rate <60–70 beats/min	Bradycardia, hypotension, constipation
Disopyramide†	++	+++	+	100 mg twice daily (sustained release formulation)	600 mg daily	Relief of symptoms	Anticholinergic effect, increase in the corrected QT interval

NYHA class III or IV with LVOTO at rest or with physiological provocation (gradient ≥50 mm Hg) are candidates for

- Primary transaortic septal myectomy or
- in selected patients, alcohol septal ablation

Myectomy

- Muscular resection from the basal ventricular septum
- remodeling of the mitral valve with plication to decrease slack and mobility,
- reconstruction of submitral intraventricular structures

- now established as one of the safest open-heart procedures
- operative mortality of 0.4%
- 95% reduction in mortality from 35 years ago.

- By abolishing subaortic gradients and normalizing LV and PA pressures, myectomy permanently reverses symptoms of heart failure (regardless of their prior duration)

- restoring quality of life in 90 to 95%
- more than 70% - completely asymptomatic.
- long-term survival equal to general population
- possible reduction in the risk of sudden death.

- Lack of symptomatic relief after the gradient is abolished

- ✓ massive hypertrophy leading to postoperative systolic or diastolic dysfunction

- ✓ Persistent atrial fibrillation.

Alcohol septal ablation

- Indications - advanced age with severe symptoms that are refractory to drug therapy who are not candidates for myectomy
- Contraindications - unfavorable anatomy of the left ventricular outflow tract and septal perforator artery
- Mechanism – basal septal thinning and LVOT enlargement

- Advantages- less invasive procedure and requiring a shorter hospital stay
- Complications –
  - 10% require a pacemaker for heart block
  - Arrhythmias may increase -septal scarring.
  - 10% require repeat ablation
- procedural mortality -1%, with survival rates that are similar to those for myectomy.

DDD Pacing

- Objective measurements of exercise capacity did not differ significantly
- Overall decrease in outflow tract gradient (25 to 40 % of baseline)
- Role of dual-chamber pacing - patients at high risk for other therapeutic modalities.
- Candidates for dual-chamber pacing
  - Significant bradycardia in which pacing may allow an increased dosage of medication
  - Patients who need ICD as a primary treatment

Table 3. Comparative Features of Septal-Reduction Therapies.

Therapy	Mortality	Residual Gradient	Effectiveness	Follow-up	Complications		Time to Resolution of Gradient
	%	*mm Hg*	*% of Patients*	*Yr*	*Type*	*% of Patients*	
Dual-chamber pacing	<1	<40	10–40	10	Infection or perforation	<2	4 wk
Septal myectomy*	<2–3	<10	>90	>30	Complete heart block Ventricular septal defect Aortic regurgitation	<3 <1 <1	Immediate
Septal ablation†	<2–3	<20	70–80	<5	Complete heart block Ventricular septal defect Large myocardial infarction	10–40 Unknown Unknown	8–12 wk

Heart Failure without Obstruction

- One third of patients
- stable and favorable prognosis.
- beta-blockers and verapamil have beneficial effects
- 10% have progressive end-stage heart failure refractory to maximum medical management
  - Transformation to systolic pump failure
  - Regression of hypertrophy due to diffuse scarring

Factors that predict end-stage heart failure

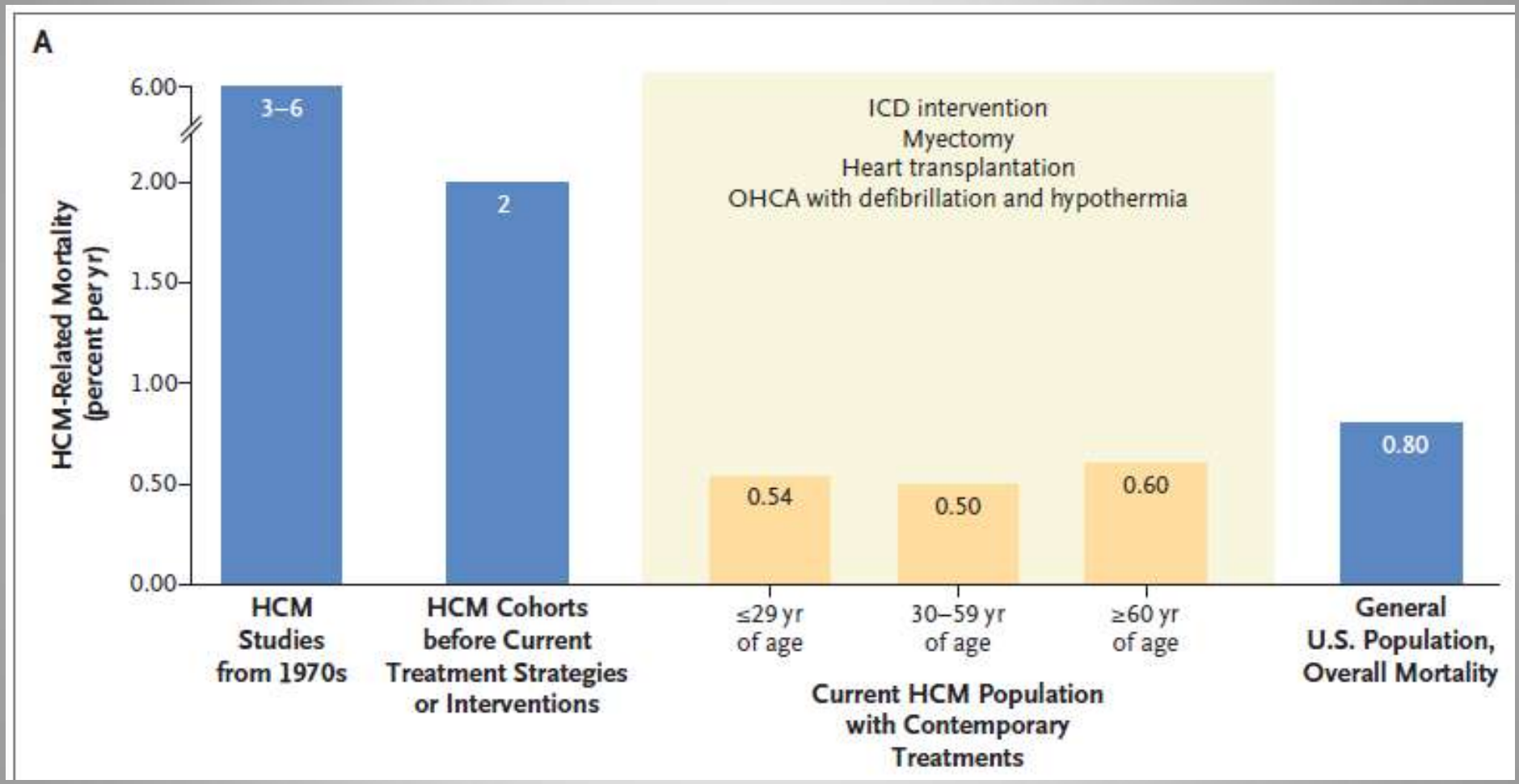
- extensive fibrosis with a borderline EF
- family history of end-stage disease.

Treatment options

1. Cardiac transplant
2. CRT
3. Apical myectomy

Outcomes

- Early clinical descriptions of HCM mortality rates (up to 6% per year),
- Present mortality rate can be as low as 0.5% per year
- 90% reduction in mortality from 35 years ago, independent of age
- Indeed most deaths in affected patients are unrelated to HCM


A
HCM-Related Mortality (percent per yr)
6.00
2.00
1.50
1.00
0.50
0.00
3–6
2
ICD intervention
Myectomy
Heart transplantation
OHCA with defibrillation and hypothermia
0.54
0.50
0.60
0.80
HCM Studies from 1970s
HCM Cohorts before Current Treatment Strategies or Interventions
≤29 yr of age
30–59 yr of age
≥60 yr of age
Current HCM Population with Contemporary Treatments
General U.S. Population, Overall Mortality

Conclusion

- Once regarded as a rare condition with an ominous prognosis and limited management options
- HCM is now recognized as a worldwide, relatively common, and treatable form of genetic heart disease that often does not affect life expectancy
- characterized by diverse clinical, genetic, and morphologic features
- risk of sudden death from arrhythmia
- Clinical diagnosis and treatment have been greatly enhanced by modern imaging techniques (MRI/DSE)

- Therapeutic armamentarium has improved life expectancy and the quality of life

Mimicking Hypertrophic Cardiomyopathy

- Chronic hypertension
- RV hypertrophy
- cardiac amyloidosis
- Athlete's heart
- Pheochromocytoma
- Long-term hemodialysis
- Fabry disease
- Friedreich ataxia.

Apical hypertrophy - apical cavity obliteration caused by hypereosinophilic syndrome or noncompaction.

Dynamic LVOT obstruction - DDs

- Elderly patients with hypertension treated with vasodilators, diuretics or digoxin
- Postoperative period intravascular volume depletion and inotropic use.
- AS after AVR
- Mitral valve prolapse after MVR
- Acute anterior-apical MI
- Some patients with apical ballooning

Athlete's Heart Vs Hypertrophic Cardiomyopathy

HCM	Athletic heart
• Can be asymmetric	• Concentric & regresses
• Wall thickness: > 15 mm	• < 15 mm
• LA: > 40 mm	
• LVEDD :< 45 mm	• < 40 mm
• Diastolic function: always abnormal	• > 45 mm • Normal

Thank You…