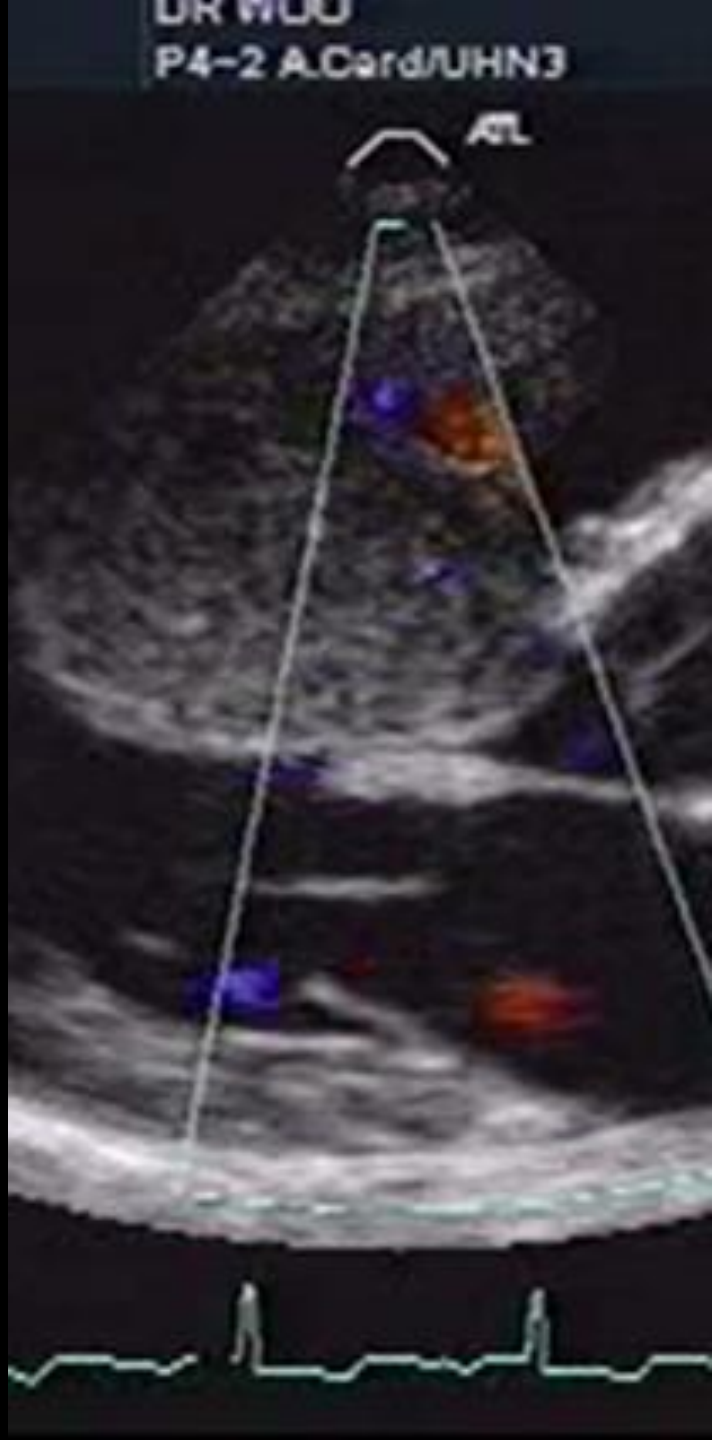
קרדיומיופטיה היפרטרופית HCM

לימודי המשך למתמחים
בקרדיולוגיה

24.09.20

דר' גיל מורבסקי



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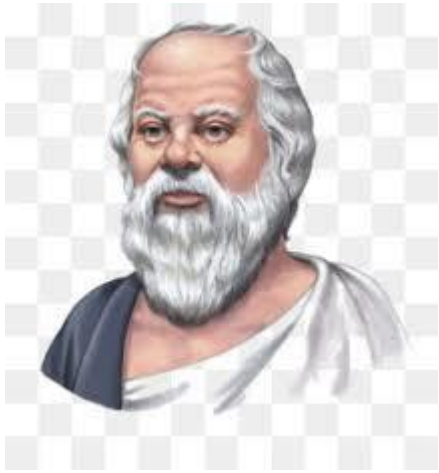


Room - MORAVSKY

על מה נשוחח היום

- הקדמה קצרה – HCM
- סיפור של מטופל
- לב של ספורטאי לעומת HCM
- ב.פיזיקלית ואקו ב-HCM
- גנטיקה ב-HCM
- הטיפול ב-HCM
- ריבוד סיכונים ל-AICD

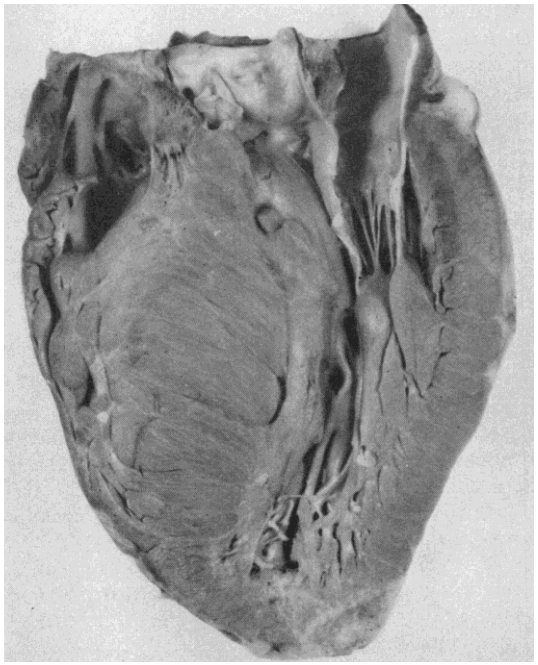
- תודות לדר' מונקיאר ולדר' מרון (בוסטון) על שיתוף סליידים

מר שמשון...

- בן 38
- הופנה למרפאתך עקב אוושה סיסטולית "חדשה" בבדיקה שגרתית אצל רופא המשפחה

Background

- In 1958, Teare described “asymmetrical hypertrophy of the heart in young adults”
- Described a 14 year old boy who had a “black out” while biking
- 5 months later he collapsed while being chased in school and was dead on arrival in hospital



Teare D. Br Heart J 1958; 20: 1-8

Historical Perspective

- HCM was initially described by Teare in 1958
  - Found massive hypertrophy of ventricular septum in small cohort of young patients who died suddenly
- Braunwald was the first to diagnose HCM clinically in the 1960s
- Many names for the disease
  - Idiopathic hypertrophic subaortic stenosis (IHSS)
  - Muscle subaortic stenosis
  - Hypertrophic obstructive cardiomyopathy (HOCM)

"At this time we are aware of no method of management that can specifically and favorably influence the course of a patient with idiopathic ventricular hypertrophy."

Eugene Braunwald
Edwin C. Brockenbrough
Andrew G. Morrow

Circulation, Volume XXVI, August 196

Definition

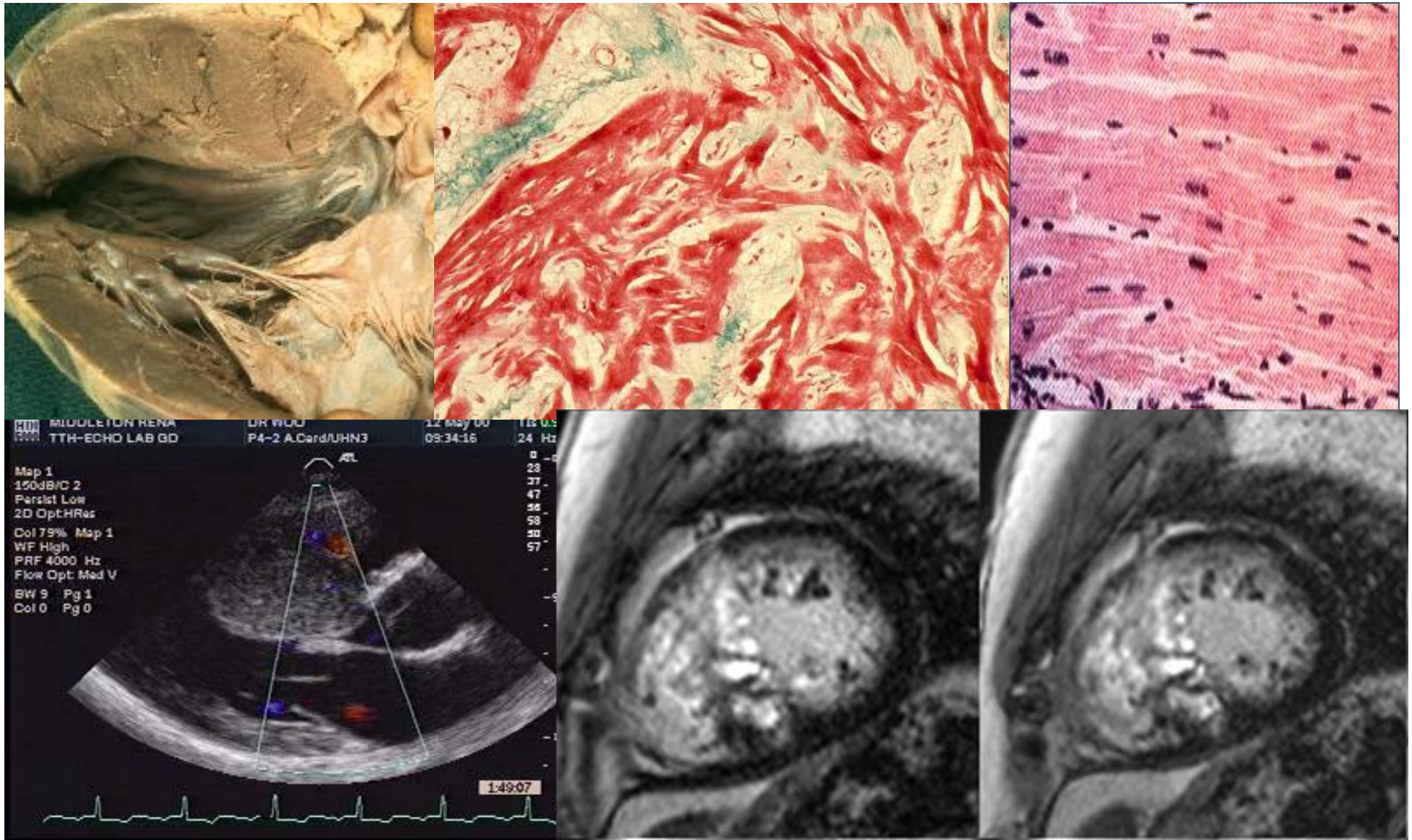
- The diagnosis of HCM is based upon
  - Unexplained LV hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy

2011 ACCF/AHA Guideline on HCM

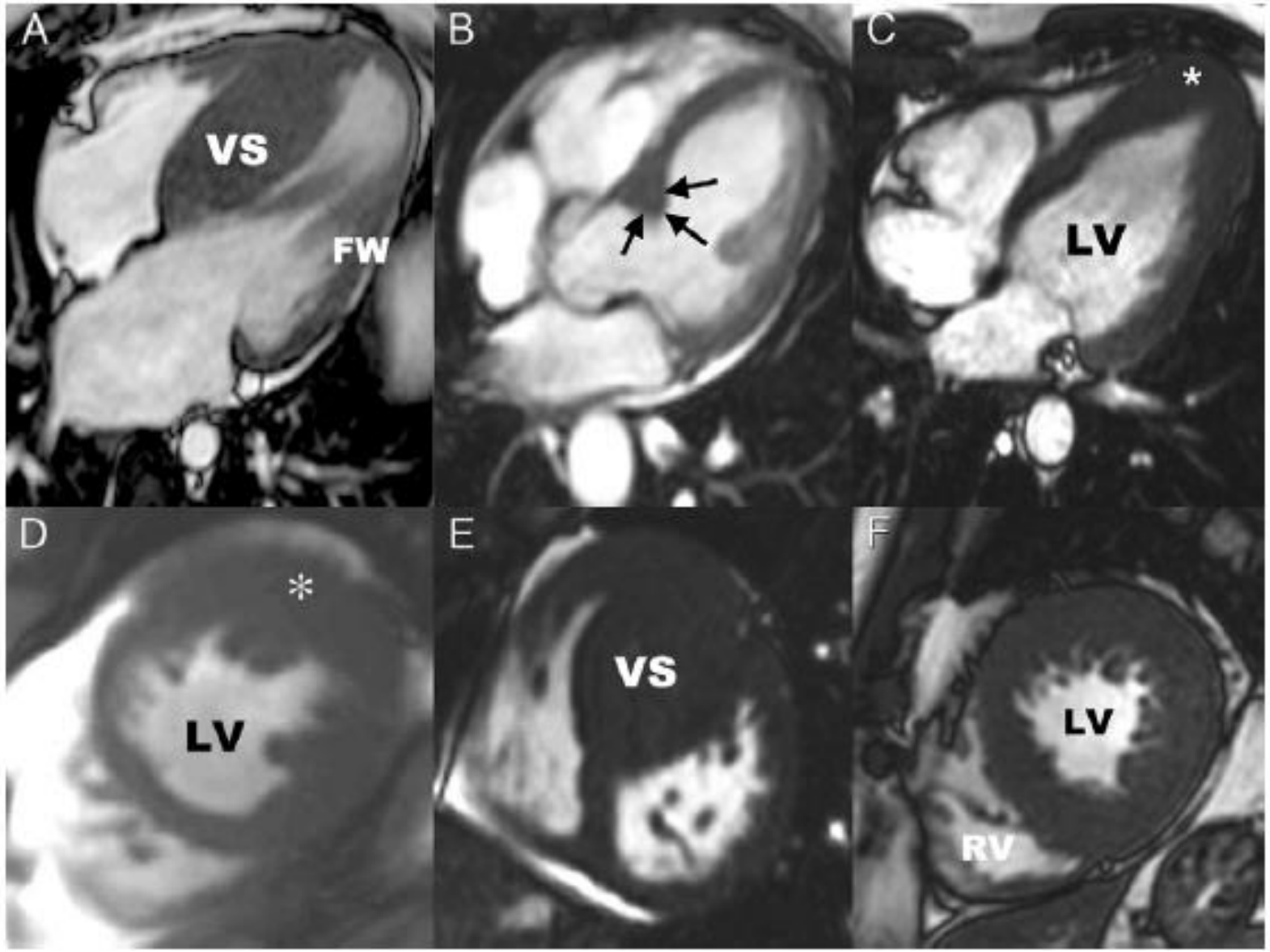
- The diagnosis of HCM is based on the presence of unexplained LV hypertrophy, defined as a maximum end-diastolic wall thickness ≥15 mm, in any myocardial segment on echocardiography, CMR, or CT imaging
- HCM may also be considered in individuals with a lesser degree of LV hypertrophy (wall thickness ≥13 mm) in the context of a family history of definite HCM or a positive genetic test

- Hypertrophic cardiomyopathy is the most prevalent, heritable cardiovascular disease (1/500) and the most common cause of sudden cardiac death in young athletes

Histopathology of Hypertrophic Cardiomyopathy: Hypertrophy, Fiber Disarray, Fibrosis



Phenotypic Variability of Hypertrophy: MRI

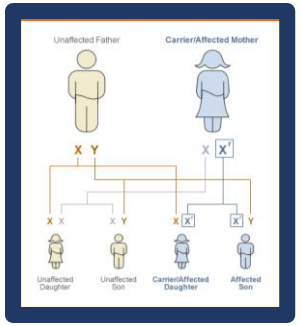


Principal causes of cardiac hypertrophy

- **Hypertension**
- **Aortic valvular stenosis**
- **Athlete’s heart (physiologic)**
- **Idiopathic/genetic**
- **Infiltrative**
- **Metabolic**

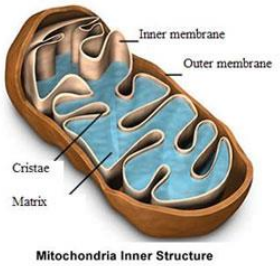
סיבות להיפרטרופיה

מחלות מטבוליות



מחלות אגירה

מיטוכונדריאליות



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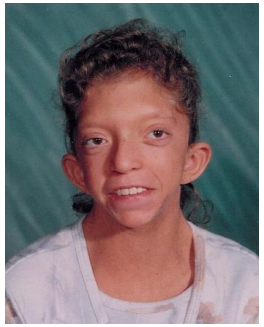
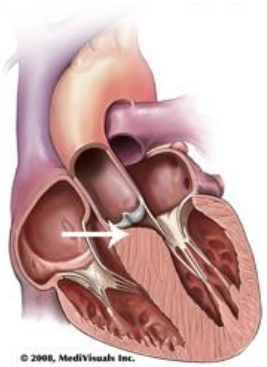
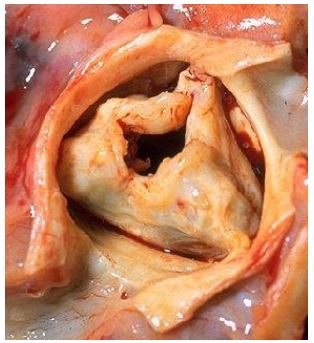


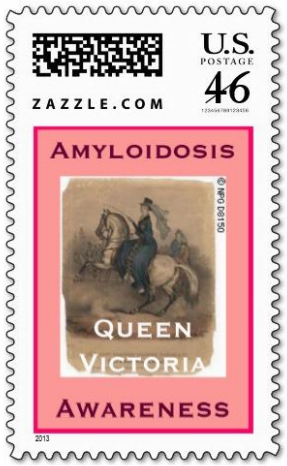
HCM

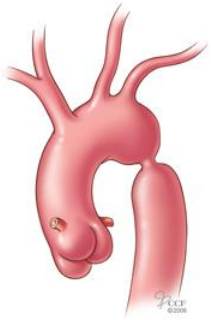


עליה בתנגודת



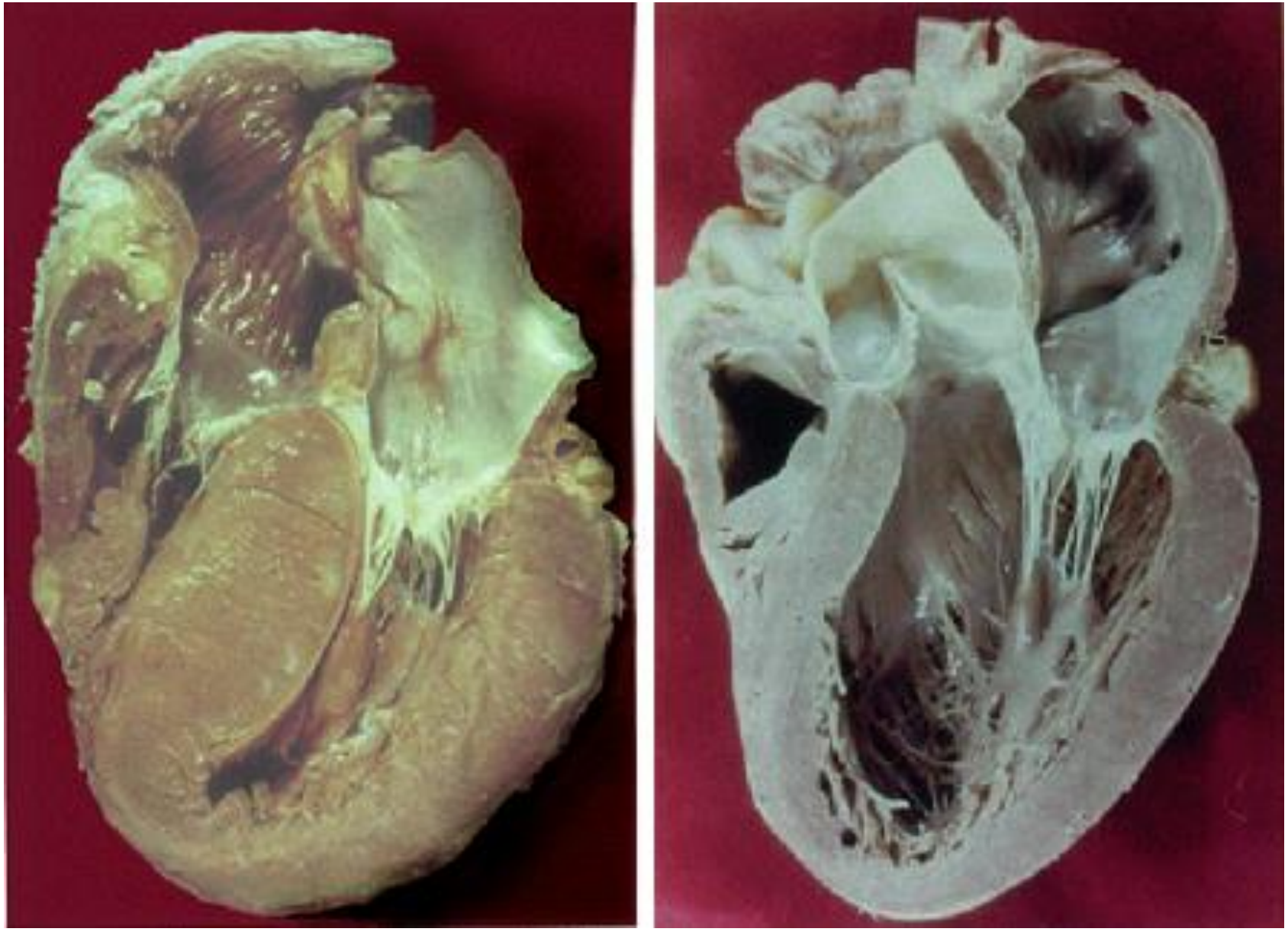
אינפילטרטיביות





מצבים פיזולוגיים

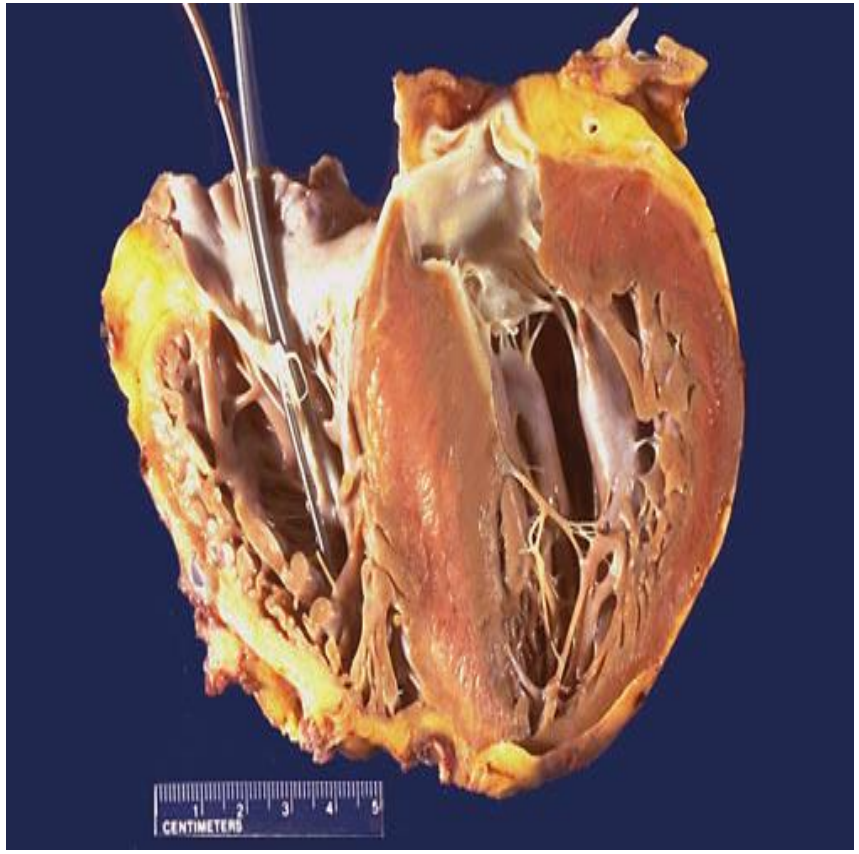
Hypertrophic Cardiomyopathy (HCM)



HCM

Gross morphology
Massive myocardial hypertrophy, usually without dilation

Asymmetric septal hypertrophy
disproportionate thickening of the ventricular septum as compared with the free wall of the left ventricle (ratio greater than 1.3)



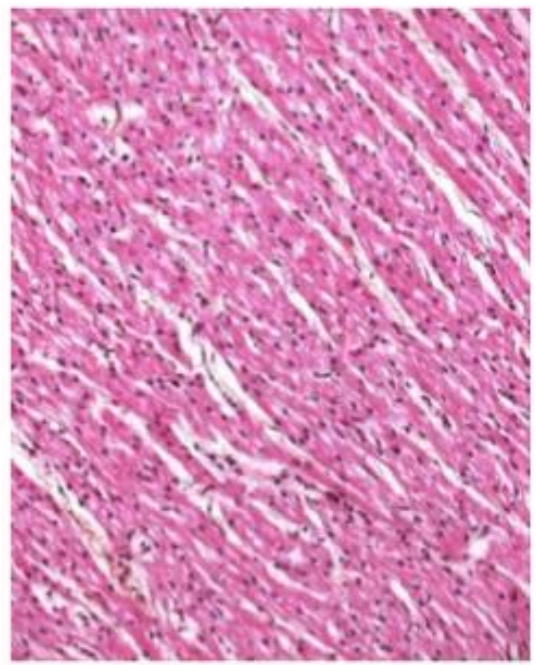
HCM-Histology

Extensive myocyte hypertrophy to a degree unusual in other conditions (transverse myocyte diameters frequently >40 µm (normal, 15 µm))

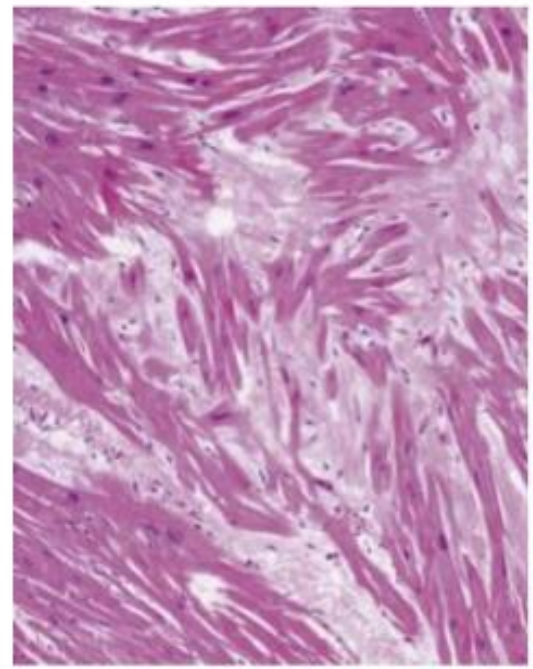
Myofiber disarray - haphazard disarray of bundles of myocytes, individual myocytes, and contractile elements in sarcomeres within cells

Interstitial and replacement fibrosis

Histopathology

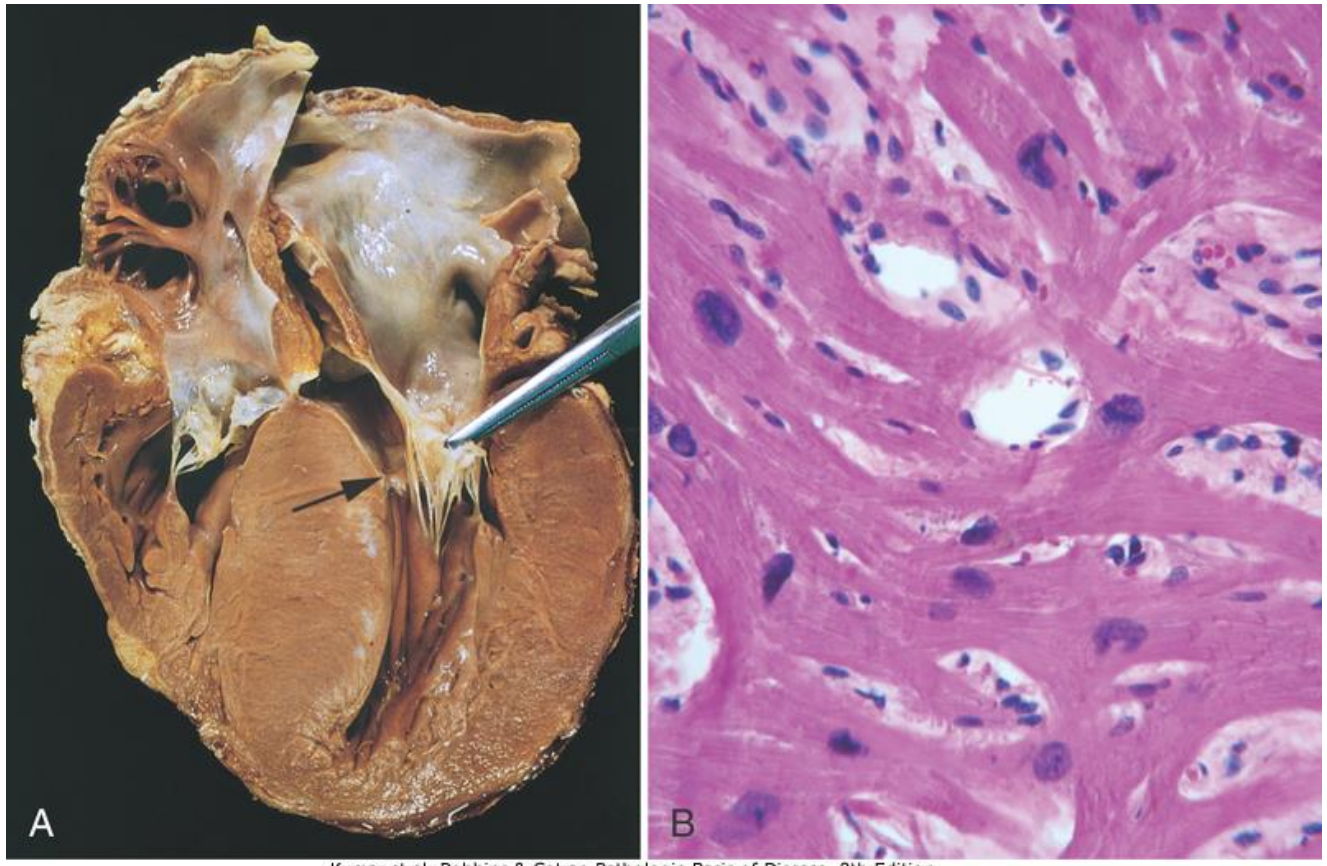


Normal myocardium



Myocardium in HCM

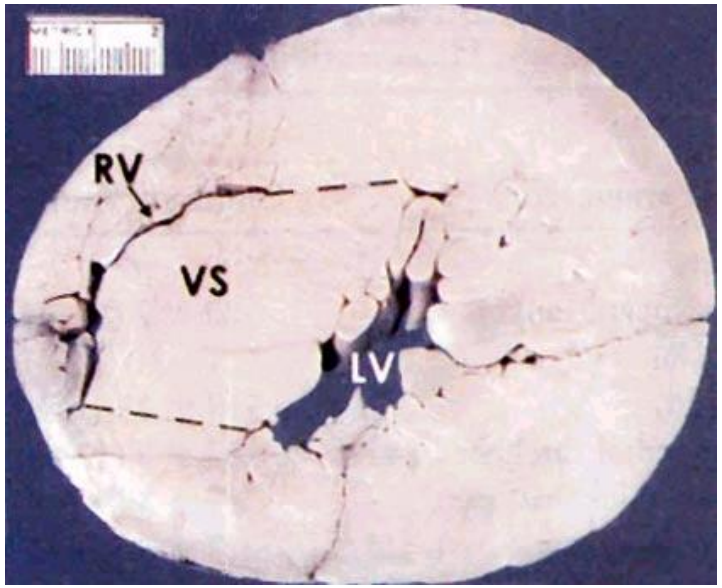
HCM

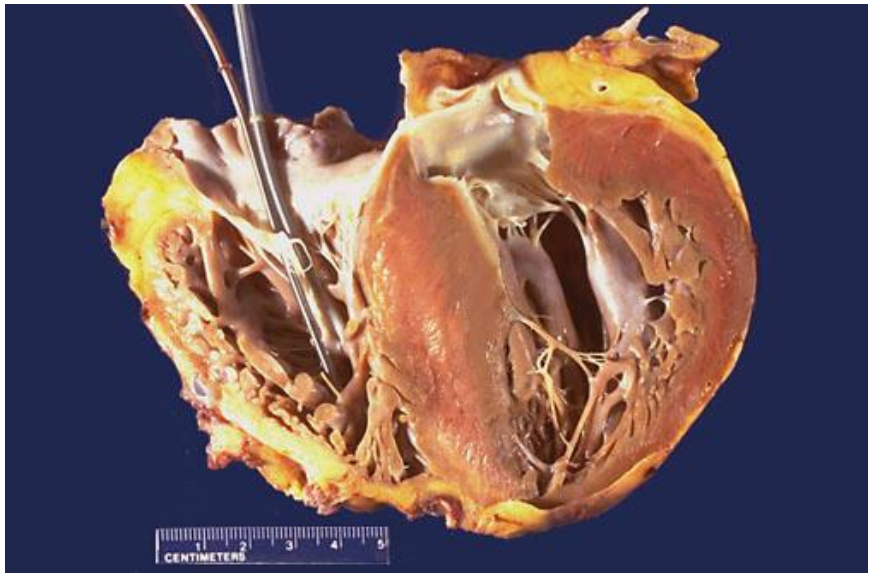


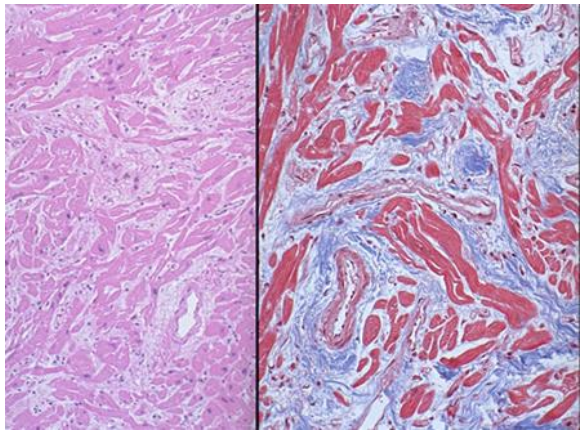
A. The septal muscle bulges into the left ventricular outflow tract, and the left atrium is enlarged. The anterior mitral leaflet has been moved away from the septum to reveal a fibrous endocardial plaque (arrow).

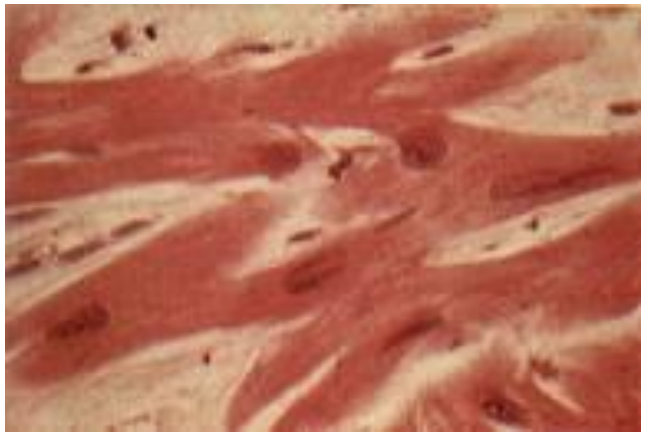
B. Histology demonstrating disarray, extreme hypertrophy, and branching of myocytes as well as the characteristic interstitial fibrosis

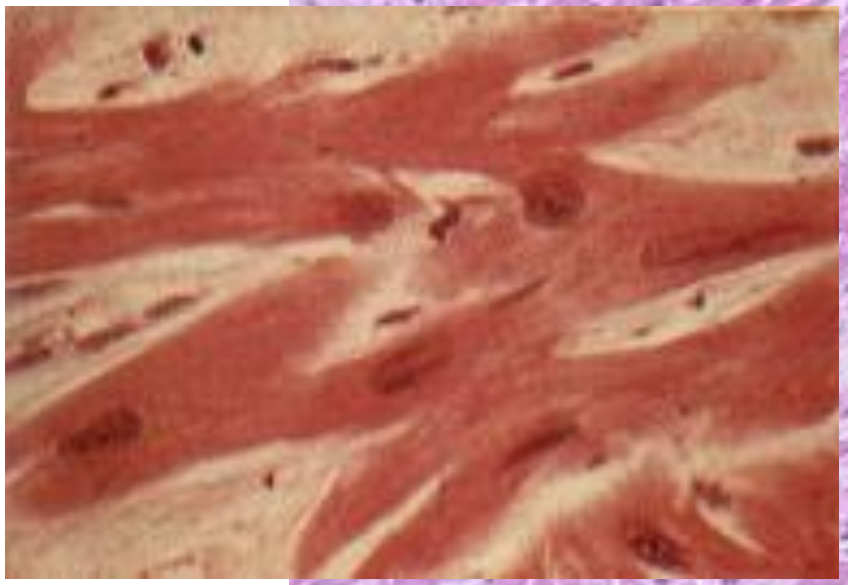
HCM











HCM Histopathology: Myofiber Dysarray and Fibrosis

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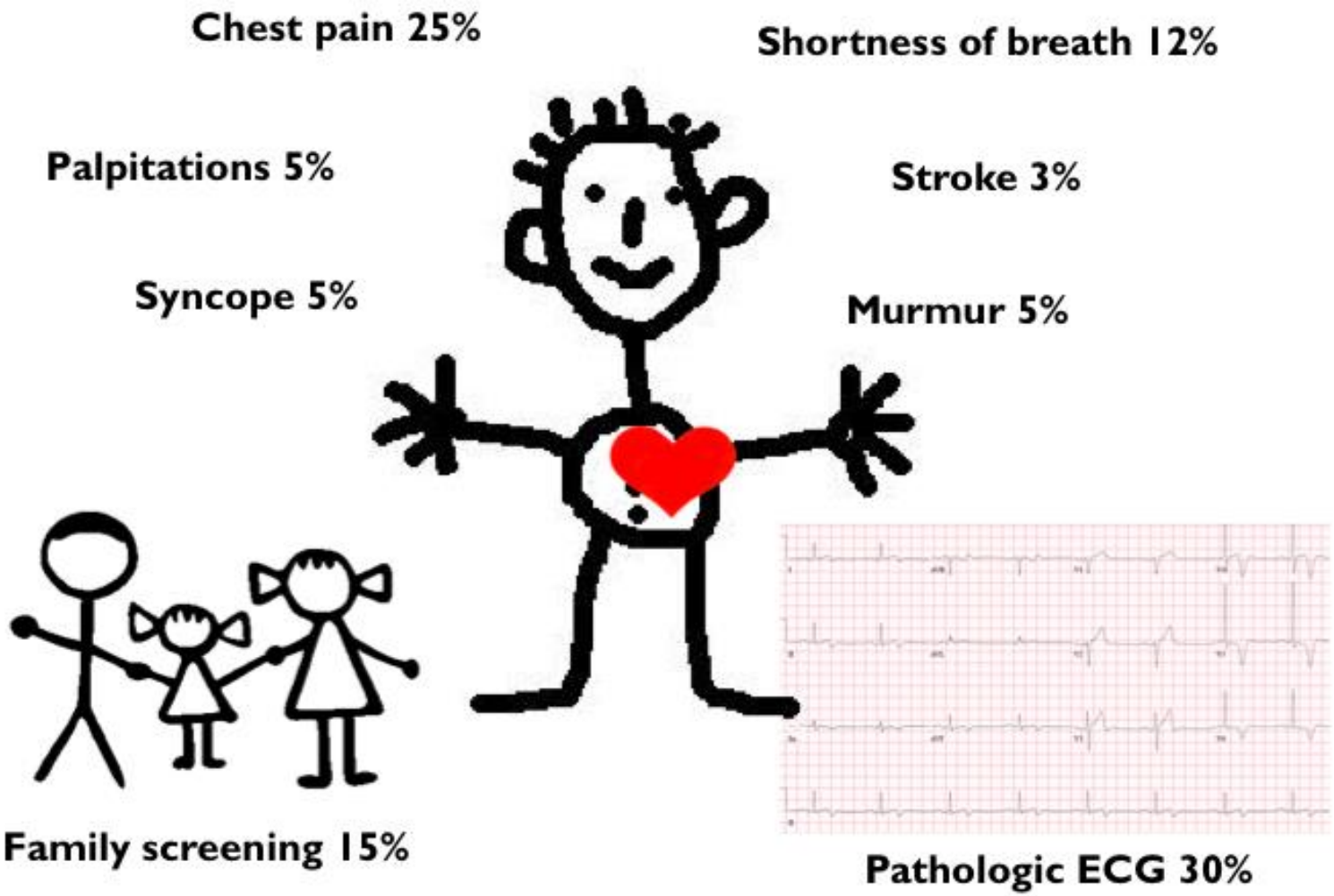
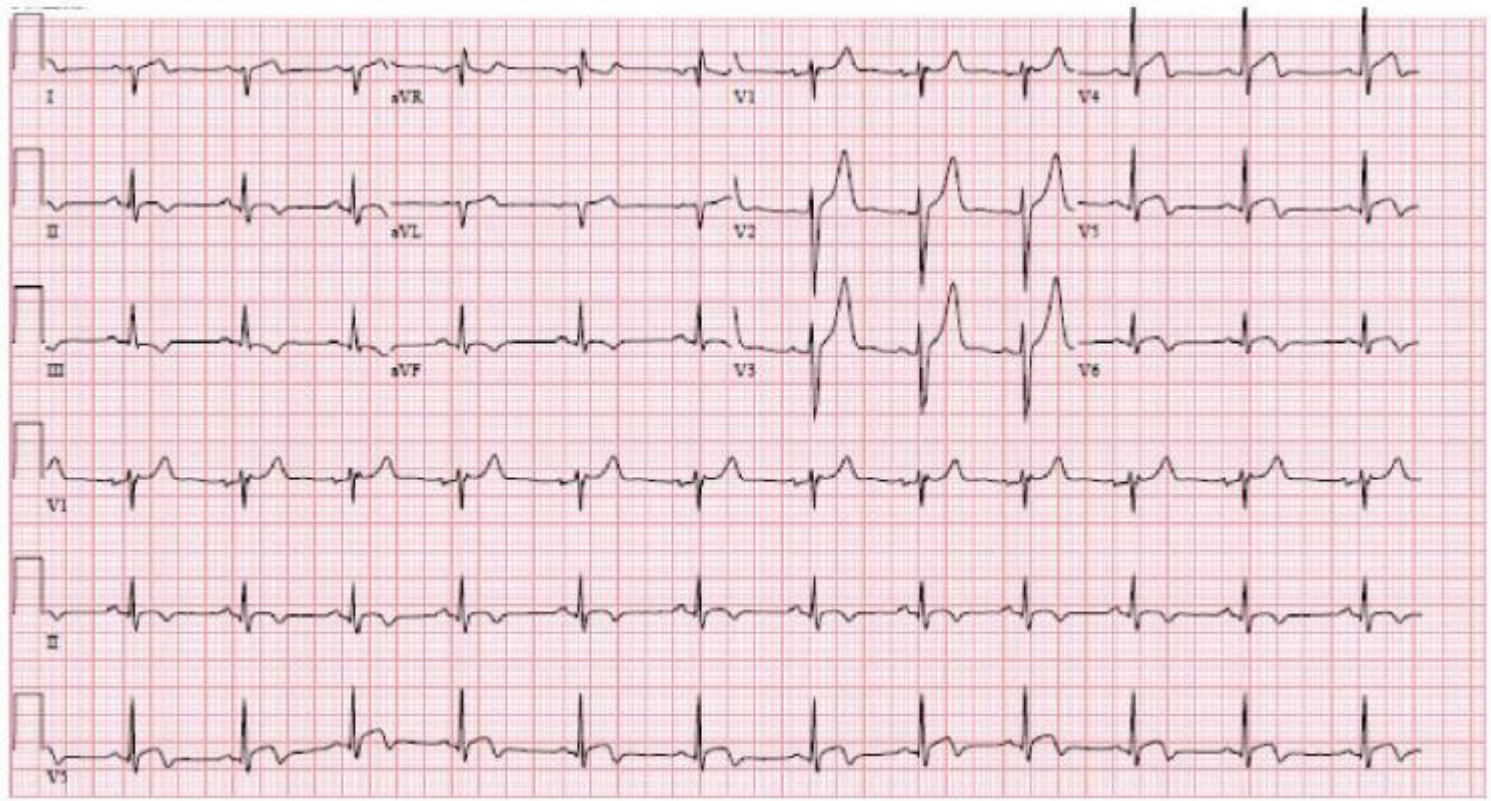
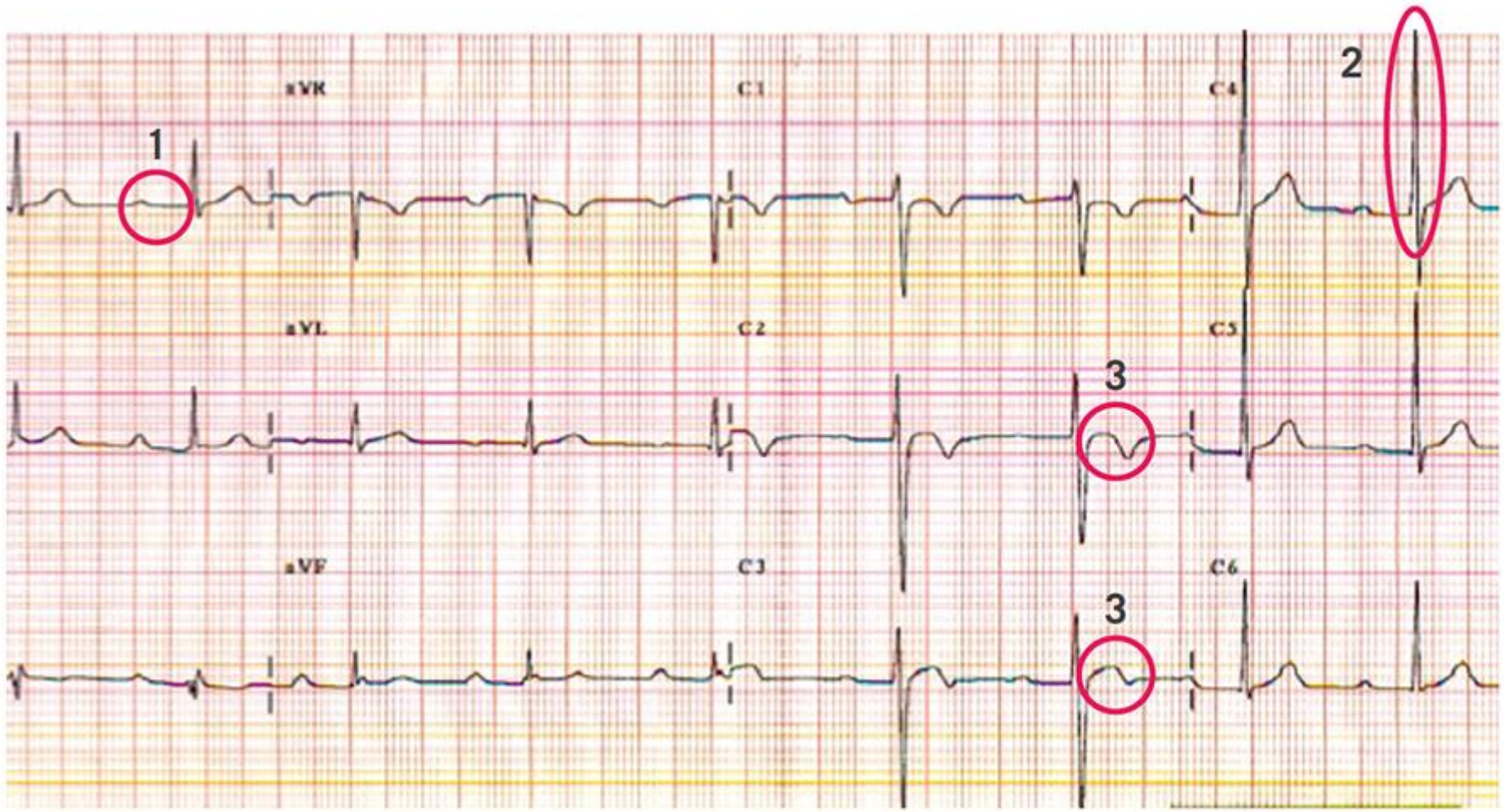
- מבצע פעילות גופנית ענפה:

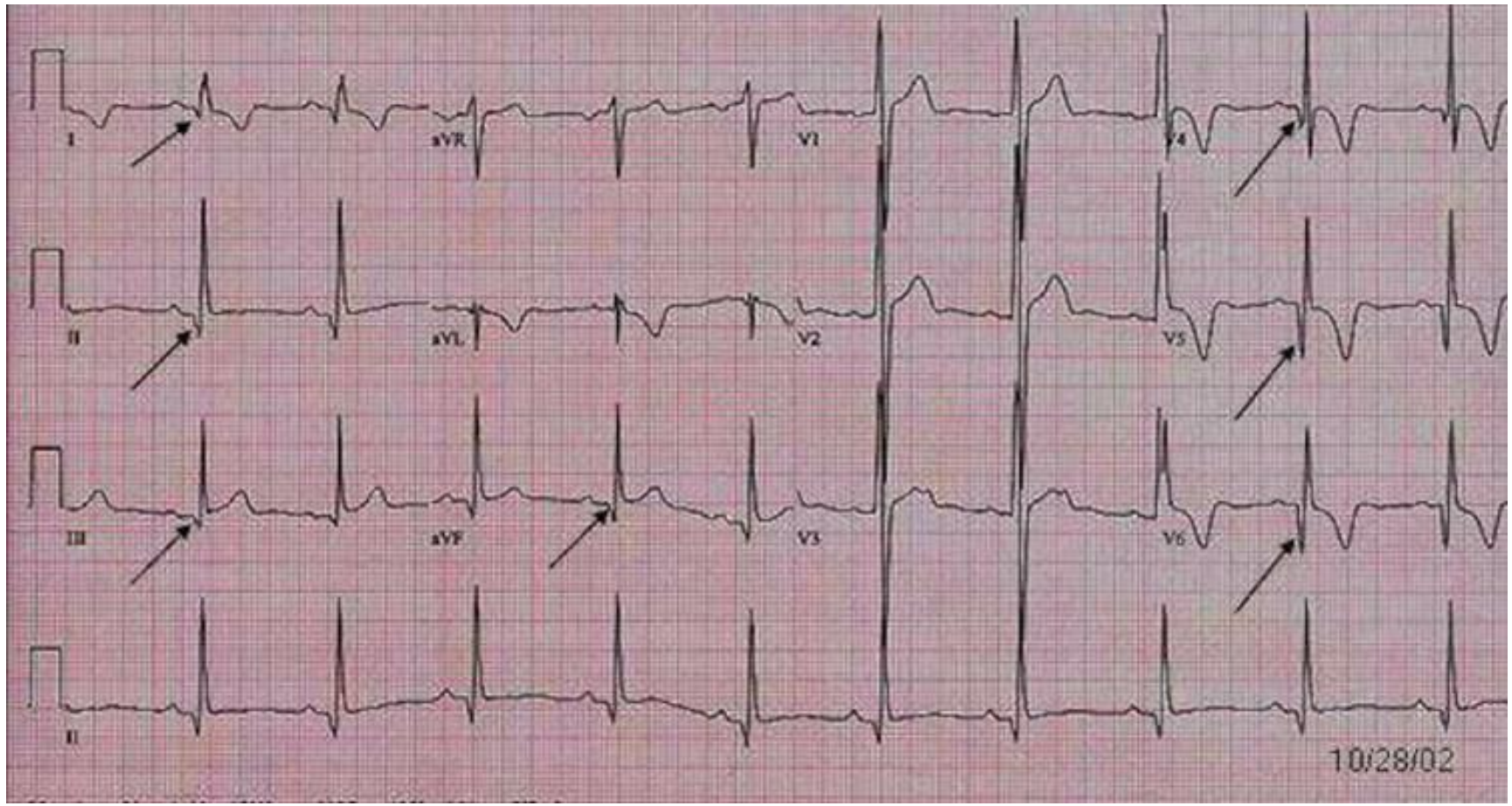
משתתף מספר שנים במירוצי תריאטלון

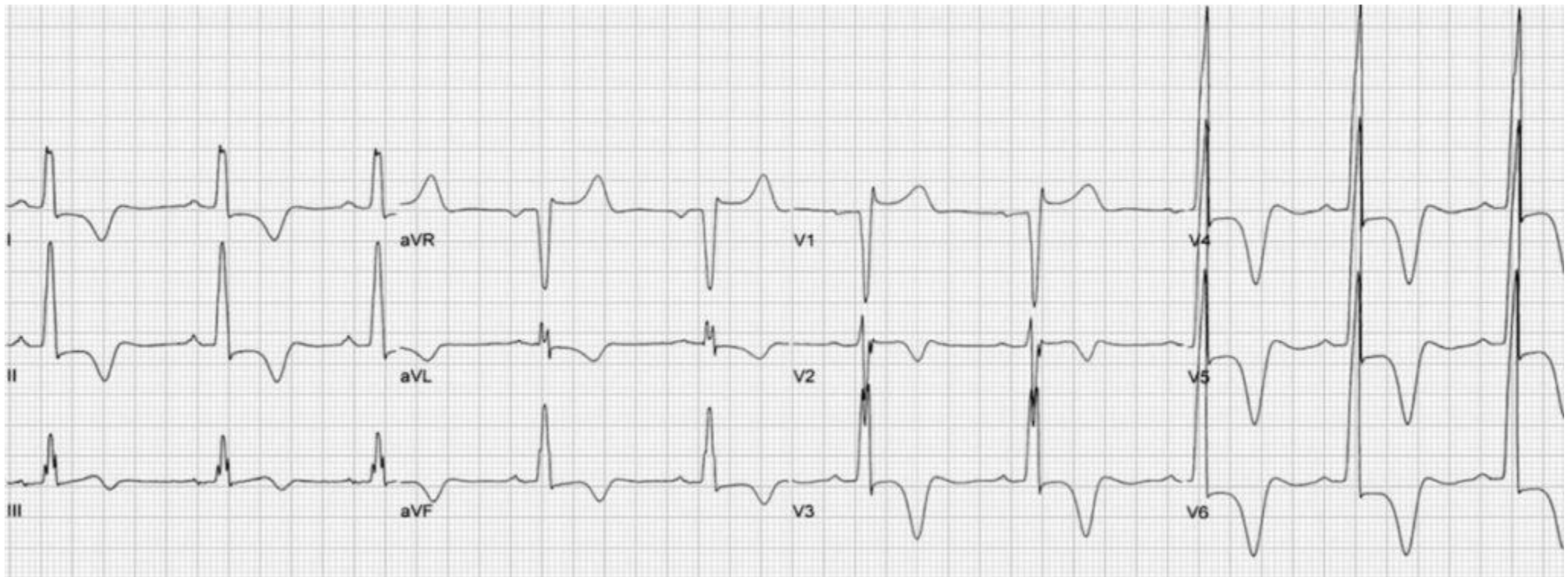
HCM- Patient Presentation




I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5


aVR
C1
C4
1
2
aVL
C2
C5
3
aVF
C3
C6
3


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
10/28/02


aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants

Finding	Comment
Short PR interval/ pre-excitation	Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.
AV block	Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.
Extreme LVH (Sokolow score ≥50)	Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.
Low QRS voltage (or normal voltages despite increased LV wall thickness)	Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.

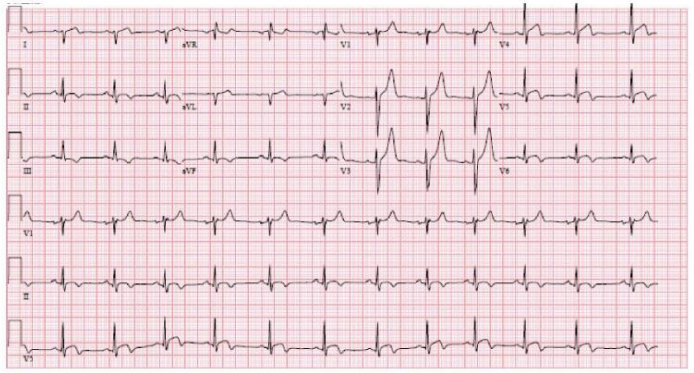
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Electrocardiographic abnormalities suggesting specific diagnoses or morphological variants (Cont.)

Finding	Comment
Extreme superior ("North West") QRS axis deviation	Seen in patients with Noonan syndrome who have severe basal hypertrophy extending into the RV outflow tract.
Giant negative T wave inversion (>10 mm)	Giant negative T wave inversion in the precordial and/or inferolateral leads suggests involvement of the LV apex.
Abnormal Q waves ≥40 ms in duration and/or ≥25% of the R wave in depth and/or ≥3 mm in depth in at least two contiguous leads except aVR	Abnormally deep Q waves in the inferolateral leads, usually with a positive T wave, are associated with an asymmetrical distribution of LVH. Q waves of abnormal duration (≥40 ms) are associated with areas of replacement fibrosis.
Coved ST-segment elevation in lateral chest leads	Some patients with apical or distal hypertrophy develop small apical aneurysms, sometimes associated with myocardial scarring. These may only be detectable on CMR, ventriculography or contrast echo, and are occasionally associated with ST-segment in the lateral chest leads.

MELAS =mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERFF =myoclonic epilepsy with ragged red fibres; PRKAG2 = gamma-2 subunit of the adenosine monophosphate-activated protein kinase.

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284



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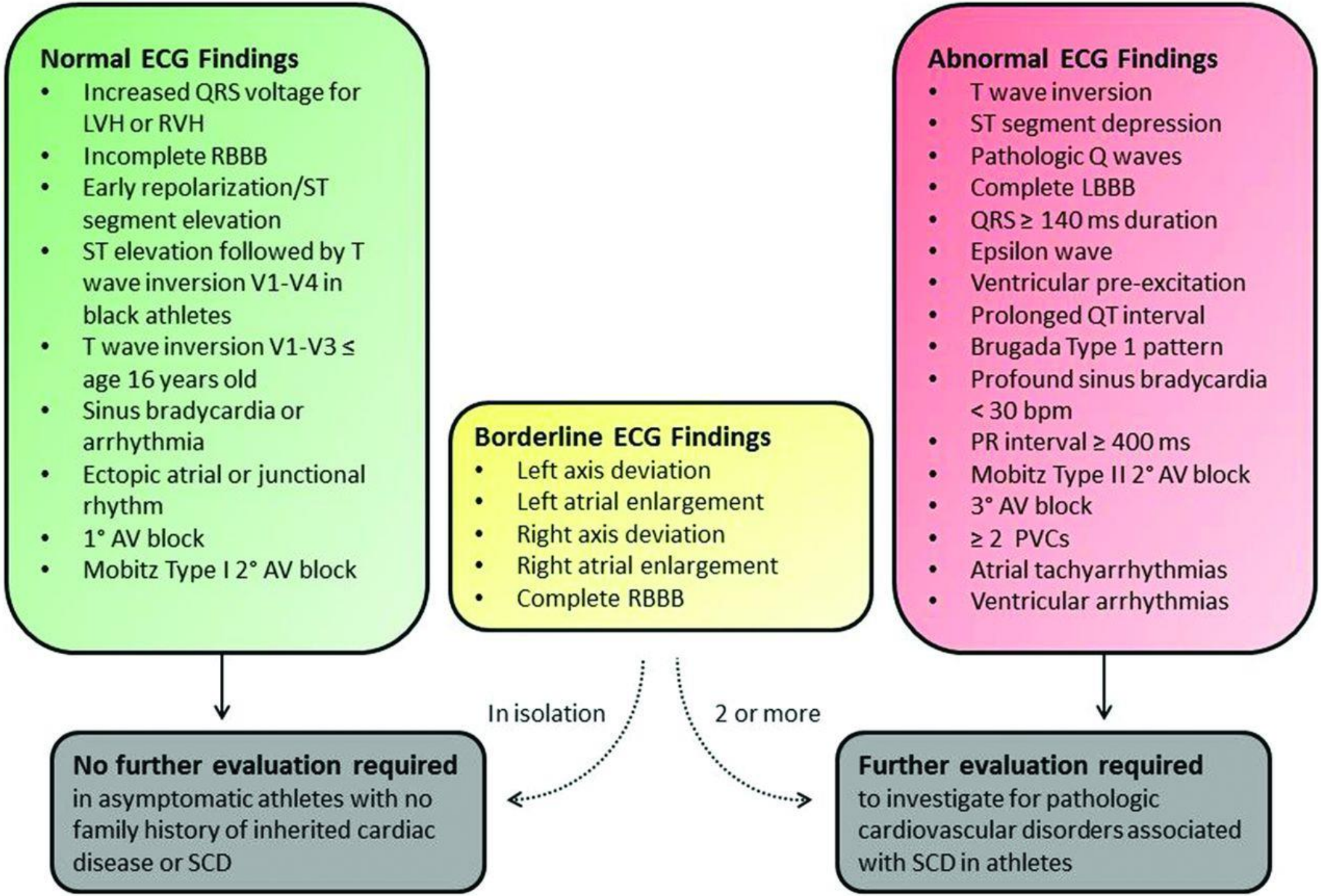
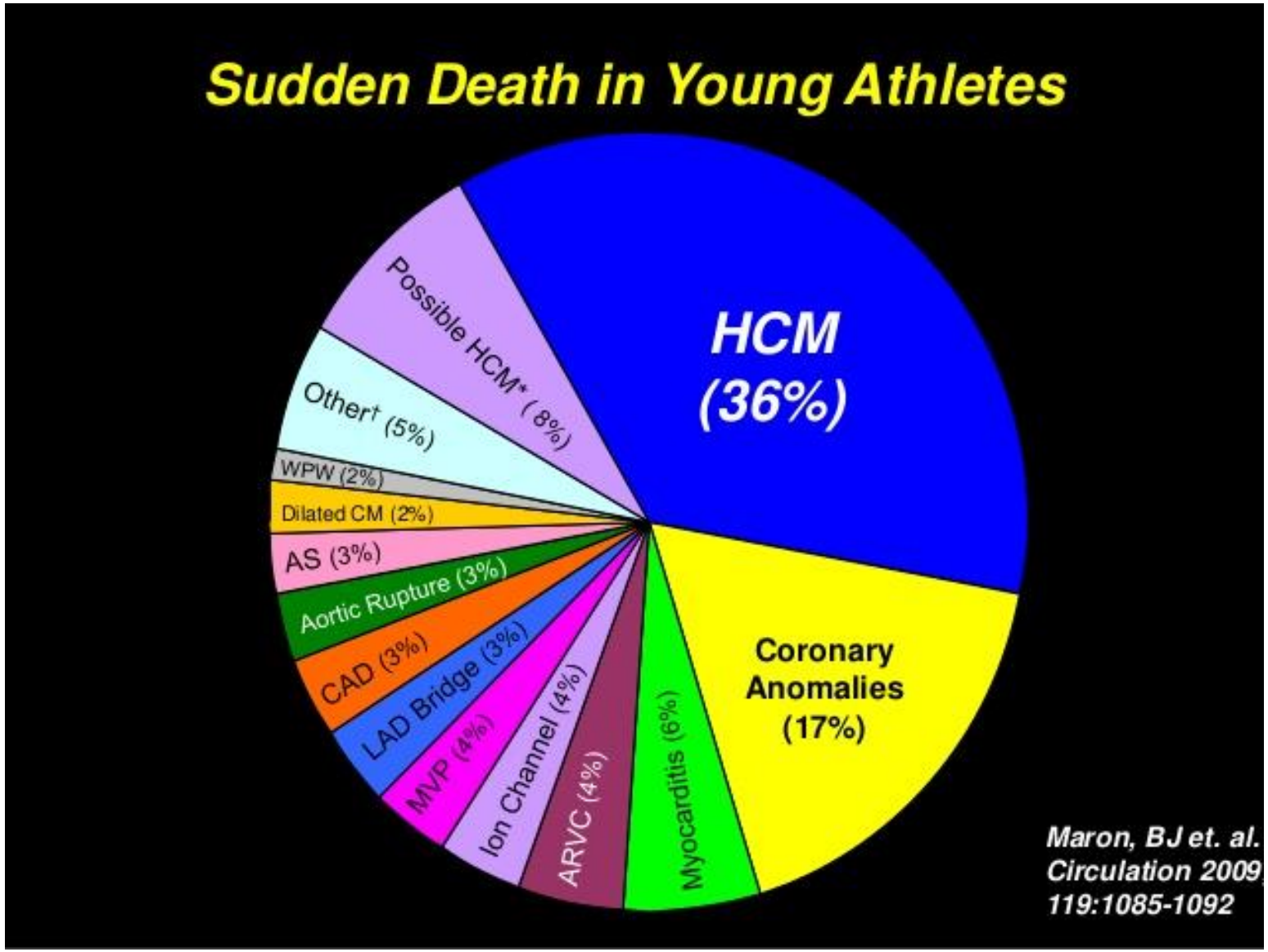
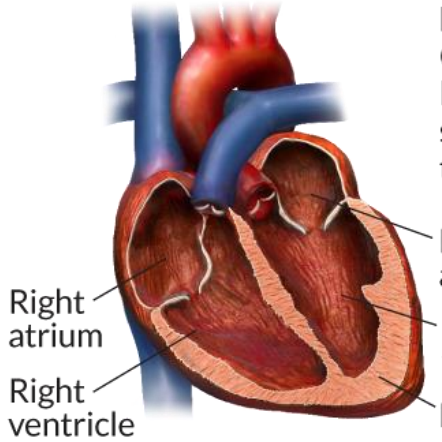
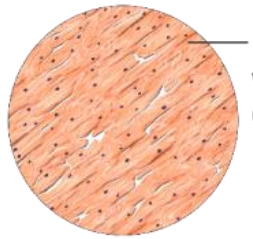
- מבקש אישור למרתון לונדון...

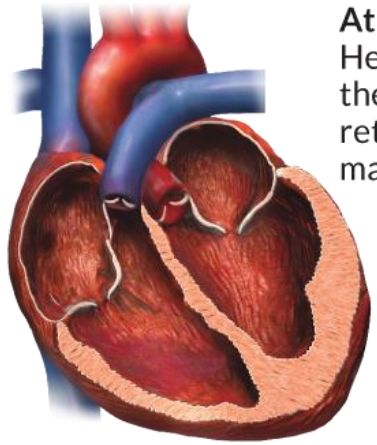

Normal ECG Findings
• Increased QRS voltage for LVH or RVH
• Incomplete RBBB
• Early repolarization/ST segment elevation
• ST elevation followed by T wave inversion V1-V4 in black athletes
• T wave inversion V1-V3 ≤ age 16 years old
• Sinus bradycardia or arrhythmia
• Ectopic atrial or junctional rhythm
• 1° AV block
• Mobitz Type I 2° AV block
Borderline ECG Findings
• Left axis deviation
• Left atrial enlargement
• Right axis deviation
• Right atrial enlargement
• Complete RBBB
Abnormal ECG Findings
• T wave inversion
• ST segment depression
• Pathologic Q waves
• Complete LBBB
• QRS ≥ 140 ms duration
• Epsilon wave
• Ventricular pre-excitation
• Prolonged QT interval
• Brugada Type 1 pattern
• Profound sinus bradycardia < 30 bpm
• PR interval ≥ 400 ms
• Mobitz Type II 2° AV block
• 3° AV block
• ≥ 2 PVCs
• Atrial tachyarrhythmias
• Ventricular arrhythmias
In isolation
2 or more
No further evaluation required in asymptomatic athletes with no family history of inherited cardiac disease or SCD
Further evaluation required to investigate for pathologic cardiovascular disorders associated with SCD in athletes


Sudden Death in Young Athletes
HCM (36%)
Coronary Anomalies (17%)
Myocarditis (6%)
ARVC (4%)
Ion Channel (4%)
MVP (4%)
LAD Bridge (3%)
CAD (3%)
Aortic Rupture (3%)
AS (3%)
Dilated CM (2%)
WPW (2%)
Other† (5%)
Possible HCM* (8%)
Maron, BJ et. al.
Circulation 2009
119:1085-1092

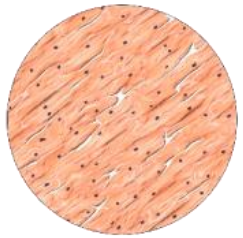


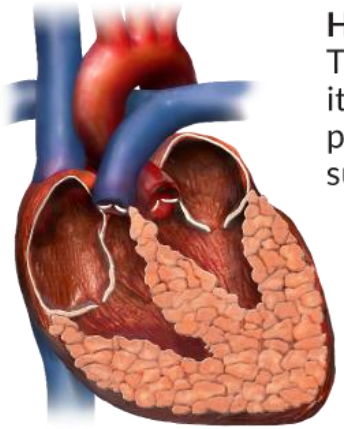
Normal
Cells in the heart wall are stacked like bricks, allowing an electrical signal to smoothly sweep across the muscle and regulate beats.



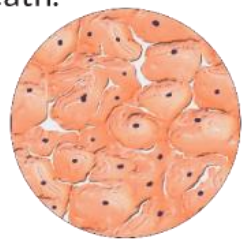


Athlete normal
Heart chambers may enlarge and the heart wall thicken, but cells retain normal structure. EKGs may flag as abnormal.





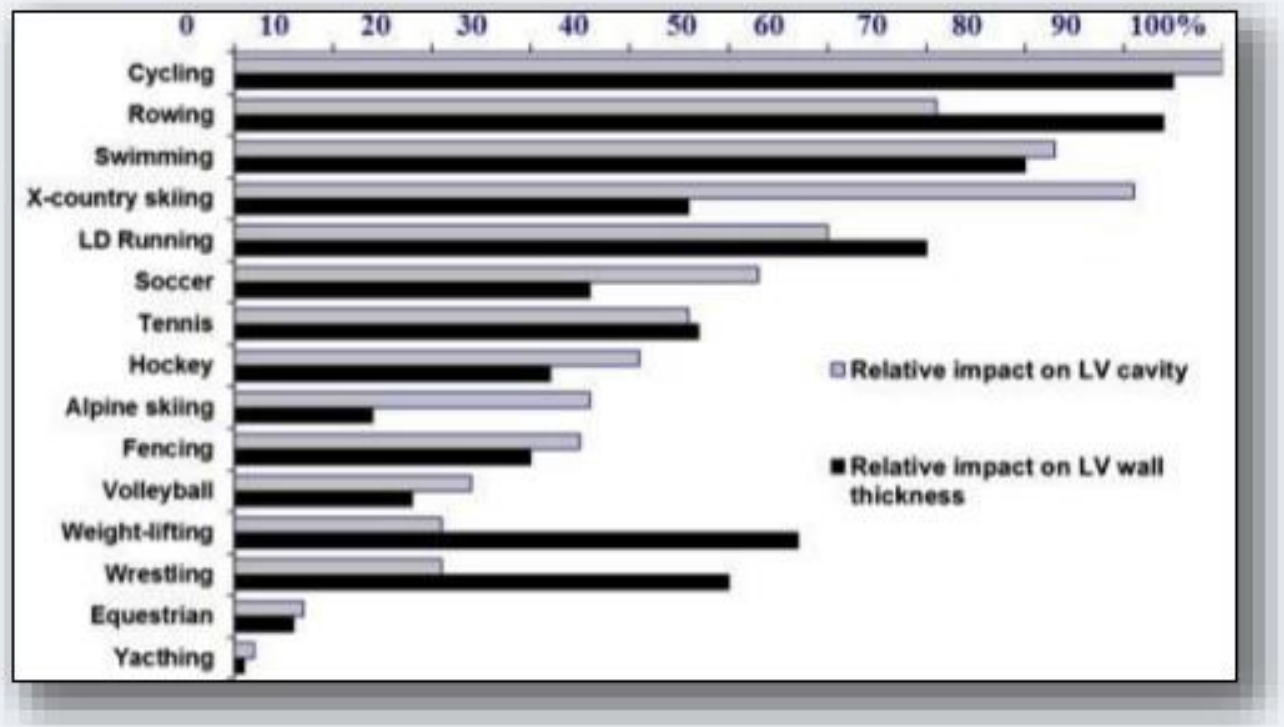
Hypertrophic cardiomyopathy
The heart wall is enlarged and its cells chaotically arranged, putting a person at risk for sudden death.



Clinical Diagnosis of H

- ***In Adults:*** **One or more LV myocardial segments 15 mm more in thickness**
- ***In Children:*** **Wall thickness > 2 standard deviations above mean**
- ***Dynamic Obstruction:*** **>30 mmHg**
- ***In Relatives:*** **One or more LV myocardial segments 13 mm or more**
- **Challenges:**
  - LVH in athlete's heart caused by training
  - LVH due to hypertension or aortic stenosis
  - Isolated basal septal hypertrophy in the elderly
  - re LVH due to infiltrative diseases
  - M compared to LV noncompaction
  - ning

Specific Sports Training Effects on Heart Size and Wall Thickness



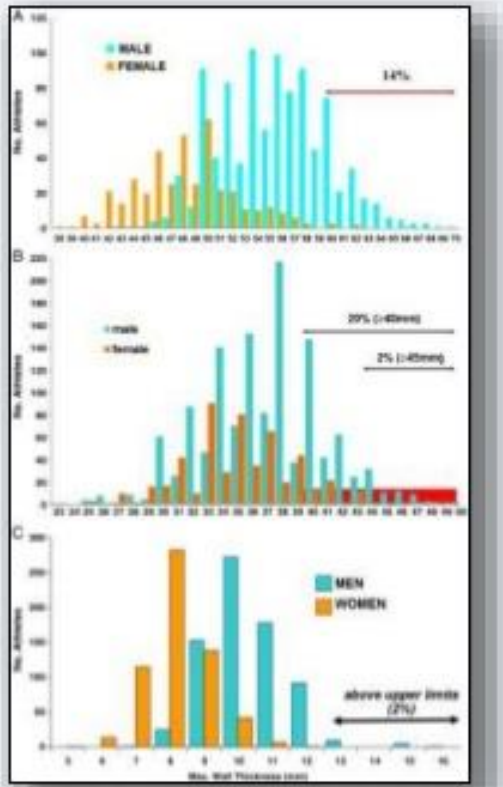
Prog CV Dis 2012;54:387

Normal Athlete Heart Sizes

LV End-diastolic Dimensions

LA Sizes

Max. Wall Thickness



14% have an LVEDD over 60 mm

20% have an enlarged LA

2% exceed 13 mm

Prog CV Dis 2012;54:387

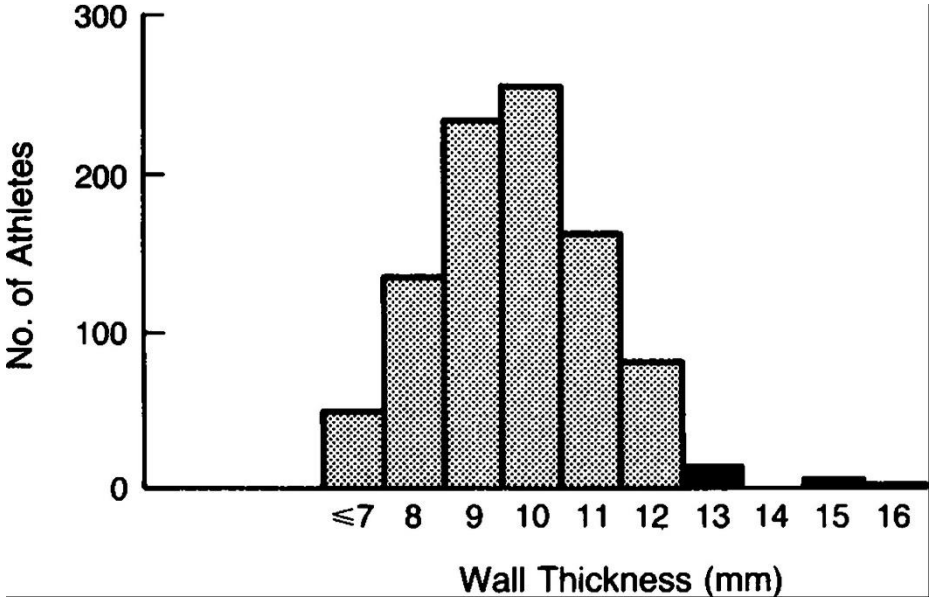
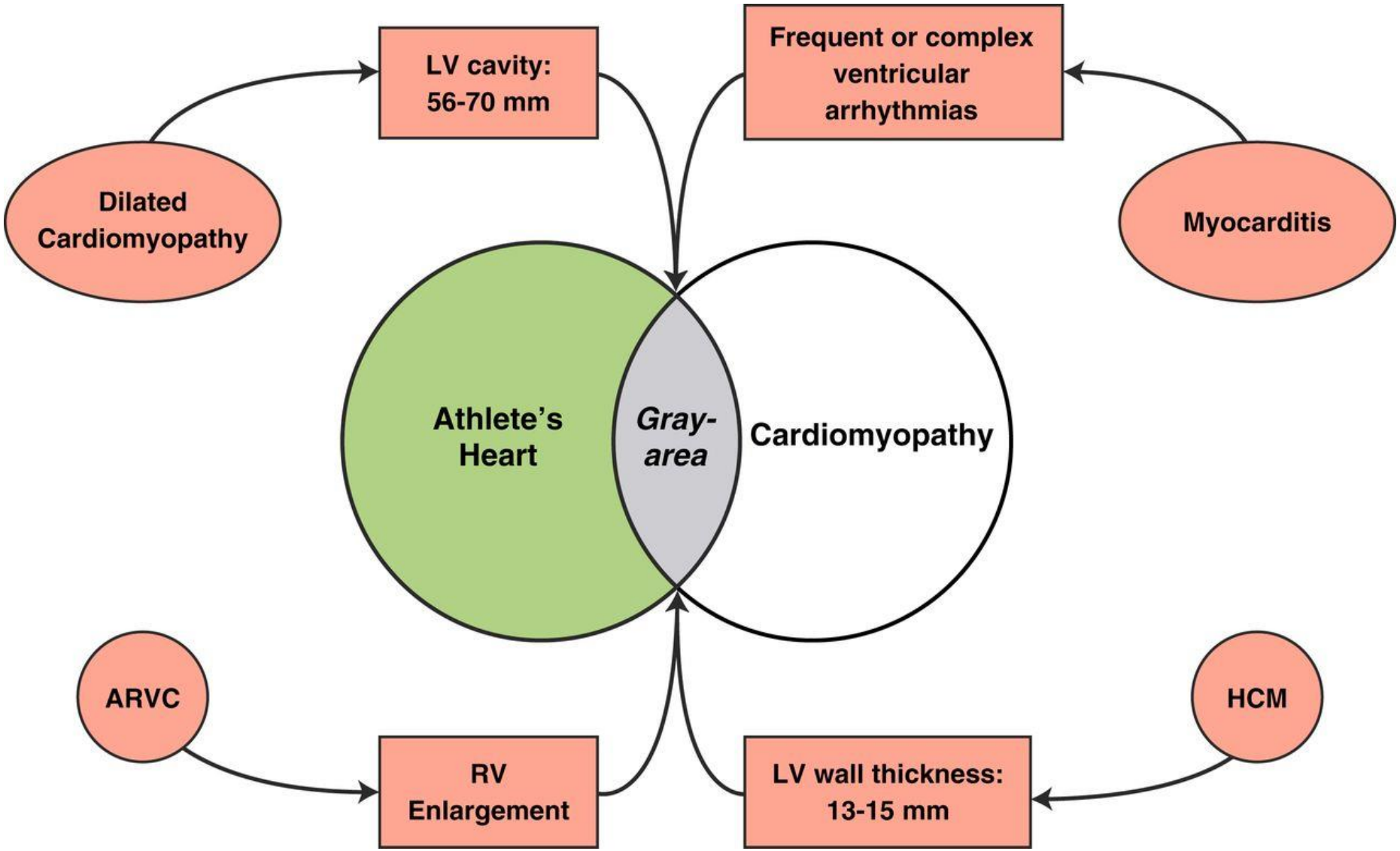
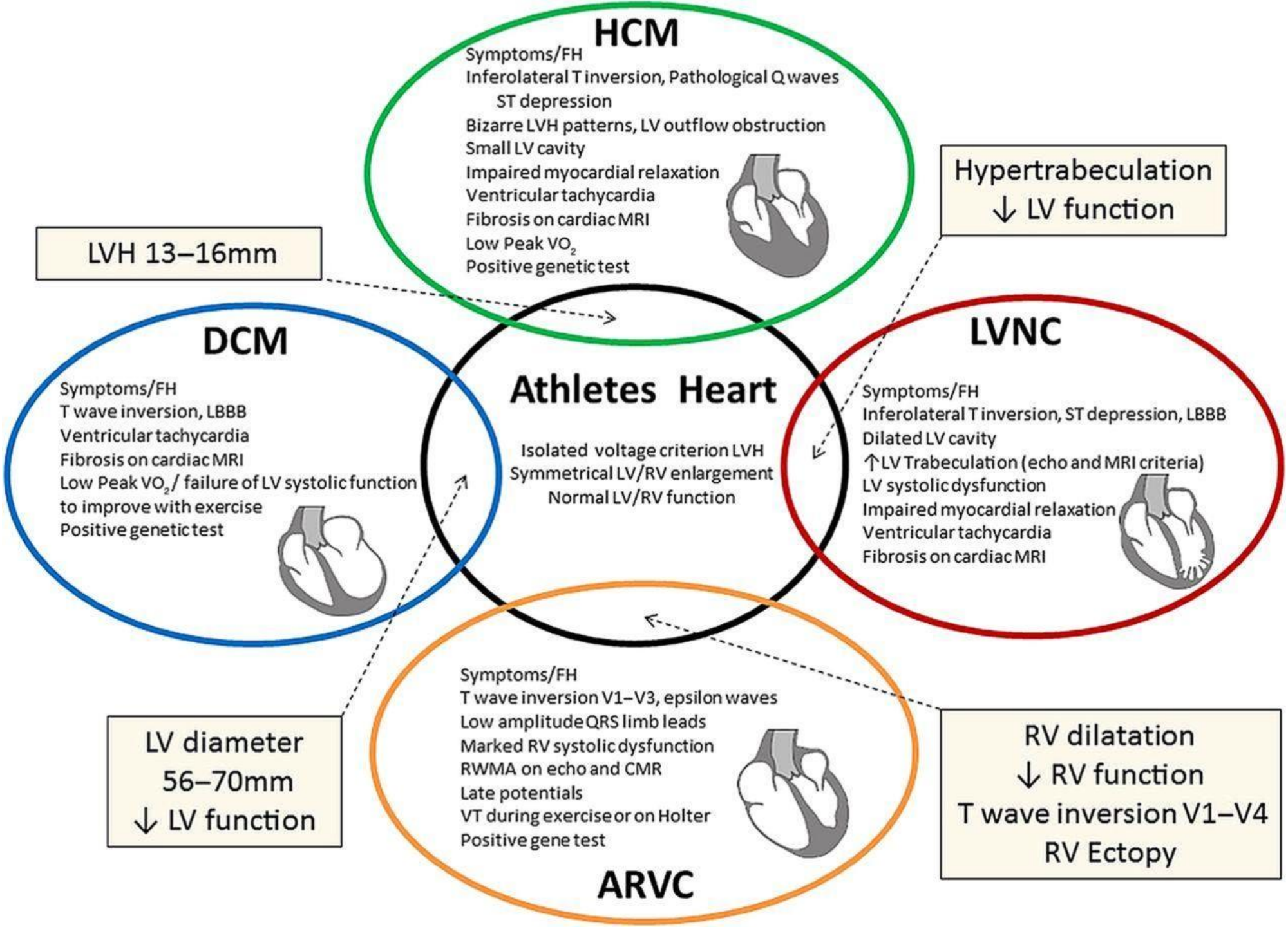


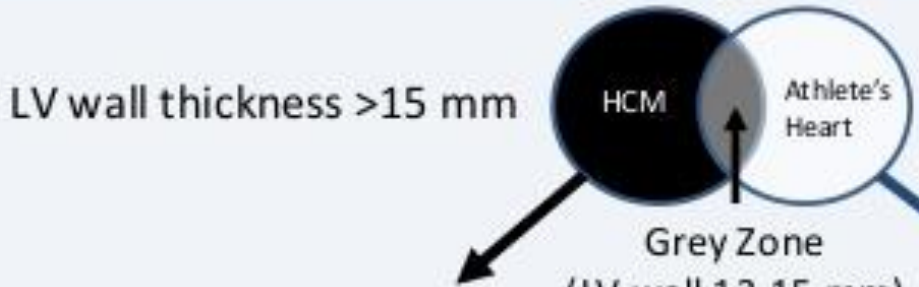
Figure 1. Distribution of Maximal Left-Ventricular-Wall Thicknesses in the 947 Elite Athletes.
Shaded bars indicate wall thicknesses within the normal range, and solid bars those within a range compatible with the diagnosis of hypertrophic cardiomyopathy (≥13 mm).

N Engl J Med. 1991 Jan 31;324(5):295-301.
The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes.
Pelliccia A[1], Maron BJ, Spataro A, Proschan MA, Spirito P.


LV cavity:
56-70 mm
Frequent or complex
ventricular
arrhythmias
Dilated
Cardiomyopathy
Myocarditis
Athlete's
Heart
Gray-
area
Cardiomyopathy
ARVC
HCM
RV
Enlargement
LV wall thickness:
13-15 mm


HCM
Symptoms/FH
Inferolateral T inversion, Pathological Q waves
ST depression
Bizarre LVH patterns, LV outflow obstruction
Small LV cavity
Impaired myocardial relaxation
Ventricular tachycardia
Fibrosis on cardiac MRI
Low Peak VO2
Positive genetic test
LVH 13–16mm
Hypertrabeculation
↓ LV function
DCM
Symptoms/FH
T wave inversion, LBBB
Ventricular tachycardia
Fibrosis on cardiac MRI
Low Peak VO2 / failure of LV systolic function to improve with exercise
Positive genetic test
Athletes Heart
Isolated voltage criterion LVH
Symmetrical LV/RV enlargement
Normal LV/RV function
LVNC
Symptoms/FH
Inferolateral T inversion, ST depression, LBBB
Dilated LV cavity
↑LV Trabeculation (echo and MRI criteria)
LV systolic dysfunction
Impaired myocardial relaxation
Ventricular tachycardia
Fibrosis on cardiac MRI
LV diameter
56–70mm
↓ LV function
Symptoms/FH
T wave inversion V1–V3, epsilon waves
Low amplitude QRS limb leads
Marked RV systolic dysfunction
RWMA on echo and CMR
Late potentials
VT during exercise or on Holter
Positive gene test
ARVC
RV dilatation
↓ RV function
T wave inversion V1–V4
RV Ectopy

Differentiating Athlete's Heart from HCM



LV wall thickness >15 mm

LV wall thickness <13 mm

Grey Zone
(LV wall 13-15 mm)

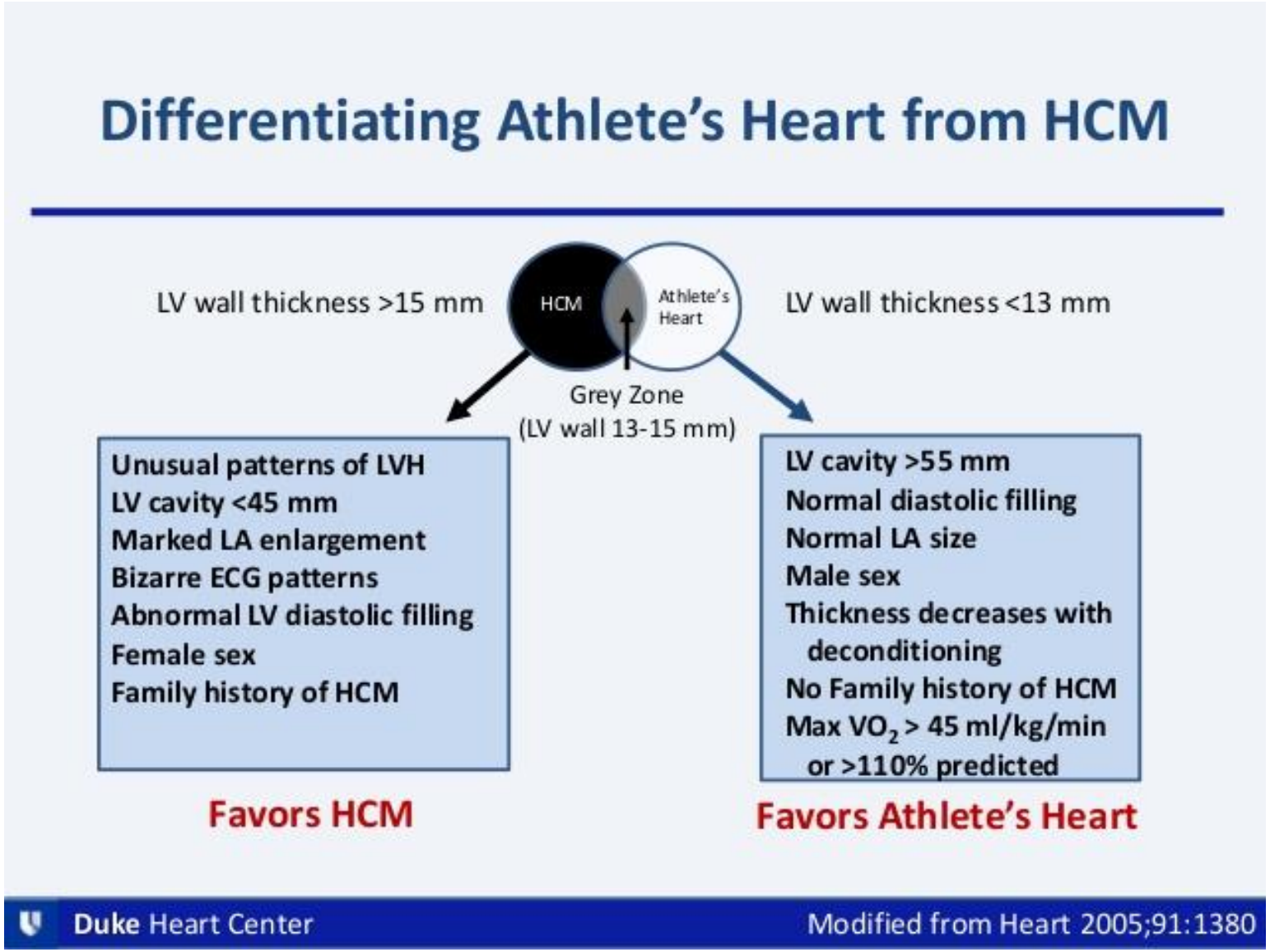
Unusual patterns of LVH
LV cavity <45 mm
Marked LA enlargement
Bizarre ECG patterns
Abnormal LV diastolic filling
Female sex
Family history of HCM

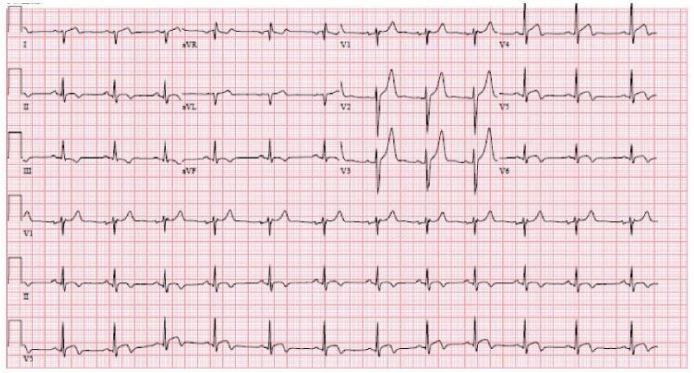
Favors HCM

LV cavity >55 mm
Normal diastolic filling
Normal LA size
Male sex
Thickness decreases with deconditioning
No Family history of HCM
Max VO_2 > 45 ml/kg/min or >110% predicted

Favors Athlete's Heart

Also- CMR-LGE..


Differentiating Athlete's Heart from HCM
LV wall thickness >15 mm
HCM
Athlete's Heart
LV wall thickness <13 mm
Grey Zone
(LV wall 13-15 mm)
Unusual patterns of LVH
LV cavity <45 mm
Marked LA enlargement
Bizarre ECG patterns
Abnormal LV diastolic filling
Female sex
Family history of HCM
LV cavity >55 mm
Normal diastolic filling
Normal LA size
Male sex
Thickness decreases with deconditioning
No Family history of HCM
Max VO2 > 45 ml/kg/min or >110% predicted
Favors HCM
Favors Athlete's Heart
Duke Heart Center
Modified from Heart 2005;91:1380



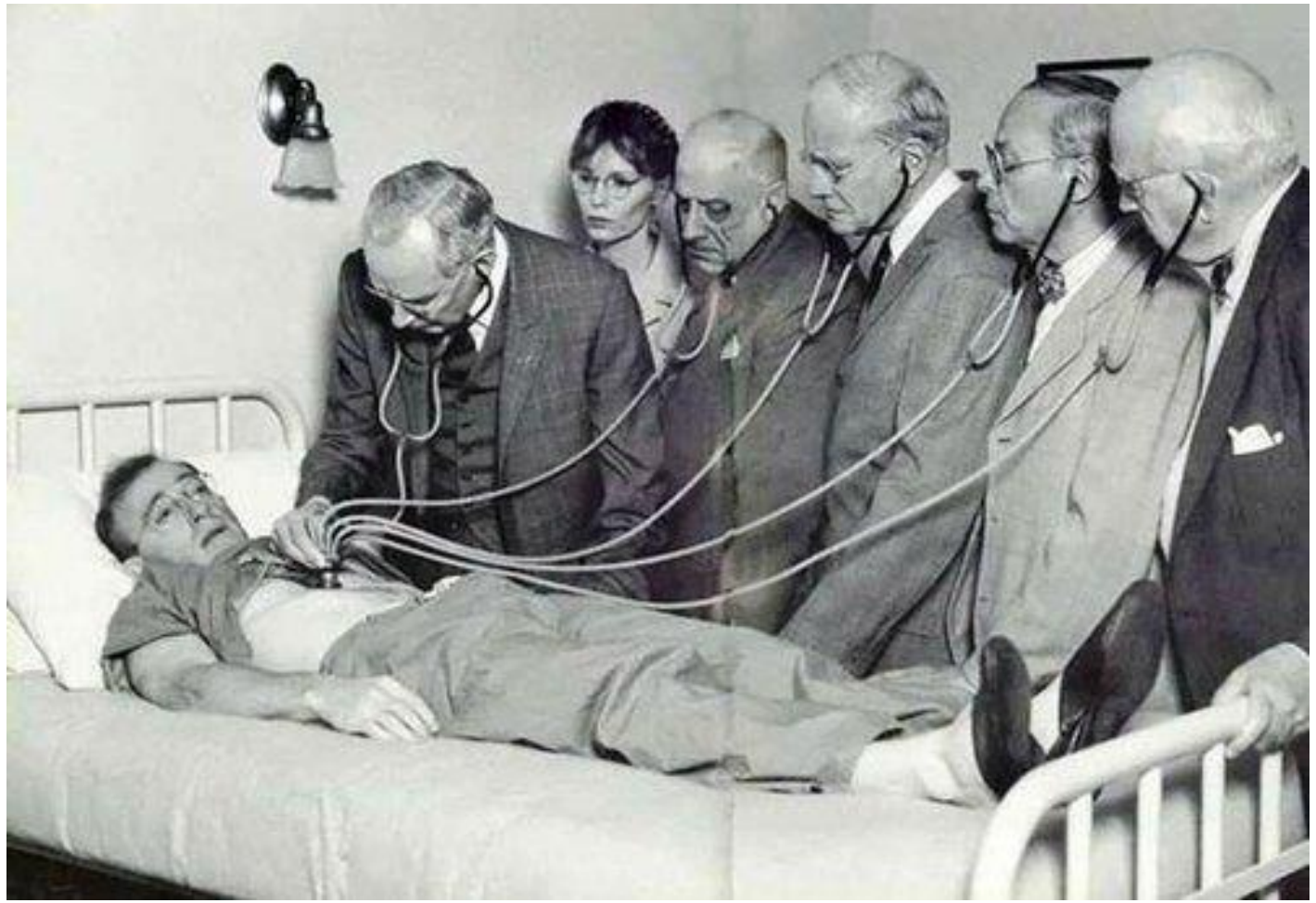
מר שמשון...

- בן 38
- הופנה למרפאתך עקב אוושה סיסטולית "חדשה" בבדיקה שגרתית אצל רופא המשפחה

- מבצע פעילות גופנית ענפה:

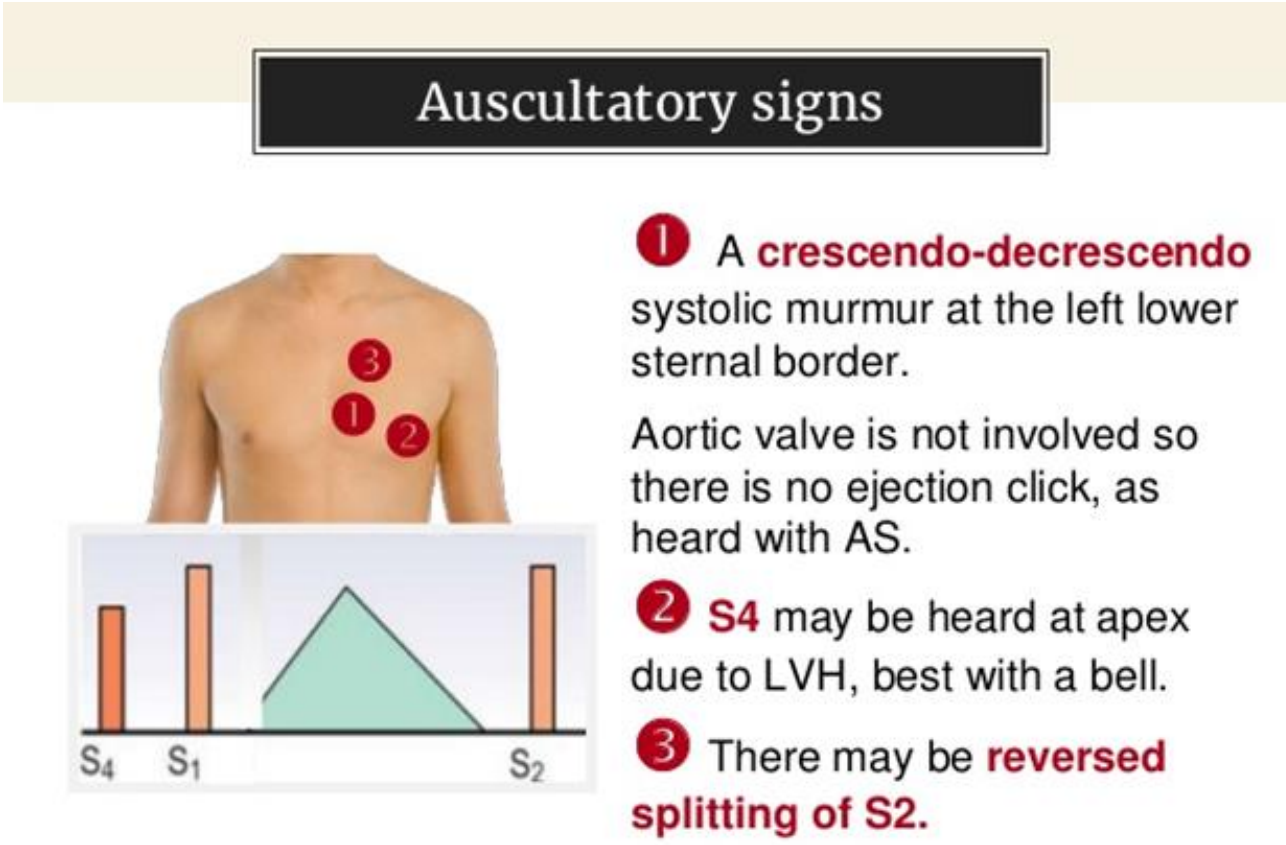
משתתף מספר שנים במירוצי תריאטלון

- מבקש אישור למרתון לונדון...



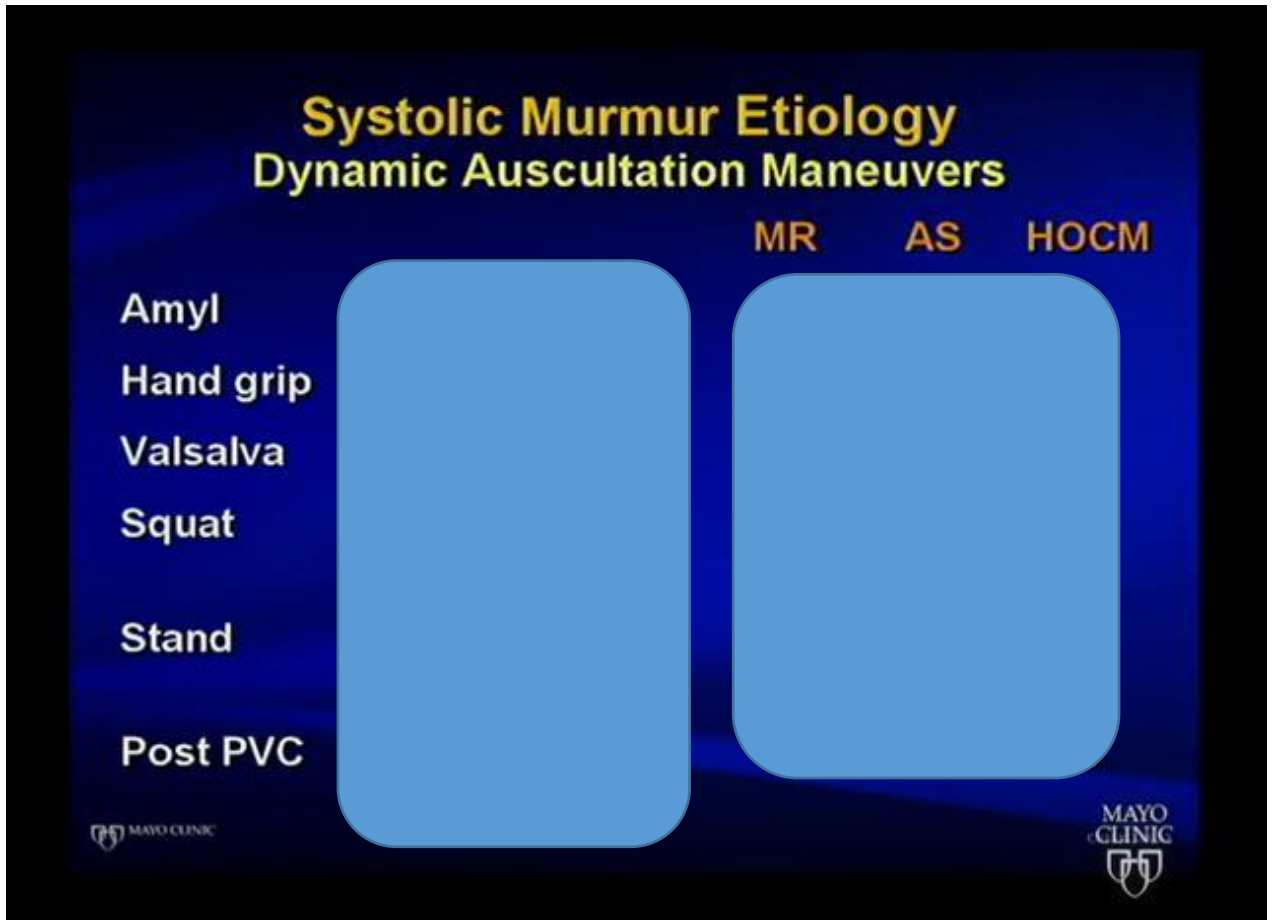
Physical Examination

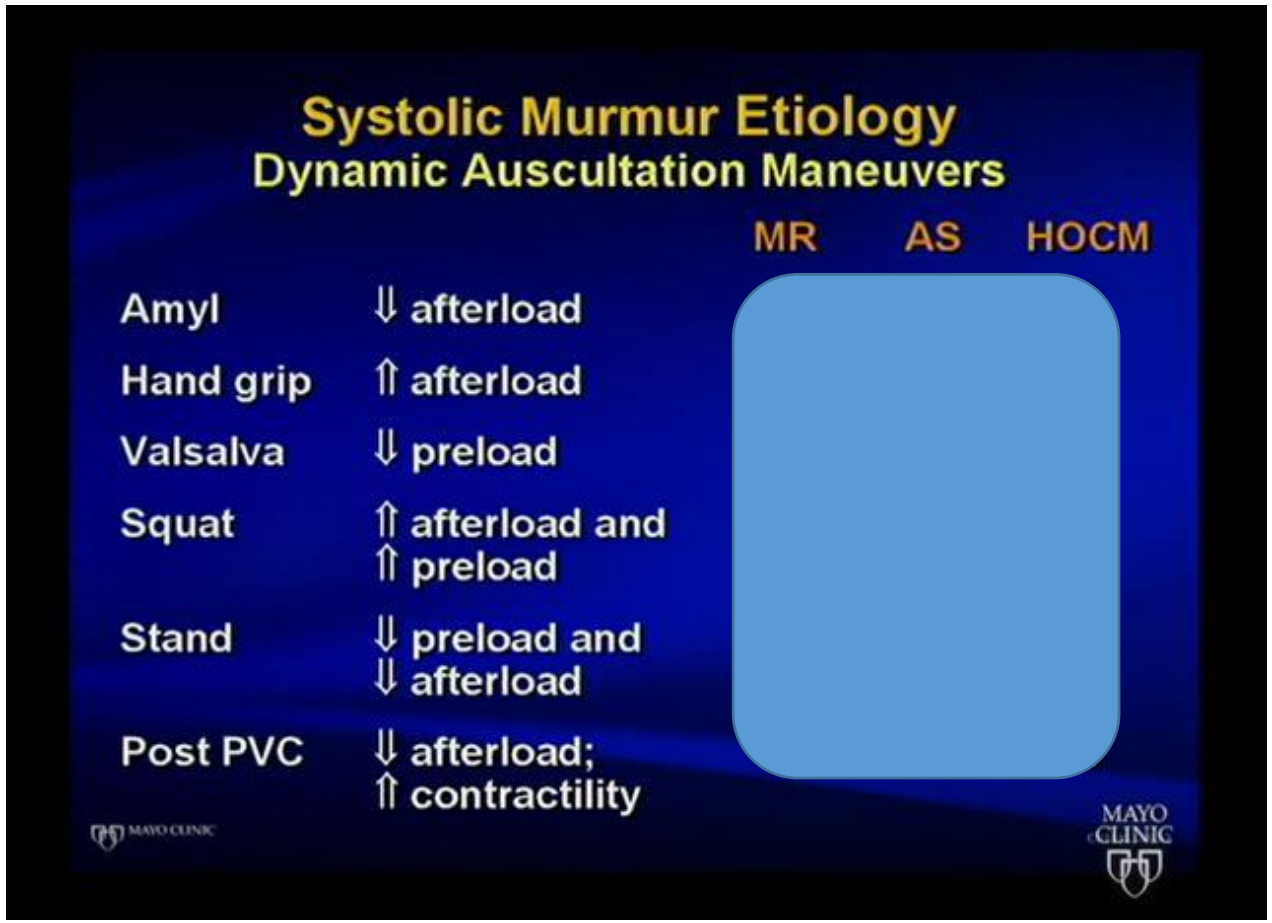
- Heart Sounds
  - S1 usually normal
  - S2 usually split but in severe stenosis – paradoxically split
  - S3 indicate heart failure
  - S4 usually present due to hypertrophy
- Murmur
  - Medium-pitch crescendo-decrescendo systolic murmur along LLSB and apex and radiates to suprasternal notch
  - Dynamic maneuvers
    - Murmur intensity increases with… decreased preload …
    - Murmur intensity decreases with…increased preload…

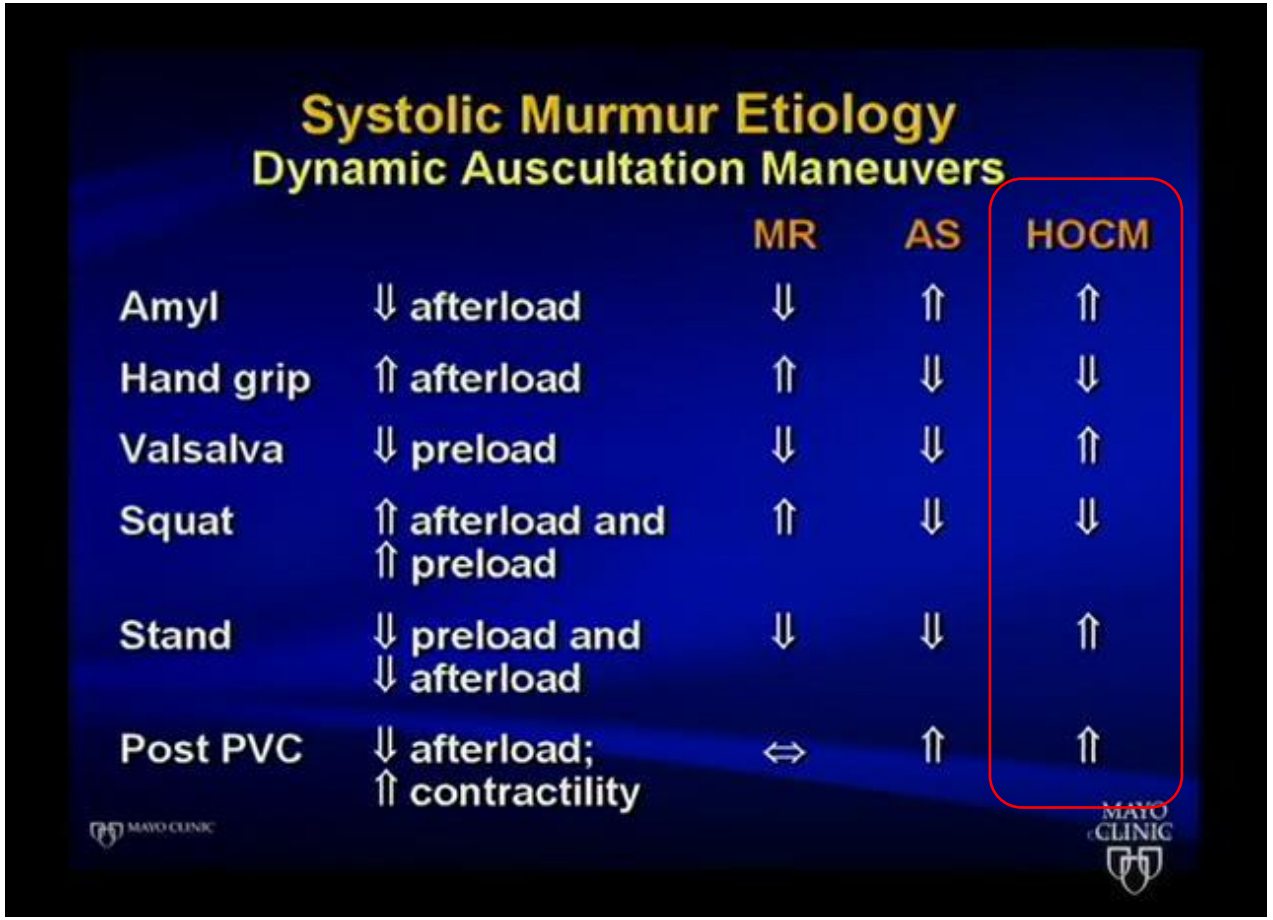


Physical Examination

- Heart Sounds
  - S1 usually normal
  - S2 usually split but in severe stenosis – paradoxically split
  - S3 indicate heart failure
  - S4 usually present due to hypertrophy
- Murmur
  - Medium-pitch crescendo-decrescendo systolic murmur along LLSB and apex and radiates to suprasternal notch
  - Dynamic maneuvers
    - Murmur intensity increases with decreased preload (i.e. Valsalva, standing, nitrates, diuretics)
    - Murmur intensity decreases with increased preload (i.e. squatting, hand grip)


Systolic Murmur Etiology
Dynamic Auscultation Maneuvers
MR
AS
HOCM
Amyl
Hand grip
Valsalva
Squat
Stand
Post PVC
MAYO CLINIC
MAYO CLINIC

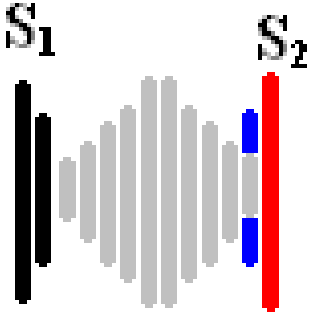

Systolic Murmur Etiology
Dynamic Auscultation Maneuvers
MR
AS
HOCM
Amyl
⇓ afterload
Hand grip
⇑ afterload
Valsalva
⇓ preload
Squat
⇑ afterload and
⇑ preload
Stand
⇓ preload and
⇓ afterload
Post PVC
⇓ afterload;
⇑ contractility
MAYO CLINIC
MAYO CLINIC


Systolic Murmur Etiology
Dynamic Auscultation Maneuvers
MR
AS
HOCM
Amyl
⇓ afterload
⇓
⇑
⇑
Hand grip
⇑ afterload
⇑
⇓
⇓
Valsalva
⇓ preload
⇓
⇓
⇑
Squat
⇑ afterload and ⇑ preload
⇑
⇓
⇓
Stand
⇓ preload and ⇓ afterload
⇓
⇓
⇑
Post PVC
⇓ afterload; ⇑ contractility
⇔
⇑
⇑
MAYO CLINIC
MAYO CLINIC

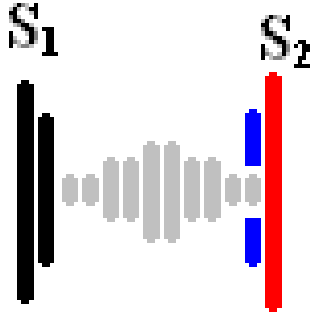
Distinguishing the murmur of HOCM and aortic stenosis

The murmur of HOCM

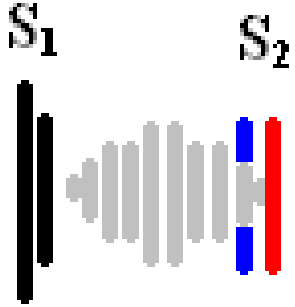
HOCM after Valsalva/standing



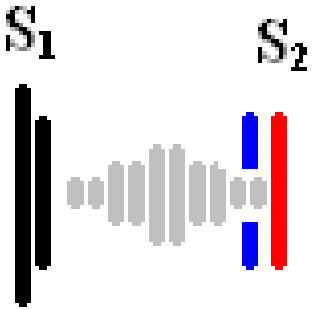
HOCM after rapid squatting



The murmur of AS



AS after Valsalva/standing



AS after rapid squatting

Aortic Valve (A2)

Pulmonic Valve (P2)

מר שמשון...

- בן 38
- הופנה למרפאתך עקב אוושה סיסטולית "חדשה" בבדיקה שגרתית אצל רופא המשפחה
- מבצע פעילות גופנית ענפה:

משתתף מספר שנים במירוצי תריאטלון

- מבקש אישור למרתון לונדון...
- אק"ג "חשוד" לקרדיומיופטיה ...
- בדיקה פיזיקלית- קול רביעי, א"ס 2/6 מתגברת לאחר ולסלבה ולאחר עמידה.

-אקו...

Hypertrophic Cardiomyopathy
Echocardiographic Diagnosis

Left Ventricular Hypertrophy ≥ 15 mm
(Asymmetric >> Symmetric)

In the absence of another cardiovascular or systemic disease associated with LVH or myocardial wall thickening

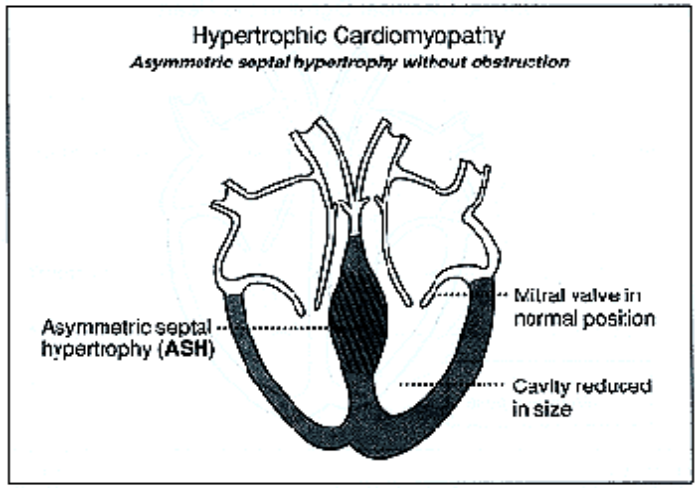
Gersh, BJ, et al. JACC 2011; 58: e212 ACC/AHA Guidelines

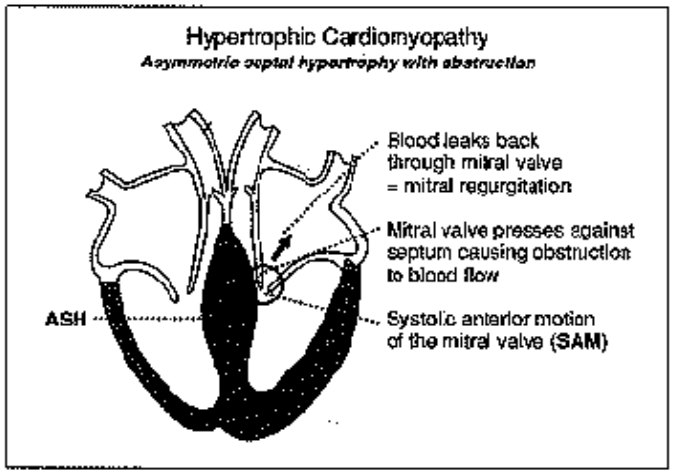
Hypertrophic Cardiomyopathy
Echocardiographic Diagnosis

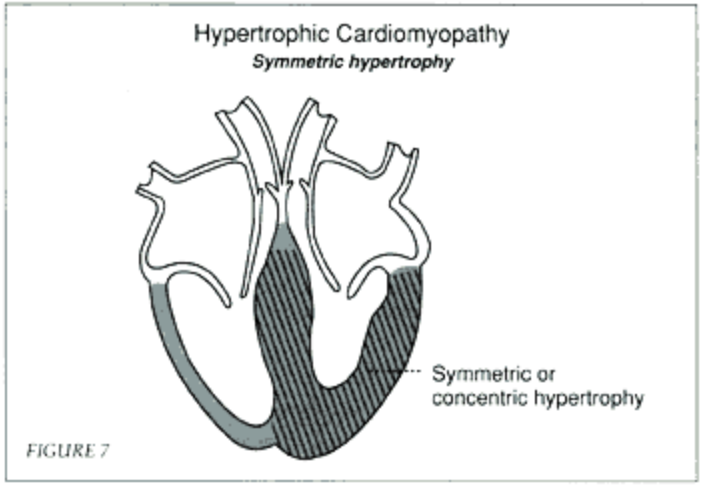
Not Mandatory for Diagnosis of HCM

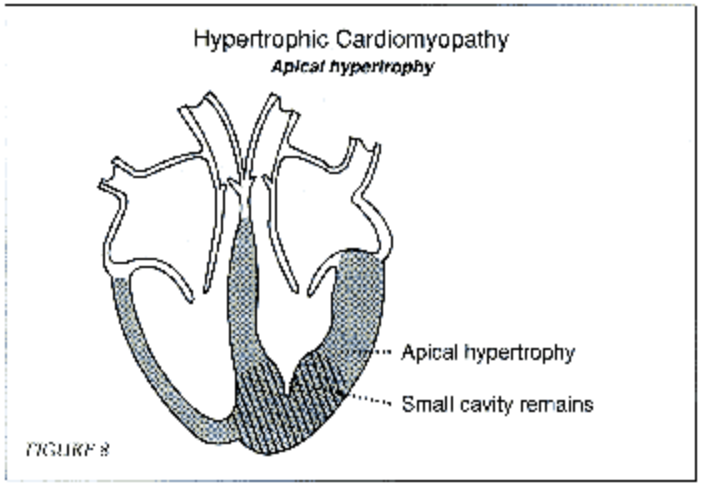
- Asymmetric Septal Hypertrophy (ASH)
- Systolic Anterior Motion (SAM)
- Dynamic LVOT obstruction

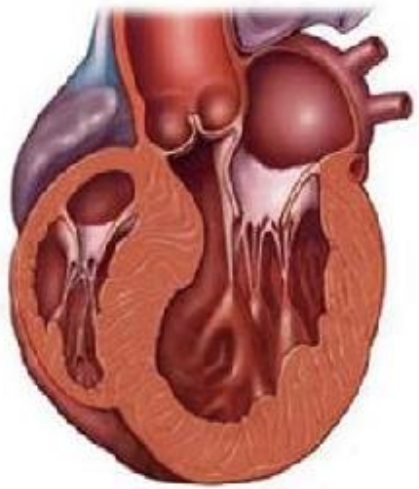
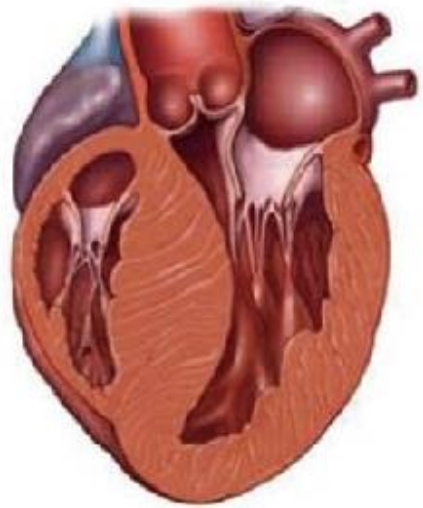
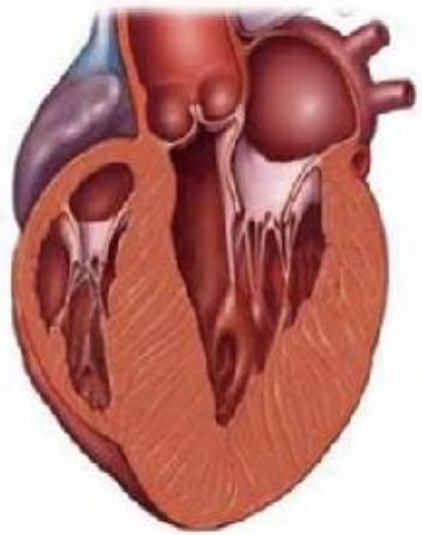
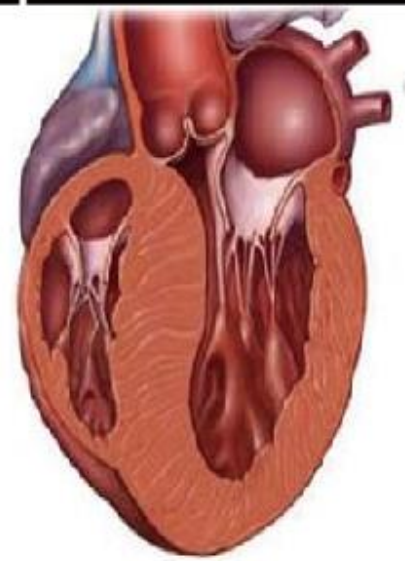
Patterns


Hypertrophic Cardiomyopathy
Asymmetric septal hypertrophy without obstruction
Asymmetric septal hypertrophy (ASH)
Mitral valve in normal position
Cavity reduced in size


Hypertrophic Cardiomyopathy
Asymmetric septal hypertrophy with obstruction
ASH
Blood leaks back through mitral valve = mitral regurgitation
Mitral valve presses against septum causing obstruction to blood flow
Systolic anterior motion of the mitral valve (SAM)

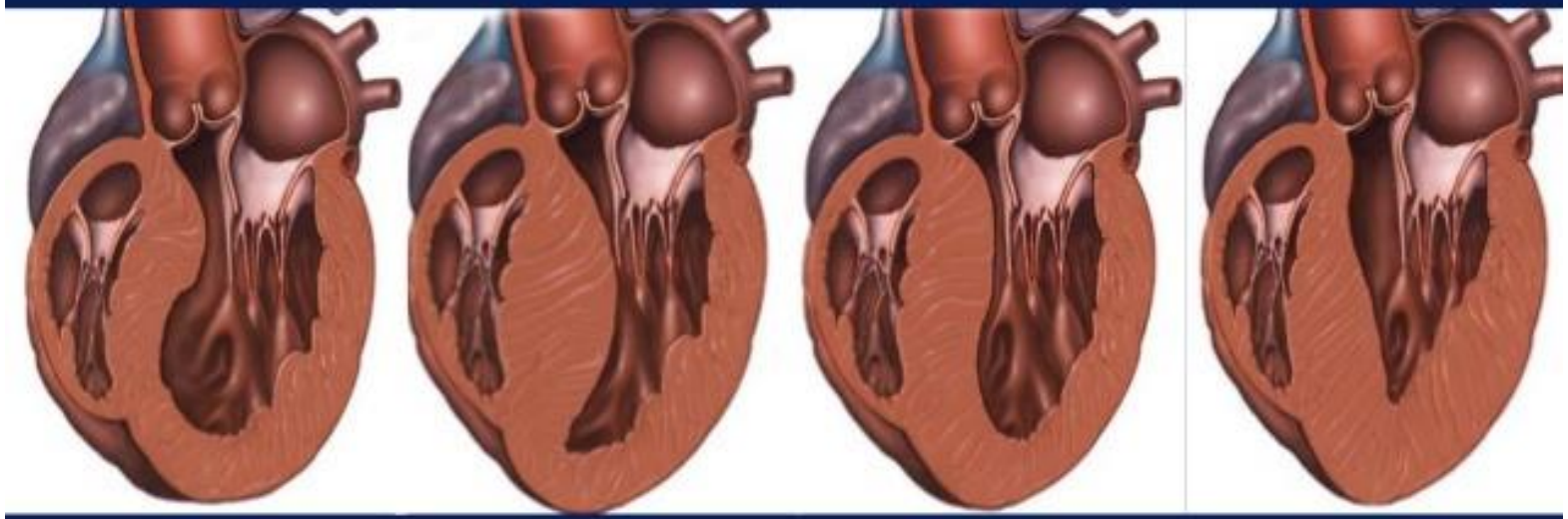

Hypertrophic Cardiomyopathy
Symmetric hypertrophy
Symmetric or concentric hypertrophy
FIGURE 7


Hypertrophic Cardiomyopathy
Apical hypertrophy
Apical hypertrophy
Small cavity remains
FIGURE 8

Sigmoidal HCM	Reverse curve HCM	Apical HCM	Neutral HCM
40-50%	30-40%	~10%	~10%
			
~ 10% Myofilament Gene +	~ 80% Myofilament Gene +	~ 30% Myofilament Gene +	~ 40% Myofilament Gene +

Left Ventricular Morphology in HCM

Sigmoid Septum	Reverse Septum	Neutral Septum	Apical Variant



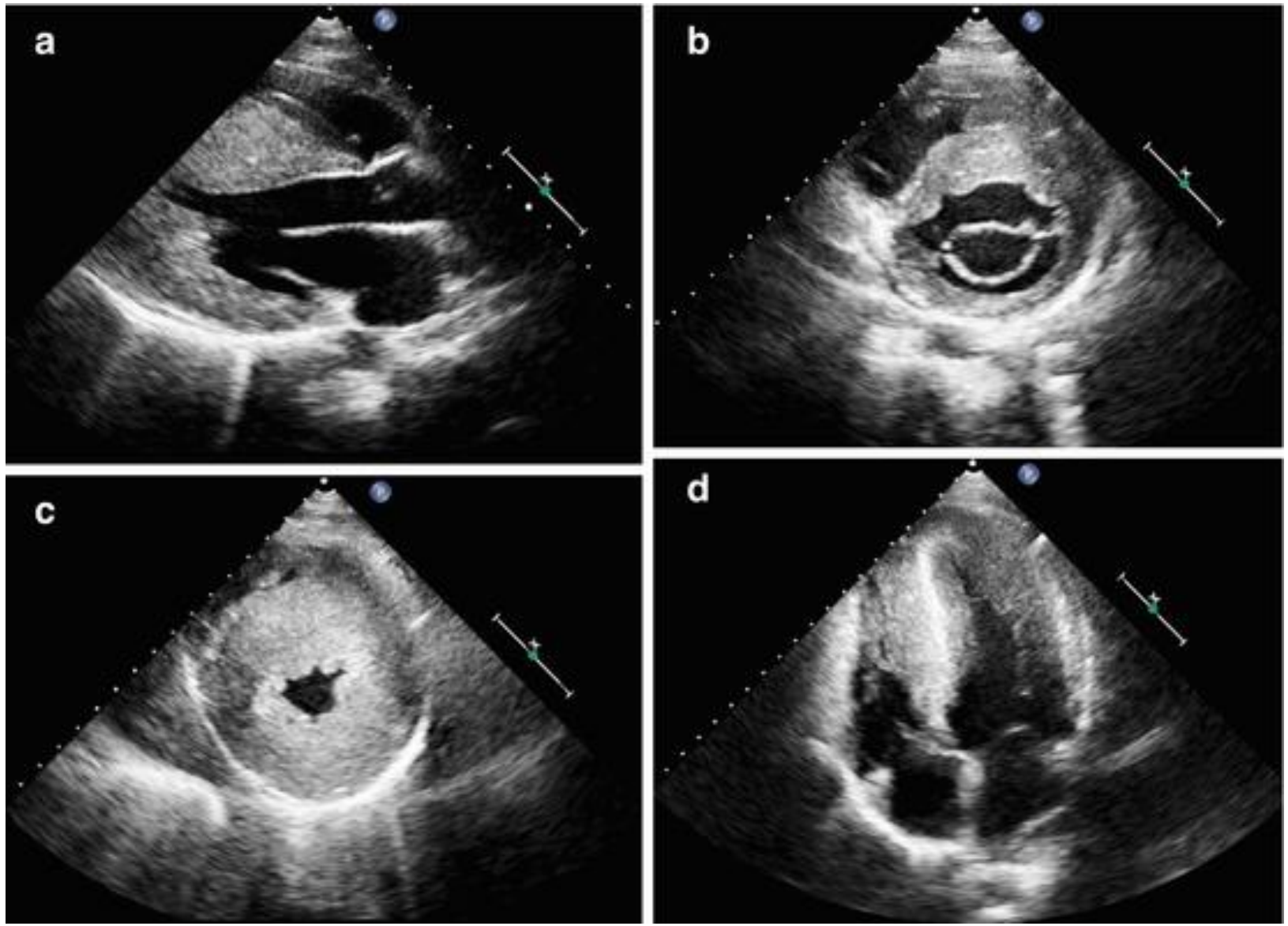
181(47%)	132(35%)	32(8%)	37(10%)
Gene + (8%)	Gene + (79%)	Gene + (41%)	Gene + (32%)

MAYO CLINIC

Binder J, et al. Mayo Clin Proc 2006; 81: 459.

Anatomic classification

Nomenclature	Sigmoidal HCM	Reverse curve HCM	Apical HCM	Neutral HCM
Prevalence	40-50%	30-40%	10%	10%
Age group	> 50-60 years	< 50-60 years	< 50-60 years	< 50-60 years
Genetics +	10-20%	80-90%	30-40%	30-40%
			Yamaguchi's disease	


a
b
c
d

European Journal of Echocardiography (2009) **10**, iii9–iii14
doi:10.1093/ejechocard/jep157

Echocardiography in hypertrophic cardiomyopathy diagnosis, prognosis, and role in management

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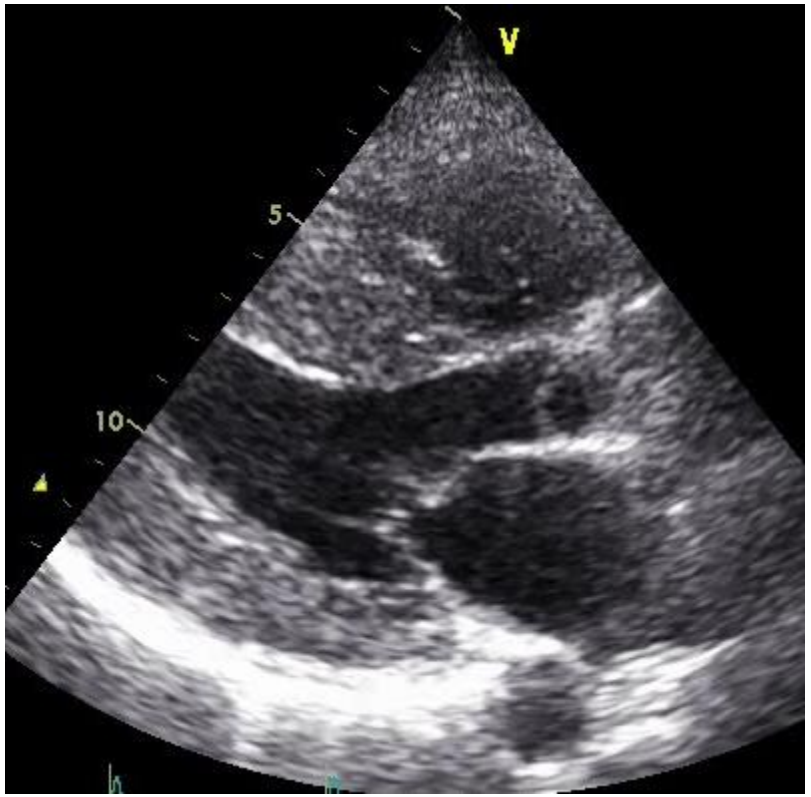
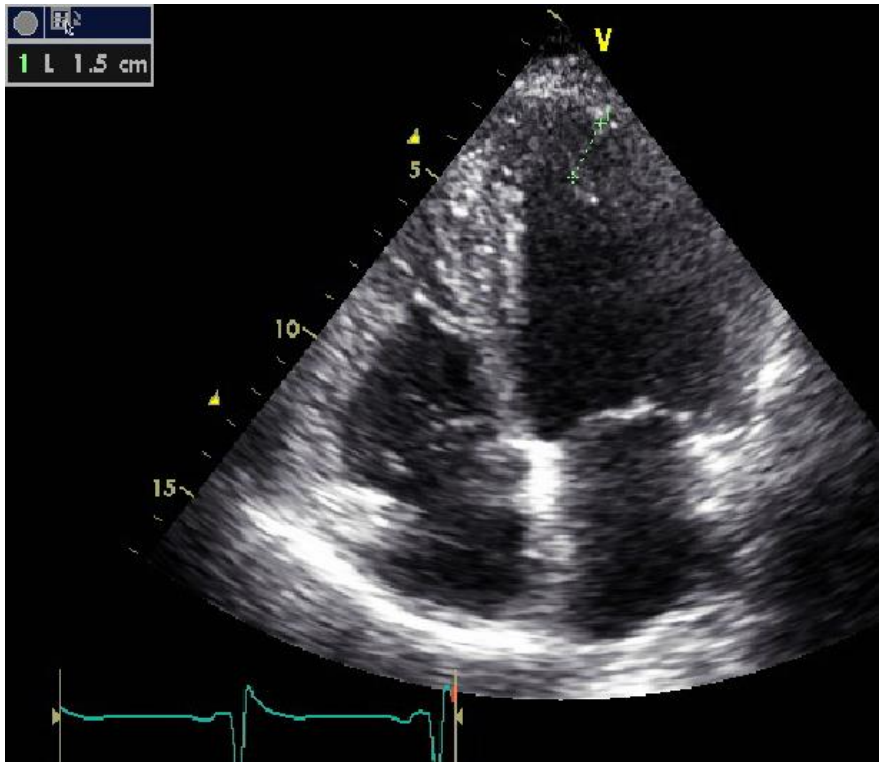
הערכה אקוקרדיוגרפית בחולים עם קרדיומיופתיה היפרטרופית

מדידות

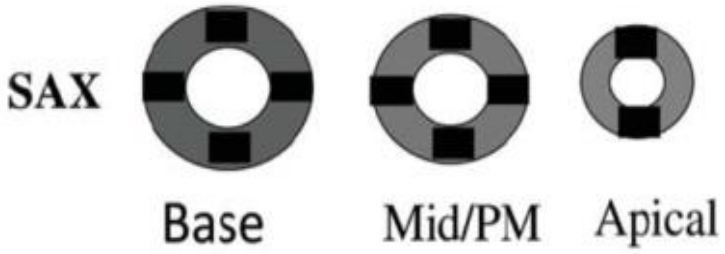
- למדוד עובי מקסימלי בסמגנטים שונים ולתאר העובי והמיקום

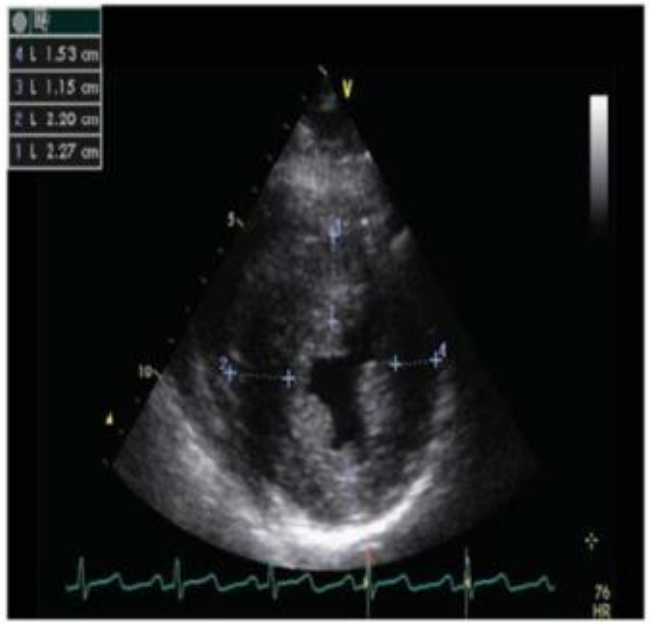


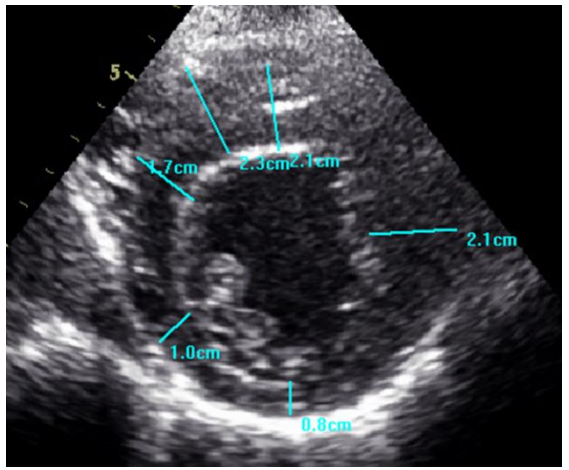


מדידות

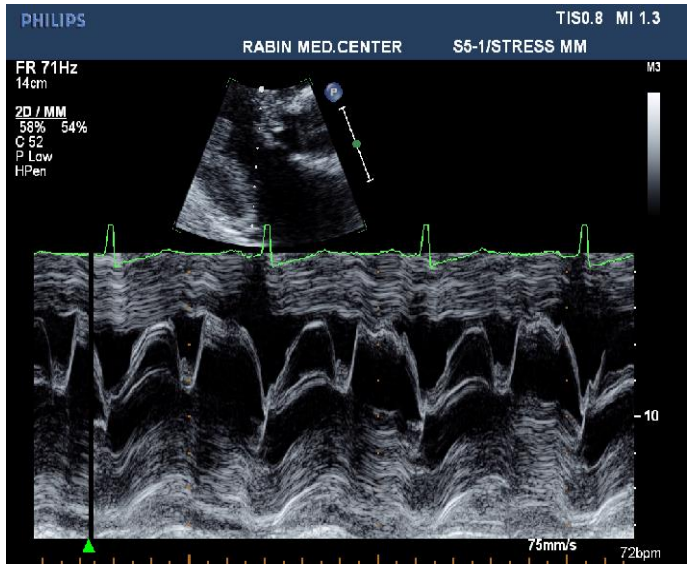
לתאר את המיקום וההיקף של ההיפרטרופיה
(כגון: ספטלית עם מעורבות קדמית וצדדית, ספטלית עם מעורבות אפיקלית)

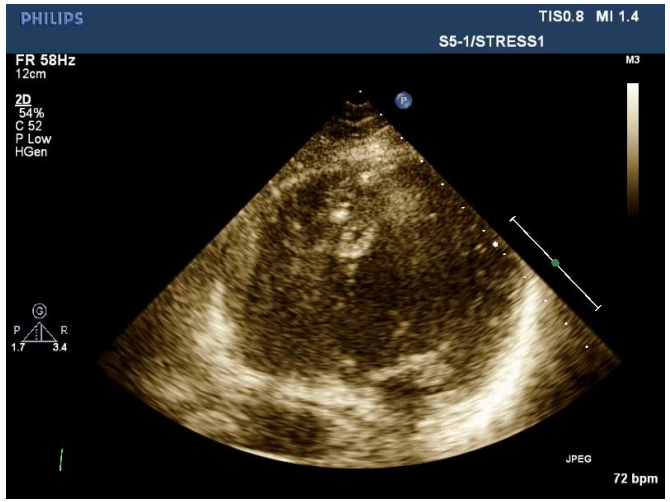






הערכת מסתם מיטרלי





: SAM

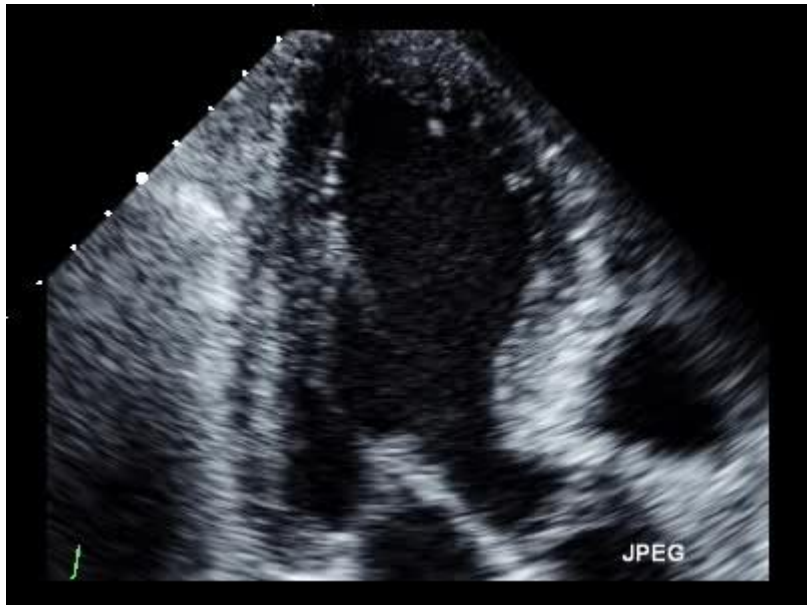
קל - אם משך המגע עם הספטום < 10% מהסיסטולה

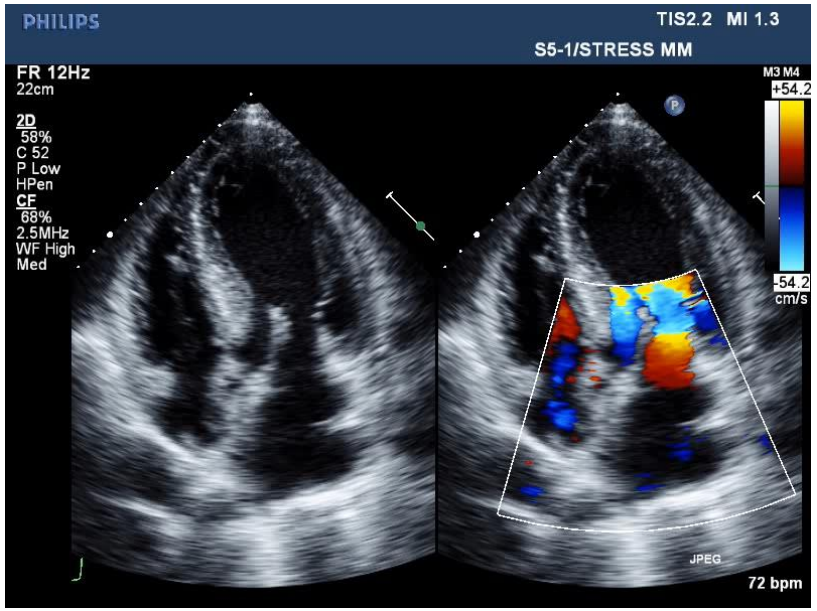
קשה- אם > 30% מהסיסטולה

לעתים עלה קדמי ארוך, קורדות ארוכות, מיקום שונה של שריר פפילרי

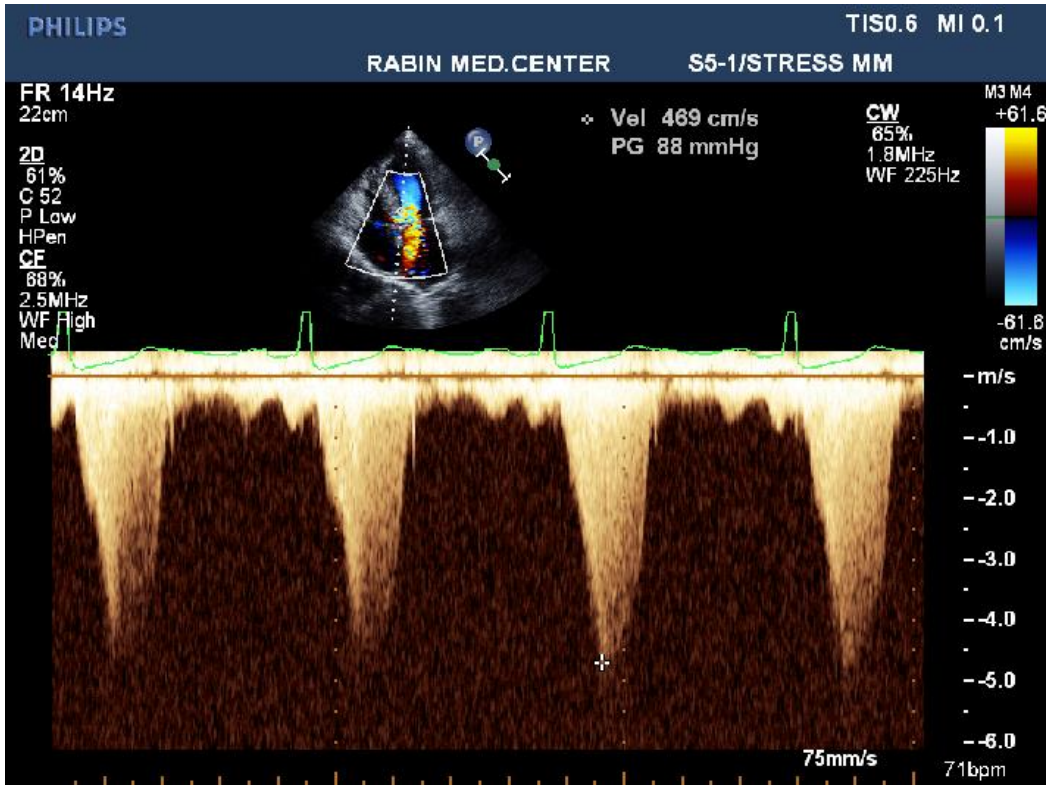
MR משני ל SAM יהיה אקצנטרי אחורי <u>אחרת</u> יש לחשוד / לתאר פתולוגיה אחרת או נוספת

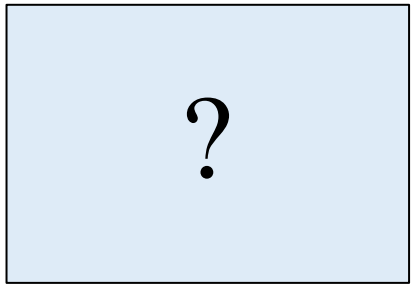
חסימה דינאמית באפיק מוצא

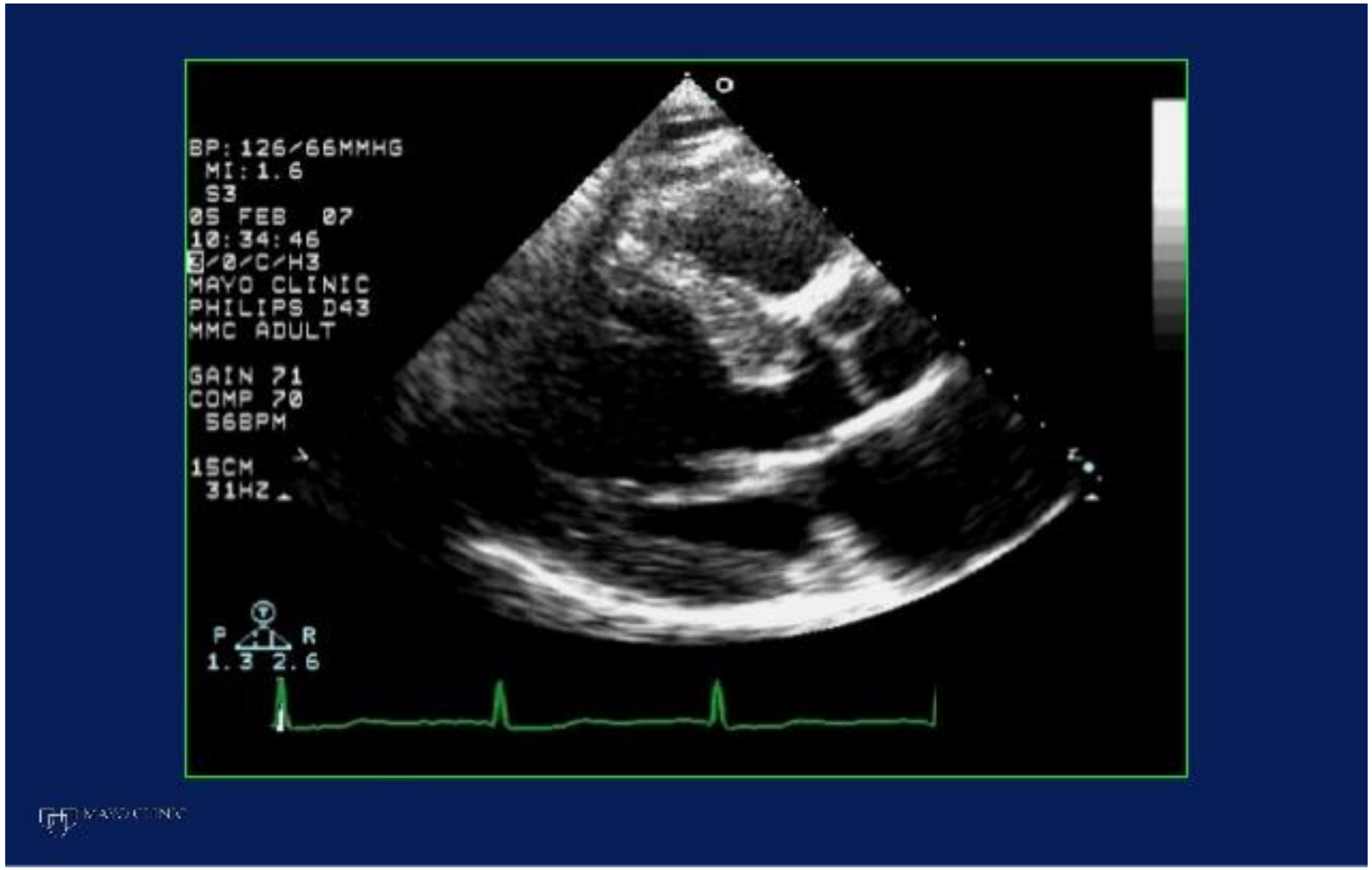




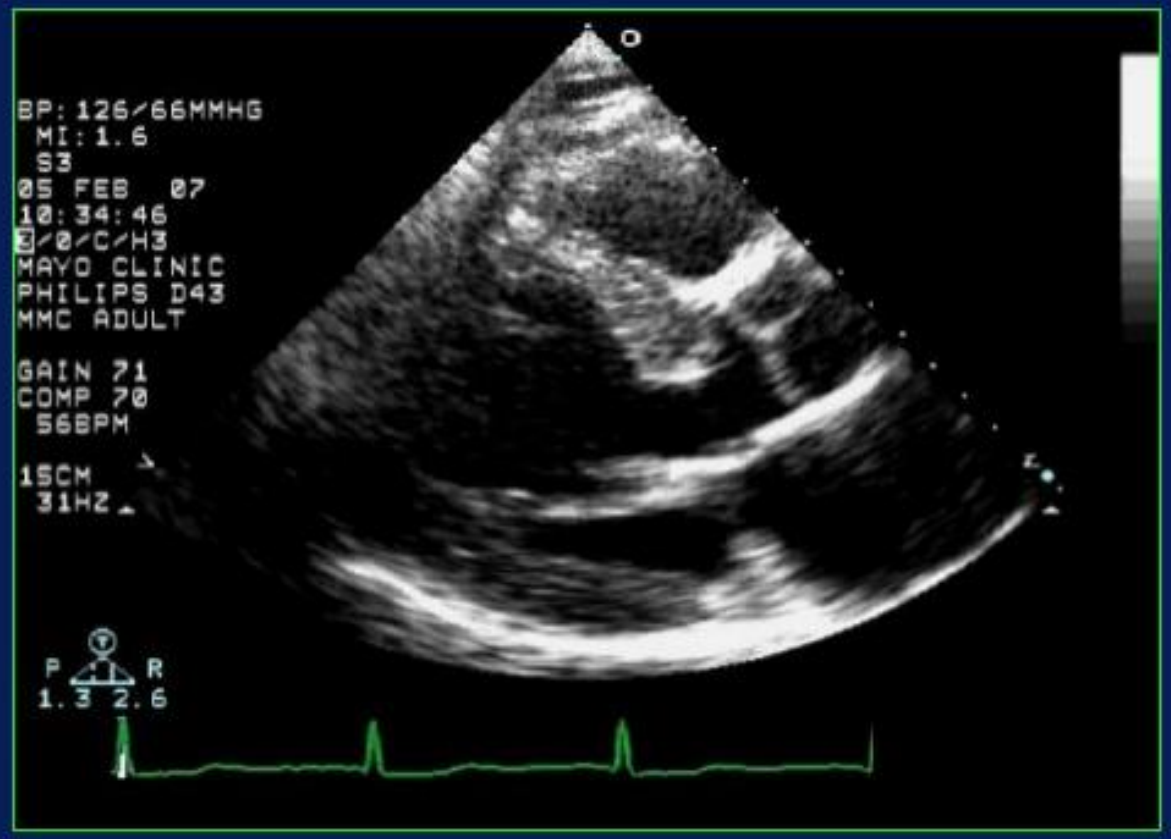
חסימה דינאמית באפיק מוצא

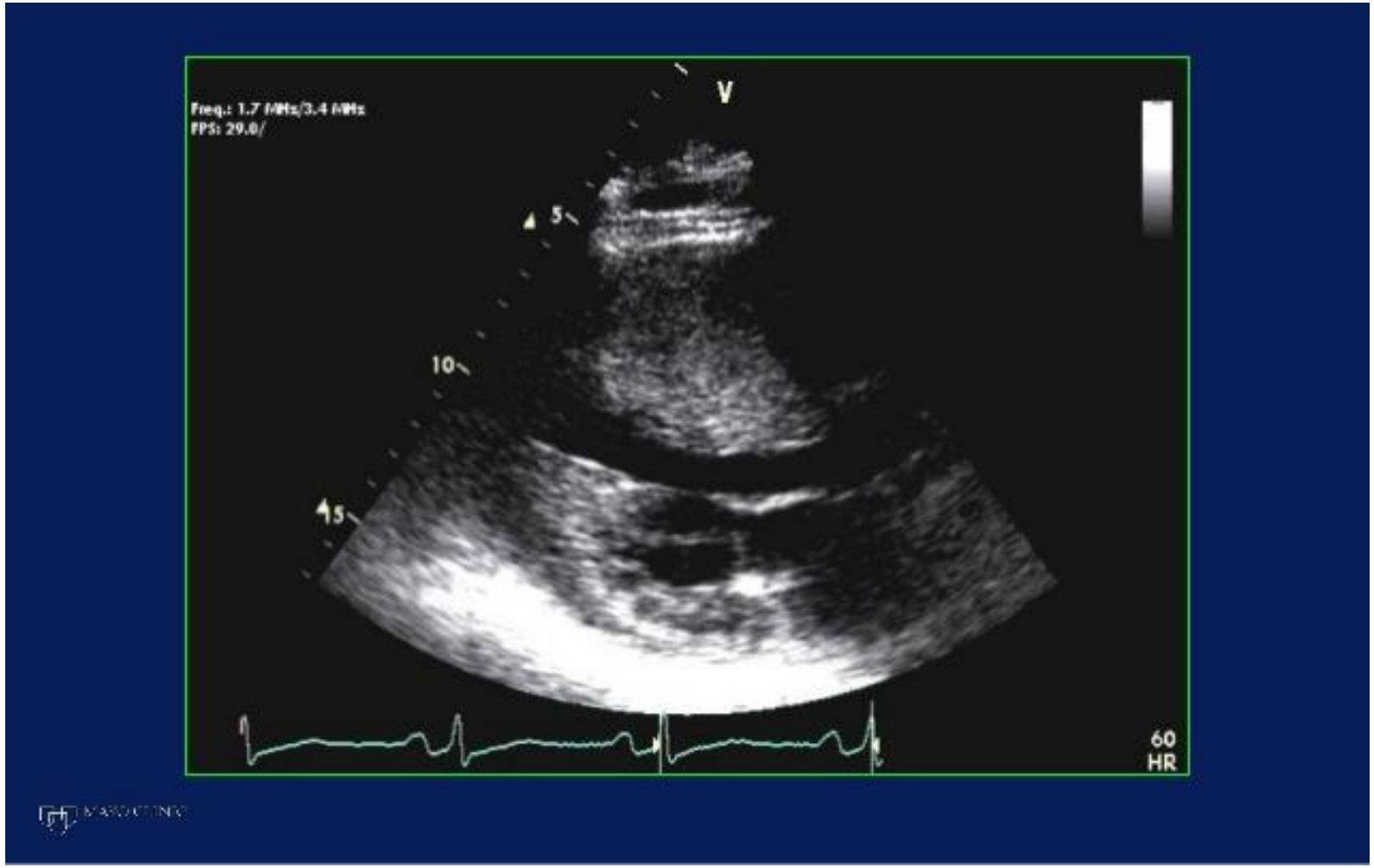




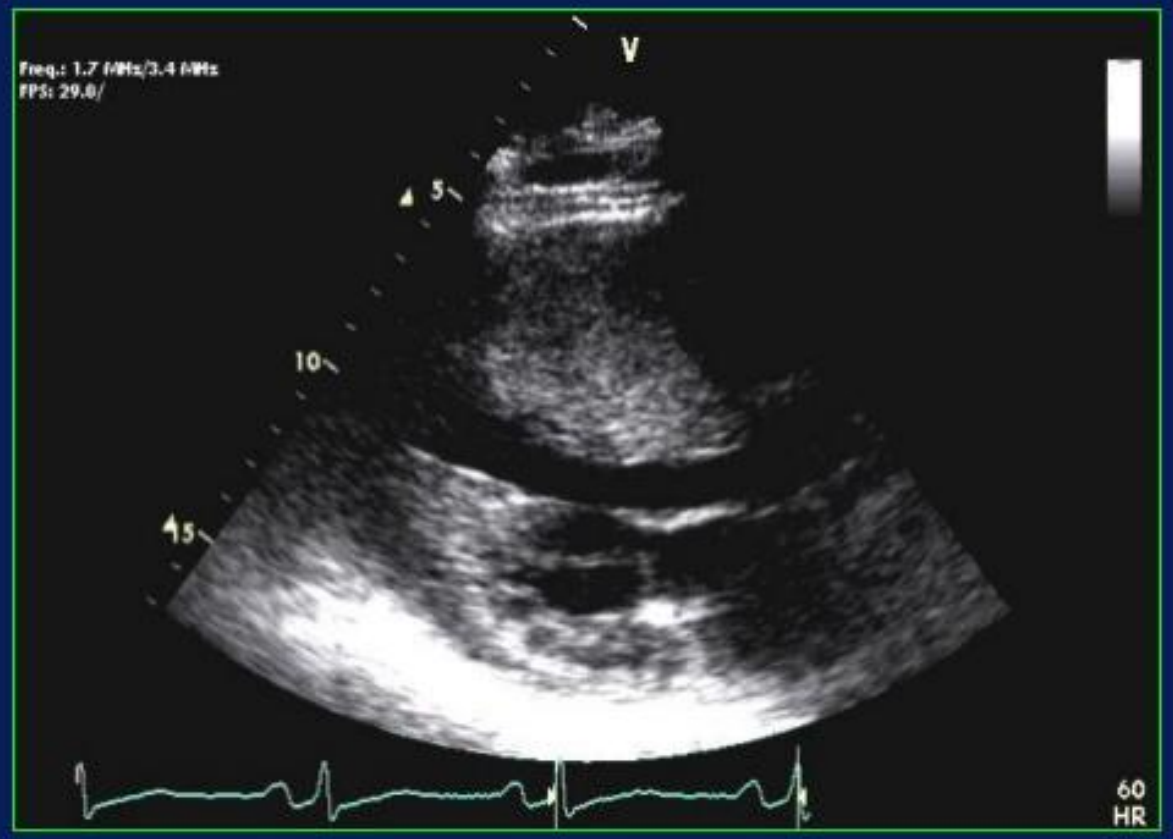

BP: 126/66MMHG
MI: 1.6
S3
05 FEB 07
10:34:46
3/0/C/H3
MAYO CLINIC
PHILIPS D43
MMC ADULT
GAIN 71
COMP 70
56BPM
15CM
31HZ
P R
1.3 2.6

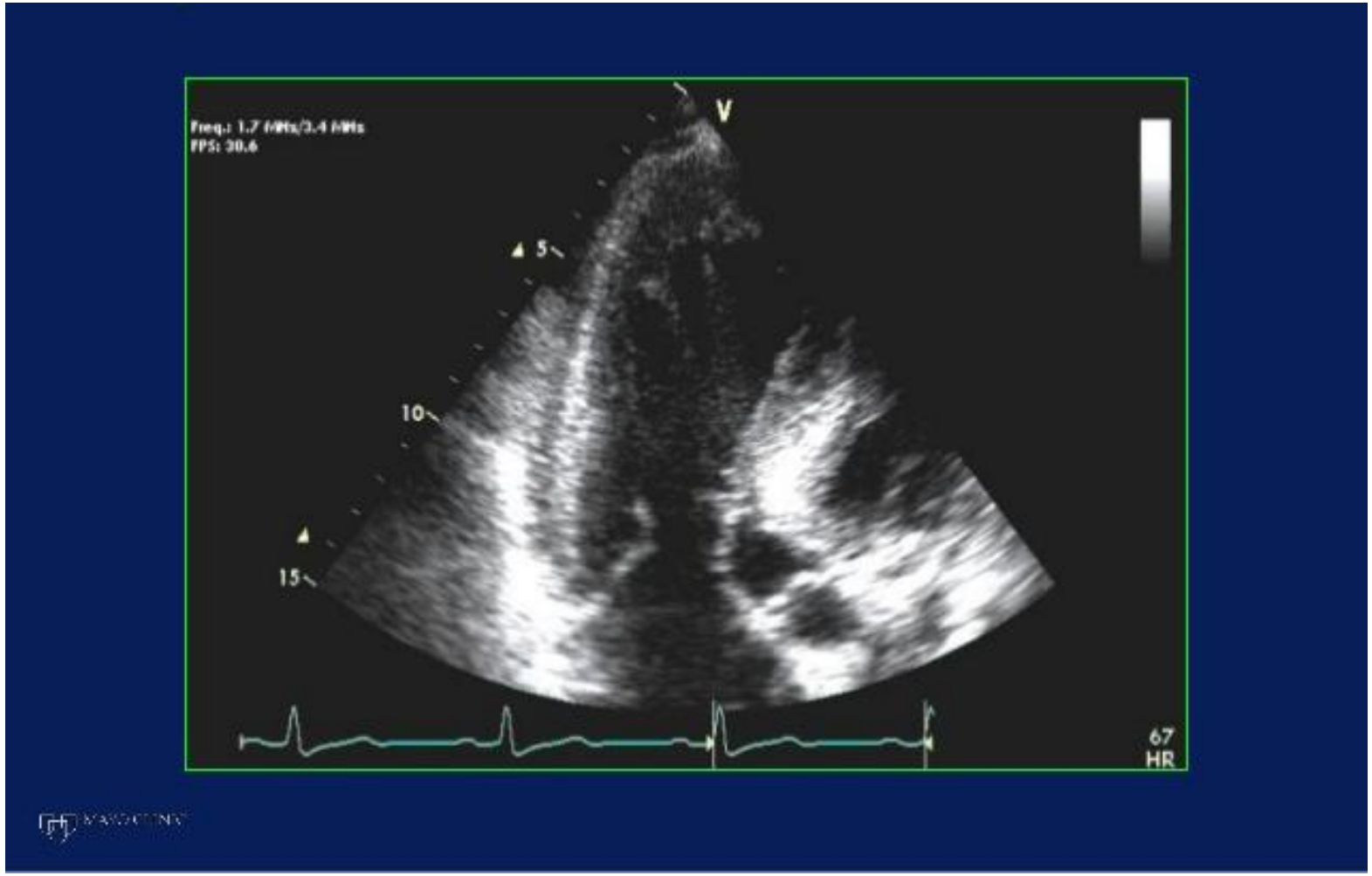
LVH in HCM: Sigmoid Septum



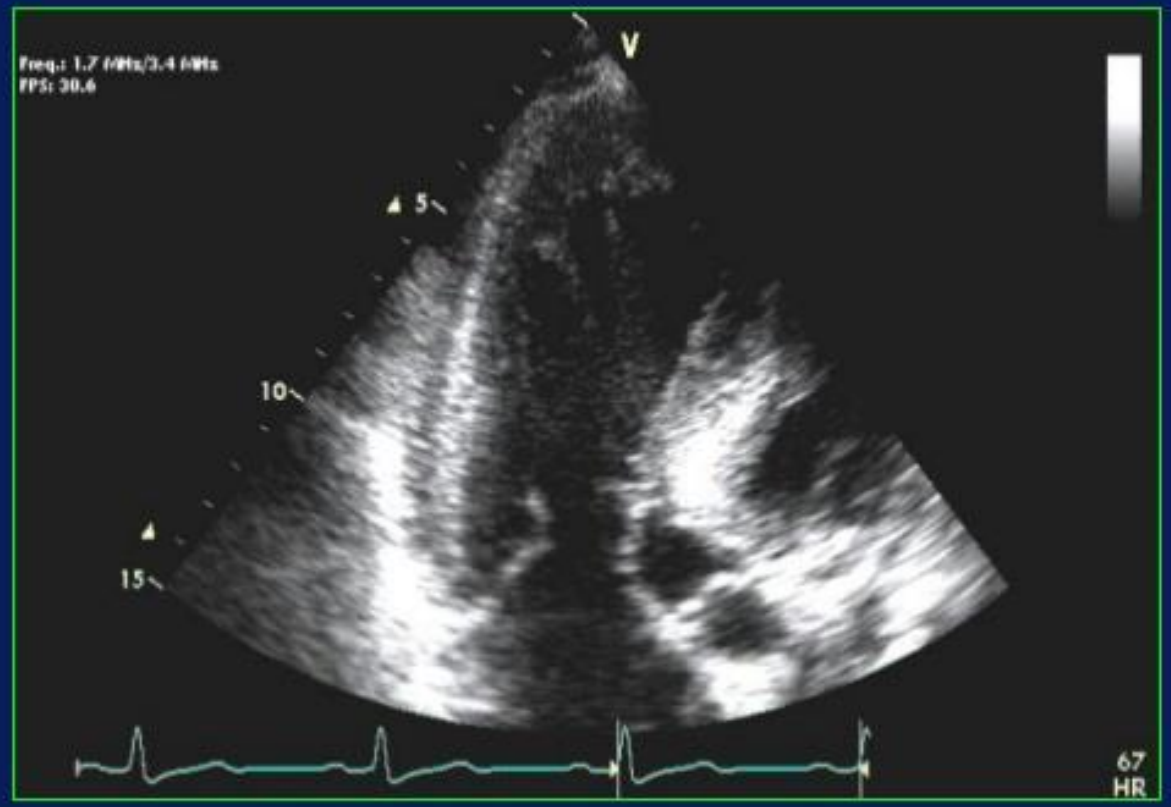

Freq.: 1.7 MHz/3.4 MHz
FPS: 29.0/
V
5
10
15
60
HR

LVH in HCM: Reversed Septum

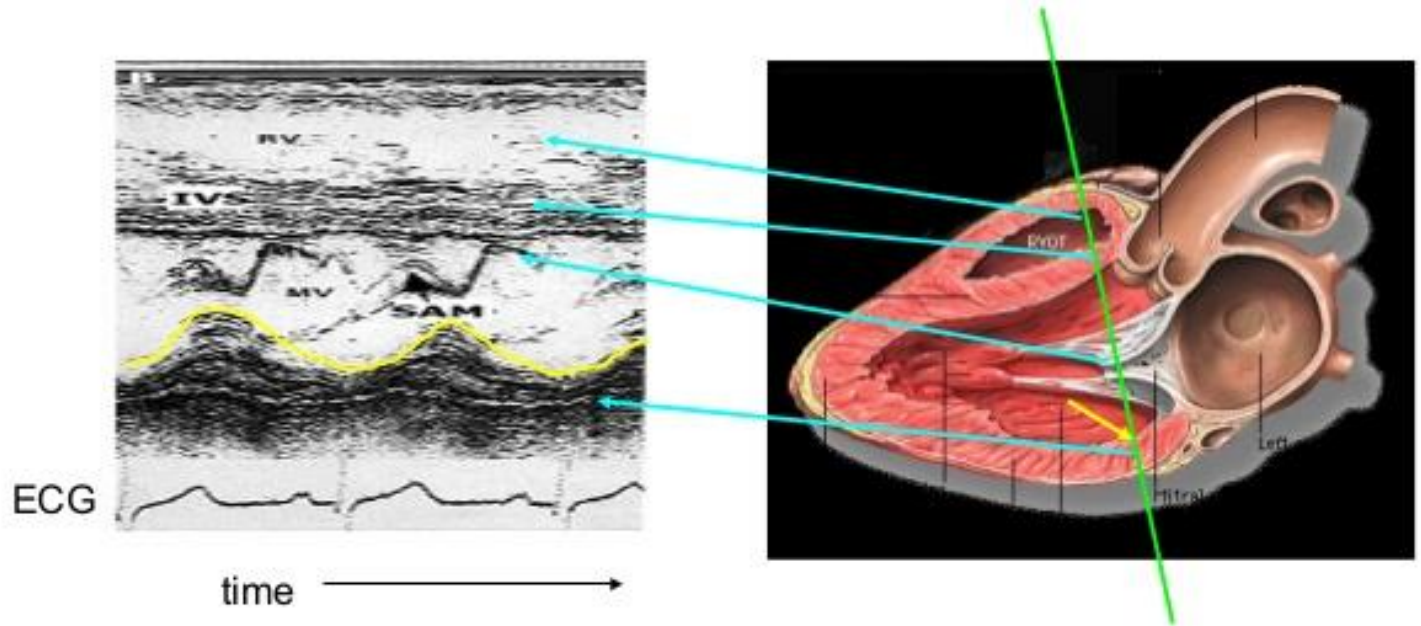


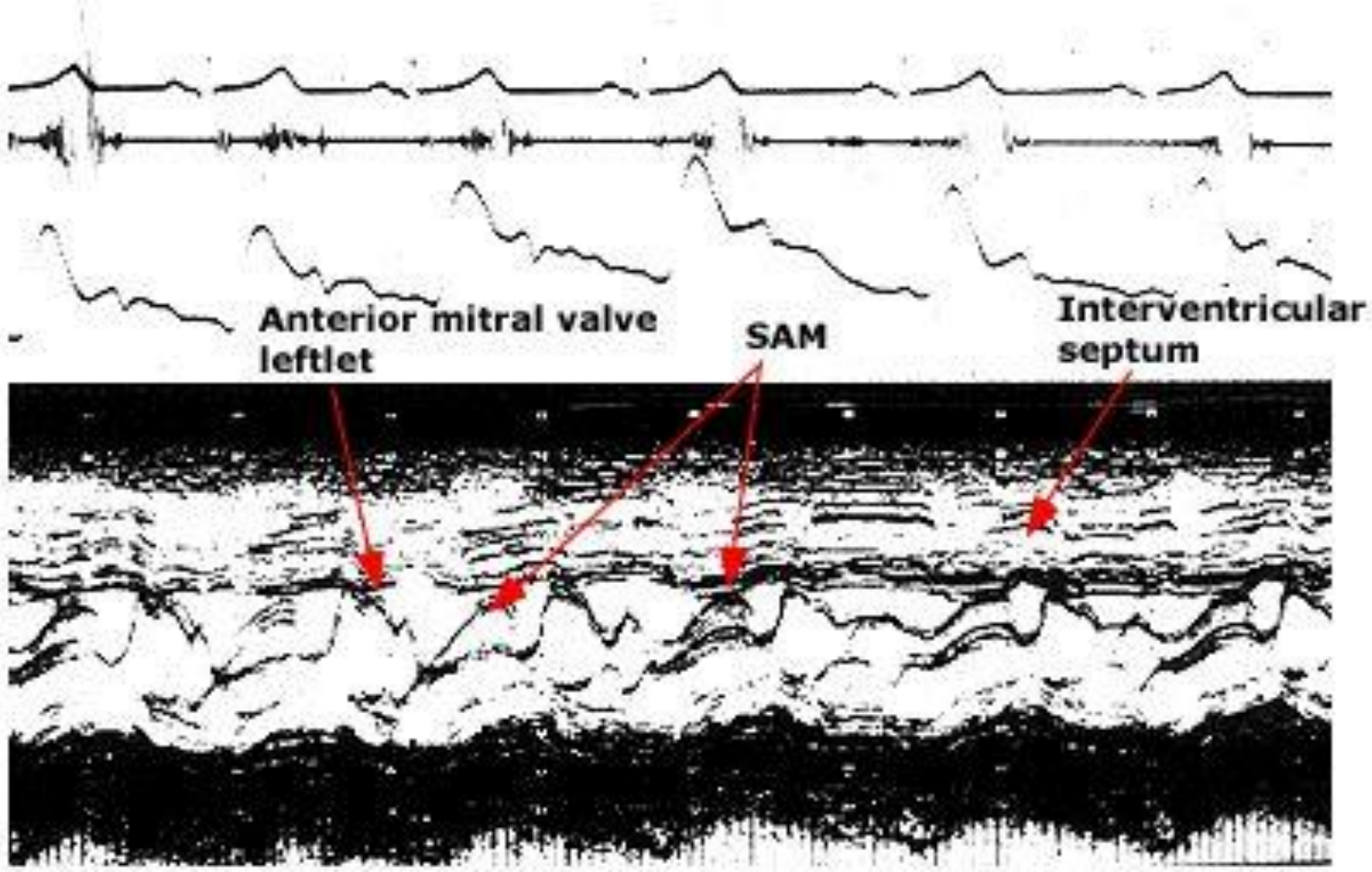

Freq.: 1.7 MHz/3.4 MHz
FPS: 30.6
V
5
10
15
67
HR

Systolic Anterior Motion (SAM)

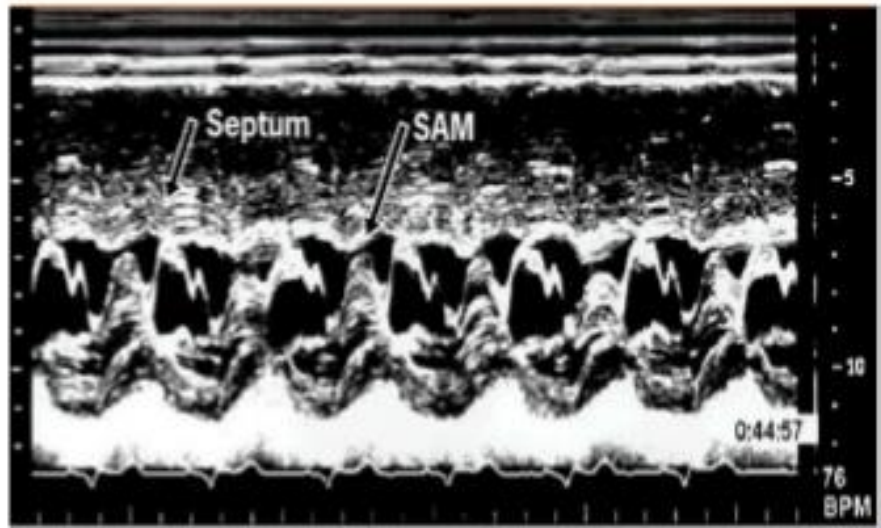


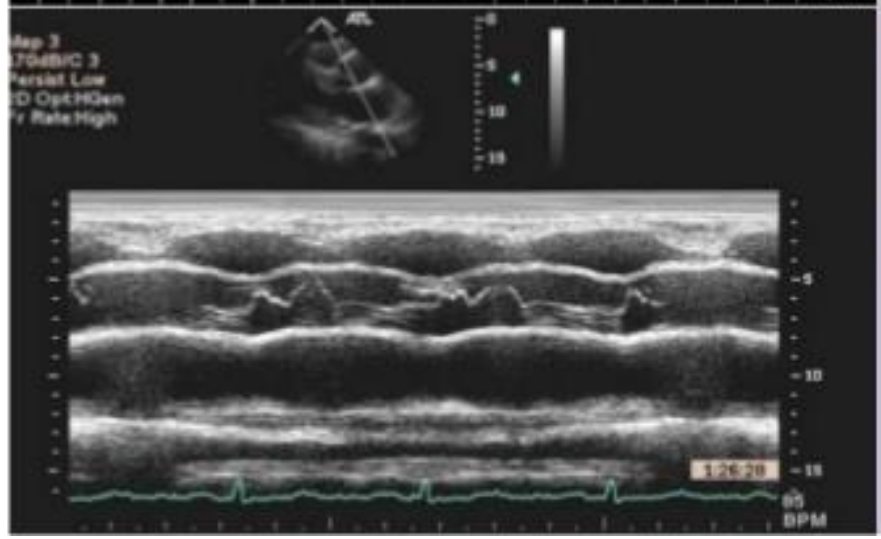
M – mode ECHO

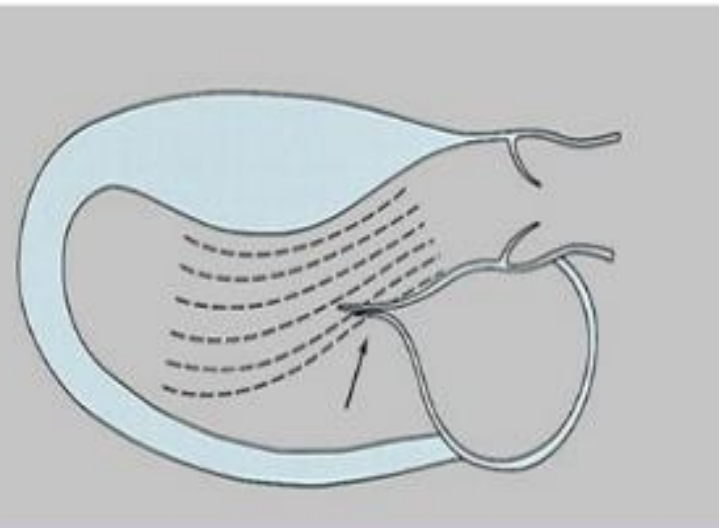



Anterior mitral valve leftlet
SAM
Interventricular septum

M MODE ECHO





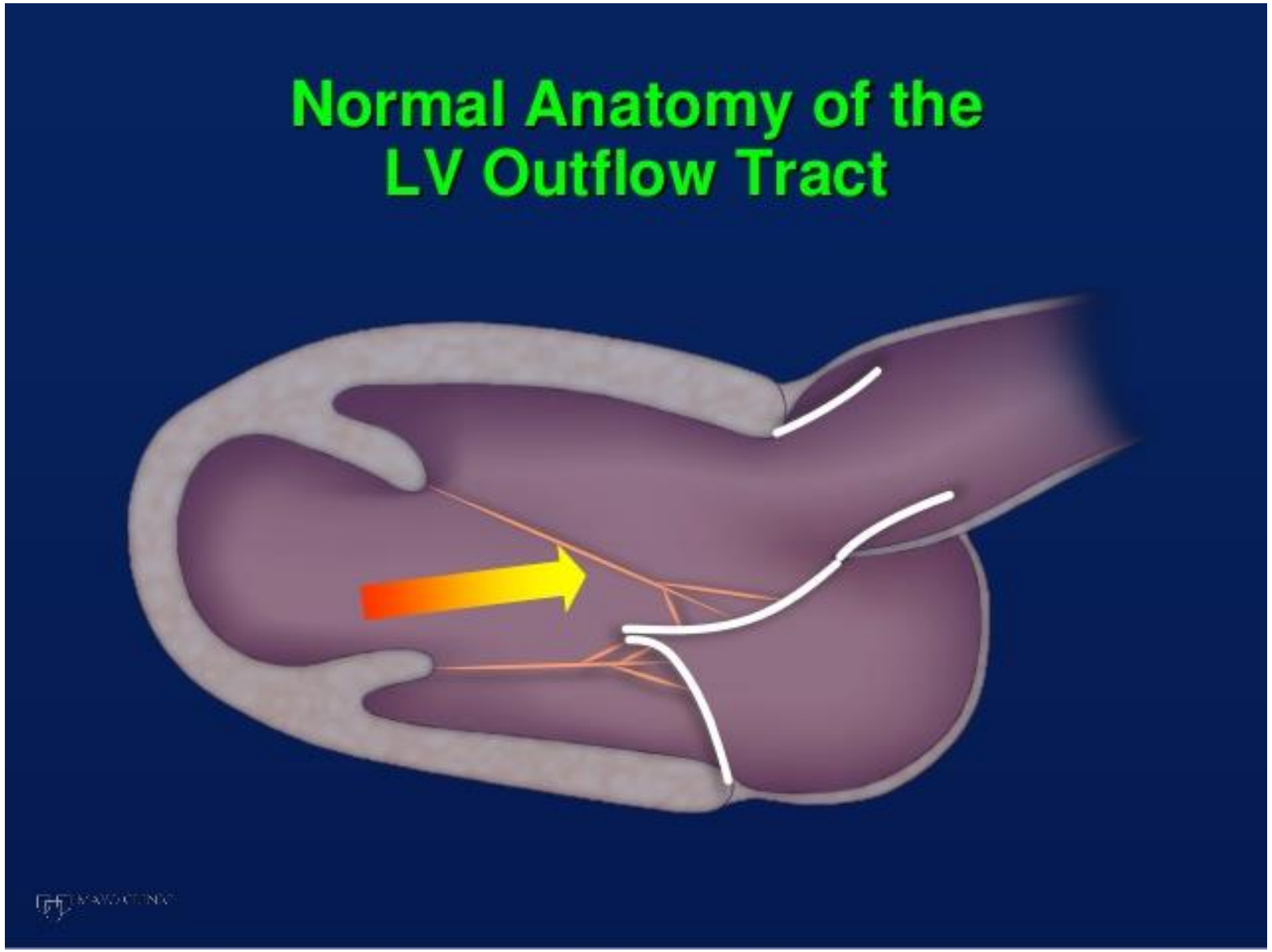


- SAM
- GRADING OF SAM
- AORTIC VALVE FLUTTERING

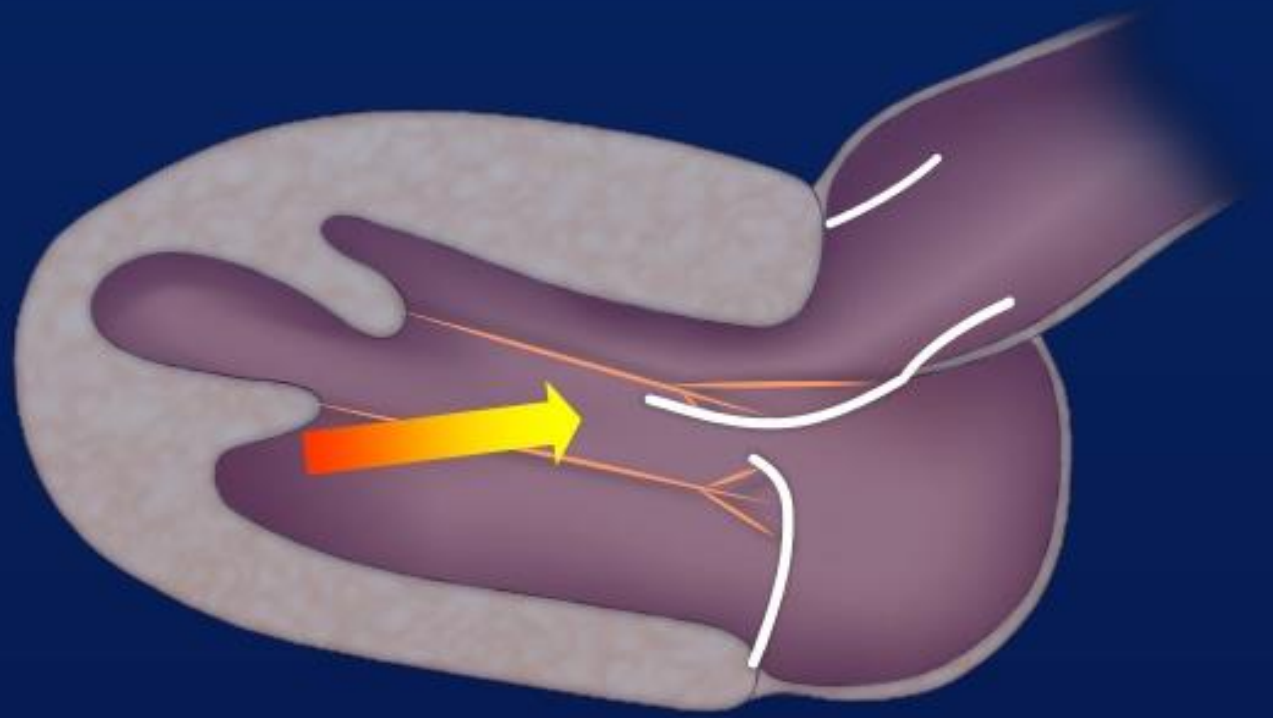
HOCM: Systolic Anterior Motion (SAM)

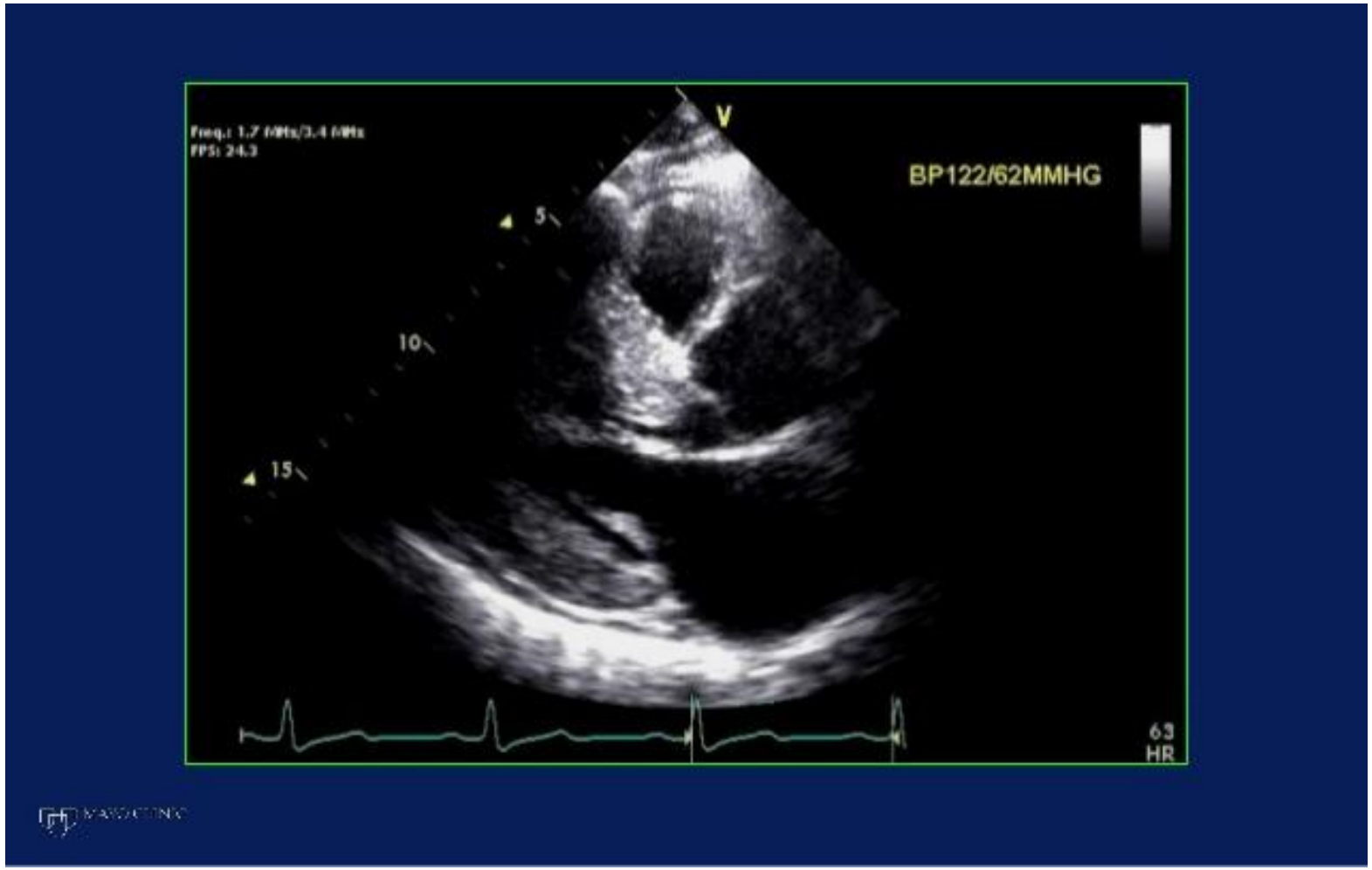
- Drag effect >>> Venturi effect
- Anterior displacement of mitral valve and support apparatus; small LV cavity
- Septal encroachment into LVOT
- Mitral valve characteristics
  - Anterior displacement of papillary muscles
  - Unusual chordal attachments
  - Elongated anterior leaflet
  - Aberrant muscle bundles

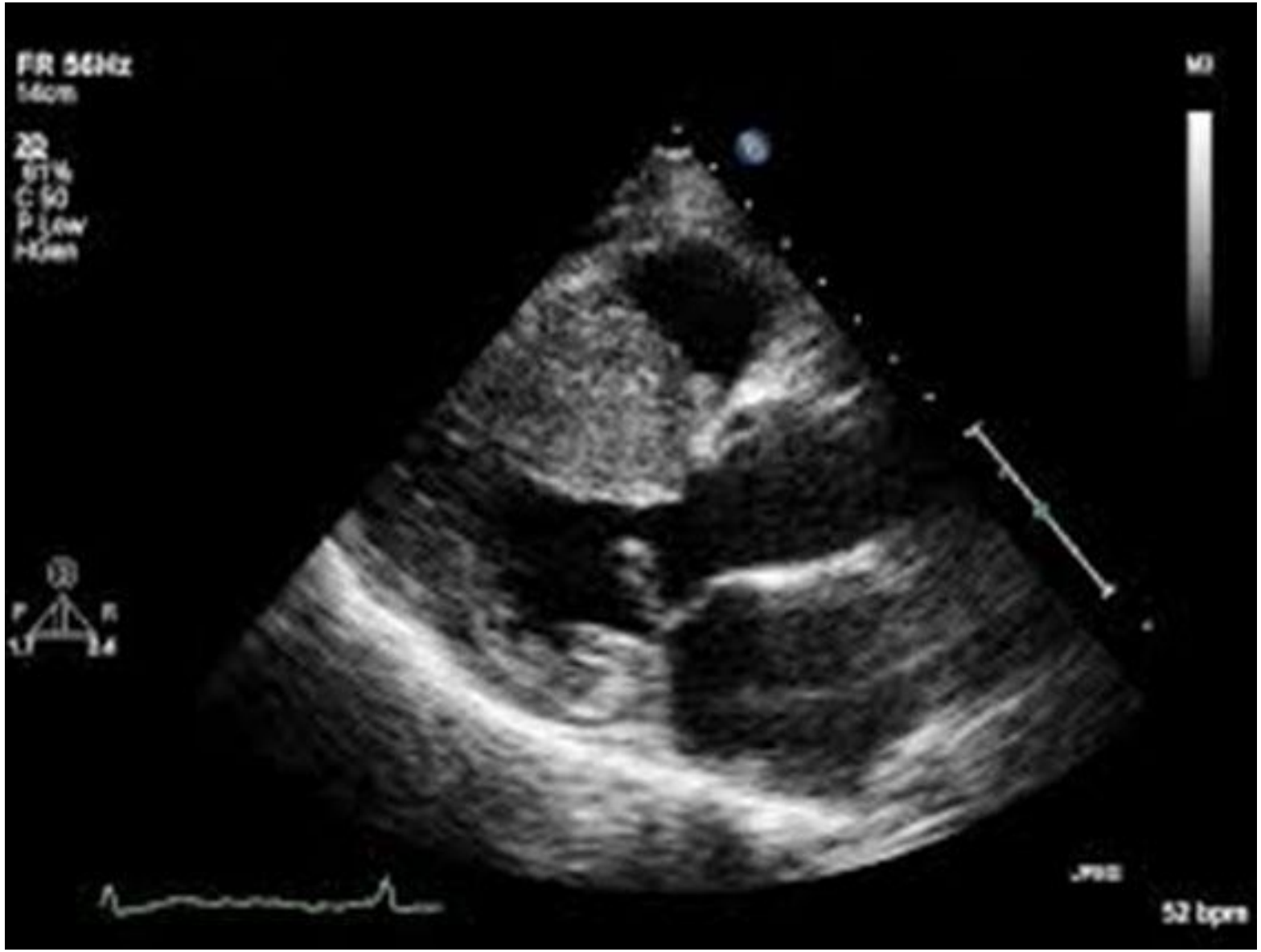
Normal Anatomy of the LV Outflow Tract



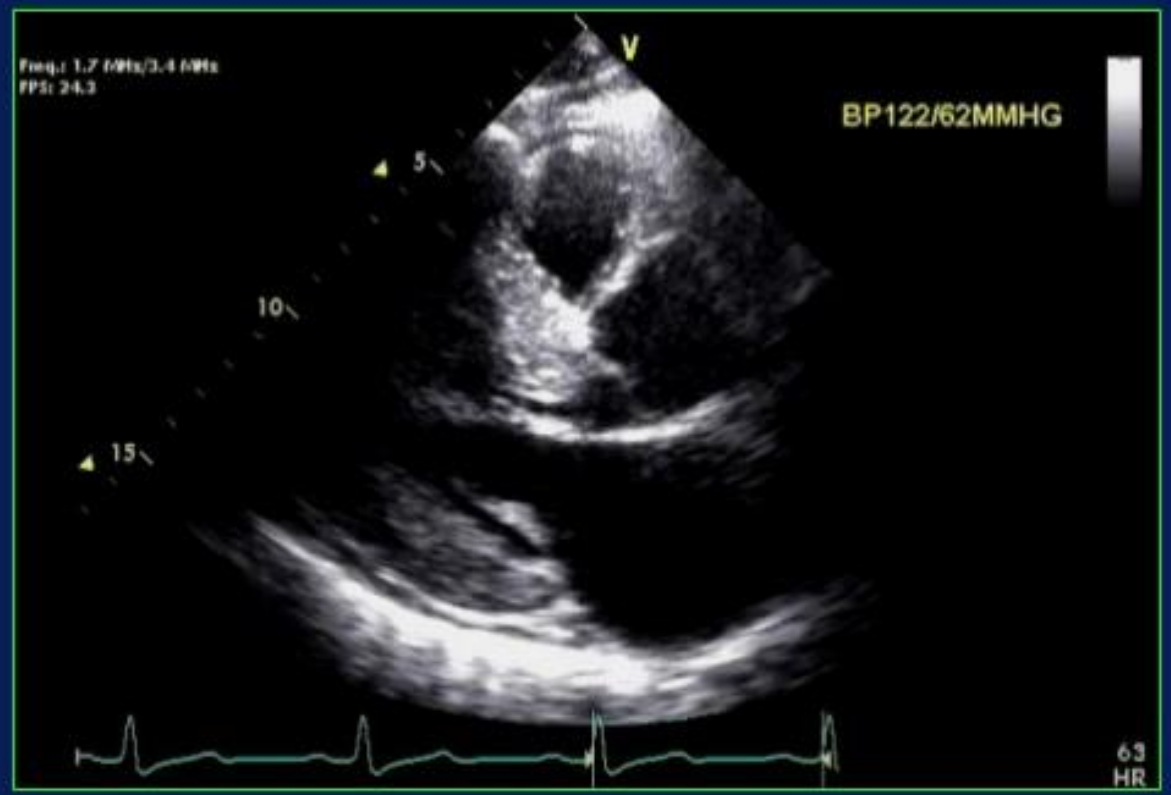
Hypertrophic Cardiomyopathy

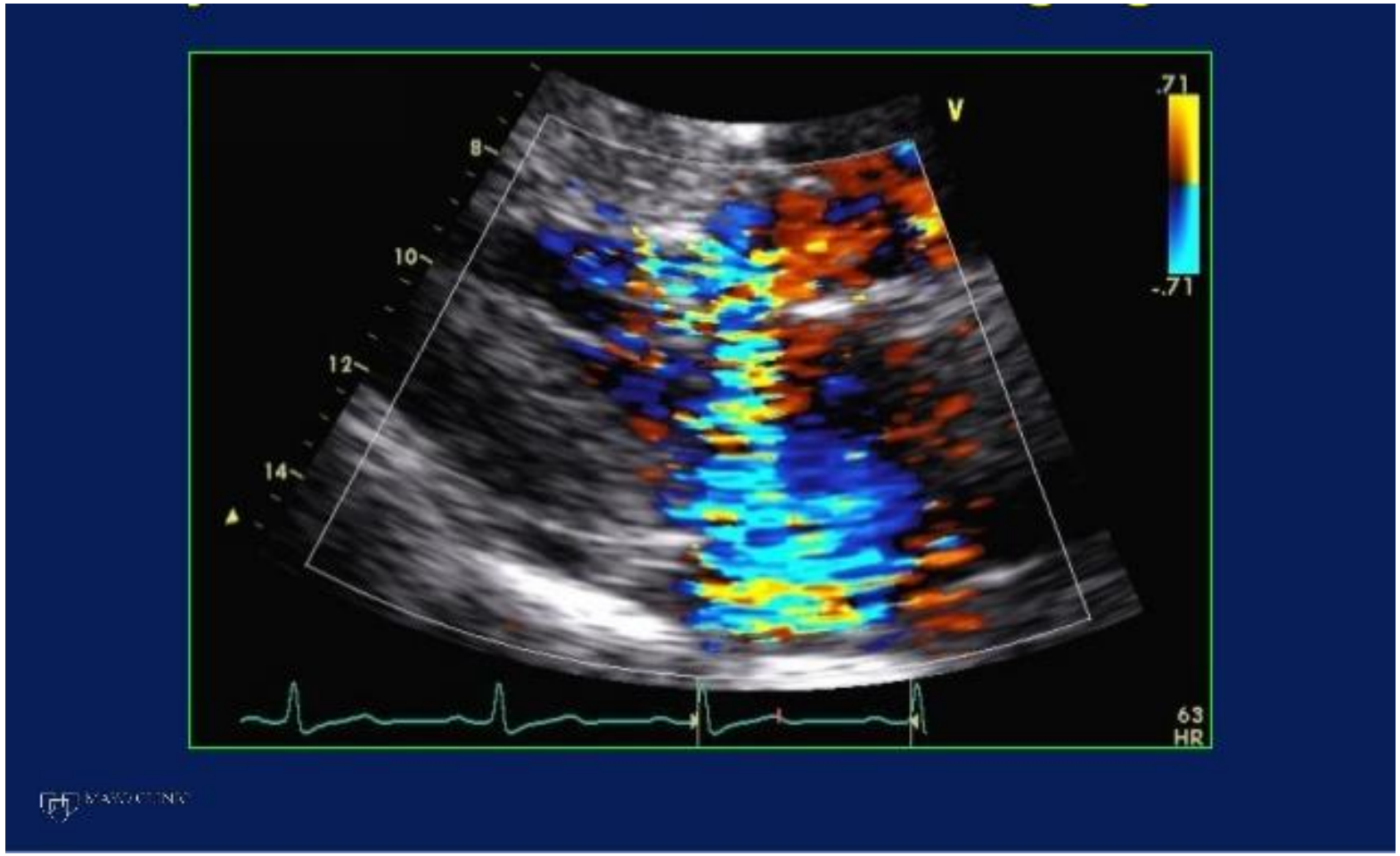



Freq.: 1.7 MHz/3.4 MHz
FPS: 24.3
V
BP122/62MMHG
5
10
15
63
HR


FR 56Hz
14cm
MI
52 bpm

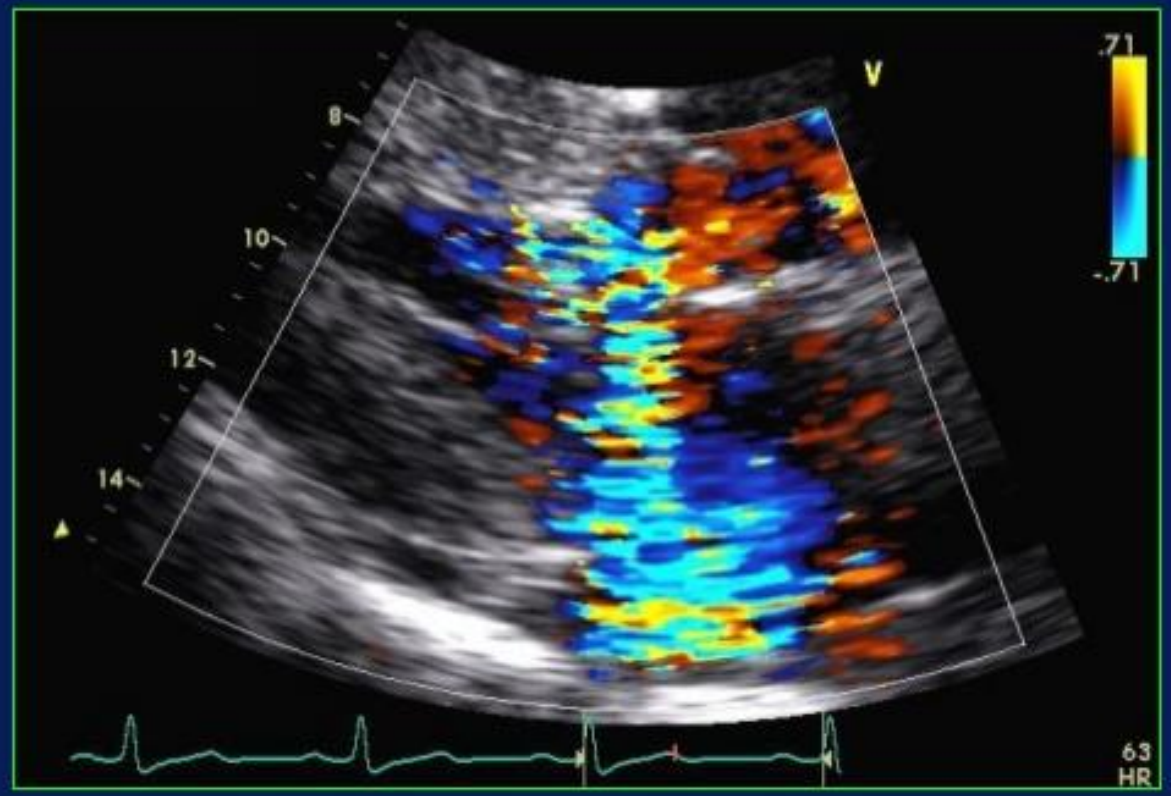
Systolic Anterior Motion (SAM)



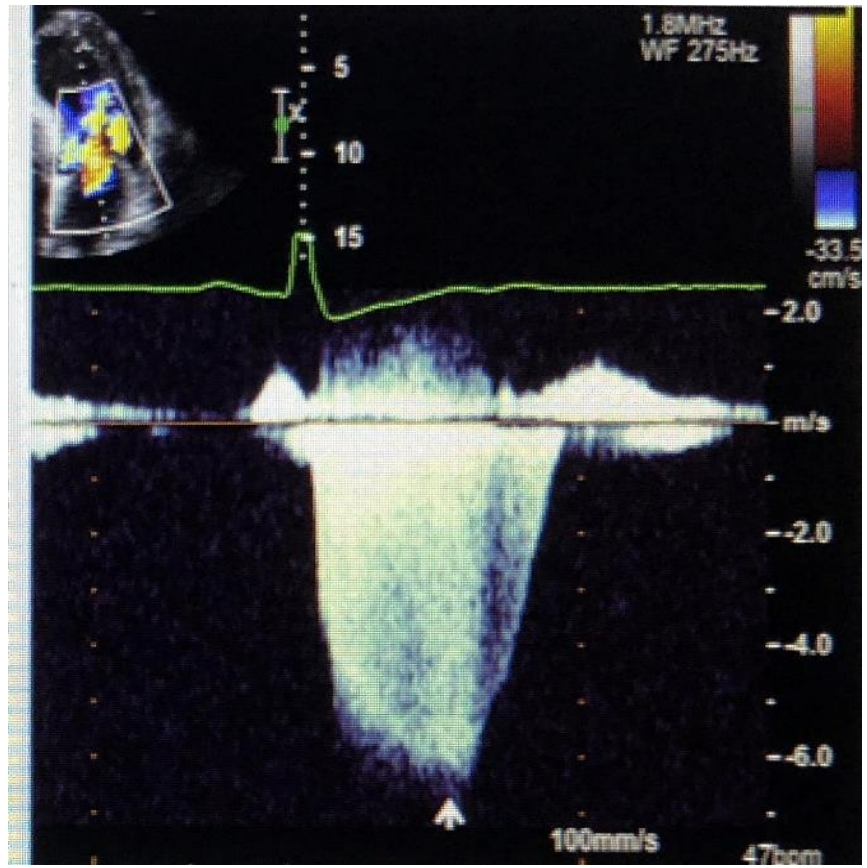

V
8
10
12
14
.71
-.71
63
HR

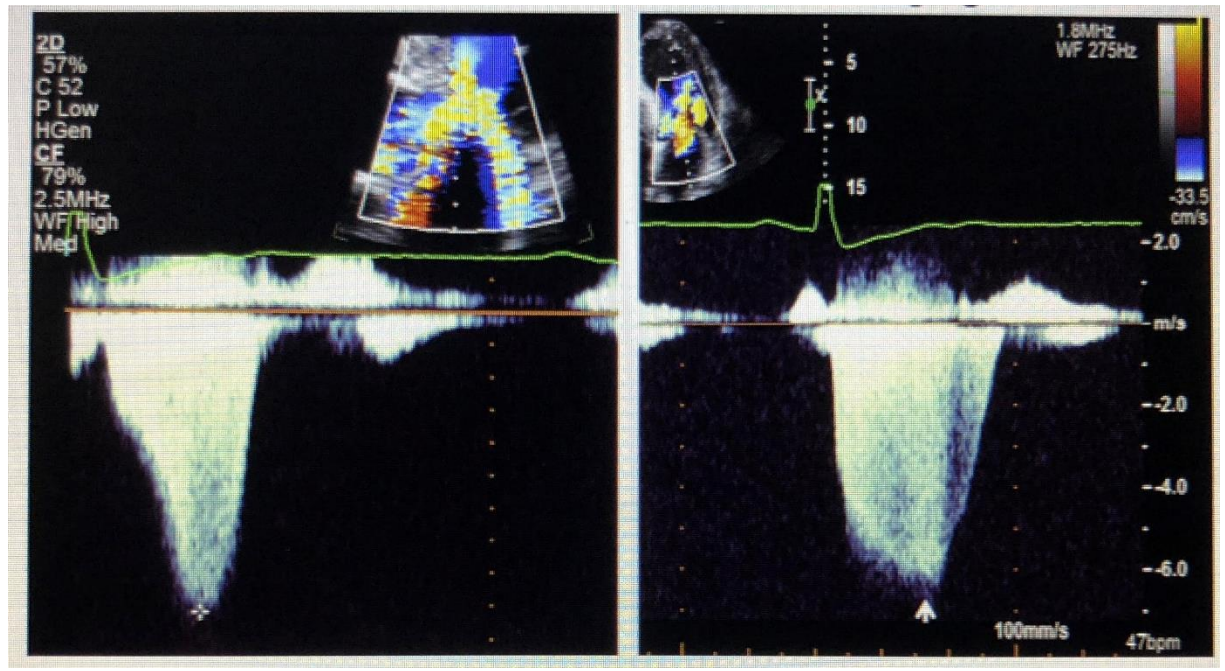
Systolic Anterior Motion (SAM):

LV Ejection ➡ Obstruction ➡ Regurgitation



איך נבצע הערכה של הגראדיאנט ב-LVOT?


1.8MHz
WF 275Hz
5
10
15
-33.5
cm/s
-2.0
m/s
--2.0
--4.0
--6.0
100mm/s
47bpm


2D
57%
C 52
P Low
HGen
CE
79%
2.5MHz
WF High
Med
1.8MHz
WF 275Hz
5
10
15
-33.5
cm/s
-2.0
m/s
-2.0
-4.0
-6.0
100mm/s
47bpm

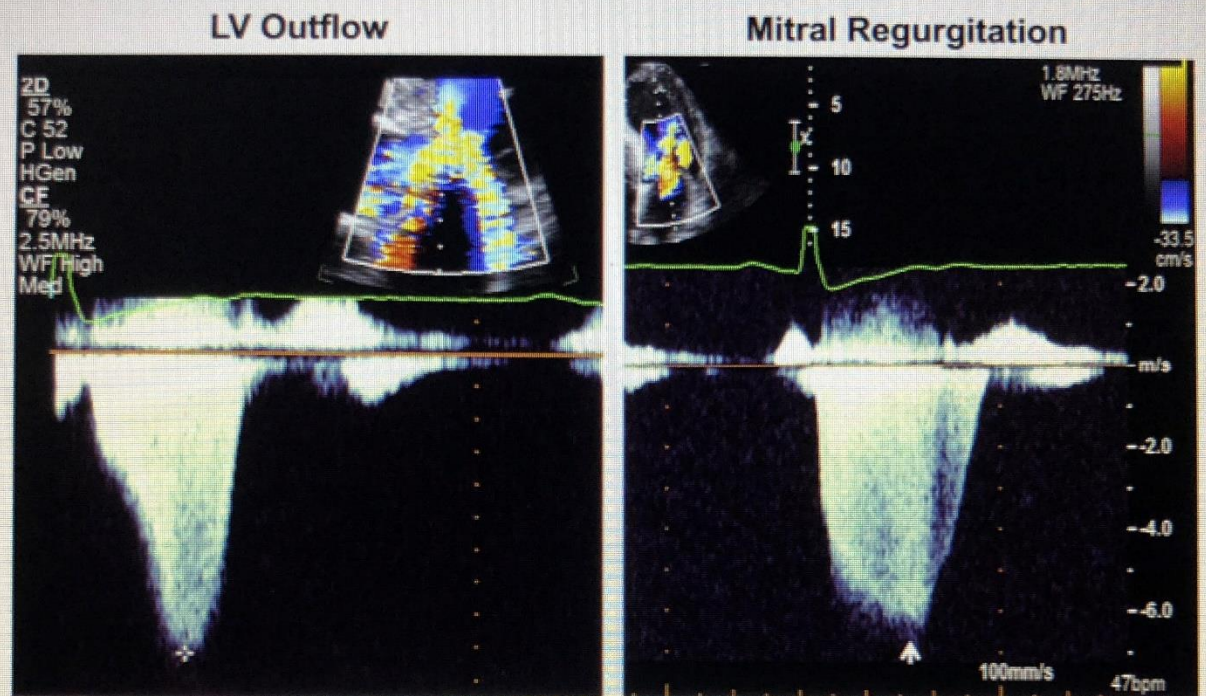
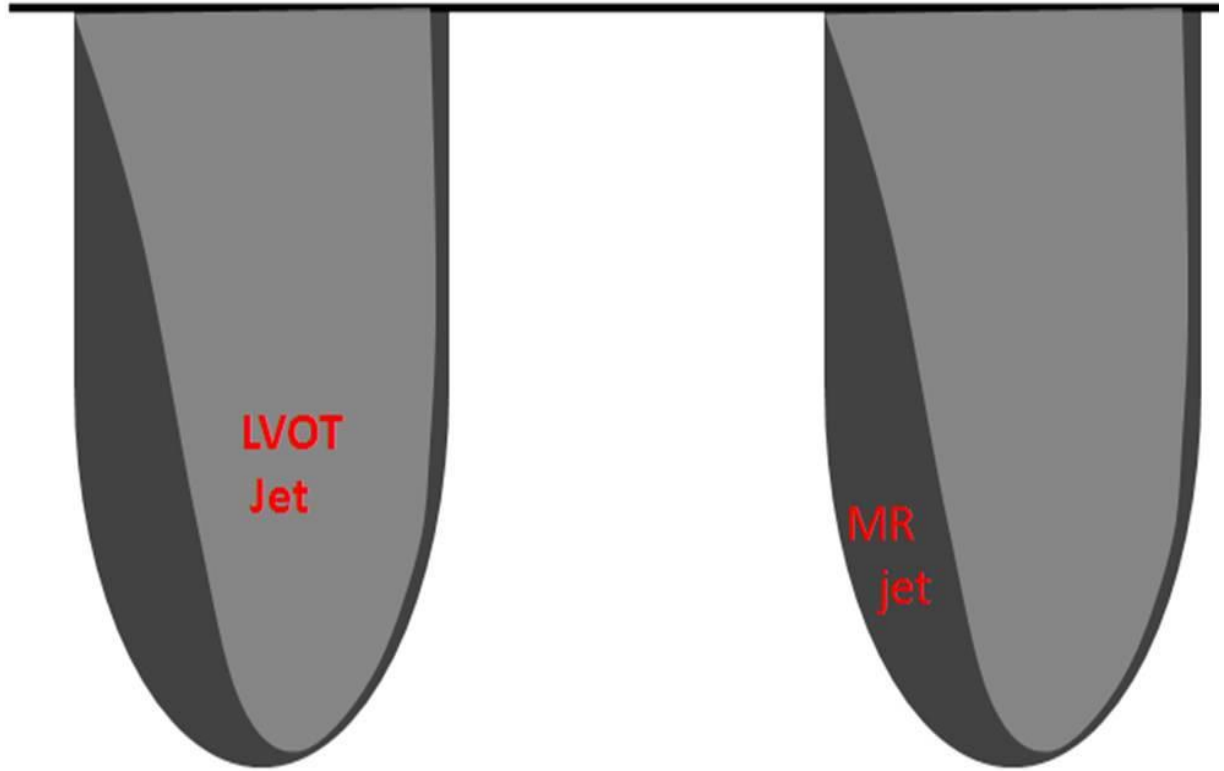
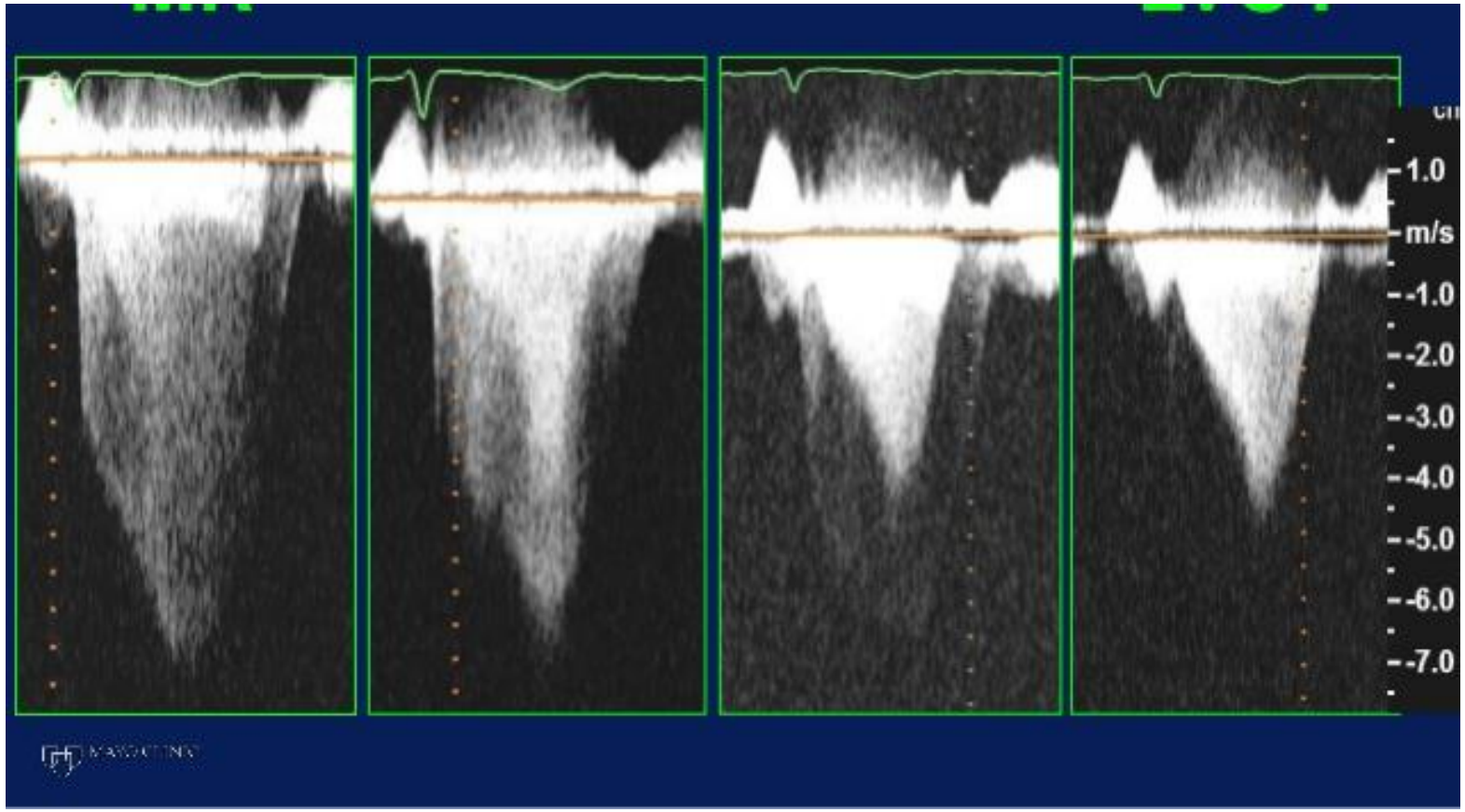


Figure 8 Continuous-wave (CW) Doppler recordings of peak velocity across the LVOT (*cross*: 4.5 m/sec) (*left*) and peak velocity of mitral regurgitation signal (*arrow*: 6.3 m/sec) (*right*). The concave-to-the-left contour of the Doppler CW jet causes a decrease in the LVOT orifice size as systole progresses and as the mitral valve is pushed further into the septum. Identification of this contour can be useful to differentiate high CW jets of dynamic LVOT obstruction from mitral regurgitation and from valvular aortic stenosis.

Doppler spectrum in *HOCM* with *MR*

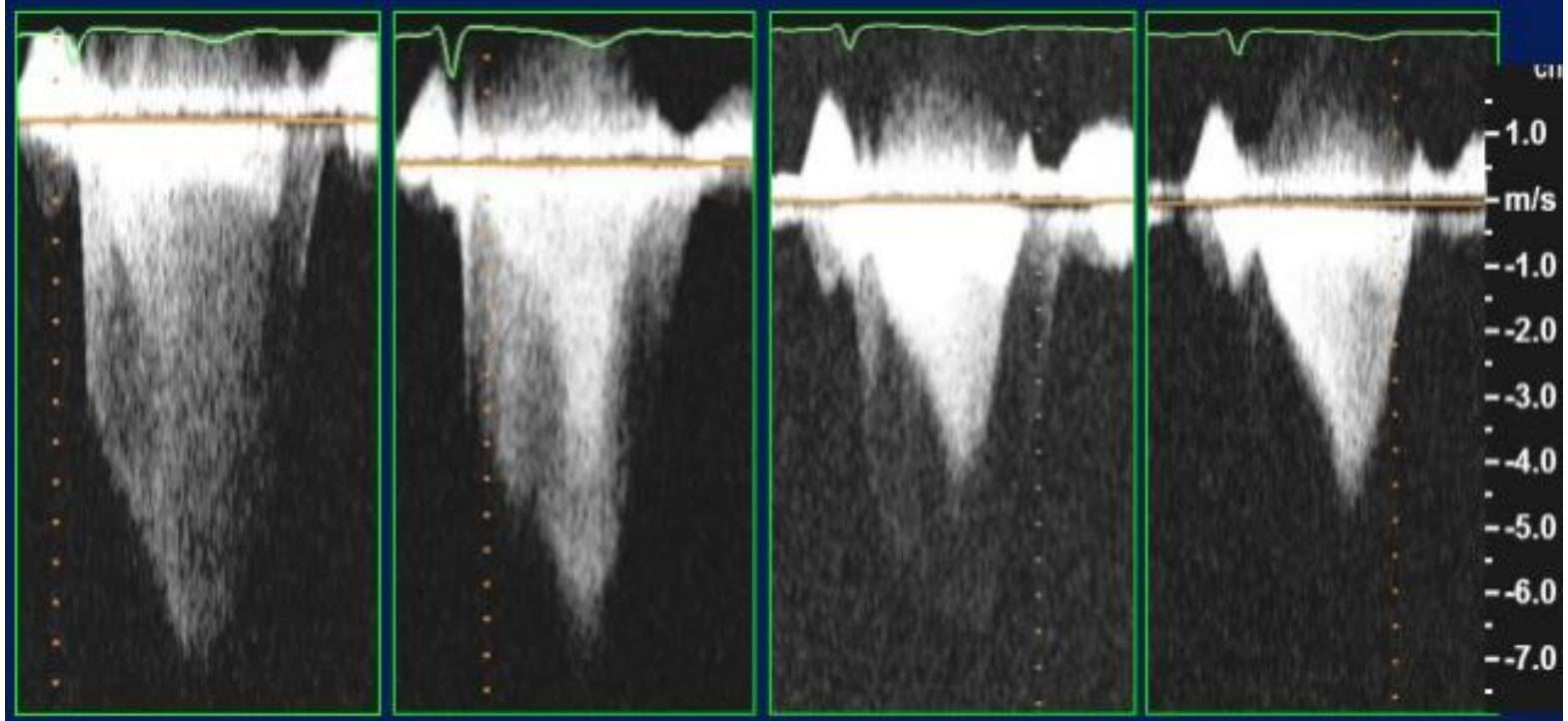



1.0
m/s
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0

Dynamic LVOT Obstruction vs. MR

CW Doppler ($\Delta P \cong 4V^2$)

MR → LVOT



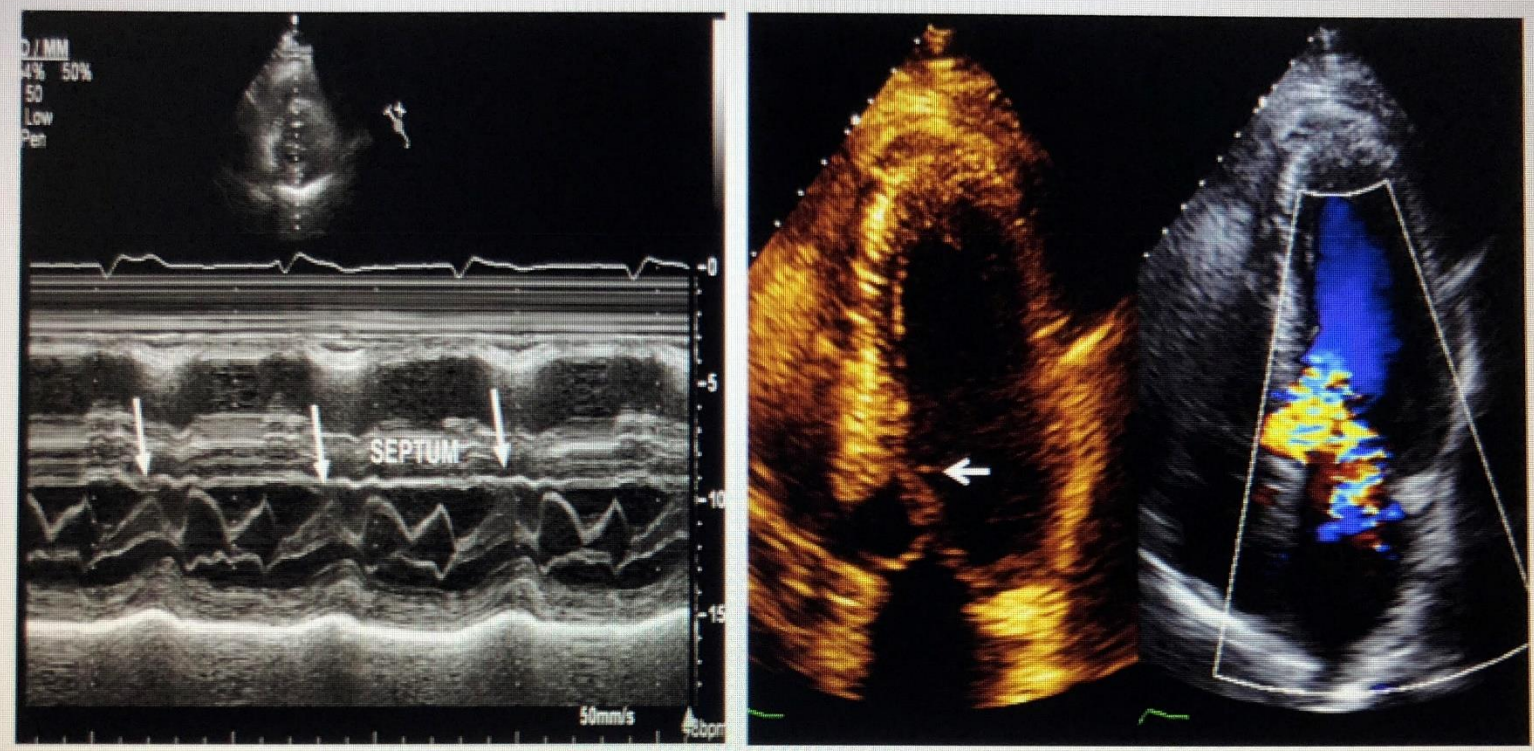
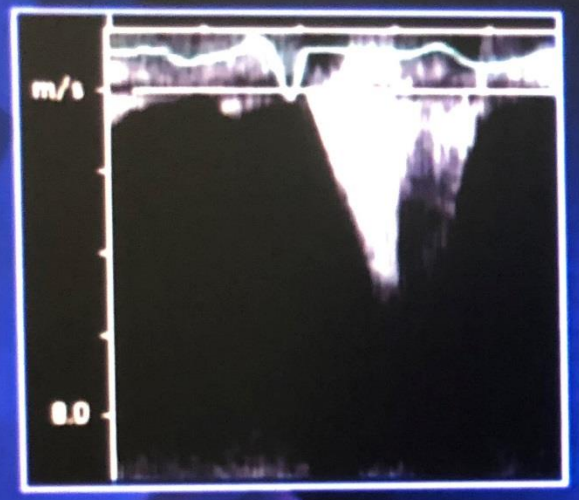


Figure 7 (*Left*) M-mode recording of SAM and mitral leaflet septal contact (*arrows*). (*Right*) SAM on 2D echocardiography (*arrow*). In the same panel, color Doppler shows the high velocities across the LVOT in mosaic color and the eccentric mitral regurgitation jet that is directed posterolaterally.

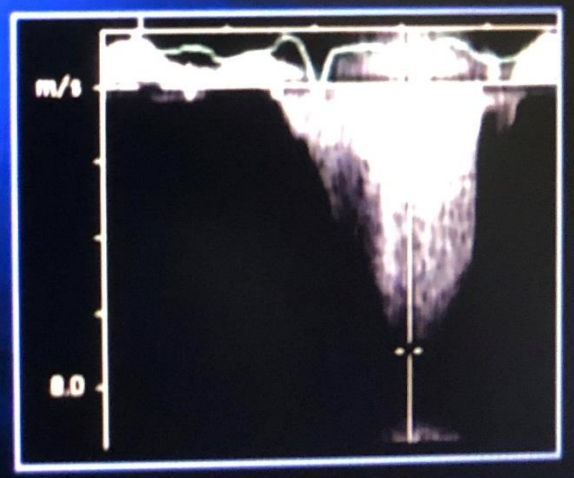
Doppler Evaluation



True LVOT signal

Vmax = 5.5 m/sec

Peak LVOT gradient = 121 mm Hg



MR signal

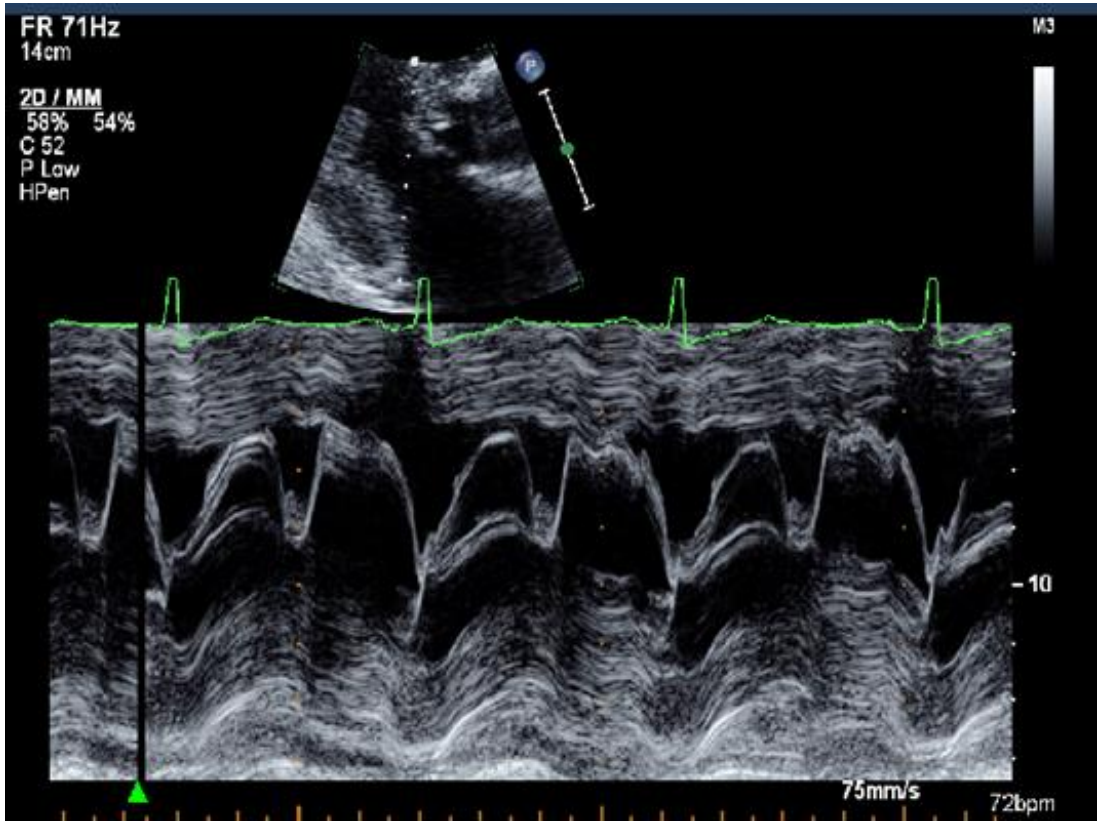
Vmax = 7.2 m/sec

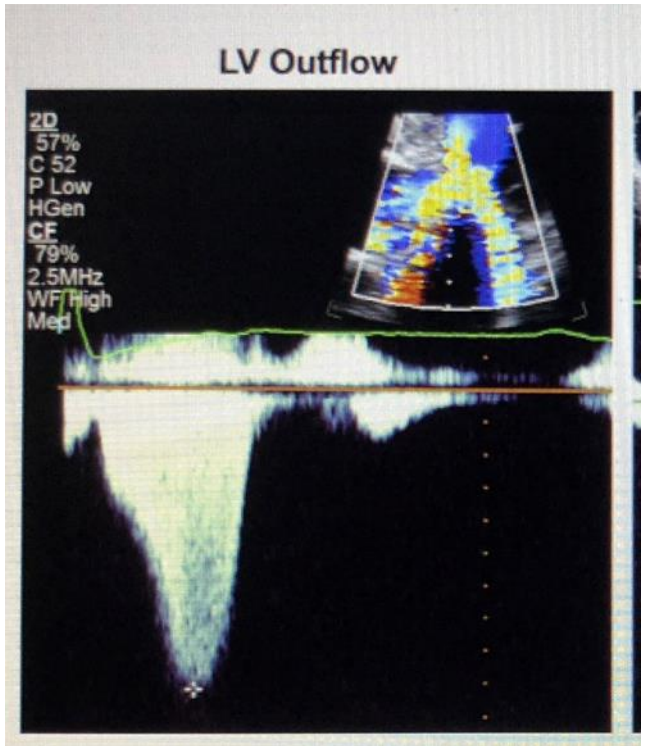
Peak LA-LV gradient = 207 mm Hg

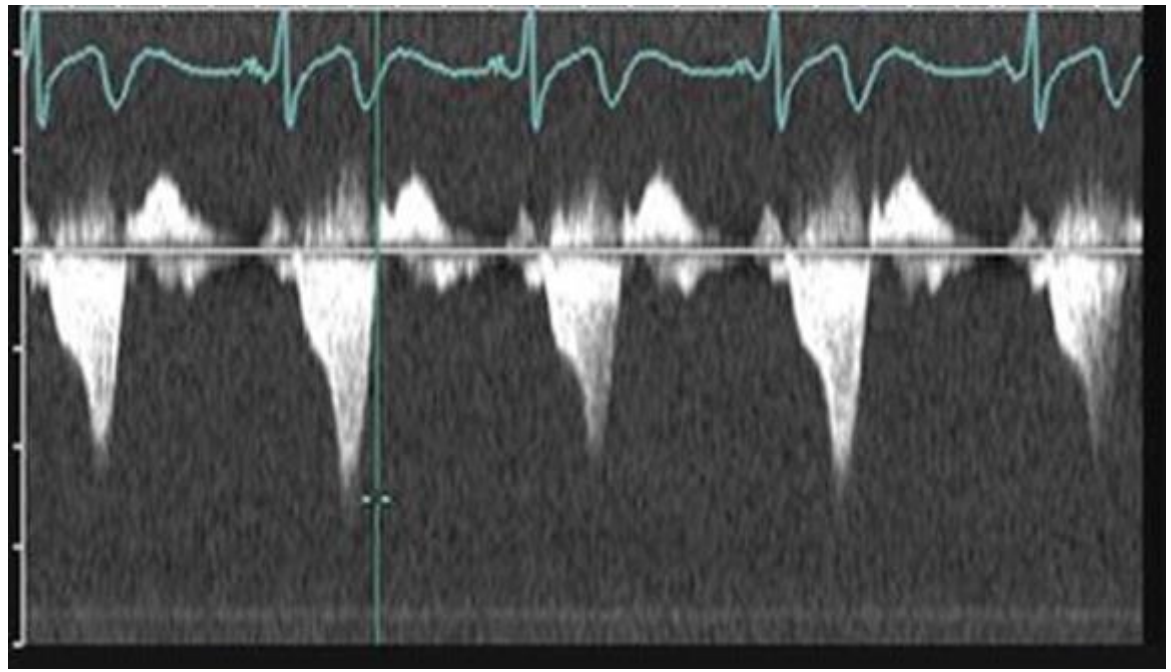
LVOT gradient ~ (207 +LA p) – SBP

~207 +15 – 105 = 117 mm Hg

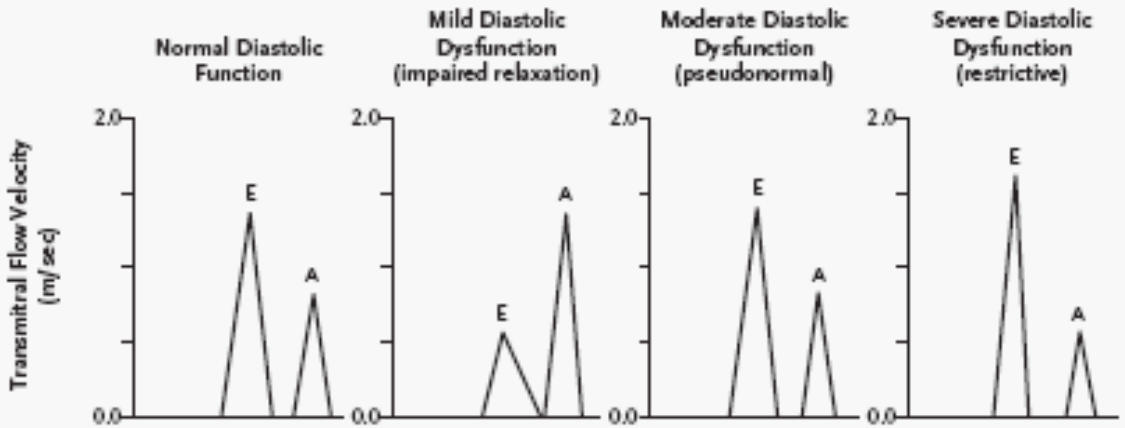
DELL


FR 71Hz
14cm
2D / MM
58% 54%
C 52
P Law
HPen
M3
10
75mm/s
72bpm


LV Outflow
2D
57%
C 52
P Low
HGen
CF
79%
2.5MHz
WF High
Med



Patterns of Left Ventricular Diastolic Filling as Shown by Standard Doppler Echocardiography



	Normal Diastolic Function	Mild Diastolic Dysfunction (impaired relaxation)	Moderate Diastolic Dysfunction (pseudonormal)	Severe Diastolic Dysfunction (restrictive)
Left Ventricular Relaxation	Normal	Impaired	Impaired	Impaired
Left Ventricular Compliance	Normal	Normal to ↓	↓↓	↓↓↓
Atrial Pressure	Normal	Normal to ↑	↑↑	↑↑↑

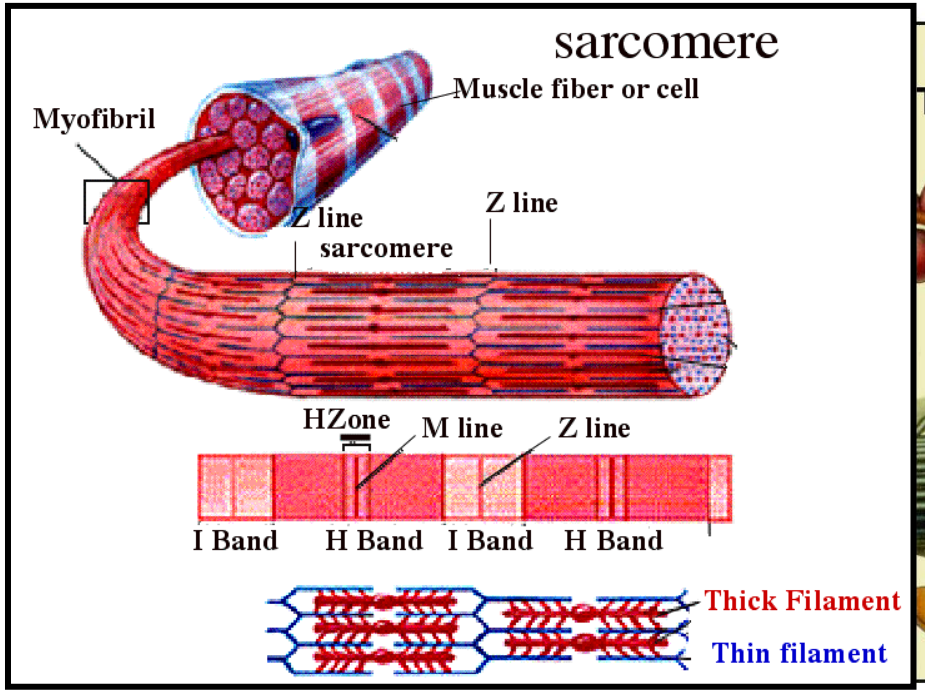
Figure 3. Patterns of Left Ventricular Diastolic Filling as Shown by Standard Doppler Echocardiography.

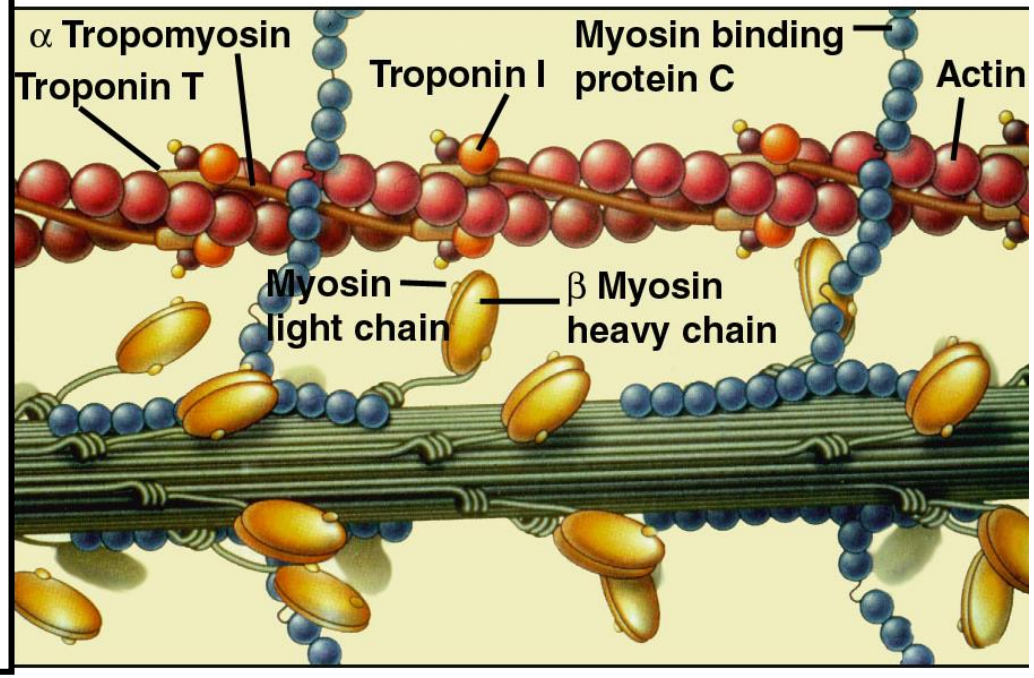
The abnormal relaxation pattern (mild diastolic dysfunction[2]) is brought on by abnormally slow left ventricular relaxation, a reduced velocity of early filling (E wave), an increase in the velocity associated with atrial contraction (A wave), and a ratio of E to A that is lower than normal. In more advanced heart disease, when left atrial pressure has risen, the E-wave velocity and E:A ratio is similar to that in normal subjects (the pseudonormal pattern). In advanced disease, abnormalities in left ventricular compliance may supervene (called the restrictive pattern because it was originally described in patients with restrictive cardiomyopathy). In these latter two instances, the E wave of normal to high velocity is a result of high left atrial pressure and a high transmitral pressure gradient in early diastole. Therefore, the use of transmitral velocity patterns alone to estimate left ventricular filling pressures in patients with diastolic heart failure is problematic.[2,32]

Molecular Genetics

The Future

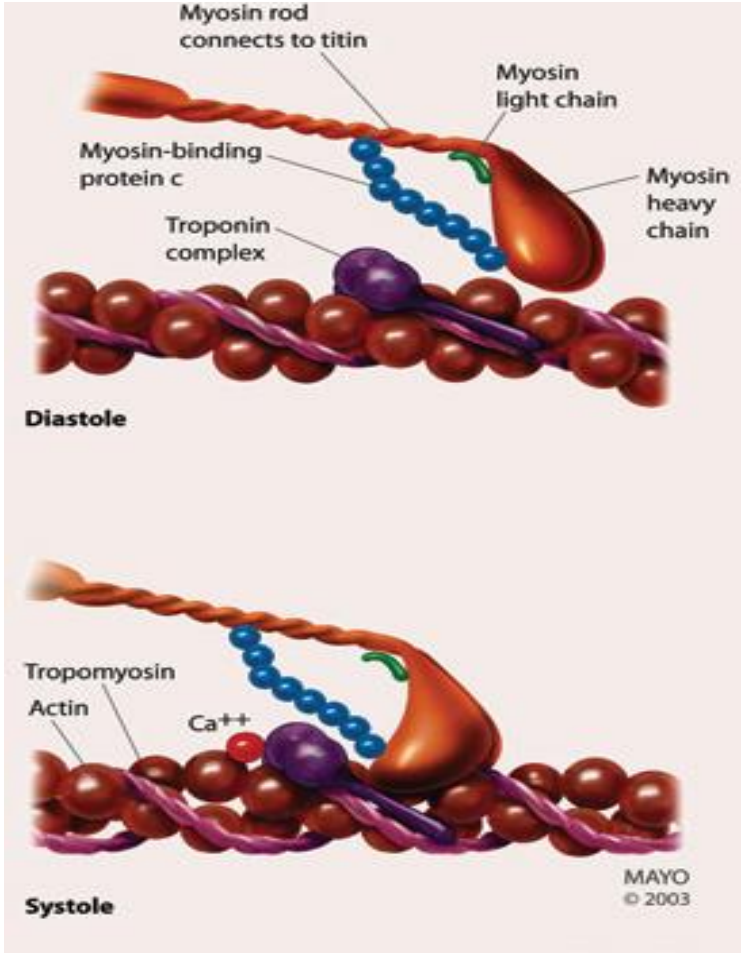
HCM is an autosomal dominant inherited disease caused by mutations in the sarcomere proteins



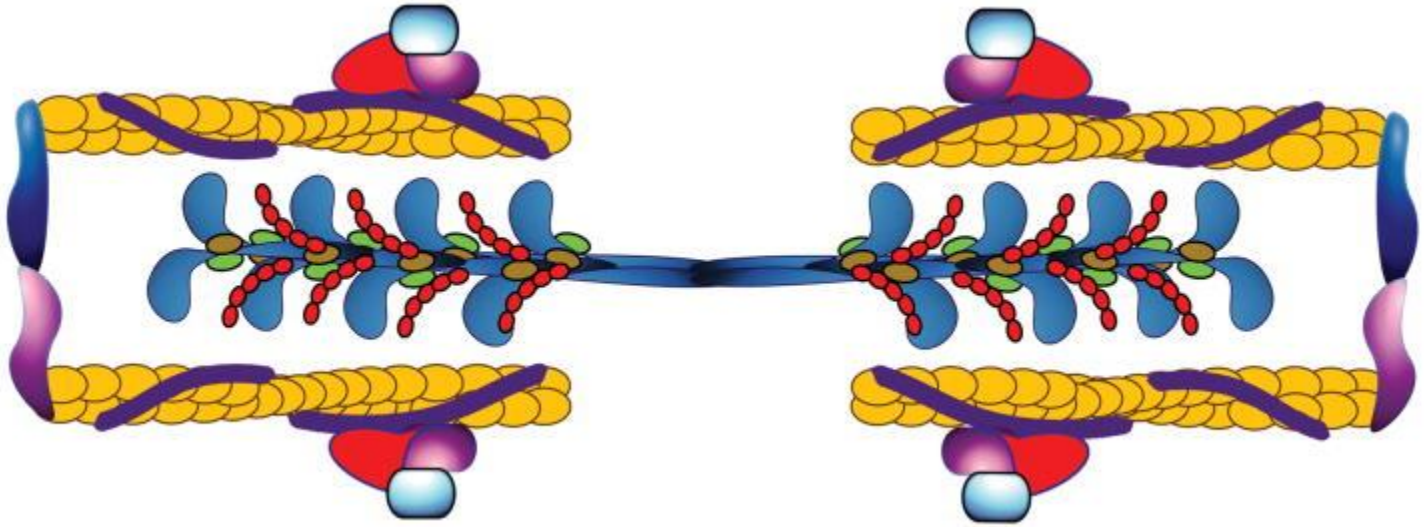


Genetic Basis of HCM

- Autosomal dominant inheritance pattern
- >>1000 mutations in 13 cardiac sarcomere & myofilament (myosin heavy chain, actin, tropomyosin, and titin) related genes identified
- Genetic basis of ventricular hypertrophy does not directly correlate with prognostic risk stratification



Alcalai et al. J Cardiovasc Electrophysiol 2008;19:104-110.



Thin myofilament proteins (~5%)
- ACTC1
- TPM1
- TNNI3
- TNNC1
- TNNT2

Thick myofilament proteins (~45%)
- MYBPC3 (25%)
- MYH7 (20%)
- MYL2 (<1%)
- MYL3 <1%)

Z disk proteins (~1%)
- CRSP3
- MYZO2

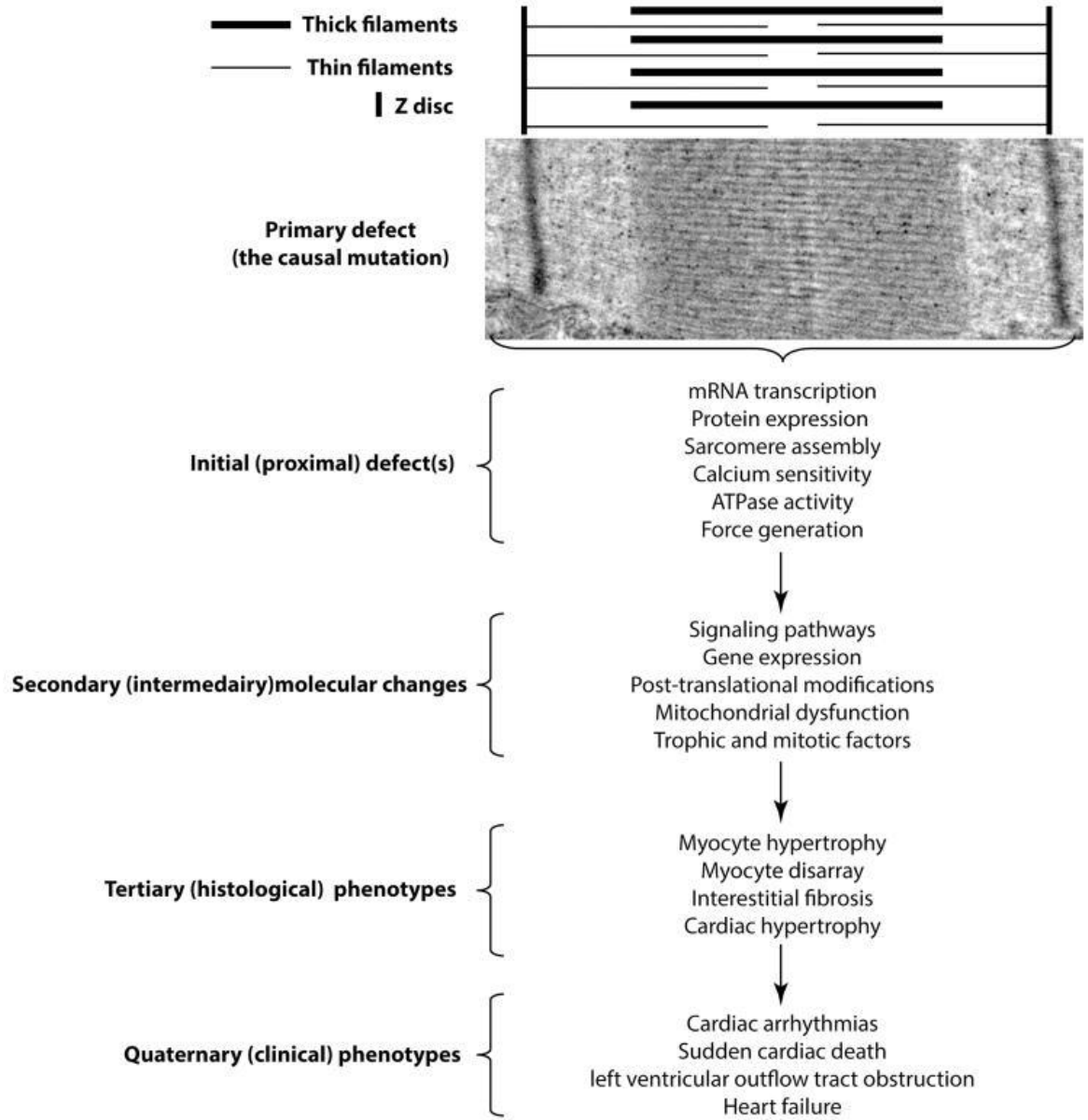
Genetics of HCM

TABLE 1

Causative Genes in Hypertrophic Cardiomyopathy

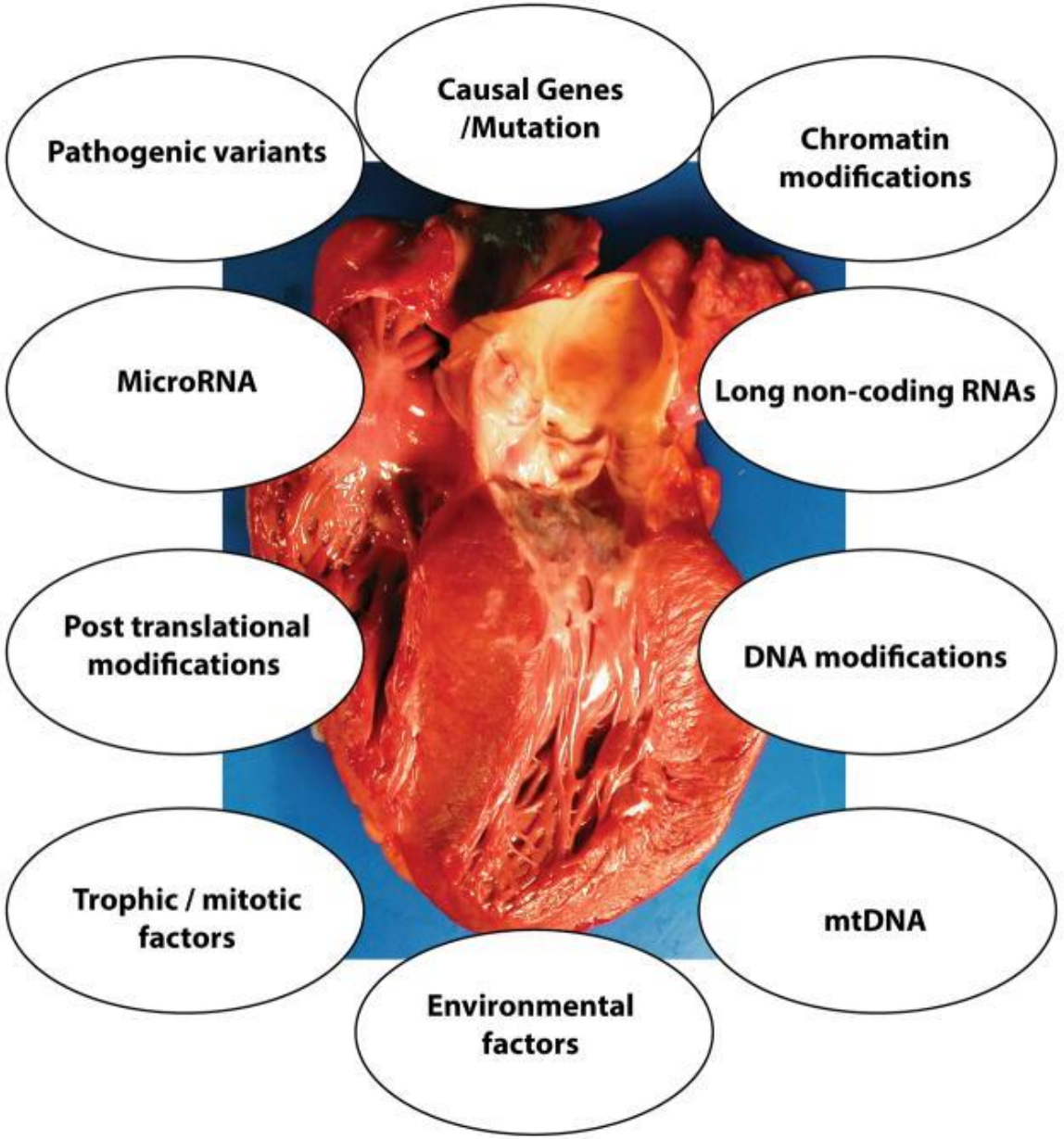
Encoded Protein	Gene Symbol	Chromosome Locus	Sarcomere Component	No. of Cases
β-Myosin heavy chain	MYH7	14q12	Thick filament	212
Myosin-binding protein C	MYBPC3	11p11.2	Thick filament	165
Troponin T	TNNT2	1q32	Thin filament	33
Troponin I	TNNI3	19q13.4	Thin filament	27
α-Tropomyosin	TPM1	15q22.1	Thin filament	12
Regulatory Myosin light chain	MYL2	12q24.3	Thick filament	10
Essential Myosin light chain	MYL3	3p21	Thick filament	5
Actin	ACTC1	15q14	Thin filament	7
Titin	TTN	2q31	Thick filament/Z-Disc	2
Muscle LIM protein	CSRP3	11p15.1	Z-Disc	3
Telethonin	TCAP	17q12	Z-Disc	2
Myozenin 2	MYOZ2	4q26	Z-Disc	1
Vinculin	VCL	10q22.1	Intercalated disc	2

Alcalai et al. J Cardiovasc Electrophysiol 2008;19:105.


Thick filaments
Thin filaments
Z disc
Primary defect
(the causal mutation)
Initial (proximal) defect(s)
mRNA transcription
Protein expression
Sarcomere assembly
Calcium sensitivity
ATPase activity
Force generation
Secondary (intermedairy)molecular changes
Signaling pathways
Gene expression
Post-translational modifications
Mitochondrial dysfunction
Trophic and mitotic factors
Tertiary (histological) phenotypes
Myocyte hypertrophy
Myocyte disarray
Interestitial fibrosis
Cardiac hypertrophy
Quaternary (clinical) phenotypes
Cardiac arrhythmias
Sudden cardiac death
left ventricular outflow tract obstruction
Heart failure

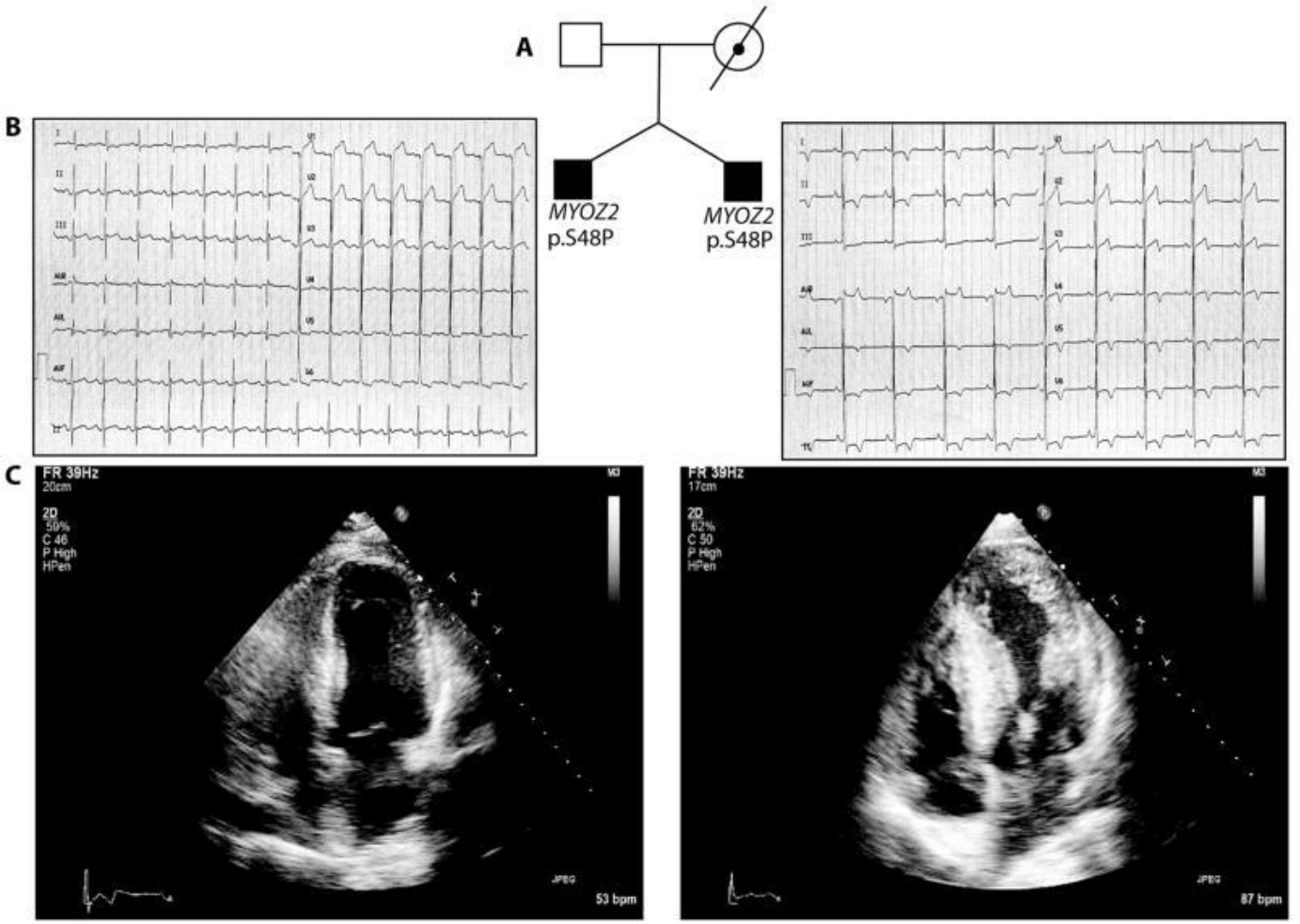
Selected factors contributing to expression of cardiac phenotype in HCM are shown

The causal mutation imparts the main effect and several others, such as other pathogenic genetic variants (modifiers), genomics (such as non-coding RNAs), proteomics (such as post-translational modifications), and environmental factors (such as isometric exercises) contributing to expression of the phenotype.

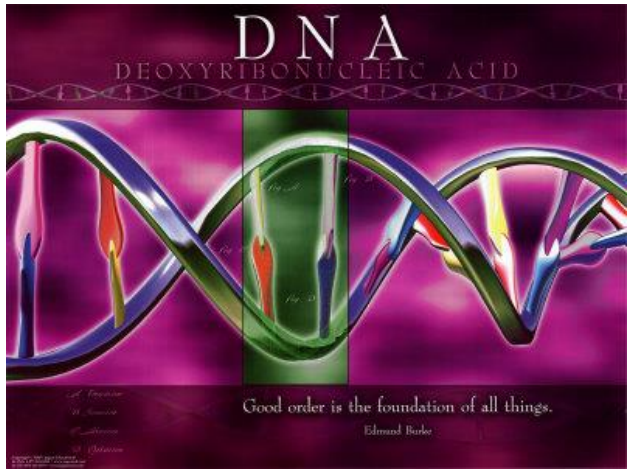


A truncated pedigree depicting dizygotic twins with HCM caused by the p.Ser48Pro mutation in the *MYOZ2* gene

Despite sharing the same causal mutation, one expresses mild and the other severe cardiac hypertrophy, as reflected in the electrocardiograms (**B**) and echocardiographic images (**C**).



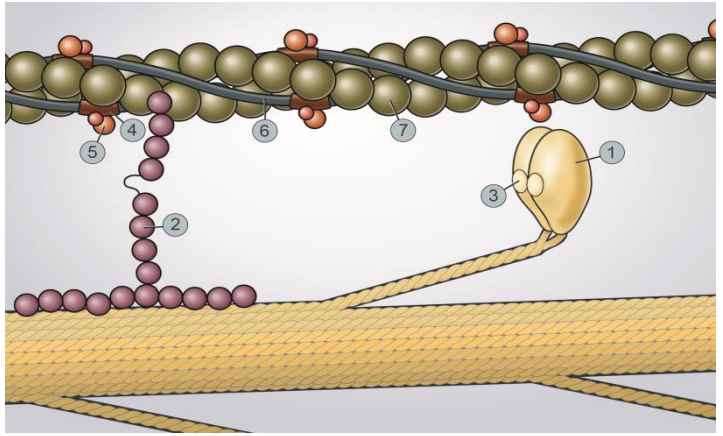
Role of Genetic Testing



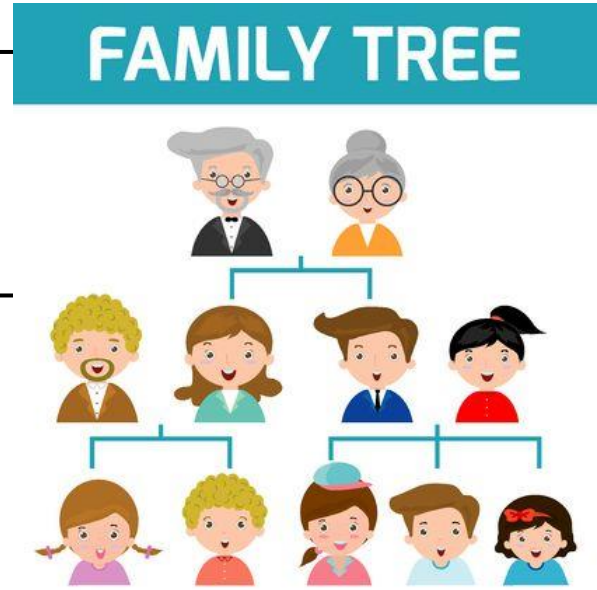
- Identify at-risk family members
- Establish the diagnosis ?
- Risk stratification ?
- Risk of sudden death ??
- Exclude HCM phenocopies
- Future genomic therapy

Genetics HCM

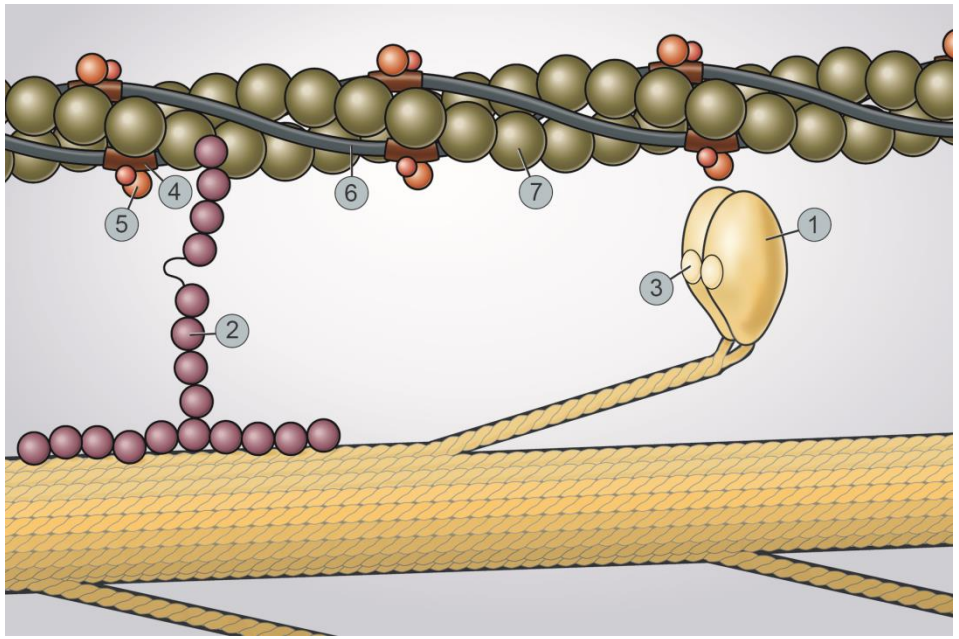
- 13 genes, > 900 mutations
- Commercially available chip:
  - sarcomere protein gene mutations
  - storage diseases: Fabry, PRKAG2, Danon
- genotype-phenotype-correlation?
- Helpful with family screening



Hereditary Disease



- Autosomal dominant: Family history is key
- Sarcomere protein gene mutations: 40% of pts



1 β-Myosin heavy chain

2 Myosin-binding protein-C

3 Myosin light chain 2 and 3

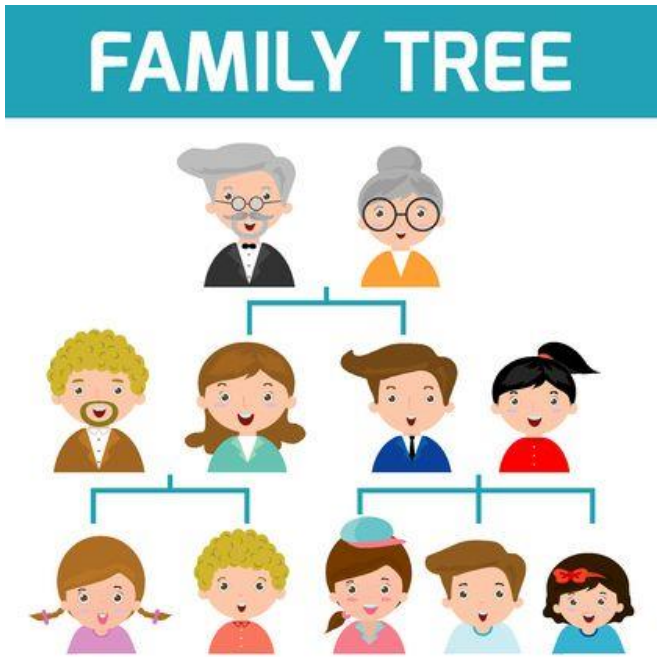
4 Troponin T

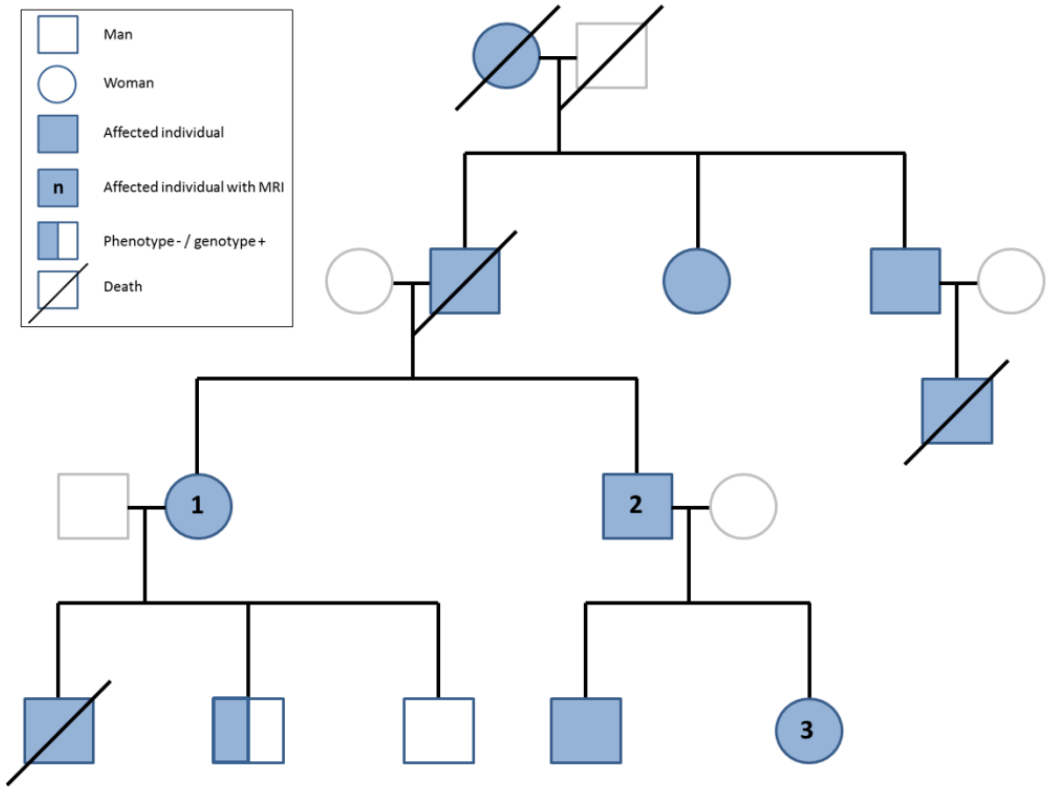
5 Troponin I

6 Tropomyosin

7 Actin

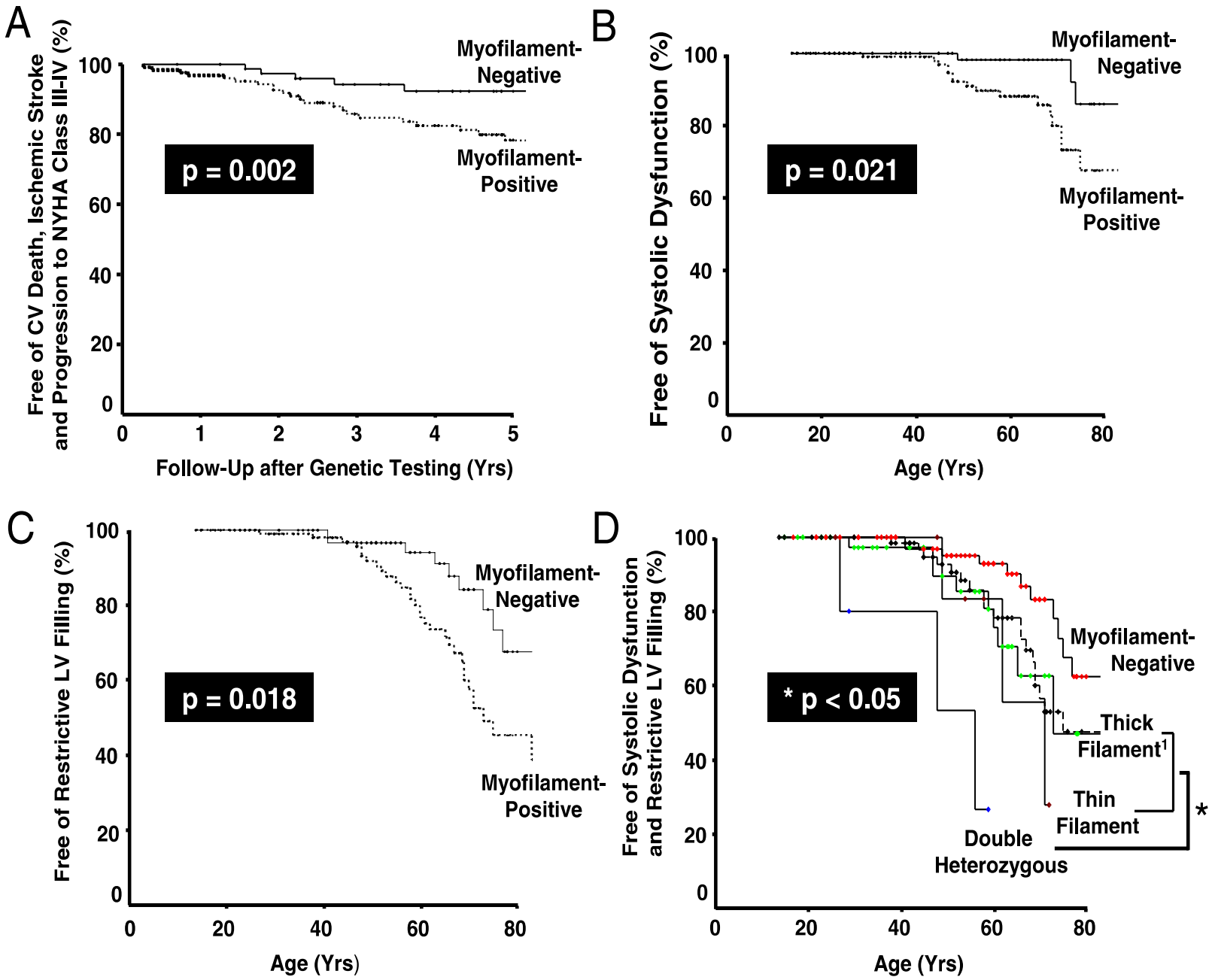
Binder et al., Mayo Clin Proc. 2006;81(4):459-467


FAMILY TREE


Man
Woman
Affected individual
n
Affected individual with MRI
Phenotype - / genotype +
Death
1
2
3

Does a Positive Genetic Test Mean Anything ?

- Olivotto et al. studied a large cohort of Italian patients with HCM and showed an increased risk of CV death, nonfatal stroke, or progression to NYHA III/IV in patients with POSITIVE myofilament gene mutation
- Gene positive patients also had higher rates of LV systolic dysfunction (EF < 50%) and restrictive LV


A
Free of CV Death, Ischemic Stroke and Progression to NYHA Class III-IV (%)
100
80
60
40
20
0
0
1
2
3
4
5
Follow-Up after Genetic Testing (Yrs)
Myofilament-Negative
Myofilament-Positive
p = 0.002
B
Free of Systolic Dysfunction (%)
100
80
60
40
20
0
0
20
40
60
80
Age (Yrs)
Myofilament-Negative
Myofilament-Positive
p = 0.021
C
Free of Restrictive LV Filling (%)
100
80
60
40
20
0
0
20
40
60
80
Age (Yrs)
Myofilament-Negative
Myofilament-Positive
p = 0.018
D
Free of Systolic Dysfunction and Restrictive LV Filling (%)
100
80
60
40
20
0
0
20
40
60
80
Age (Yrs)
Myofilament-Negative
Thick Filament[1]
Thin Filament
Double Heterozygous
*
* p < 0.05

Gene Dosage

- Gene Dosage
  - 3-5% of HCM probands have >1 sarcomere mutation
    - Compound heterozygotes: two different mutations within a single HCM gene
    - Double heterozygotes: mutations in 2 HCM genes
    - Homozygotes: inheriting the same mutation from both parents
  - They have more severe disease expression and increased incidence of SCD
  - Many of the compound heterozygotes involve 1 mutation in MYBPC3
  - Triple mutations are also associated with more severe disease, 14 fold risk of progression to end-stage HF

Identifying At-Risk Family Members

Detection Rate ~40%

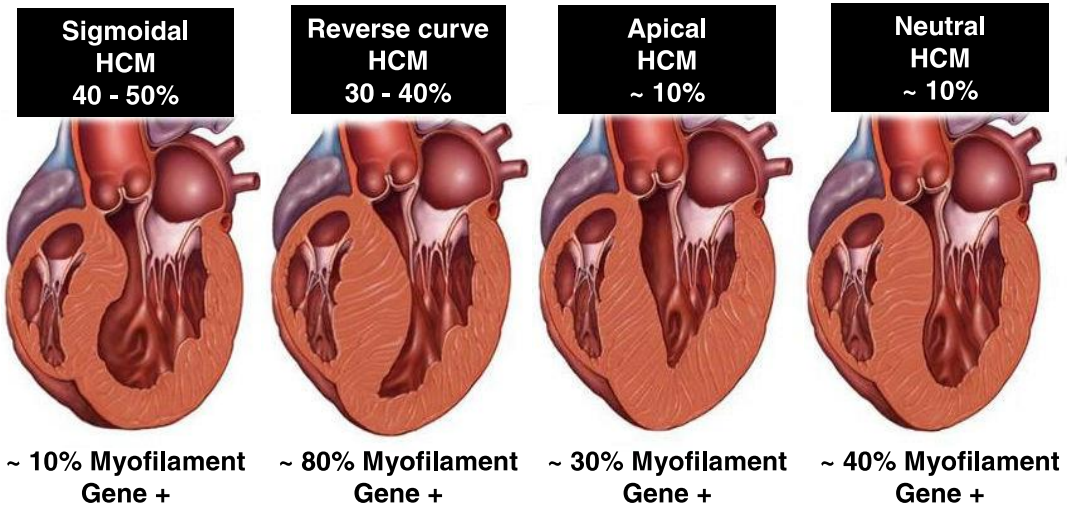
Not all gene variants are associated with disease

Some families have multiple mutations – possibly in genes not yet discovered

Little value in predicting sudden death

Genotype – Phenotype Heterogeneity

- Binder et al. examined 400 unrelated patients with HCM and observed correlations between LV morphology and the probability of a positive genetic test.
- Septal contour was the strongest predictor of a positive HCM genetic test with odds ratio of 21



Binder et al. Mayo Clin Proc 2006; 81: 459

Predicting mutation carriers?

	Overall (n=200)	Positive Results (n=79)	Negative Results (n=95)
Mean Age at Diagnosis*	35.5 y	35.5 y	49.5 y
Reported Hx Hypertension**	40 (20%)	10 (12.7%)	30 (31.3%)
Positive Family History*	99 (49.5%)	60 (75.9%)	39 (41.1%)

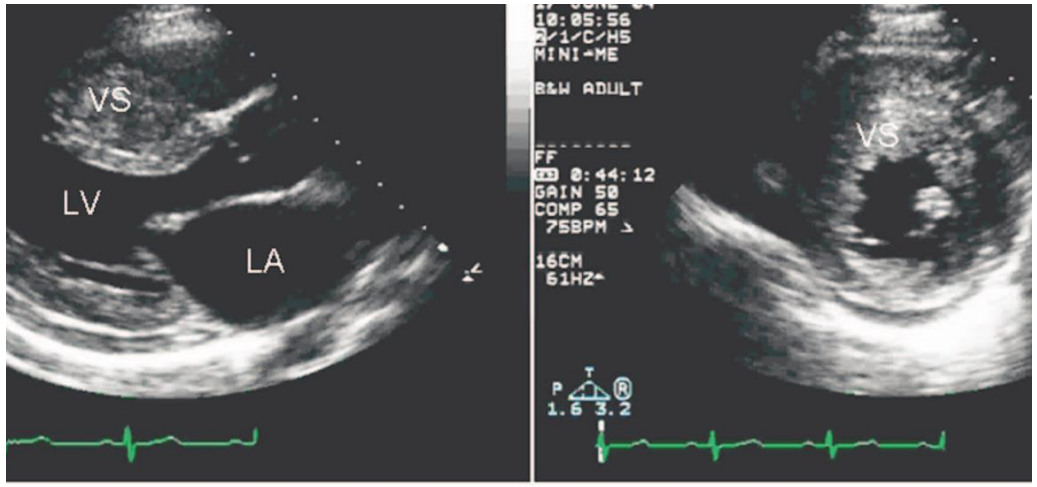
*Significant difference; $p<0.001$ **Significant difference; $p<0.01$

Another Use of Genetic Testing

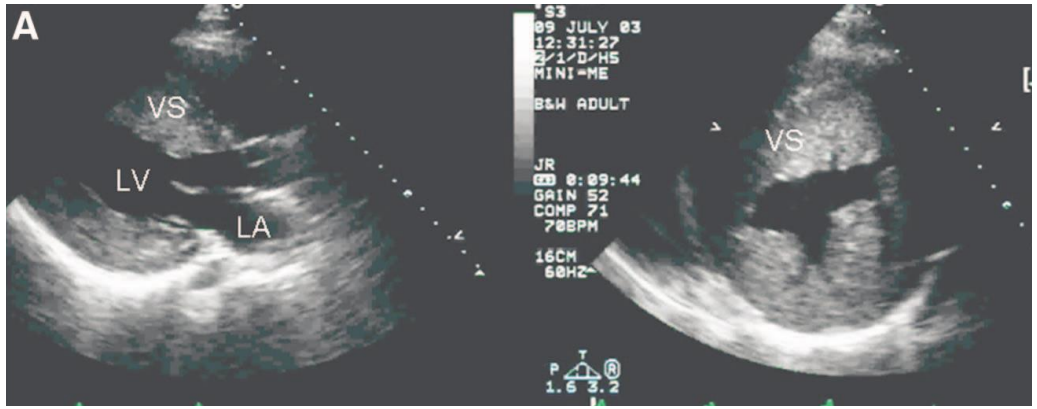
- Cardiac hypertrophy is a final common pathway for a number of different disease

Protein	Gene	Chromomosome	Disease
Adenosine Monophosphate Protein Kinase	PRKAG2	7q	Preexcitation and conduction disease
Lysosome associated membrane protein	LAMP2	Xq	Cardiomyopathy, skeletal myopathy, preexcitation, high risk SCD
Alpha-Galactosidase	GLA	Xq	Fabry Disease

Mimickers of HCM



LAMP mutation



Fabry disease

GLA mutation

Cost Effectiveness of Genetic Testing

- HCM follows autosomal dominant inheritance
- Penetrance is age-dependent
- All first degree relatives need serial clinical screening
- Cost: $2214 / proband testing; $314 / relative
- Ingles et al. performed cost effectiveness ratio
  - quality adjusted life years
  - life years gained
  - Genetic testing results in the discharge of geno-negative patients from serial clinical f/u

Ingles et al. Heart 2012, 98: 625

Cost Effectiveness of Genetic Testing

- The addition of genetic testing to the management of HCM families is cost-effective in comparison with the conventional approach of regular clinical screening.
- This has important implications for the evaluation of families with HCM, and suggests that all should have access to specialised cardiac genetic clinics that can offer genetic testing

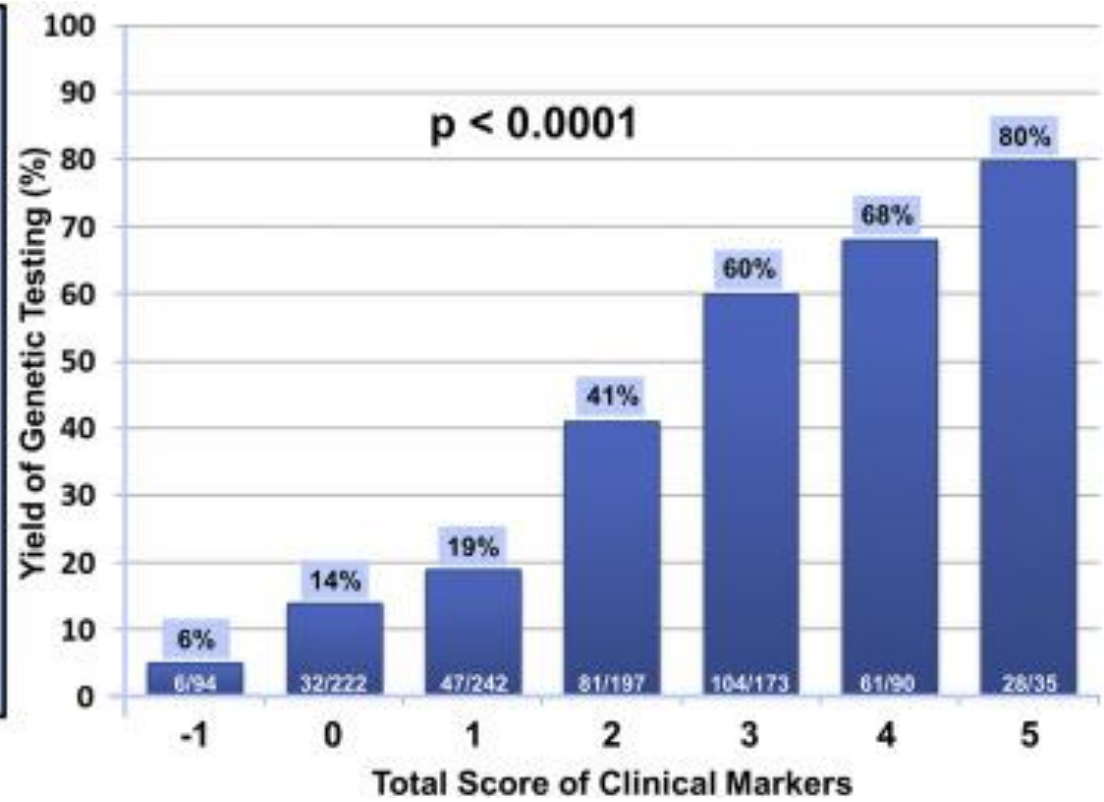
Ingles et al. Heart 2012, 98: 625

Prediction Score?

Clinical Markers for Positive Genetic Test

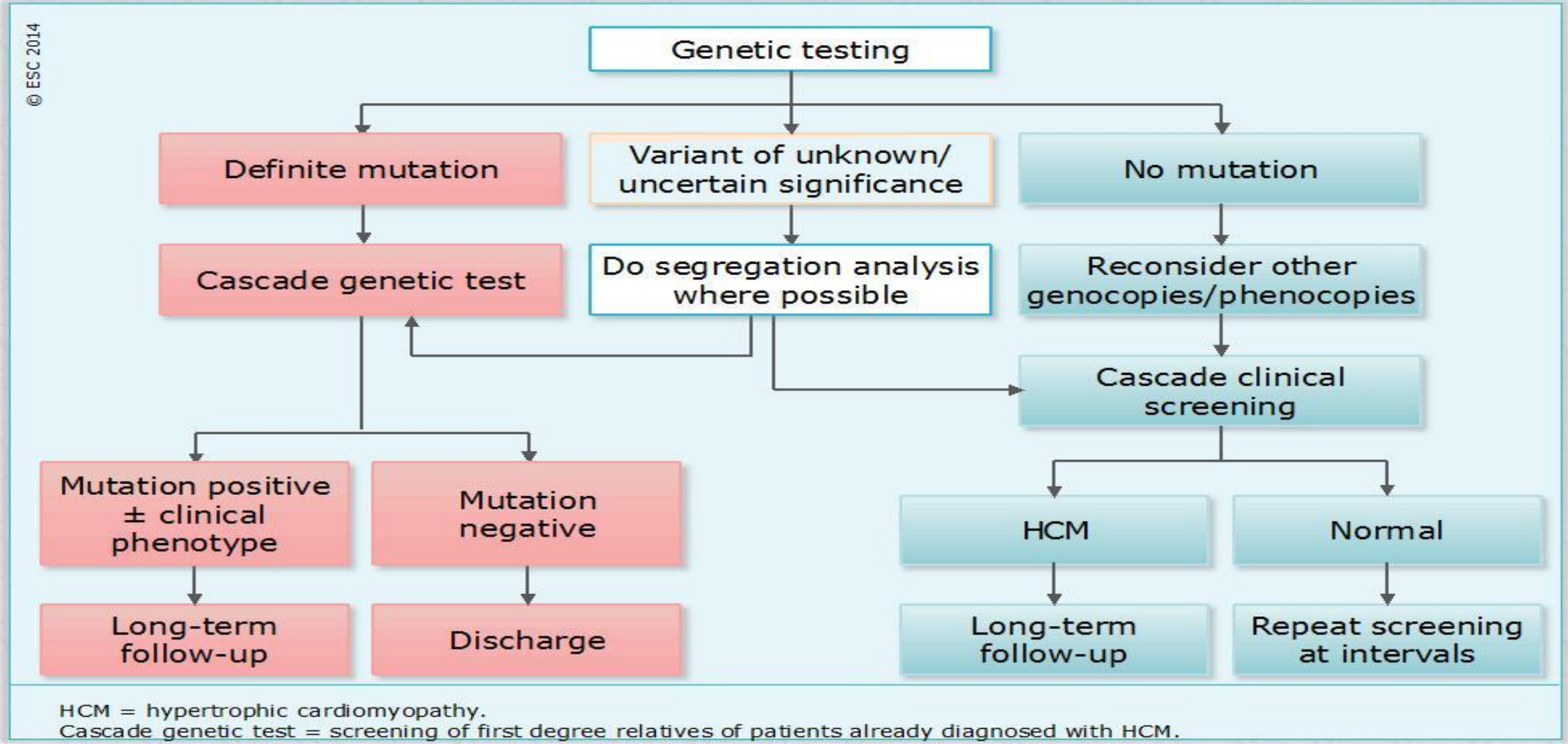
Marker	Pts
❑ Age Dx < 45 yrs	1
❑ MLVWT ≥ 20 mm	1
❑ FH of HCM	1
❑ FH SCD	1
❑ Reverse-curve HCM	1
❑ Hx of Hypertension	-1

Scoring range: -1 to 5 pts



המלצות לגבי
בדיקה גנטית
ומעקב ילדים?

Flow chart for the genetic and clinical screening of probands and relatives



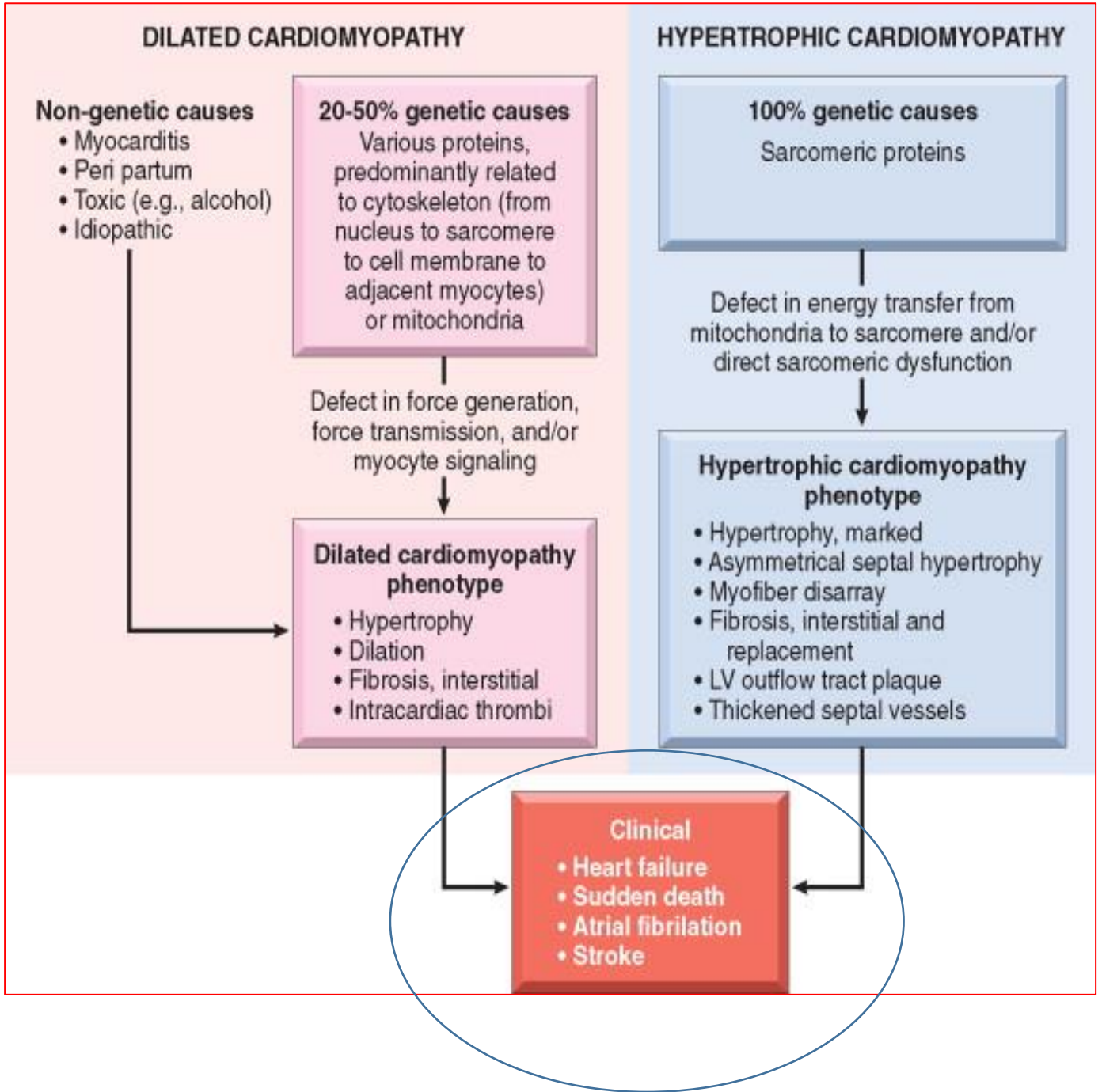
HCM = hypertrophic cardiomyopathy.
Cascade genetic test = screening of first degree relatives of patients already diagnosed with HCM.

Genetic and clinical screening in children

Recommendations	Class	Level
The children of patients with a definite disease-causing mutation should be considered for predictive genetic testing—following pre-test family counselling—when they are aged 10 or more years and this should be carried out in accordance with international guidelines for genetic testing in children.	IIa	C
In first-degree child relatives aged 10 or more years, in whom the genetic status is unknown, clinical assessment with ECG and echocardiography should be considered every 1–2 years between 10 and 20 years of age, and then every 2–5 years thereafter.	IIa	C
If requested by the parent(s) or legal representative(s), clinical assessment with ECG and echocardiography may precede or substitute for genetic evaluation after counselling by experienced physicians and when it is agreed to be in the best interest of the child.	IIb	C
When there is a malignant family history in childhood or early-onset disease or when children have cardiac symptoms or are involved in particularly demanding physical activity, clinical or genetic testing of first-degree child relatives before the age of 10 years may be considered.	IIb	C

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

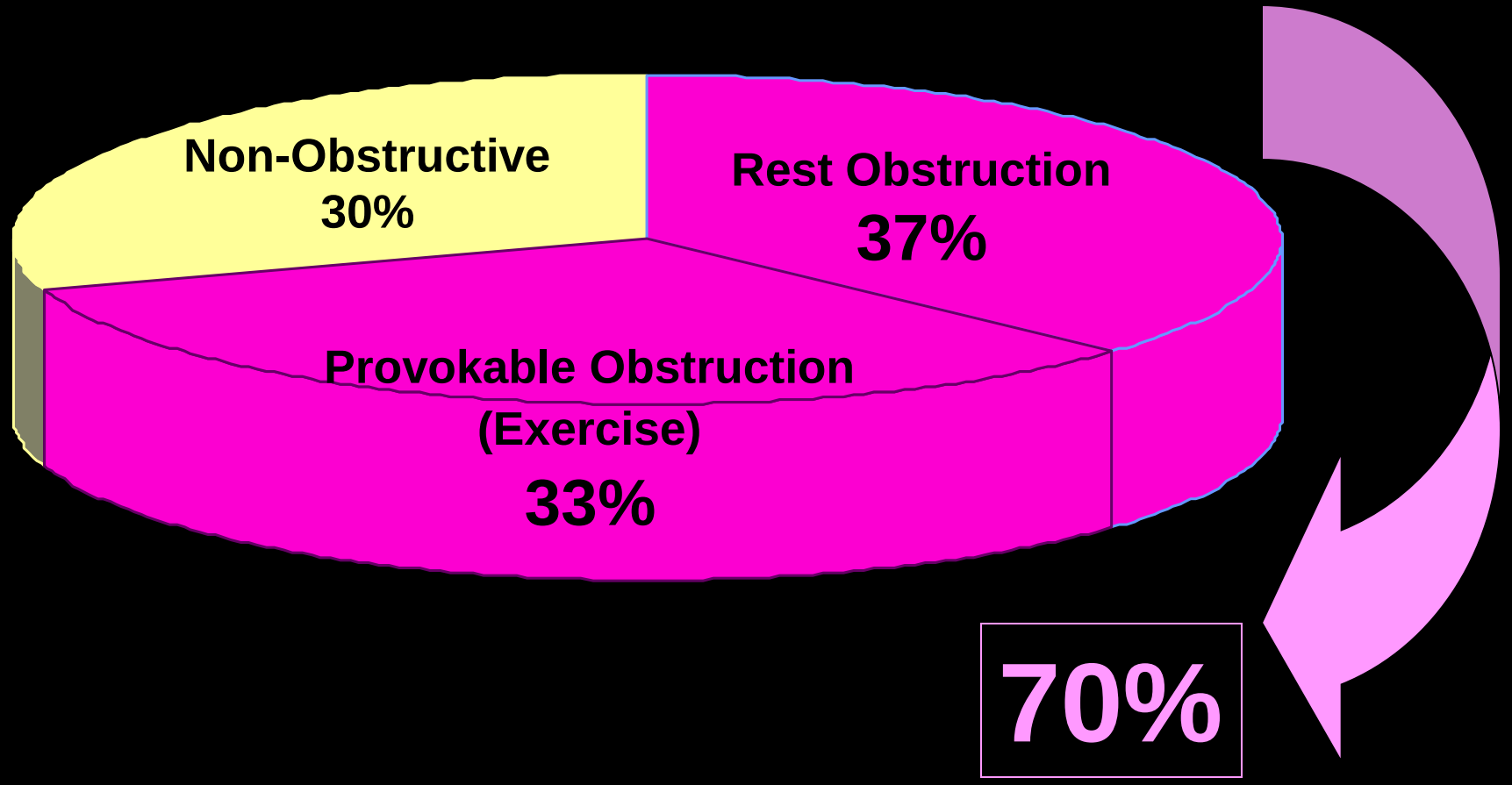
HCM vs DCM


DILATED CARDIOMYOPATHY
HYPERTROPHIC CARDIOMYOPATHY
Non-genetic causes
• Myocarditis
• Peri partum
• Toxic (e.g., alcohol)
• Idiopathic
20-50% genetic causes
Various proteins, predominantly related to cytoskeleton (from nucleus to sarcomere to cell membrane to adjacent myocytes) or mitochondria
100% genetic causes
Sarcomeric proteins
Defect in energy transfer from mitochondria to sarcomere and/or direct sarcomeric dysfunction
Defect in force generation, force transmission, and/or myocyte signaling
Dilated cardiomyopathy phenotype
• Hypertrophy
• Dilation
• Fibrosis, interstitial
• Intracardiac thrombi
Hypertrophic cardiomyopathy phenotype
• Hypertrophy, marked
• Asymmetrical septal hypertrophy
• Myofiber disarray
• Fibrosis, interstitial and replacement
• LV outflow tract plaque
• Thickened septal vessels
Clinical
• Heart failure
• Sudden death
• Atrial fibrilation
• Stroke

- מהו הסיכוי של המטופל להיות עם מפל לחצים ב-LVOT?
- האם יש לכך משמעות מבחינה פרוגנוסטית? סימפטומים?

HCM is a Predominantly Obstructive Disease

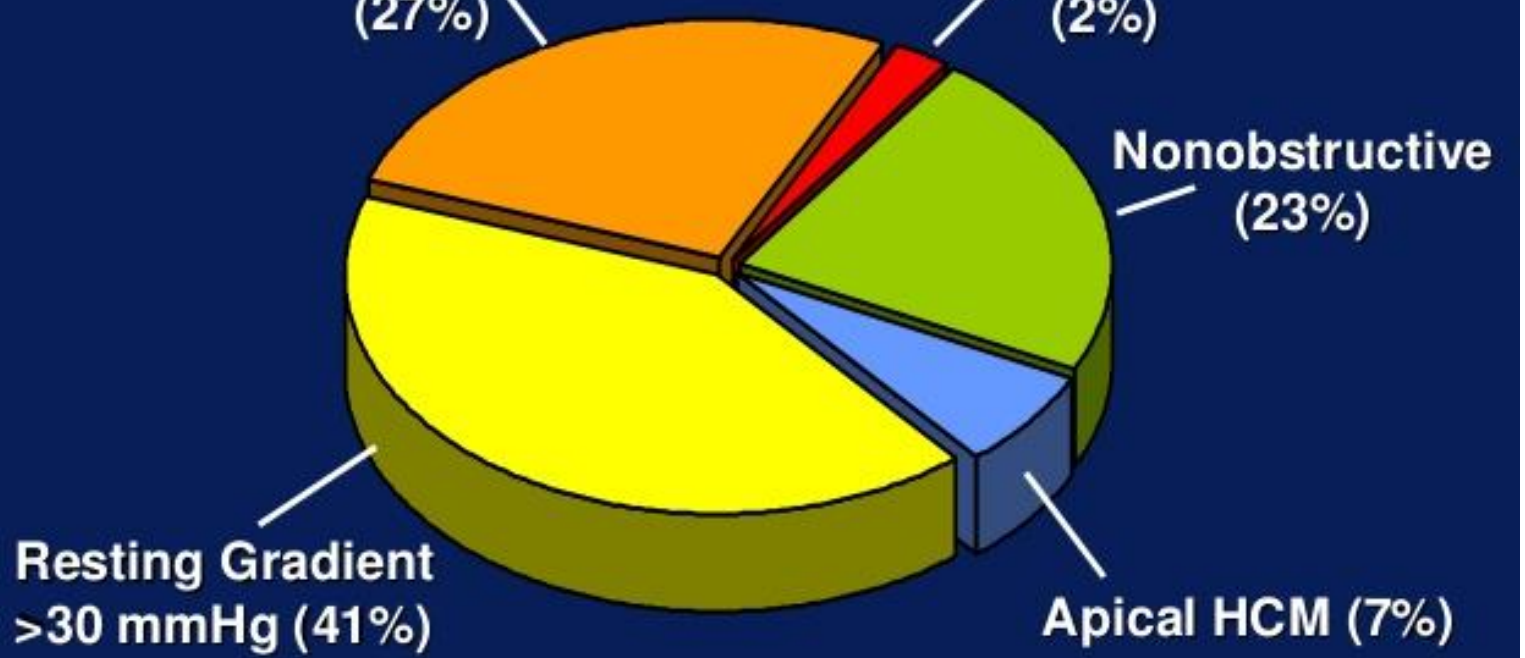
(based on rest and exercise gradients)



Maron MS et al Circulation 2007

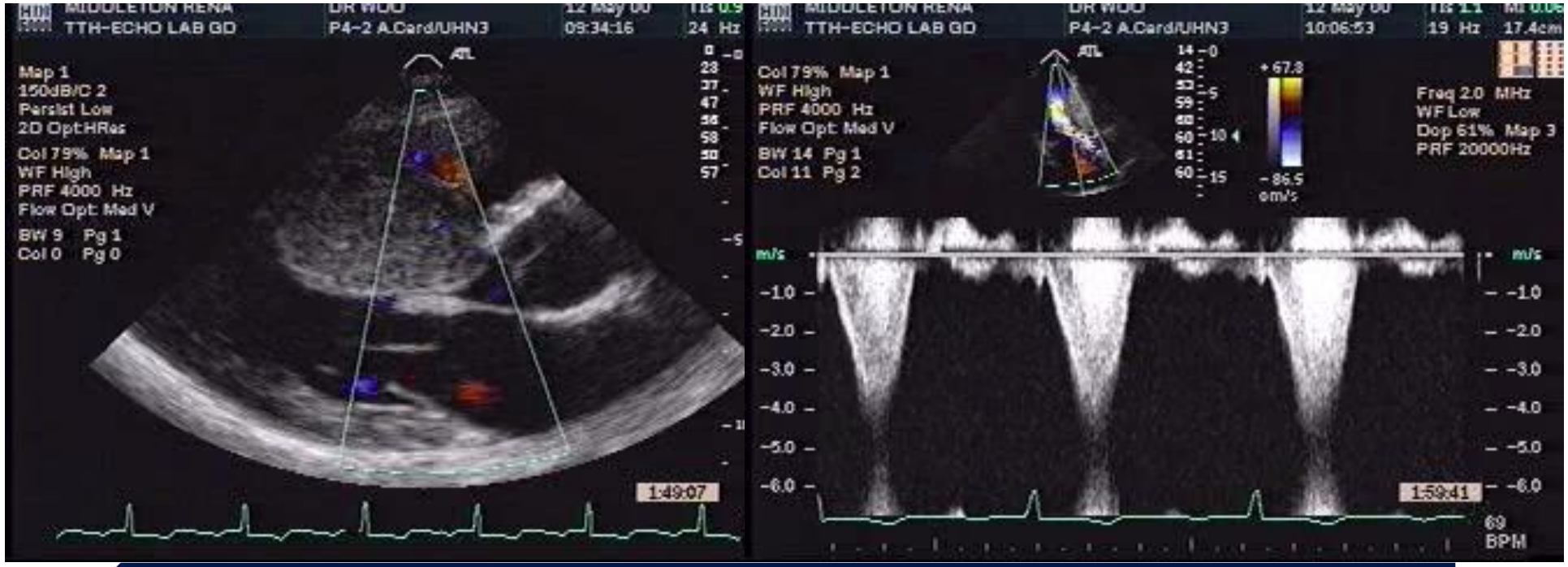
HCM Morphology and LVOT Obstruction

Mayo Clinic HCM Database (2,856 Patients)



Ommen SR, et al. 2006

Obstructive HCM

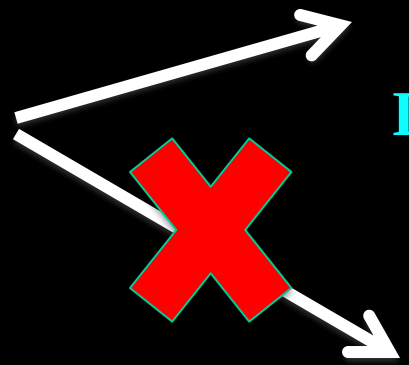


LVOTO increased Relative Risk of

NYHA 3-4	4.4
HCM CV death	1.6-2.14

Maron et al NEJM2003;348: 295-303Autore et al JACC,2005;1076-80

“Congestive Heart Failure”



CONVENTIONAL CHF:
Systolic and/or Diastolic Dysfunction

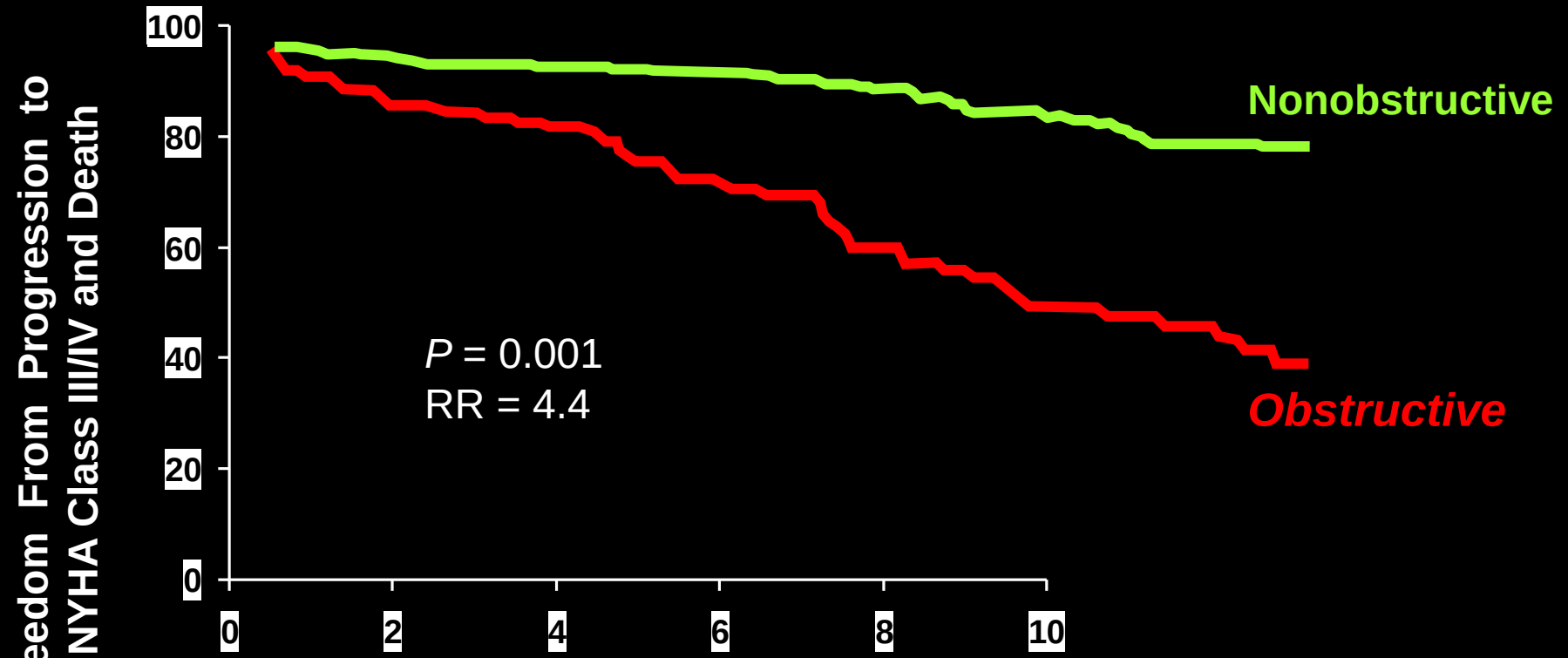
HCM

NOT the Correct Term?...

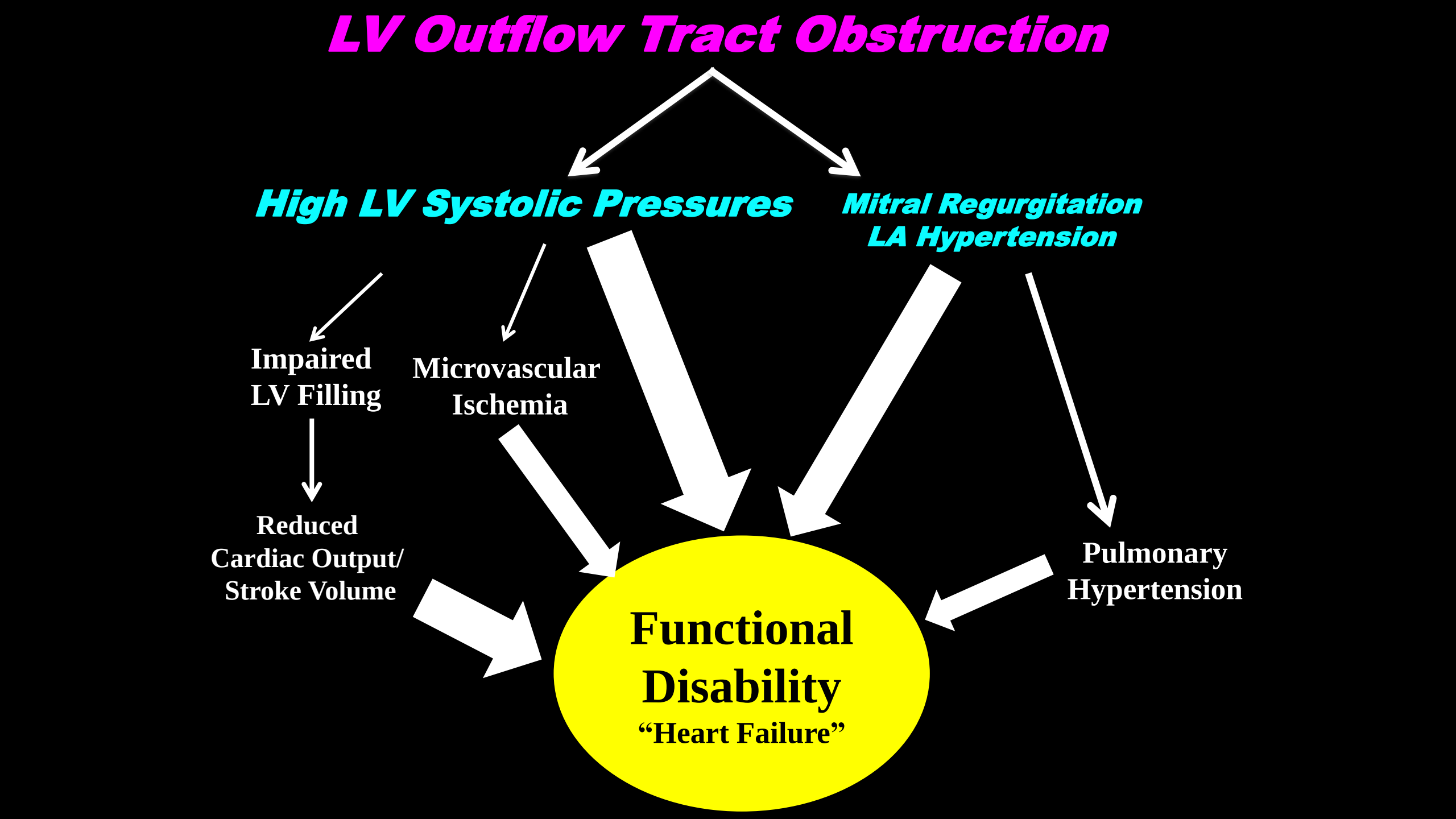
	Conventional CHF (Non-HCM)	HCM
Vol. Overload	Very Common	Virtually Absent
Hospitalization/ Diuresis	Very Common (1M)	Virtually Absent
Associated Renovascular Dz.	Common	Virtually Absent
Annual Mortality	10%	0.5%
Preserved EF	50%	95%
Reversibility	Uncommon	Majority

Maron MS et al. JACC in press

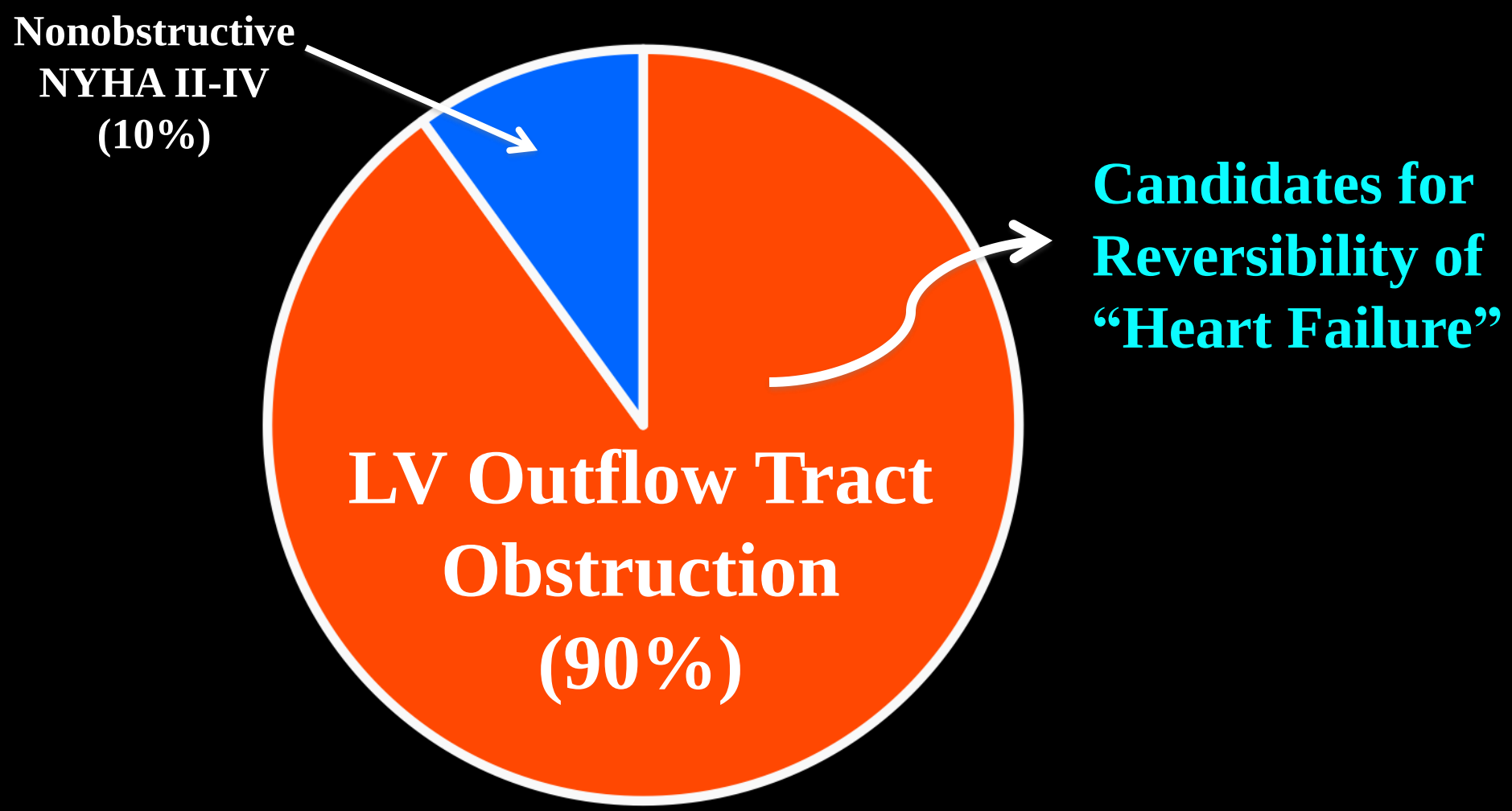
Impact of LV Outflow Obstruction (≥30 mmHg) on Heart Failure Symptoms and Death



Maron MS et al. *N Engl J Med.* 2003; 348(4):295-303.


LV Outflow Tract Obstruction
High LV Systolic Pressures
Mitral Regurgitation
LA Hypertension
Impaired
LV Filling
Microvascular
Ischemia
Reduced
Cardiac Output/
Stroke Volume
Pulmonary
Hypertension
Functional
Disability
"Heart Failure"

Majority of HCM Patients with "Heart Failure" Symptoms (Class III-IV) Have LV Outflow Tract Obstruction



Fundamental Principle

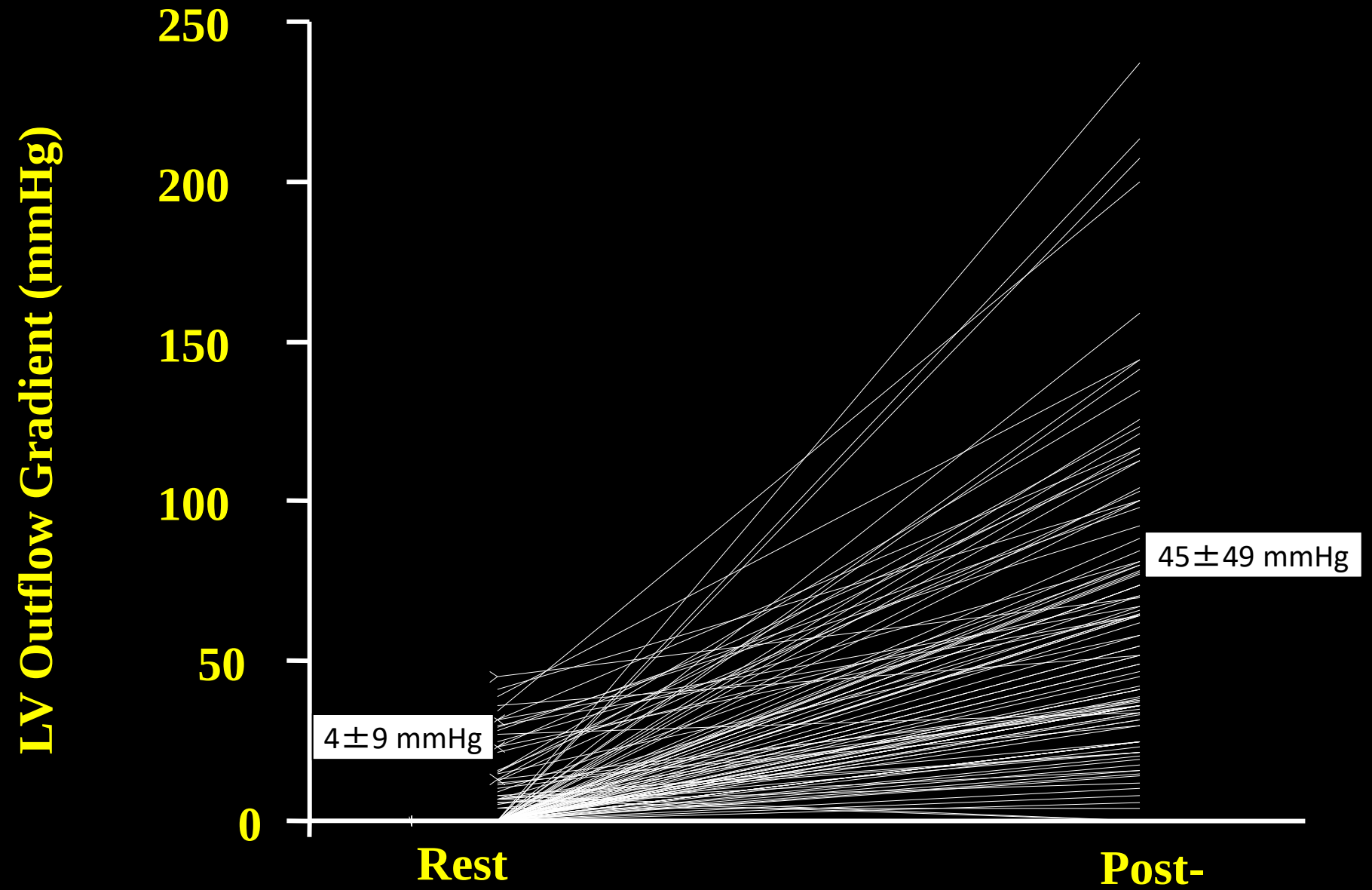
LV Outflow Tract Obstruction is the Determinant of Functional Disability in *nearly all* HCM and Represents a *reversible* Form of "Heart Failure"

Provoking Gradients in HCM for the Purpose of Management Decisions

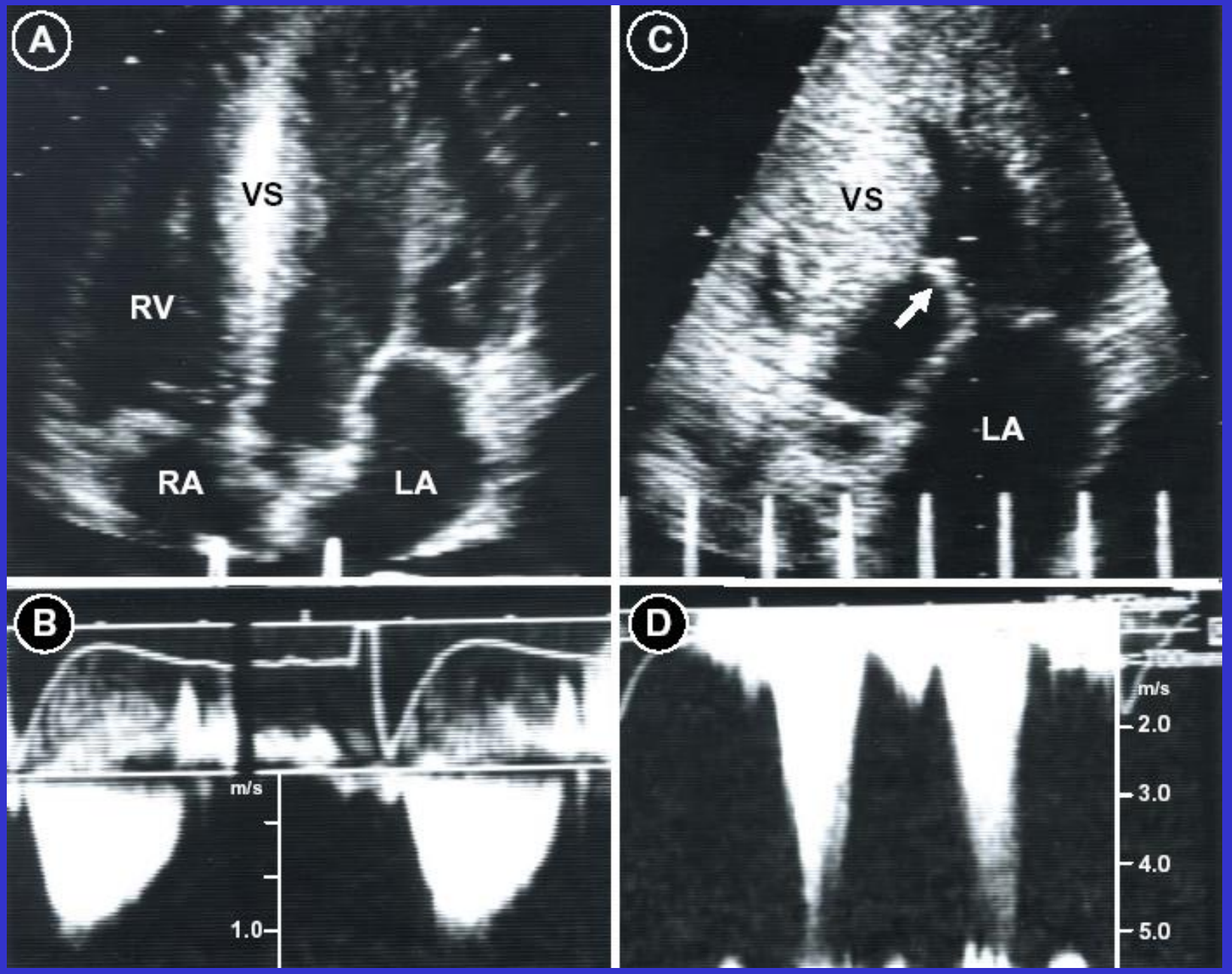
- Post-PVC response
- Isoproterenol infusion
- Amyl nitrite inhalation
- Valsalva maneuver
- Dobutamine infusion

- *Exercise Echocardiography*

Change in Gradient Among 304 Exercised HCM Pts without Obstruction at Rest



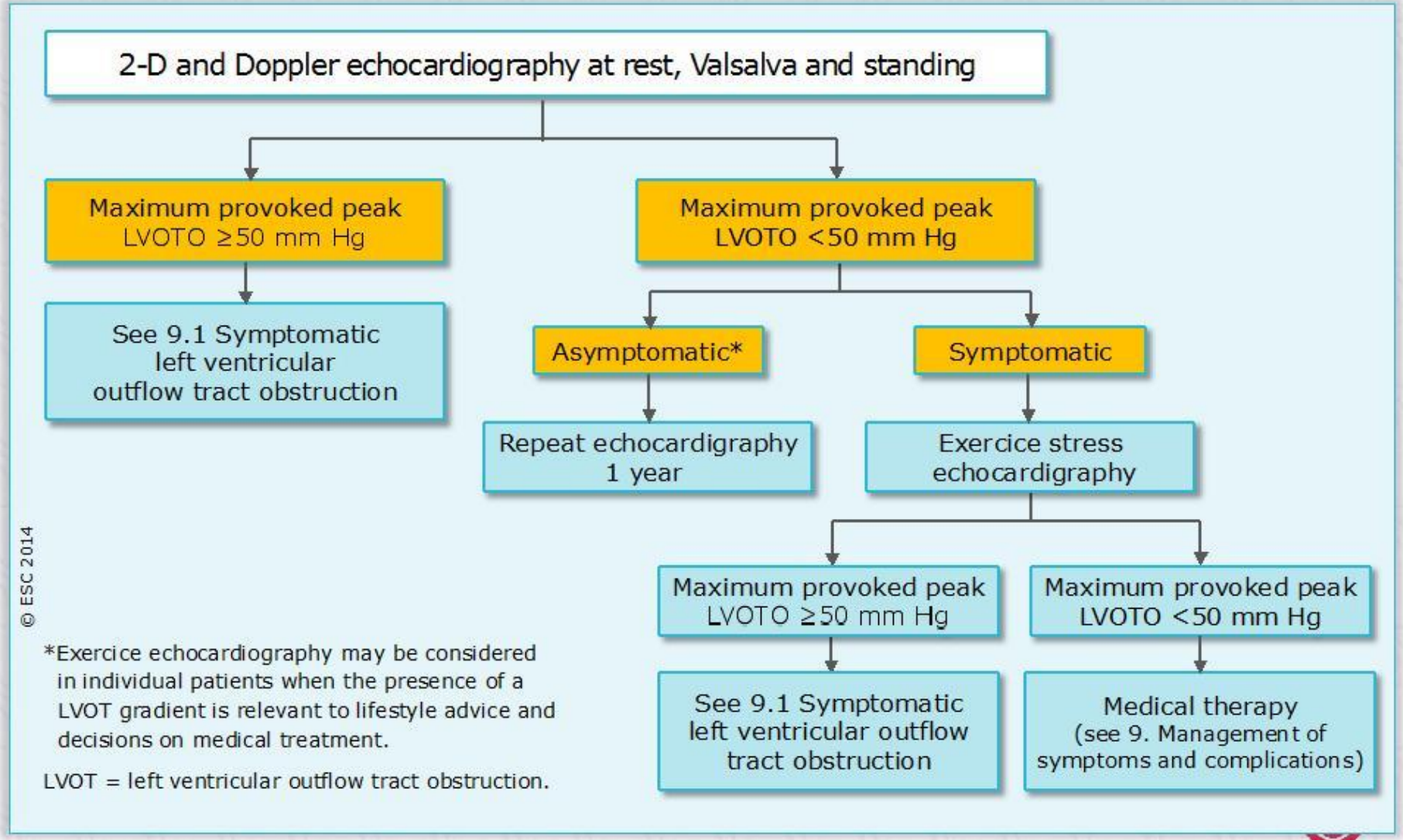
Maron MS et al Circulation 2007



Rest

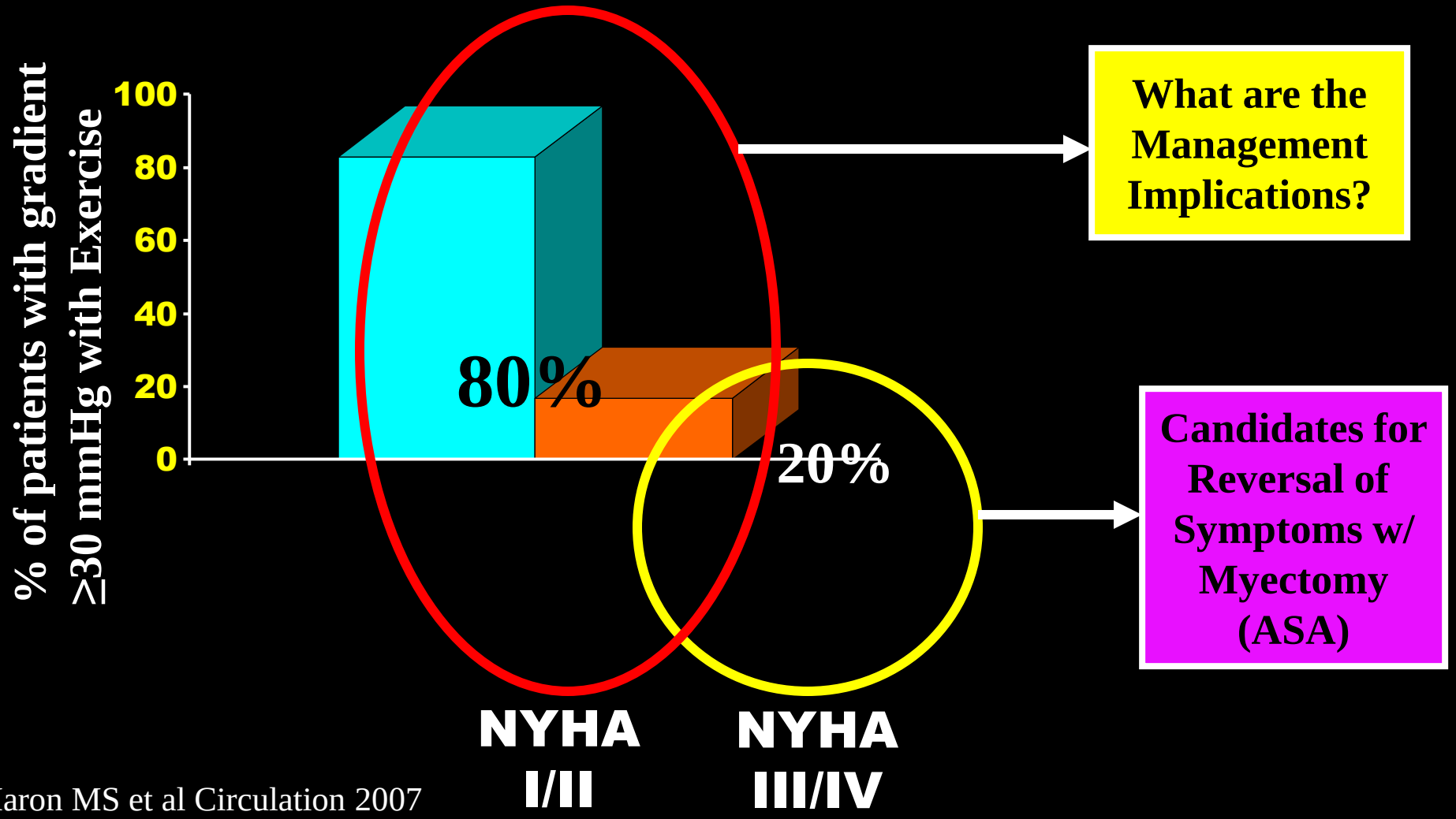
Exercise

Protocol for the assessment and treatment of left ventricular outflow tract obstruction



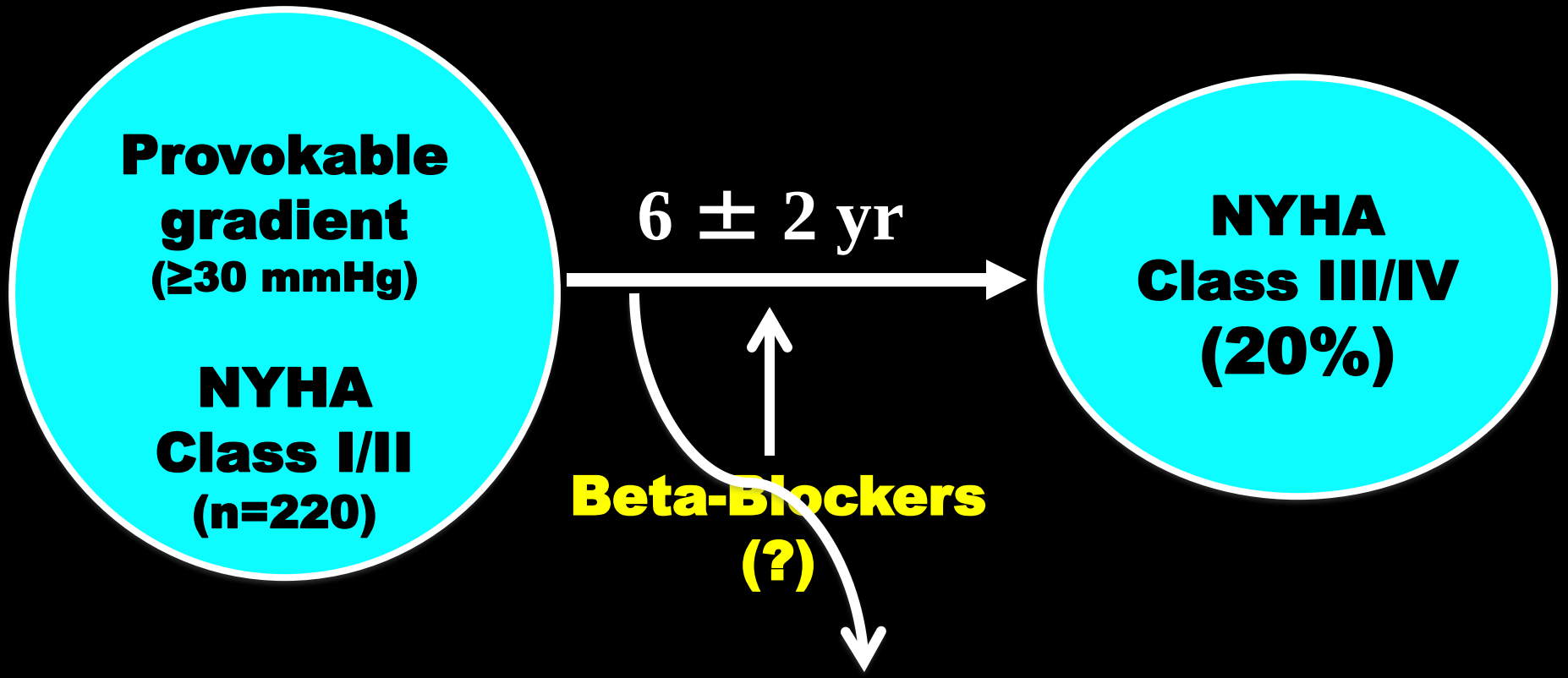
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Provocable (Exercise) Gradients and Symptoms



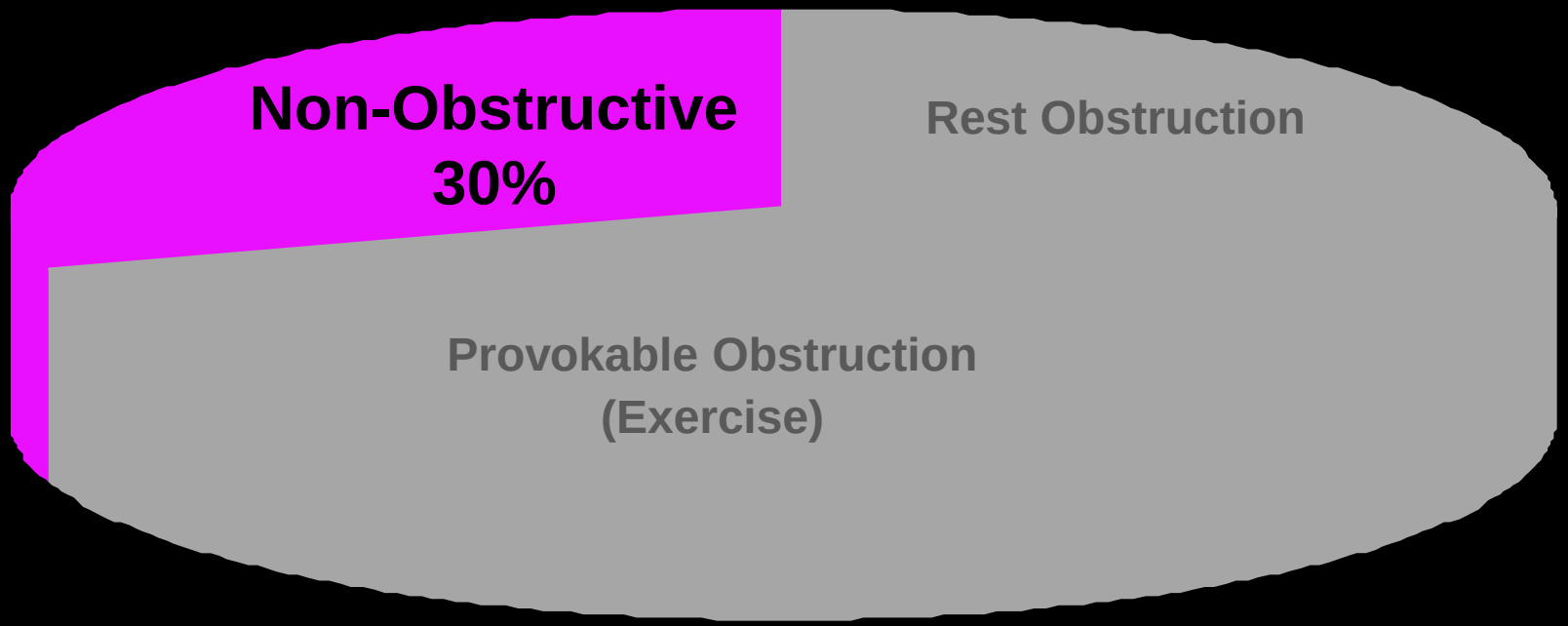
Maron MS et al Circulation 2007

Clinical Significance of Provokable Gradients in Asymptomatic or Mildly Asymptomatic HCM Patients

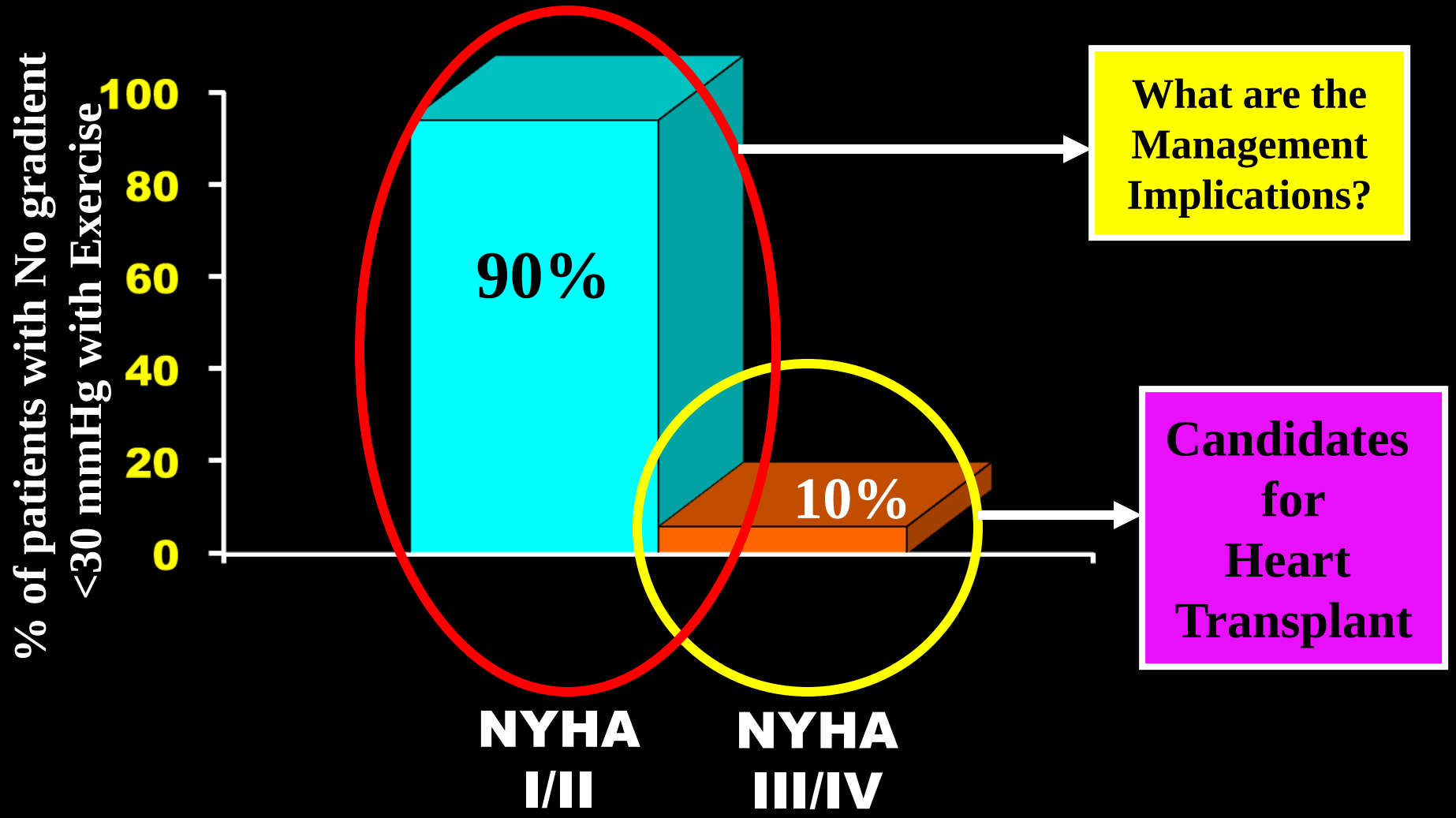


Provokable Gradients:
Rate of Heart Failure Progression
3%/year

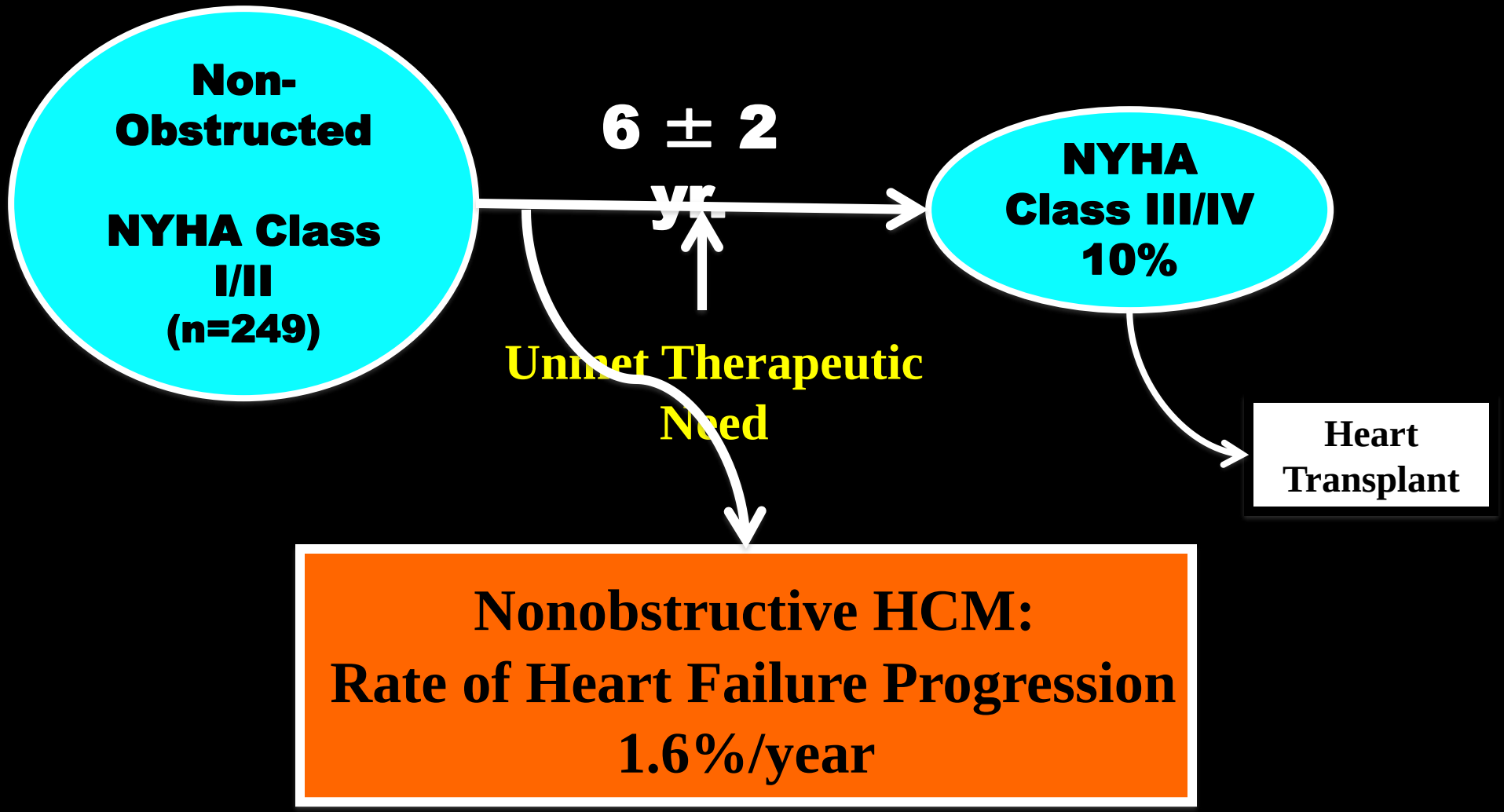
Natural History of Patients with Non-Obstructive HCM



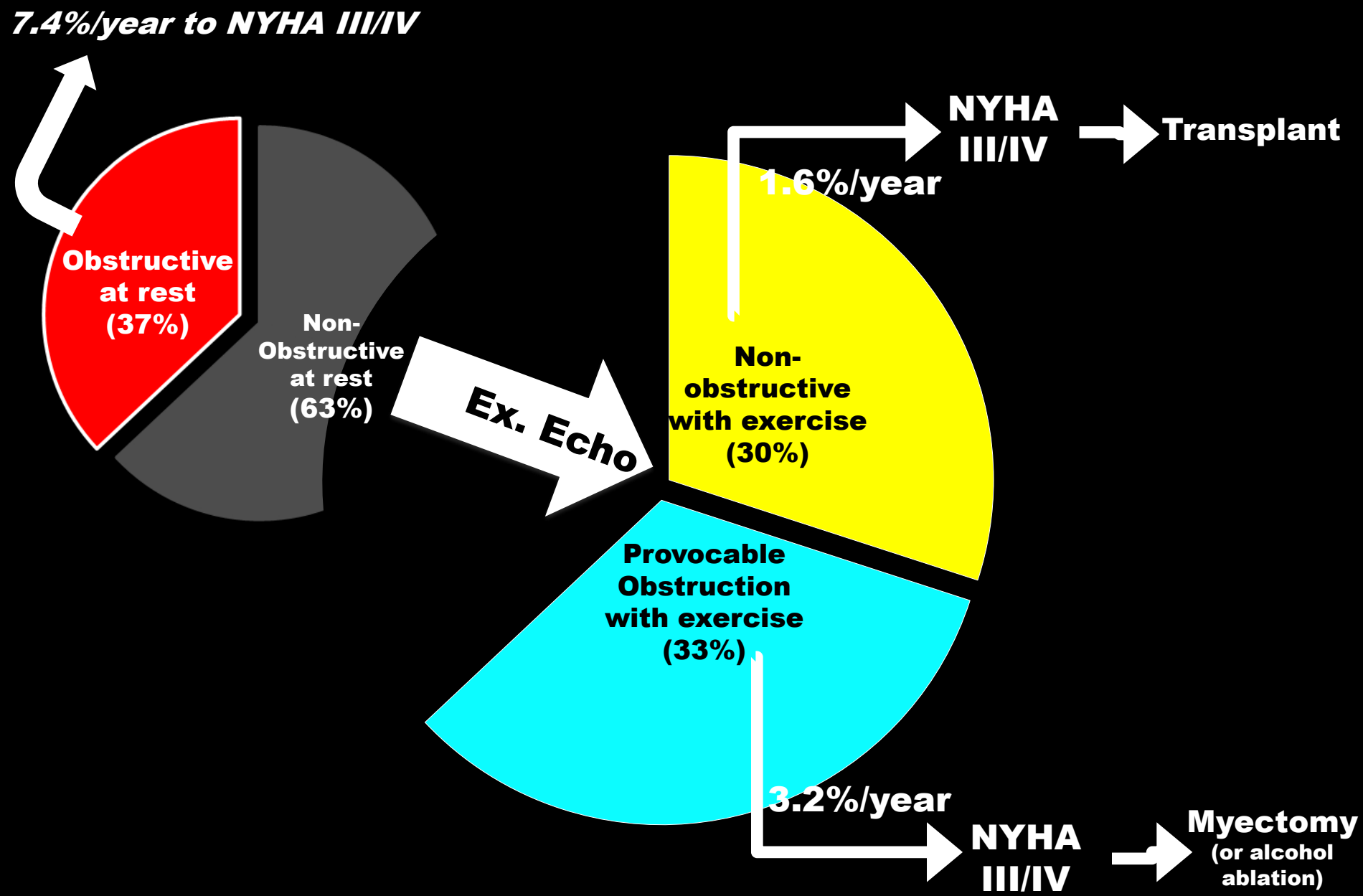
Nonobstructive (<30 mmHg) HCM and Symptoms

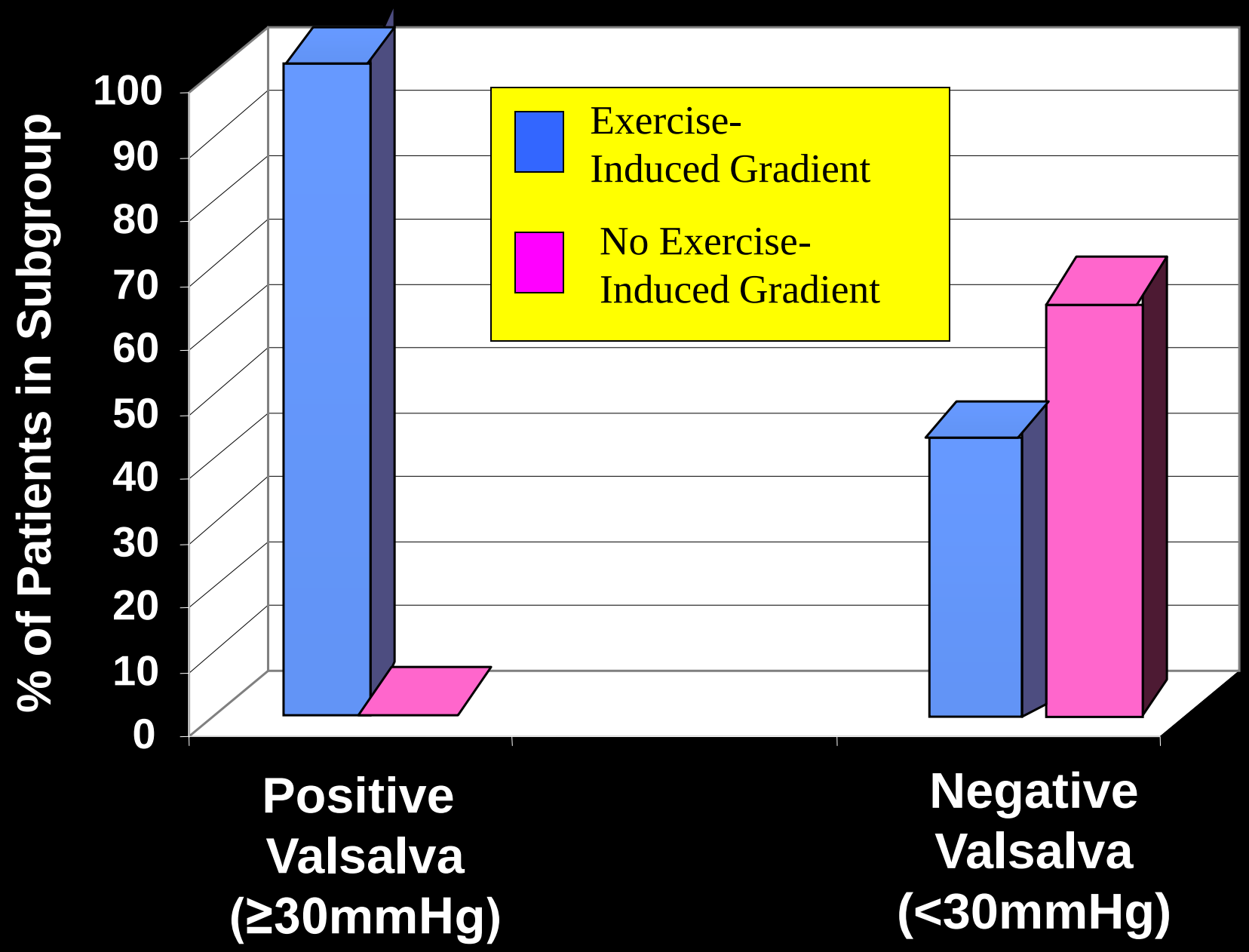


Clinical Significance of Nonobstructive HCM Patients



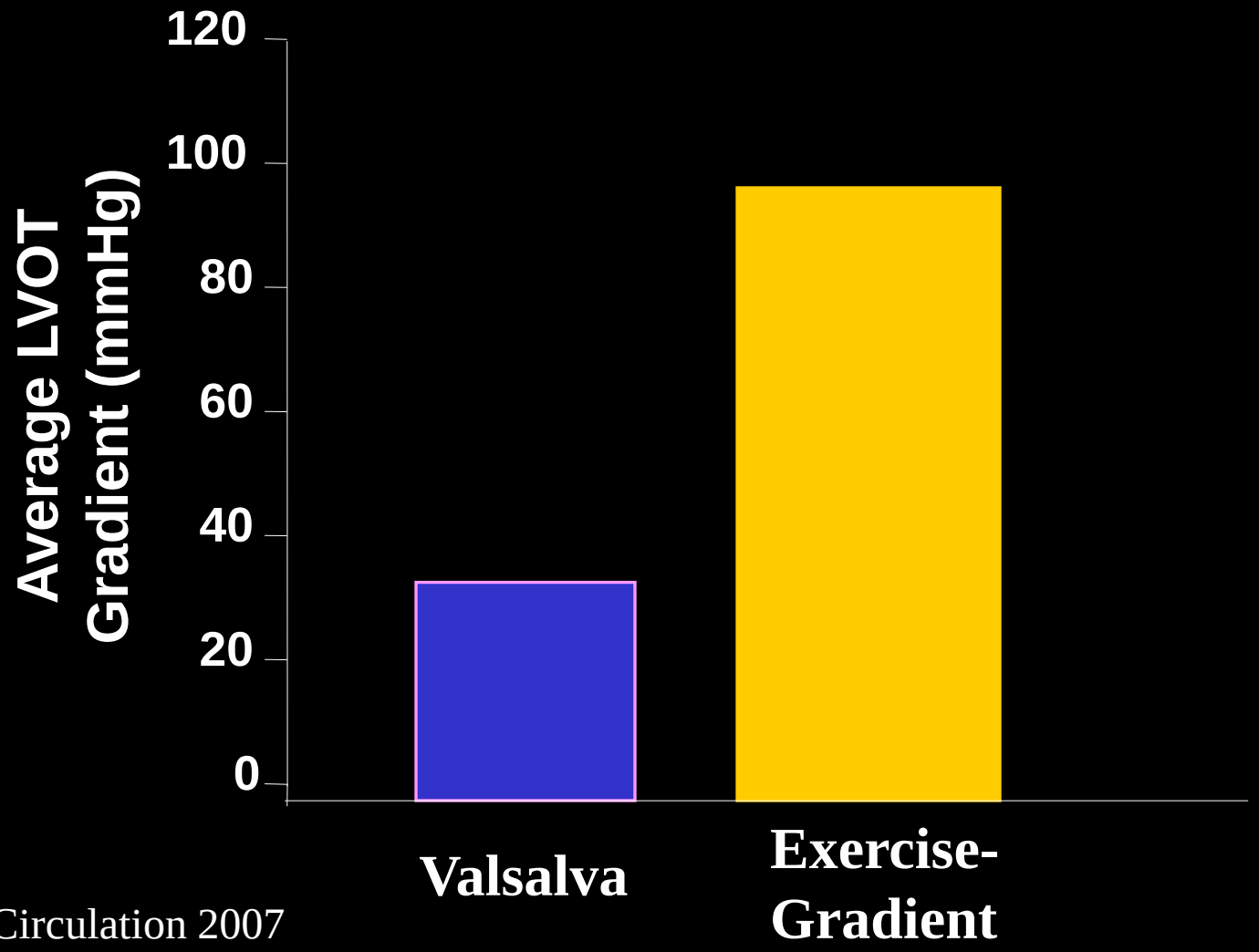
Exercise Echocardiography is a *KEY* Test in HCM



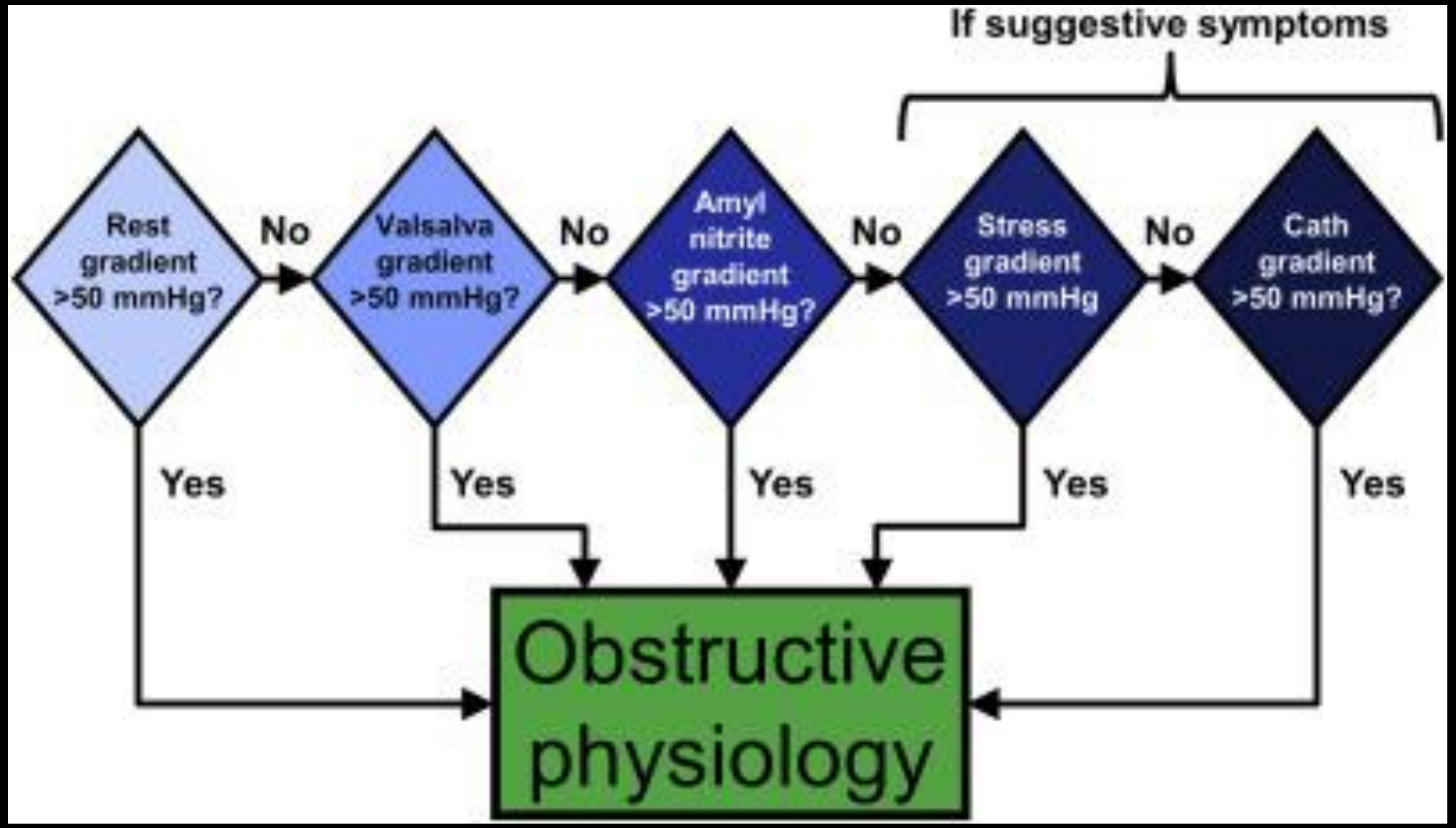


Maron et al Circulation 2007

Relation of Valsalva to Exercise Gradients In HCM Patients with Both

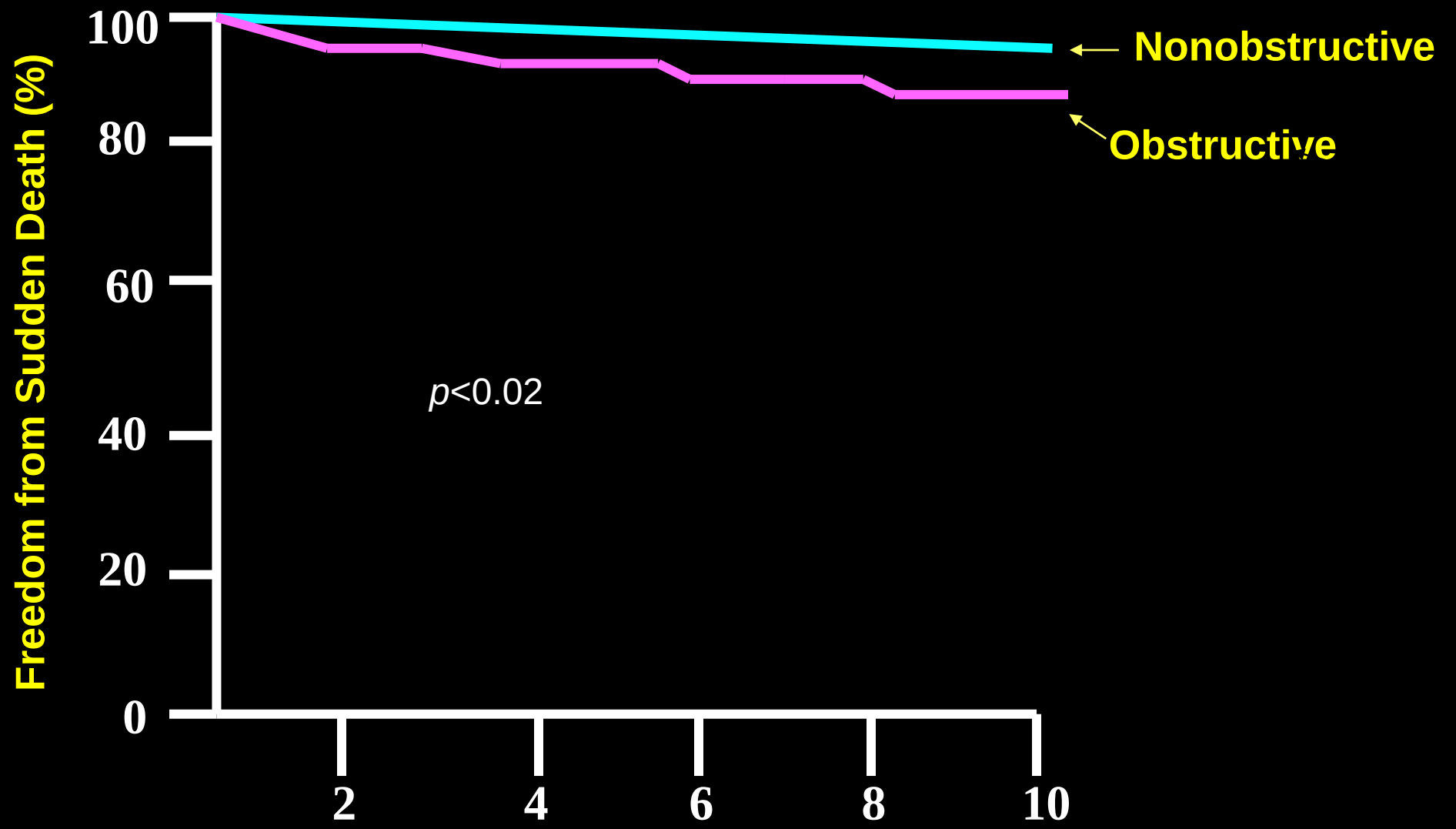


Maron et al Circulation 2007


If suggestive symptoms
Rest gradient >50 mmHg?
No
Valsalva gradient >50 mmHg?
No
Amyl nitrite gradient >50 mmHg?
No
Stress gradient >50 mmHg
No
Cath gradient >50 mmHg?
Yes
Yes
Yes
Yes
Yes
Obstructive physiology

Obstruction and Sudden Death

Impact of Outflow Obstruction (≥ 30mmHg) on *Sudden Death* Risk



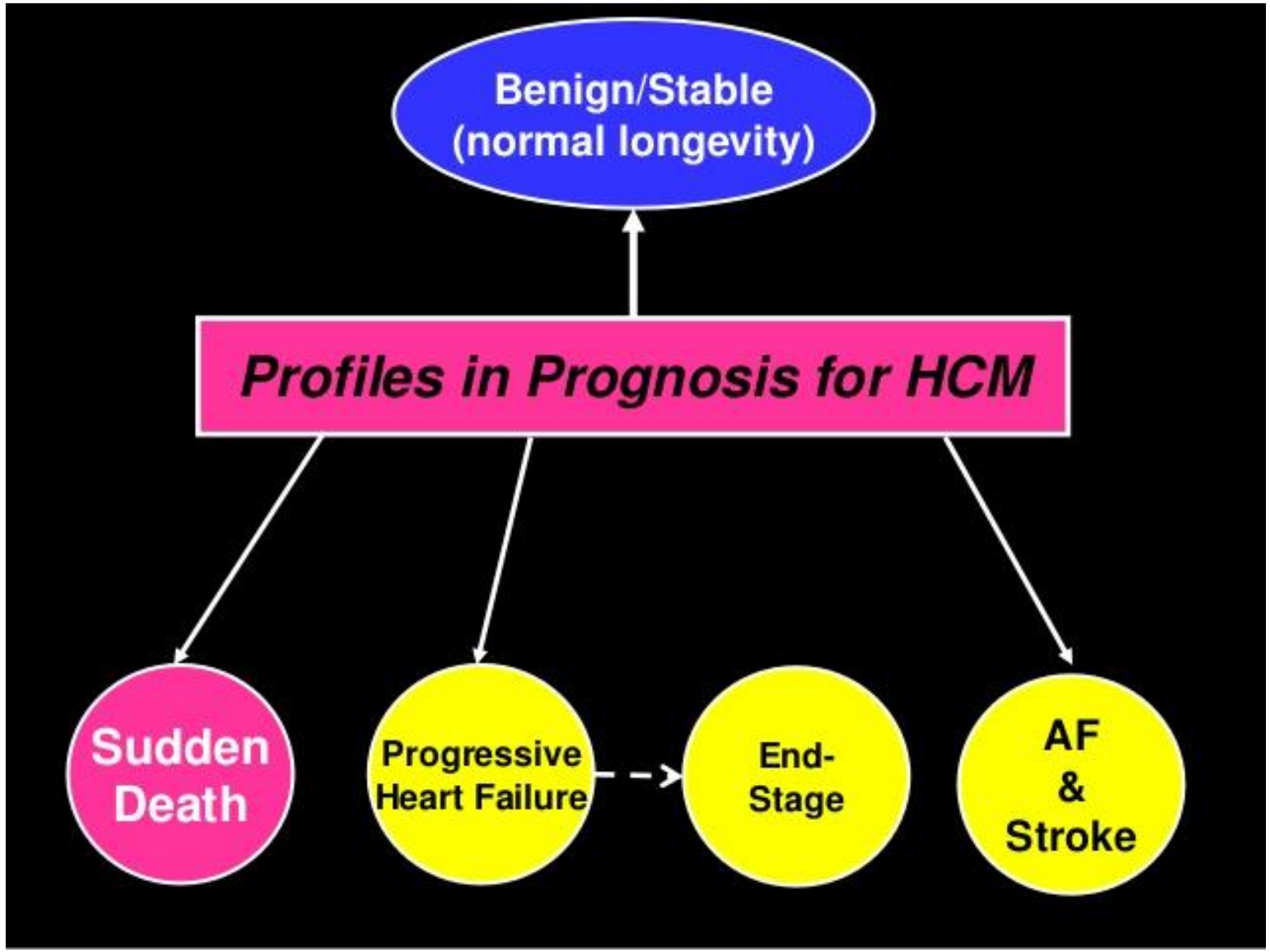
Maron MS et al. NEJM, 2003

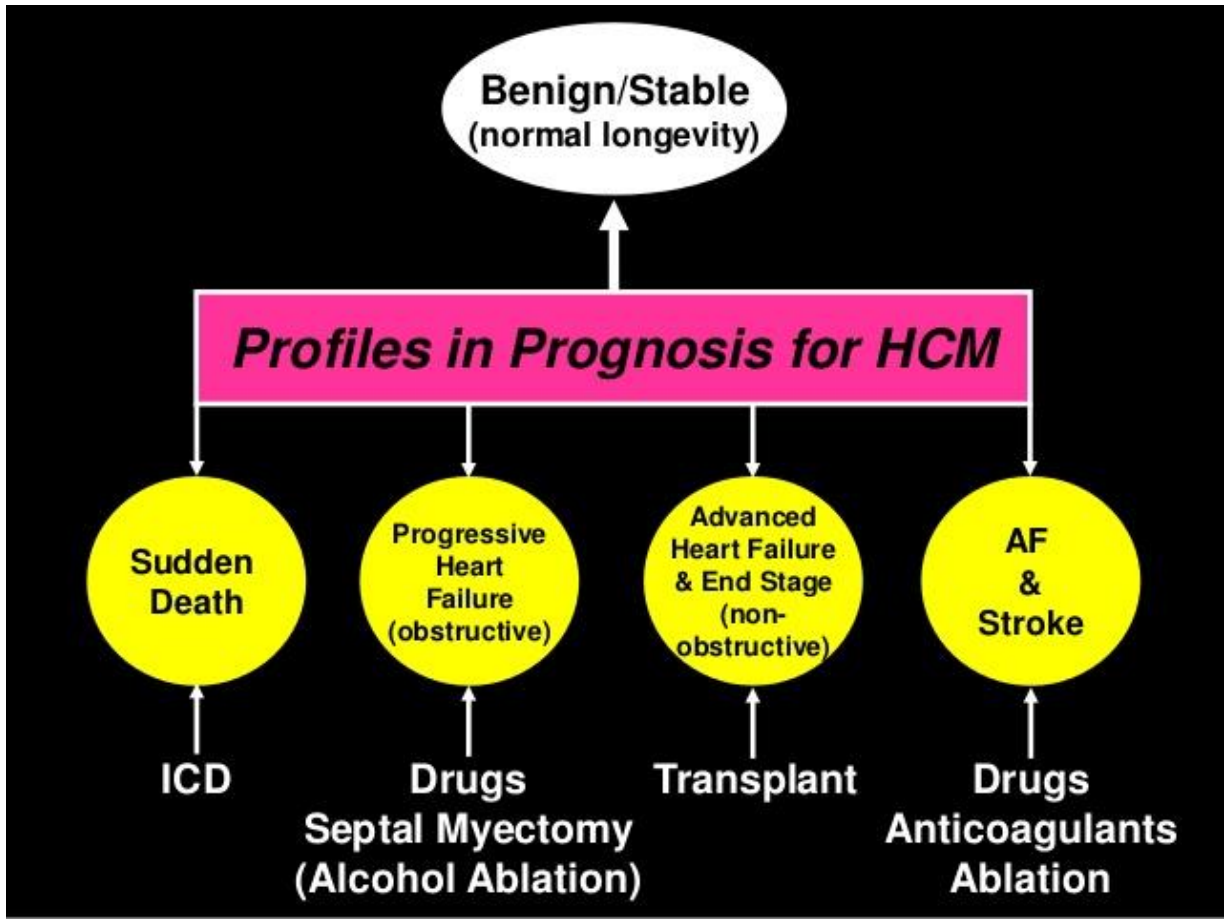
Obstruction is not a Feasible Primary Risk Factor for *Sudden Death*

- Gradients are dynamic and modifiable by treatment
- Substantial proportion of patients with either rest or provocable gradients (70%)
- Therefore, virtually all HCM patients would be considered for ICD

LV Outflow Tract Obstruction in HCM:

- Although controversial early on, has evolved to a highly prevalent (70%) and predominant disease feature
- Whether present at rest or exercise, responsible for 90% of severe “heart failure”
- Permanently *reversible* with low risk myectomy (ASA) by, conveying long-term benefit in quality of life and survival... *Functional Disability not “Congestive Heart Failure”*
- Majority of nonobstructive HCM have little to no symptoms; transplant for small subgroup who develop advanced heart failure


Benign/Stable
(normal longevity)
Profiles in Prognosis for HCM
Sudden Death
Progressive Heart Failure
End-Stage
AF & Stroke


Benign/Stable
(normal longevity)
Profiles in Prognosis for HCM
Sudden Death
Progressive Heart Failure (obstructive)
Advanced Heart Failure & End Stage (non-obstructive)
AF & Stroke
ICD
Drugs
Septal Myectomy
(Alcohol Ablation)
Transplant
Drugs
Anticoagulants
Ablation

Treatment?
NYHA CLASS II

- IVS- 22 mm; PW- 14 mm
- LVOT gradient-
- REST -60mmHg.
- Post Valsalva -100 mmHg
- SAM with Mod+ MR

Treatment?

Meds? +/-

PPM?

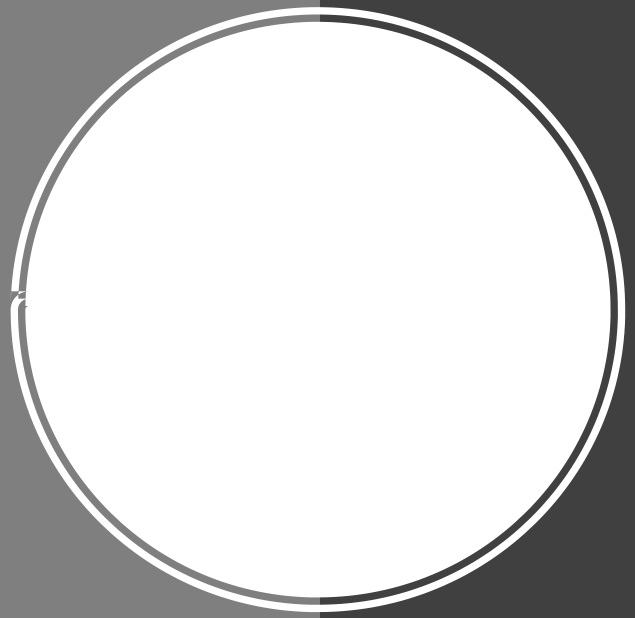
Operation?

Treatment of left ventricular outflow tract obstruction: General measures

Recommendations	Class	Level
Arterial and venous dilators, including nitrates and phosphodiesterase inhibitors, should be avoided if possible in patients with resting or provocable LVOTO.	IIa	C
Restoration of sinus rhythm or appropriate rate control should be considered before considering invasive therapies in patients with new-onset or poorly controlled atrial fibrillation.	IIa	C
Digoxin is not recommended in patients with resting or provocable LVOTO.	III	C

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

איזה תרופה מהווה קו ראשון?



- איזה חוסם ביטא תעדיף?

- CARVEDILOL
- BISOPROLOL
- PROPANOLOL
- LABETOLOL

- איזה חוסם סידן?

Medical treatment of left ventricular outflow tract obstruction

Recommendations	Class	Level
Non-vasodilating ß-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in symptomatic patients with resting or provoked LVOTO.	I	B
Verapamil, titrated to maximum tolerated dose, is recommended to improve symptoms in symptomatic patients with resting or provoked[a] LVOTO, who are intolerant or have contra-indications to ß-blockers.	I	B

Medical treatment of left ventricular outflow tract obstruction

Recommendations	Class	Level
Non-vasodilating ß-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in symptomatic patients with resting or provoked LVOTO.	I	B
Verapamil, titrated to maximum tolerated dose, is recommended to improve symptoms in symptomatic patients with resting or provoked[a] LVOTO, who are intolerant or have contra-indications to ß-blockers.	I	B
Disopyramide, titrated to maximum tolerated dose[b], is recommended in addition to a ß-blocker (or, if this is not possible, with verapamil) to improve symptoms patients with resting or provoked[a] LVOTO.	I	B
Disopyramide, titrated to maximum tolerated dose[b], may be considered as monotherapy to improve symptoms in symptomatic patients with resting or provoked[a] LVOTO (exercise or Valsalva manoeuvre) taking caution in patients with–or prone to–AF, in whom it can increase ventricular rate response.	IIb	C
ß-Blockers or verapamil may be considered in children and *asymptomatic* adults with resting or provoked[a] LVOTO, to reduce left ventricular pressures.	IIb	C

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

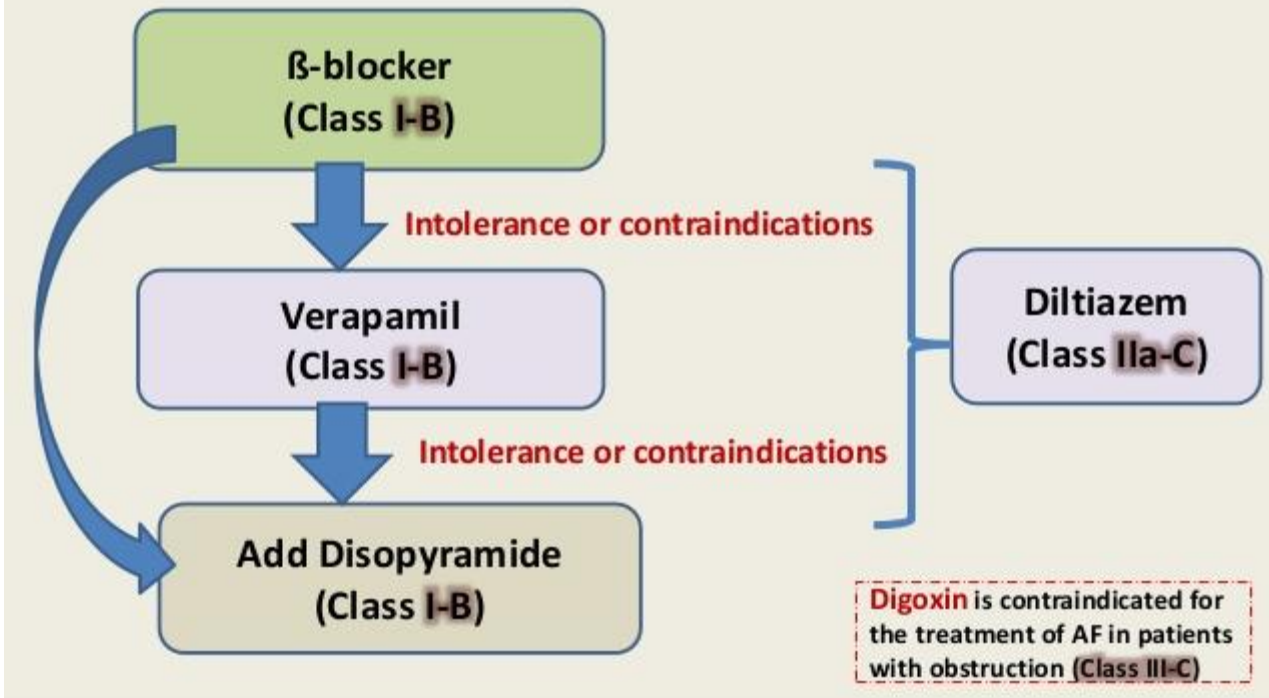
Medical treatment of left ventricular outflow tract obstruction *(Cont.)*

Recommendations	Class	Level
Low-dose loop–or thiazide diuretics may be used with caution in symptomatic LVOTO, to improve exertional dyspnoea.	IIb	C
Diltiazem, titrated to maximum tolerated dose, should be considered in symptomatic patients with resting or provoked[a] LVOTO, who are intolerant or have contra-indications to ß-blockers and verapamil to improve symptoms.	IIa	C
Oral or i.v. ß-blockers and vasoconstrictors should be considered in patients with severe provocable LVOTO presenting with hypotension and pulmonary oedema.	IIa	C

[a]Provocation with Valsalva manoeuvre, upright exercise or oral nitrates if unable to exercise.
[b]QTc interval should be monitored during up-titration of disopyramide and the dose reduced if it exceeds 480 ms.

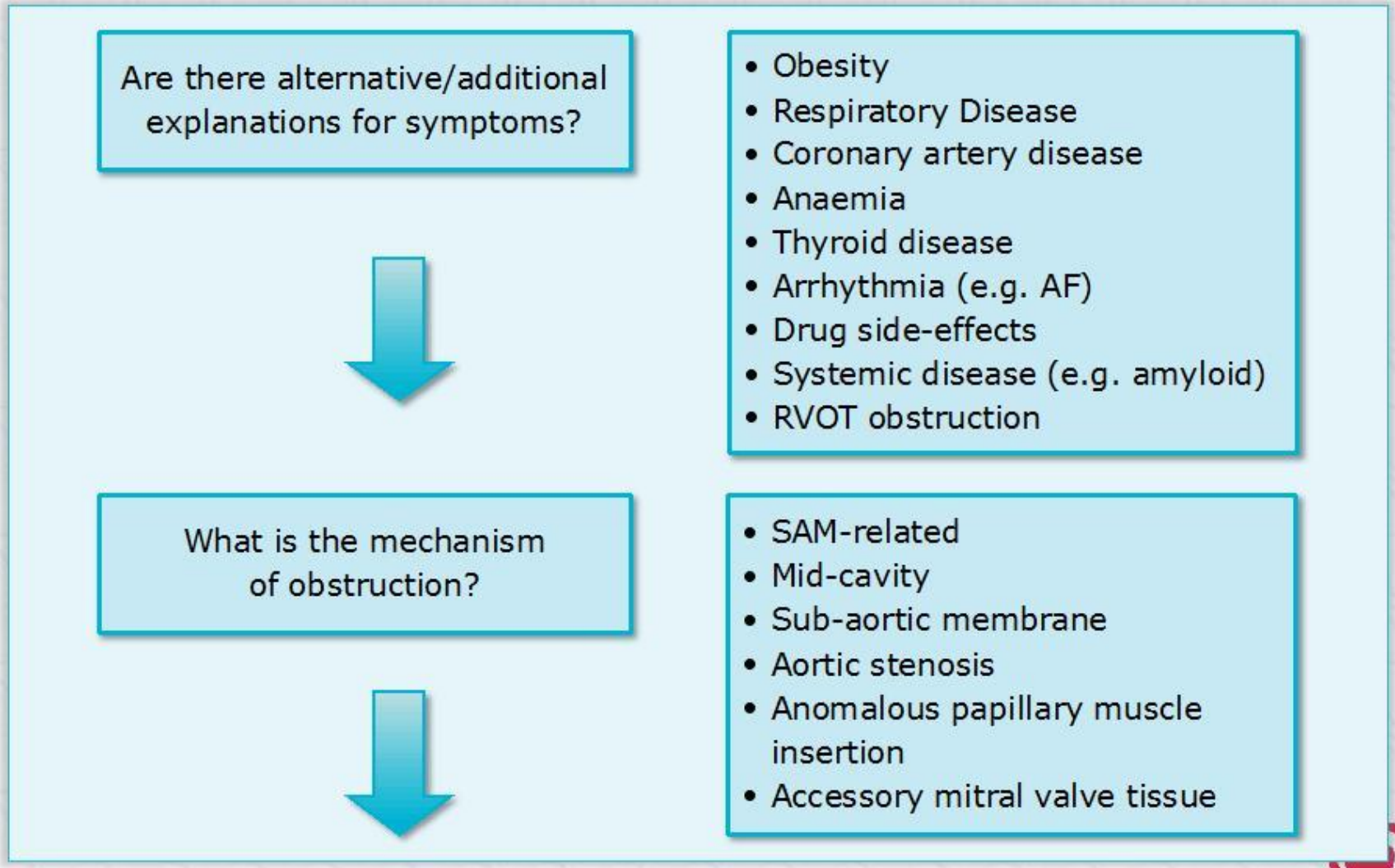
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

5 Management of Left Ventricular Outflow Tract Obstruction : *Medical Treatment*



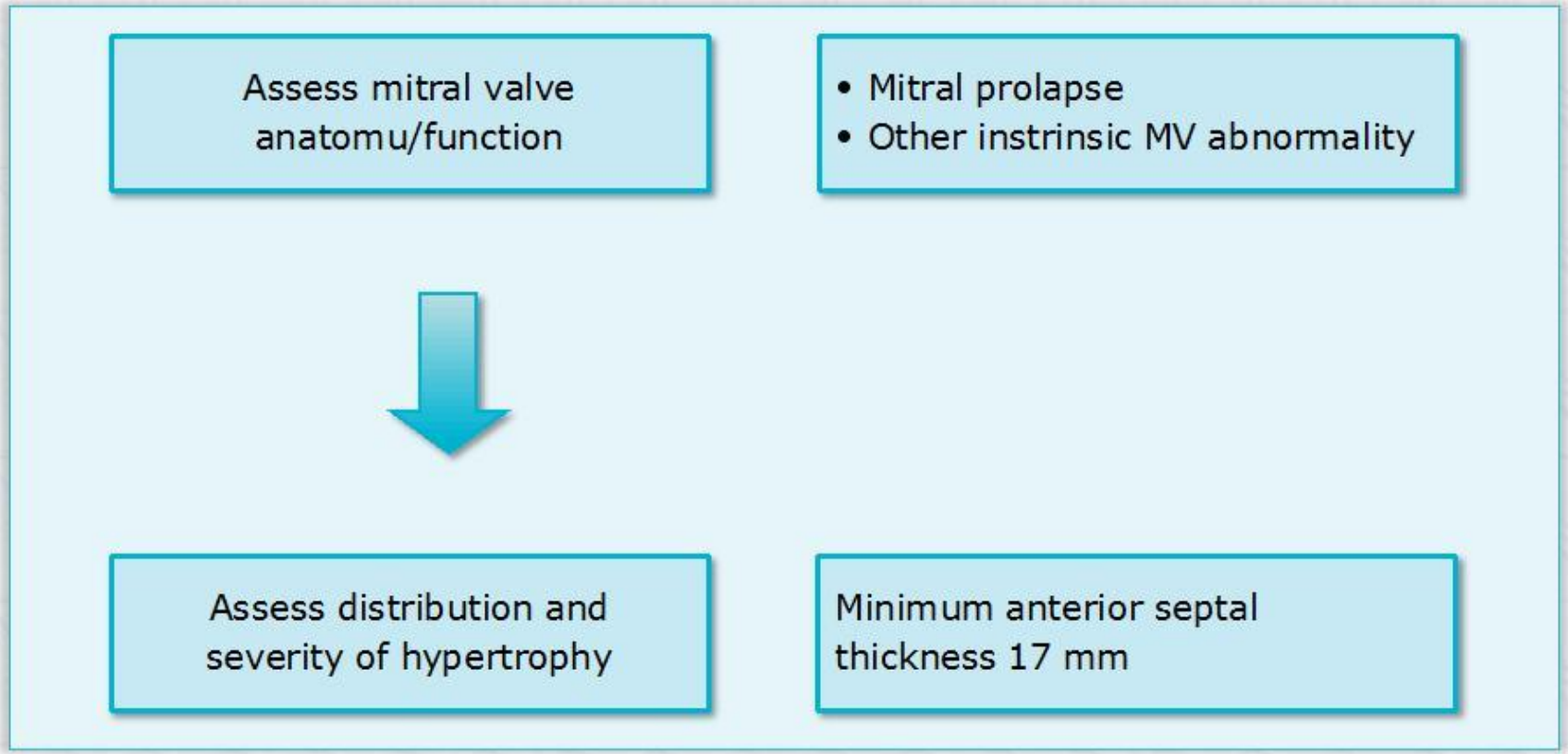
חולה עדיין סימפטומטי.....
NYHA CLASS III

Pre-assessment check list for patients being considered for invasive septal reduction therapies



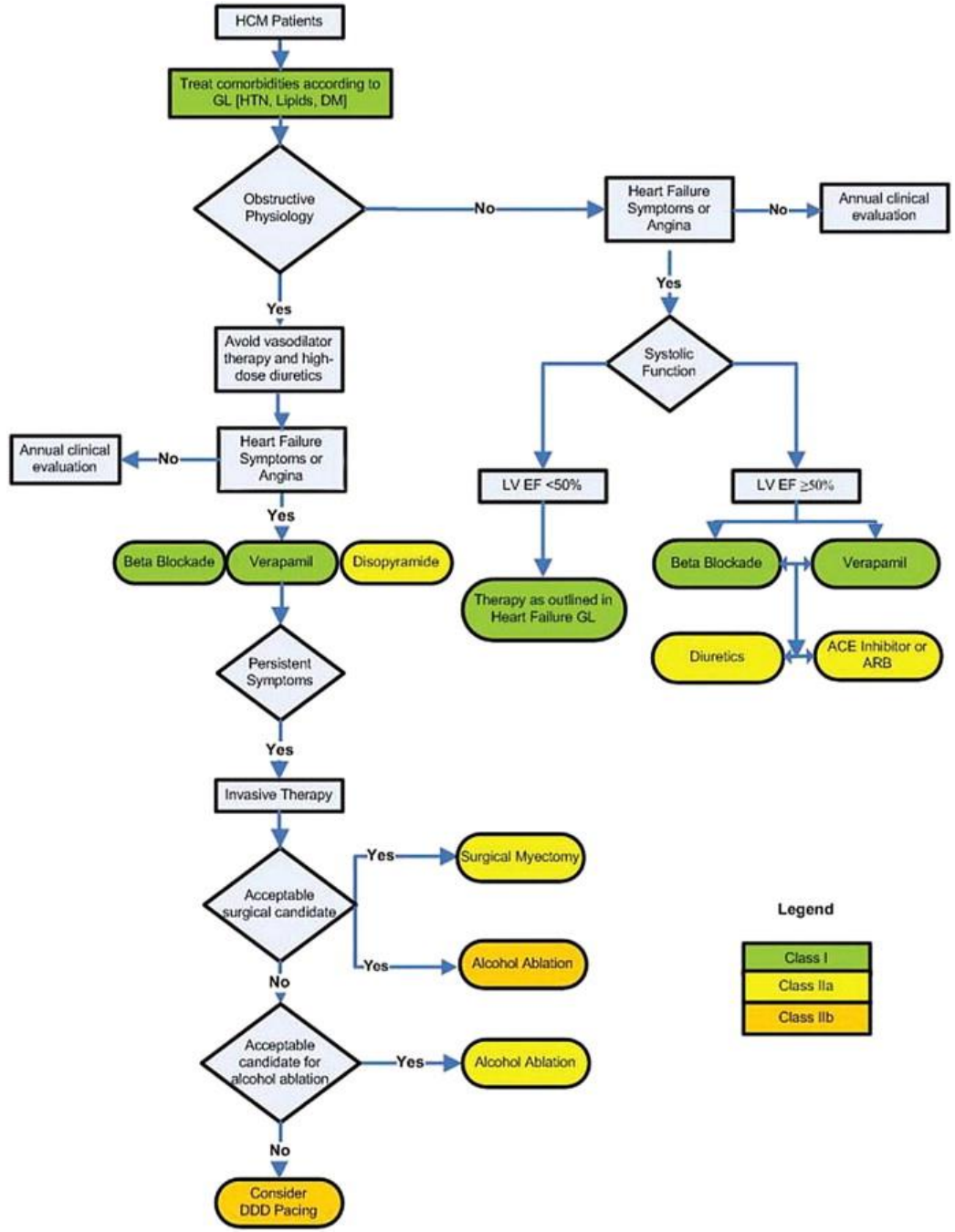
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Pre-assessment check list for patients being considered for invasive septal reduction therapies *(Cont.)*



European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

אלכוהול? ניתוח קוצב?


HCM Patients
Treat comorbidities according to GL [HTN, Lipids, DM]
Obstructive Physiology
No
Heart Failure Symptoms or Angina
No
Annual clinical evaluation
Yes
Systolic Function
LV EF <50%
LV EF ≥50%
Therapy as outlined in Heart Failure GL
Beta Blockade
Verapamil
Diuretics
ACE Inhibitor or ARB
Yes
Avoid vasodilator therapy and high-dose diuretics
Heart Failure Symptoms or Angina
No
Annual clinical evaluation
Yes
Beta Blockade
Verapamil
Disopyramide
Persistent Symptoms
Yes
Invasive Therapy
Acceptable surgical candidate
Yes
Surgical Myectomy
Yes
Alcohol Ablation
No
Acceptable candidate for alcohol ablation
Yes
Alcohol Ablation
No
Consider DDD Pacing
Legend
Class I
Class IIa
Class IIb

Eligible patients for invasive therapy

Clinical: NYHA functional classes III or IV, syncope or other symptoms that interfere with quality of life despite optimal medical therapy.

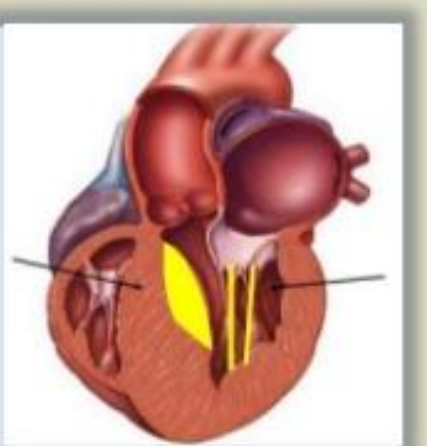
Hemodynamic: LVOT gradient ≥50 mmHg (at rest or provoked) associated with septal hypertrophy and systolic anterior motion of the mitral valve.

Anatomic: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator.

Surgery vs. alcohol ablation

- For the first time, **septal alcohol ablation** is assigned the same class of recommendation (I-B) as **myectomy** in expert centers.
- The 2 procedures have similar efficacy and complications rates. Septal alcohol ablation has a higher rate of atrioventricular block than surgery (12% vs 5%).

Septal myectomy, rather than **septal alcohol ablation**, is recommended in patients with an indication for septal reduction therapy and other lesions requiring surgical intervention (e.g. mitral valve repair/replacement, papillary muscle intervention). (Class I-C)



Septal reduction therapy

Recommendations	Class	Level
It is recommended that septal reduction therapies be performed by experienced operators, working as part of a multidisciplinary team expert in the management of HCM.	I	C
Septal reduction therapy to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mm Hg, who are in NYHA functional Class III–IV despite maximum tolerated medical therapy.	I	B
Septal reduction therapy should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mm Hg despite optimal medical therapy.	IIa	C
Septal myectomy, rather than SAA, is recommended in patients with an indication for septal reduction therapy and other lesions requiring surgical intervention (e.g. mitral valve repair/replacement, papillary muscle intervention).	I	C
Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient ≥50 mm Hg and moderate-to-severe mitral regurgitation not caused by SAM of the mitral valve alone.	IIa	C
Mitral valve repair or replacement may be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mm Hg and a maximum septal thickness ≤16 mm at the point of the mitral leaflet–septal contact or when there is moderate-to-severe mitral regurgitation following isolated myectomy.	IIb	C

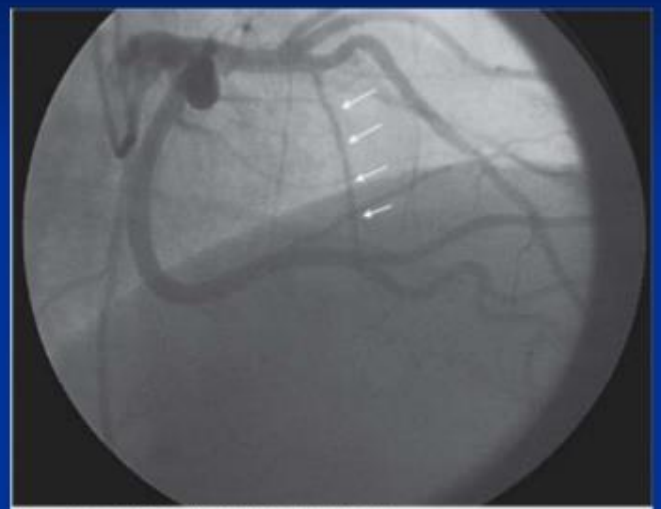
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Indications for cardiac pacing in patients with obstruction

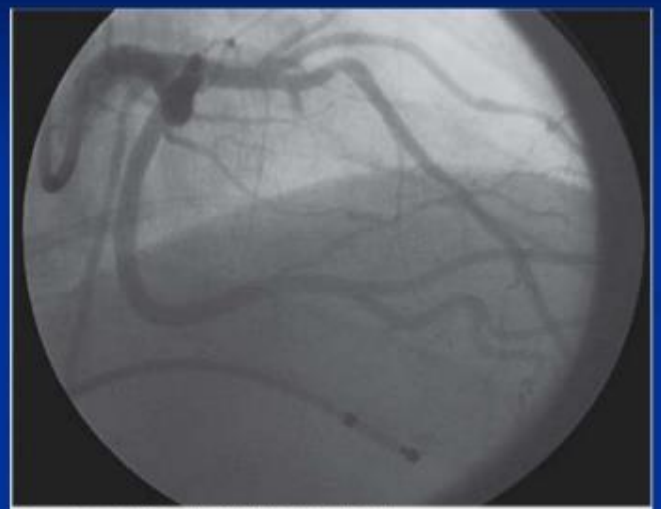
Recommendations	Class	Level
Sequential AV pacing, with optimal AV interval to reduce the LV outflow tract gradient or to facilitate medical treatment with ß-blockers and/or verapamil, may be considered in selected patients with resting or provocable LVOTO ≥50 mm Hg, sinus rhythm and drug-refractory symptoms, who have contra-indications for septal alcohol ablation or septal myectomy or are at high-risk of developing heart block following septal alcohol ablation or septal myectomy.	**IIb**	C
In patients with resting or provocable LVOTO ≥50 mm Hg, sinus rhythm and drug-refractory symptoms, in whom there is an indication for an ICD, a dual-chamber ICD (instead of a single-lead device) may be considered, to reduce the LV outflow tract gradient or to facilitate medical treatment with ß-blockers and/or verapamil.	**IIb**	C

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Alcohol Septal Ablation



Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

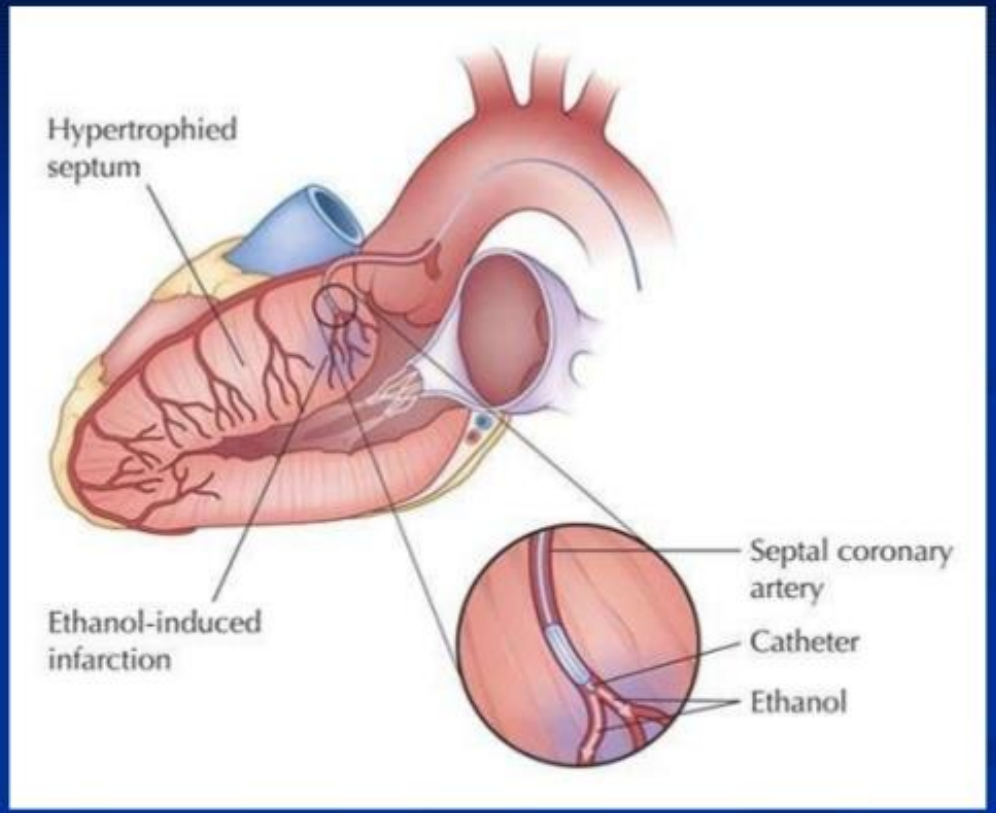


Source: Fuster V, O'Rourke RA, Walsh RA, Poole-Wilson P: *Hurst's The Heart*, 12th Edition: http://www.accessmedicine.com

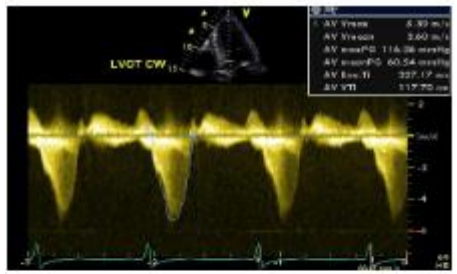
Before

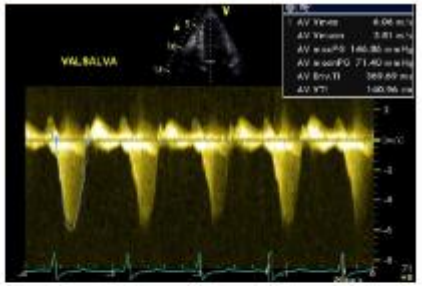
After

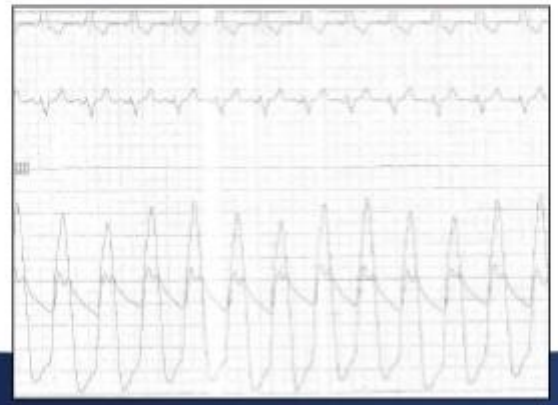
Alcohol Septal Ablation



Braunwald. Atlas of Heart Diseases: Cardiomyopathies, Myocarditis, and Pericardial Disease. 1998.

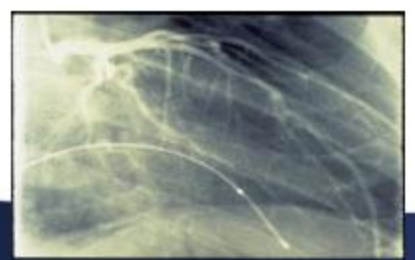

LVOT CW

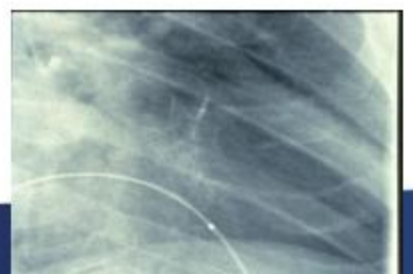

VALSALVA



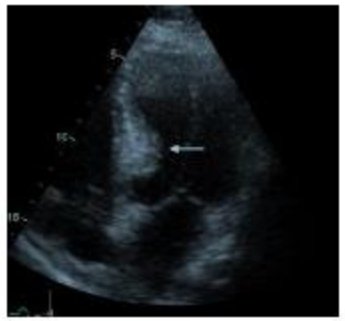
ASA
Septal angiogram

- Inject contrast with 3 cc syringe
- Look for target distribution of the septal
- Look for collaterals to RCA or other vessels
- Confirm that no contrast leaks around the balloon into the parent vessel (LAD)
- Assess hemodynamics with balloon inflated
  - Reduction of the LVOT gradient and normalization of the bisferiens contour of the Ao tracing is an encouraging sign

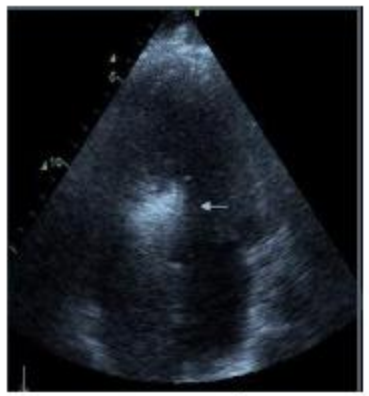


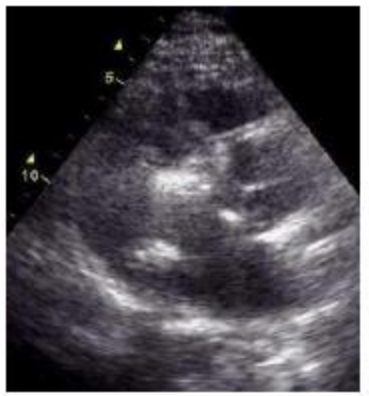


ASA
Echo localization of target infarct



Before agitated contrast





After agitated contrast

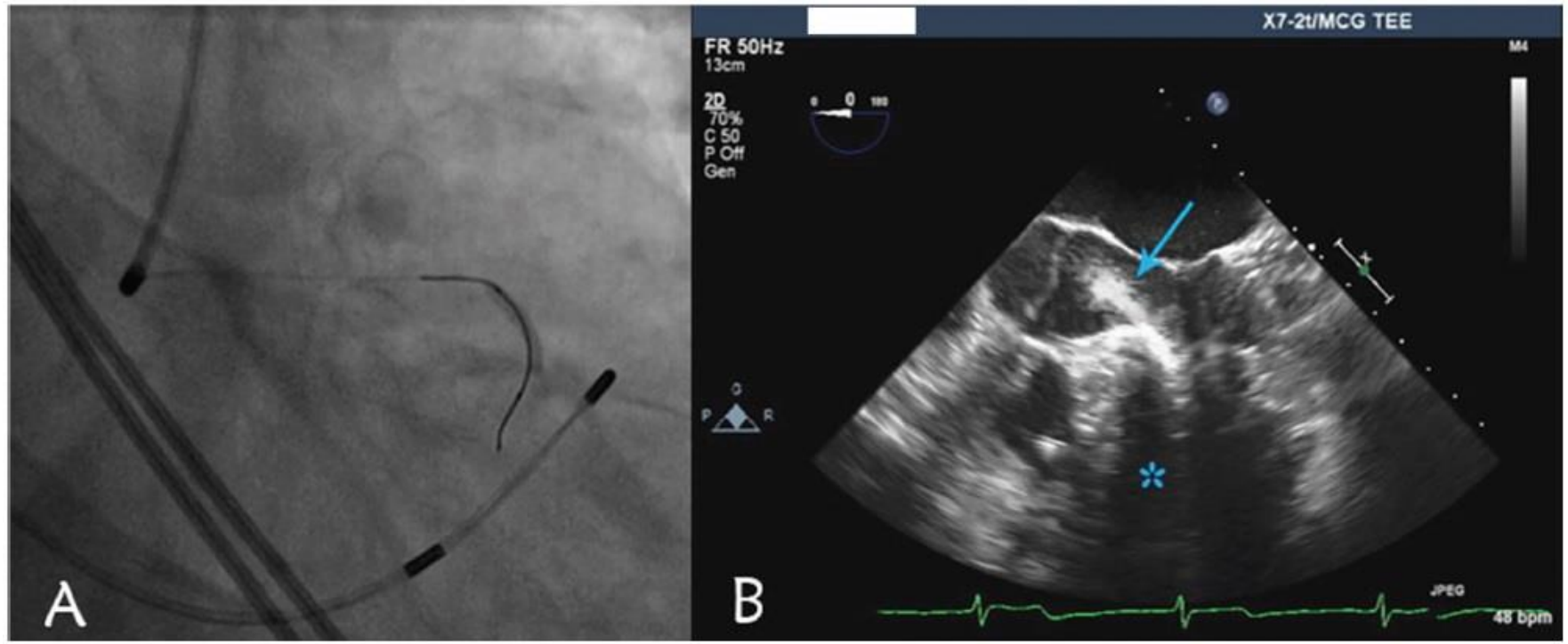
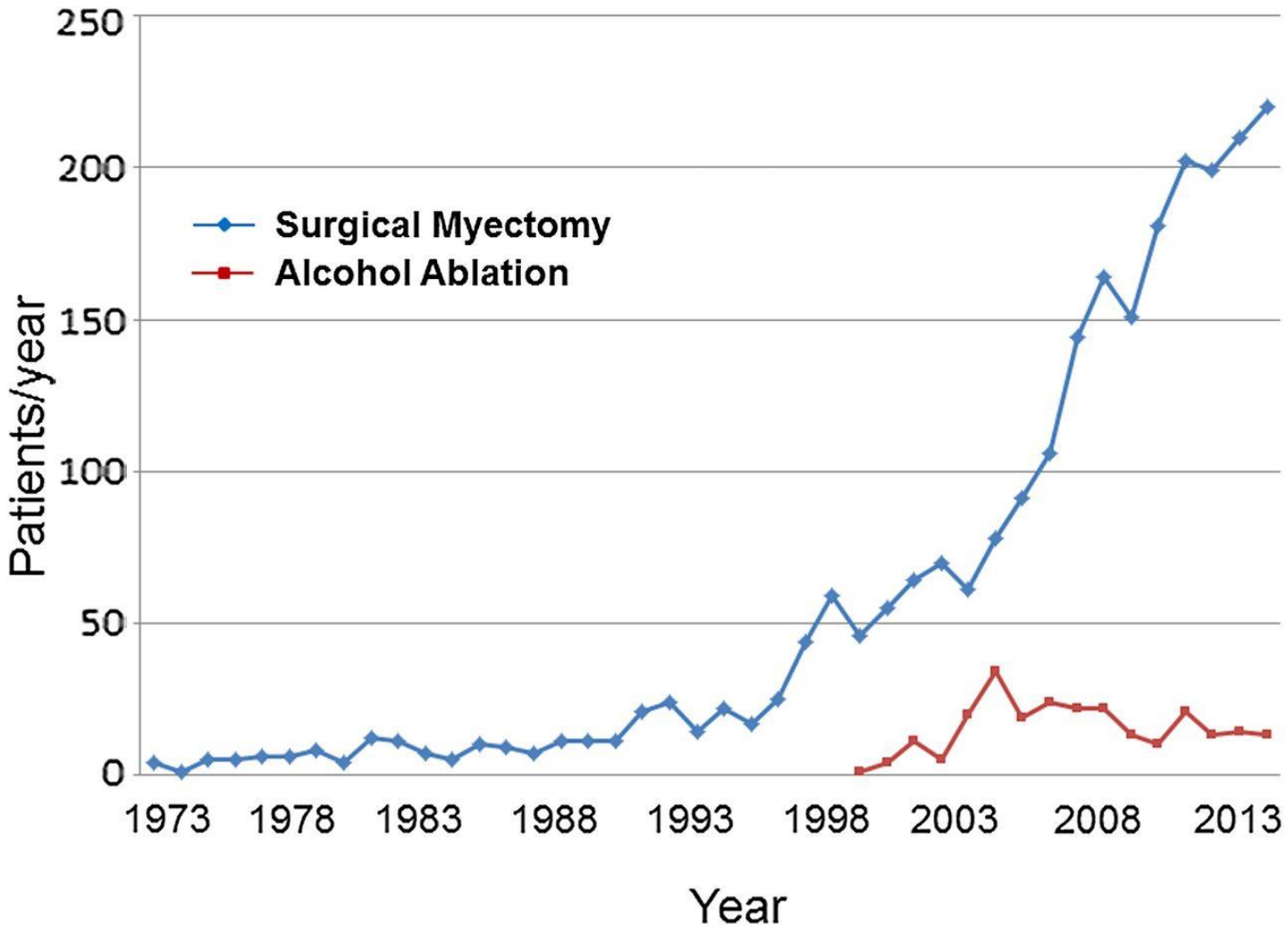
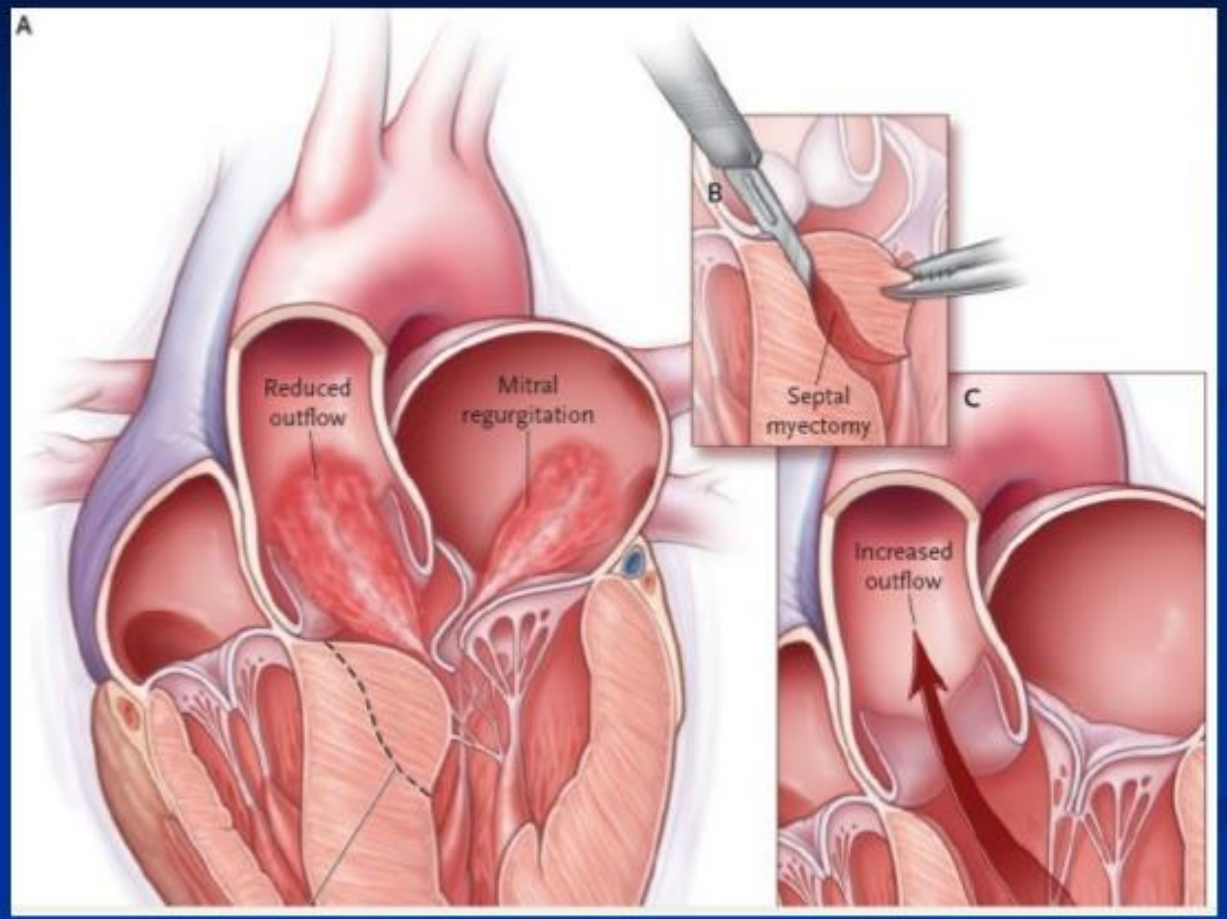


Figure 2. (A) Fluoroscopic image showing a wire placed in the patient's first septal perforator with an Apex 1.5 mm over-the-wire balloon (Boston Scientific), inflated for septal occlusion. (B) Jet of echo contrast is seen emanating from the septal wall into the LV cavity on transesophageal imaging as the first septal artery is injected with Definity (Lantheus Medical Imaging).



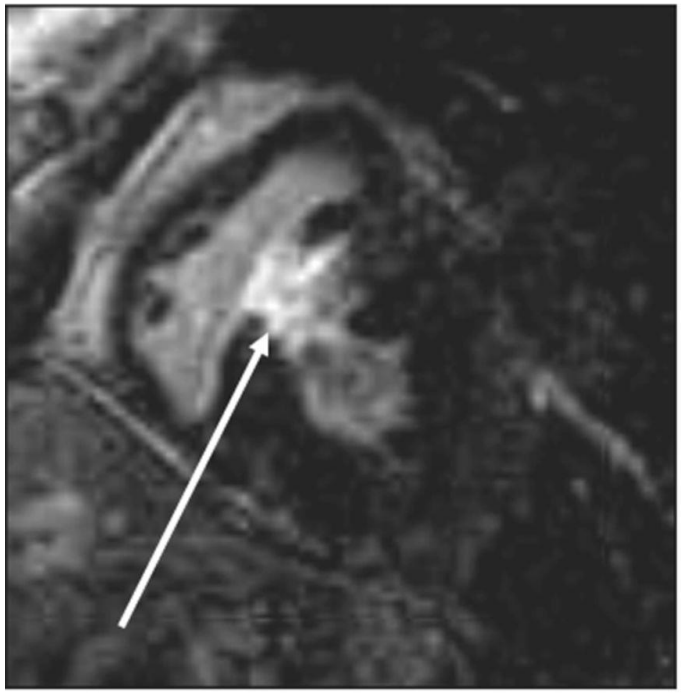
Barry J. Maron, and Rick A. Nishimura JCHF 2014;2:637-640

Surgical Septal Myectomy

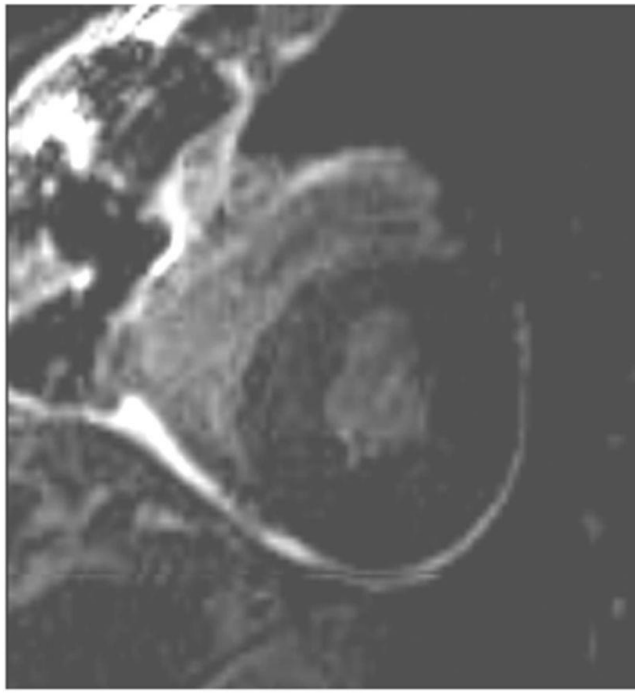


Nishimura RA et al. NEJM. 2004. 350(13):1320.

Post-ablation



Post-myectomy



Septal Scar

VS = 30%

LV = 10%

No Scar

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JACC Heart Failure

Operator experience

Patient shared decision making

Elderly

Comorbidities

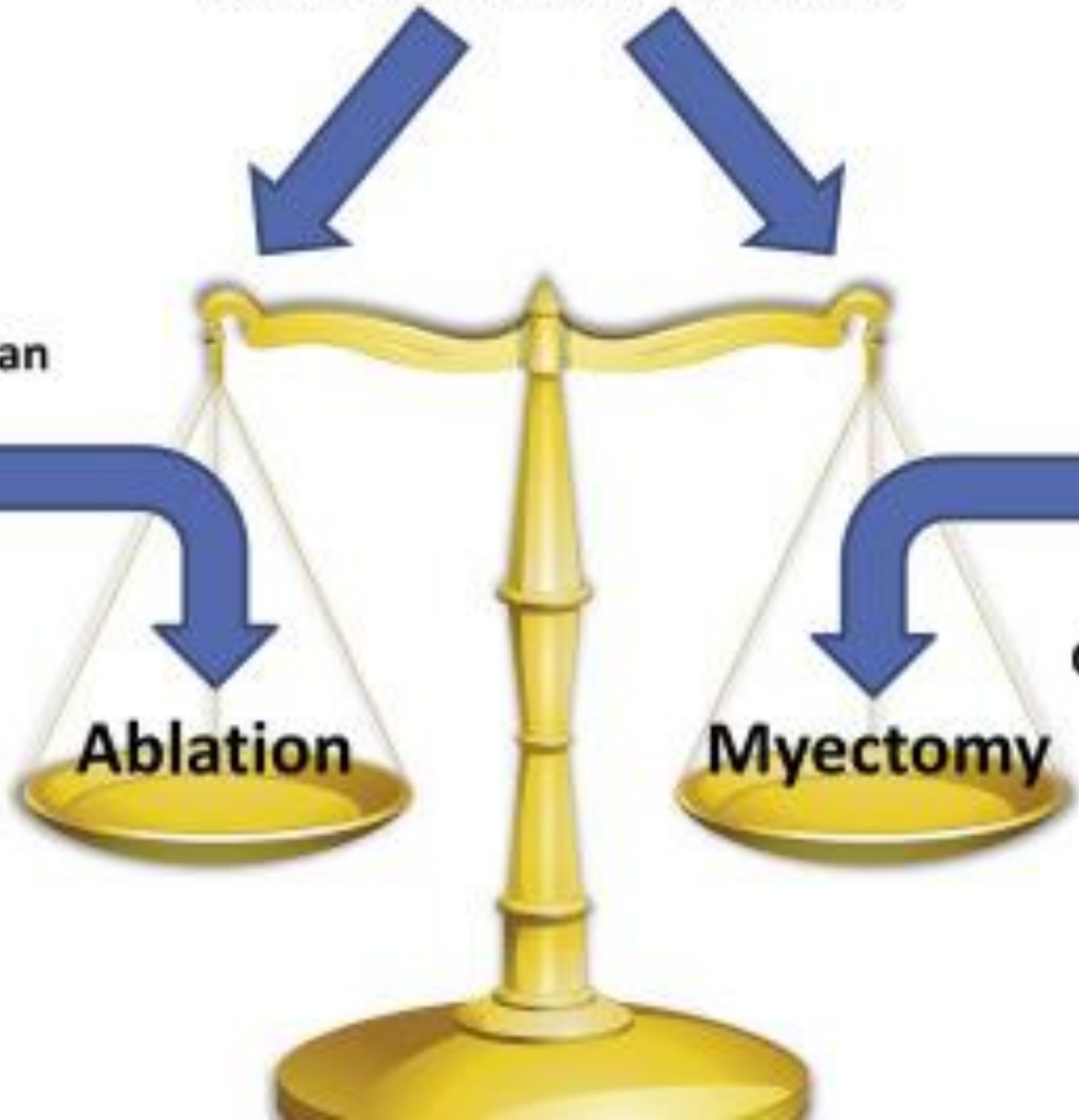
Limited expected lifespan

Sedentary

Lower gradient

Lesser thickness

Influence on SCD risk?



Younger

Healthy

Long expected lifespan

Active

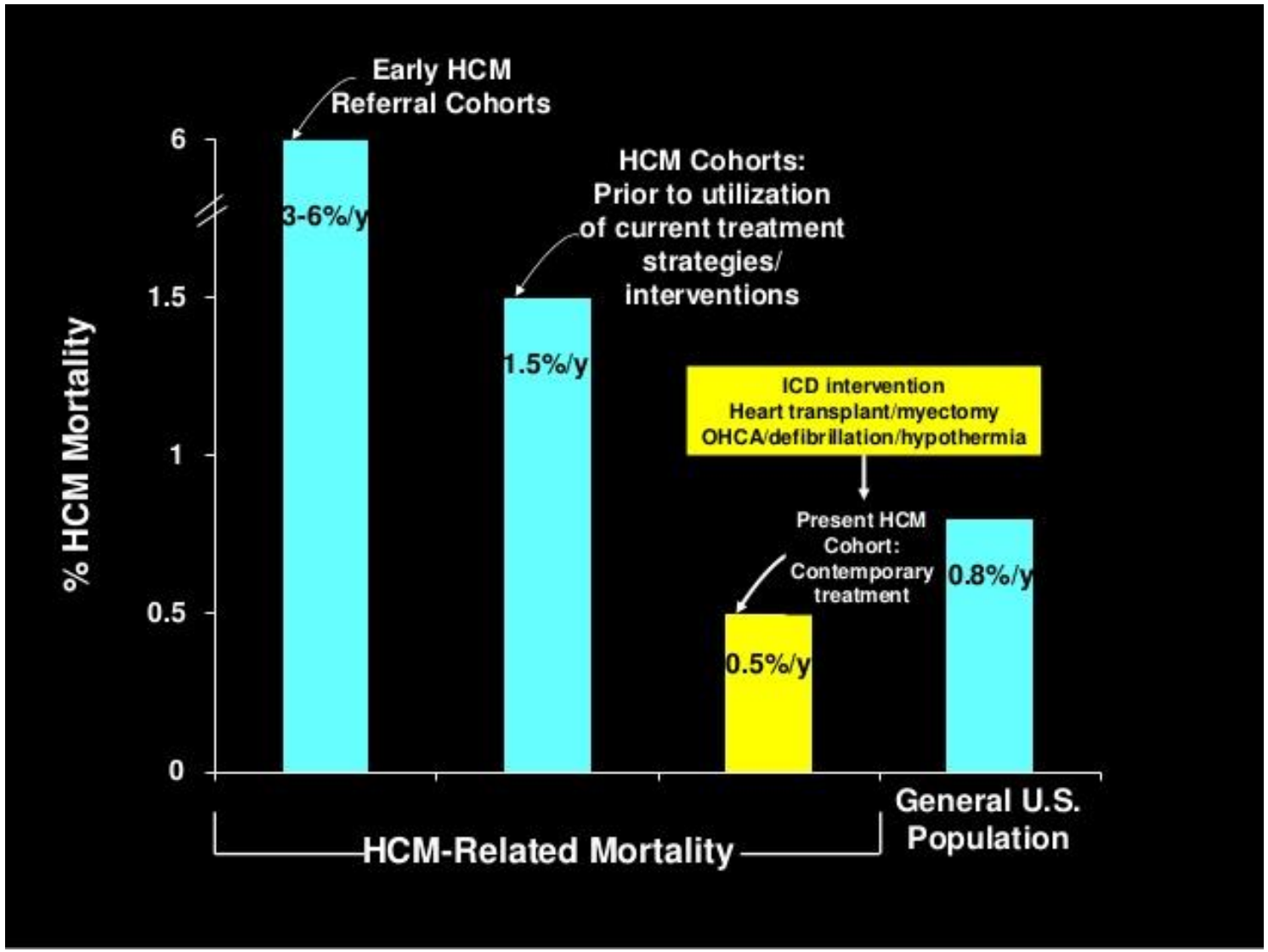
Higher gradient

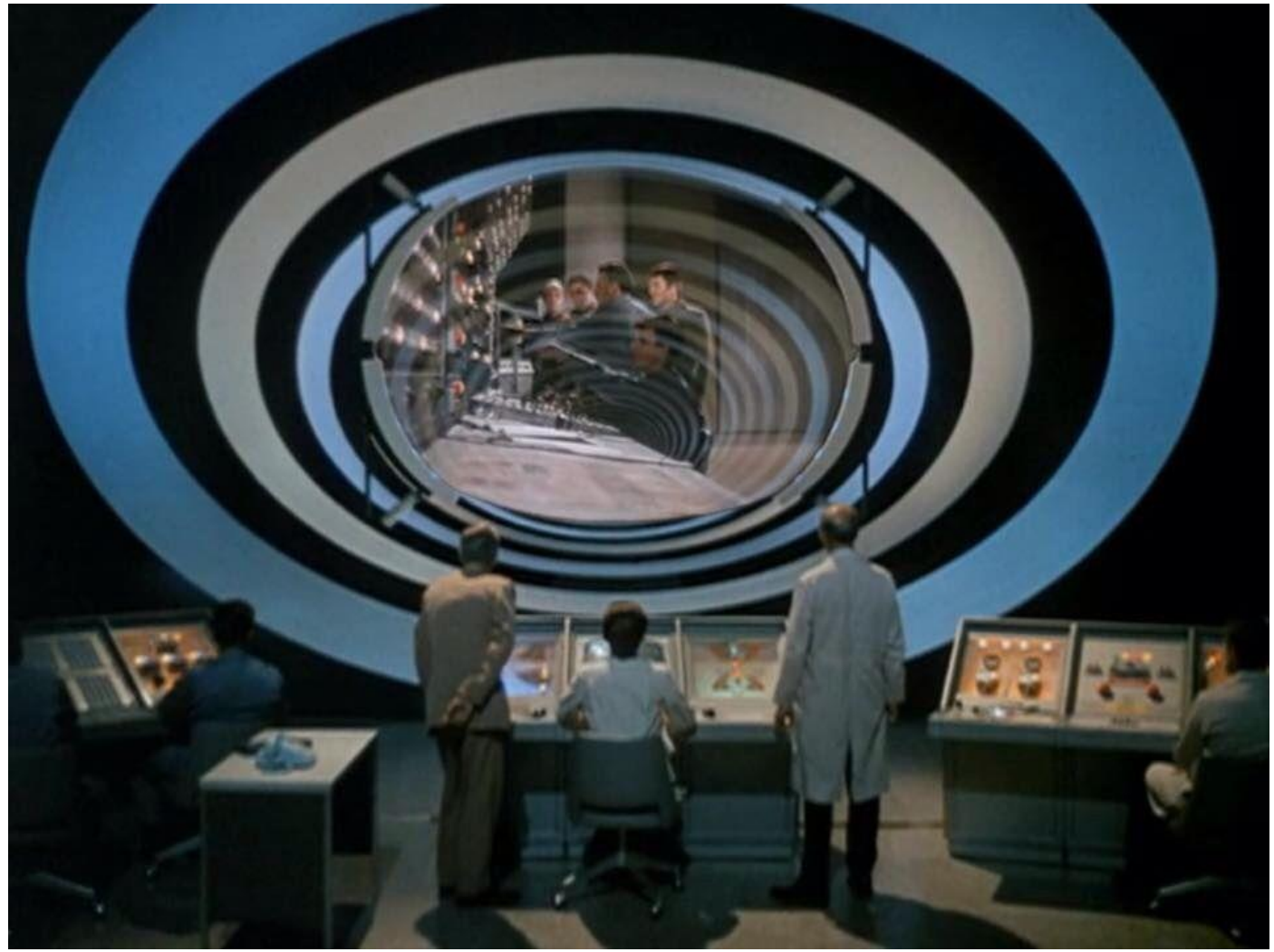
Greater thickness

Coexistent structural disease

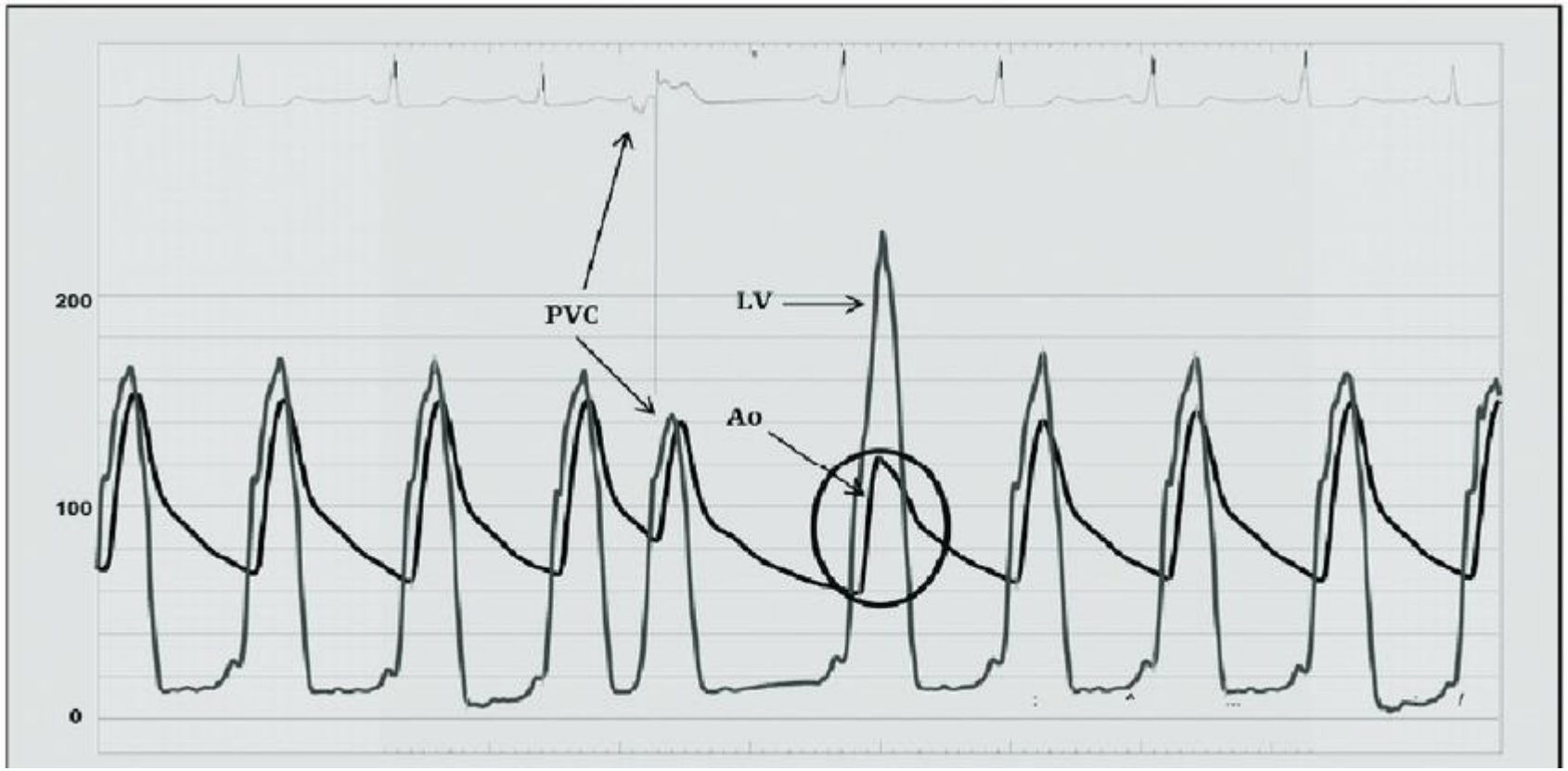
Sequential DDD-AV right ventricular pacing

- Hypotheses to explain the beneficial effects include:
- 1) negative inotropic effect and reduced hypercontractility of the LV
- 2) asynchronous septal activation and delayed septal thickening
- 3) limitation of abnormal mitral valve motion
- 4) interactions with LV filling
- 5) ventricular remodelling

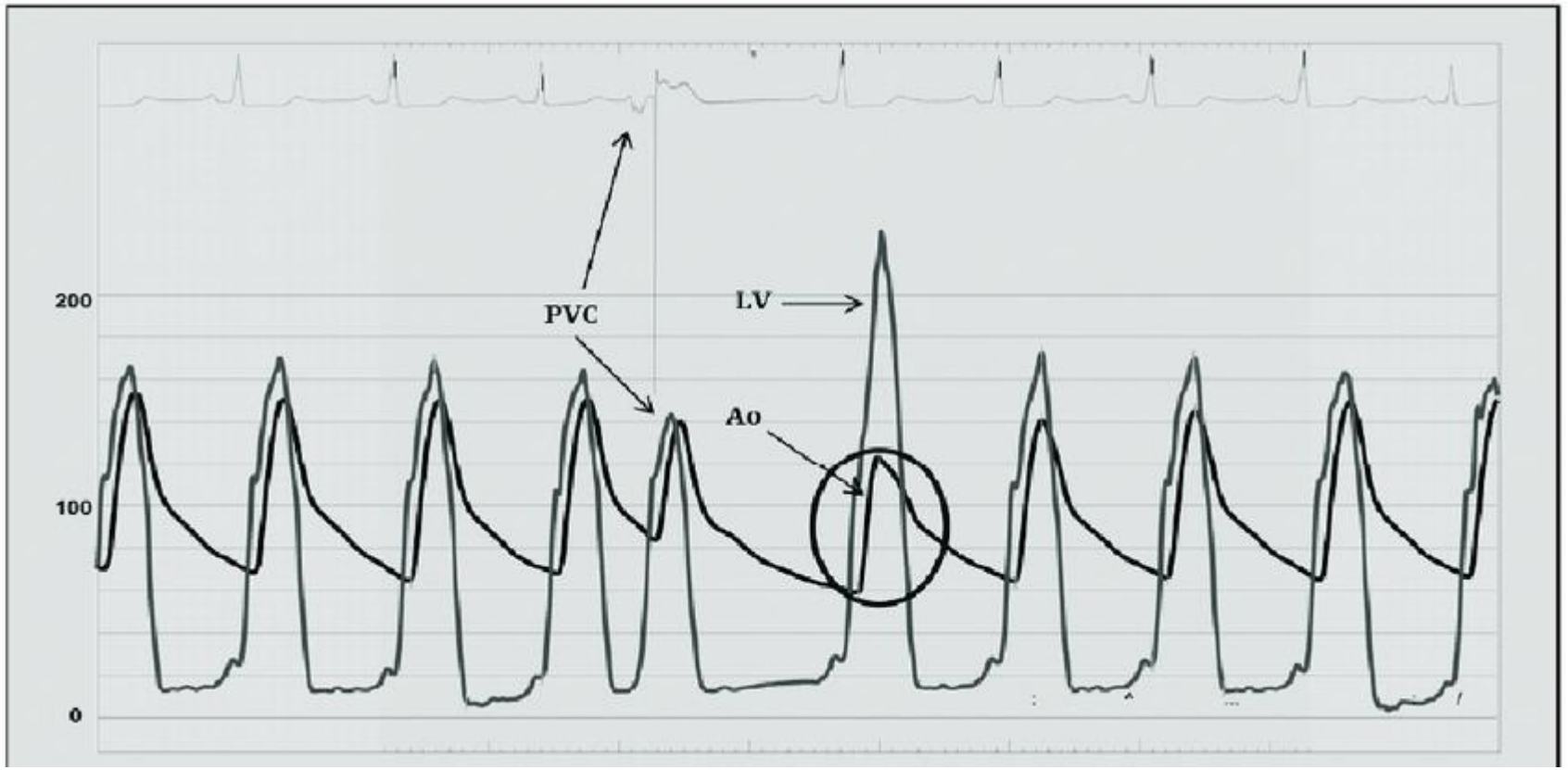

Early HCM
Referral Cohorts
HCM Cohorts:
Prior to utilization
of current treatment
strategies/
interventions
ICD intervention
Heart transplant/myectomy
OHCA/defibrillation/hypothermia
Present HCM
Cohort:
Contemporary
treatment
% HCM Mortality
6
1.5
1
0.5
0
3-6%/y
1.5%/y
0.5%/y
0.8%/y
HCM-Related Mortality
General U.S.
Population



?


200
100
0
PVC
LV
Ao

The Brockenbrough-Braunwald-Morrow sign

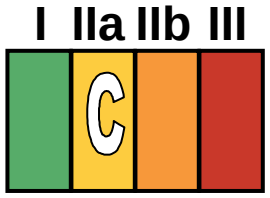


Management of HCM

Asymptomatic Patients

Asymptomatic Patients

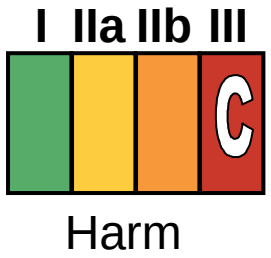
For patients with HCM, it is recommended that comorbidities that may contribute to cardiovascular disease (e.g., hypertension ,diabetes, hyperlipidemia, obesity) be treated in compliance with relevant existing guidelines.



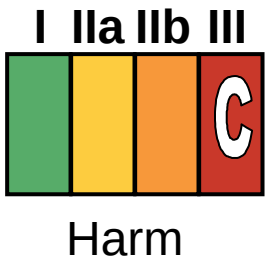
Low-intensity aerobic exercise is reasonable as part of a healthy lifestyle for patients with HCM.

The usefulness of beta blockade and calcium channel blockers to alter clinical outcome is not well established for the management of asymptomatic patients with HCM with or without obstruction.

Asymptomatic Patients



Septal reduction therapy should not be performed for asymptomatic adult and pediatric patients with HCM with normal effort tolerance regardless of the severity of obstruction.

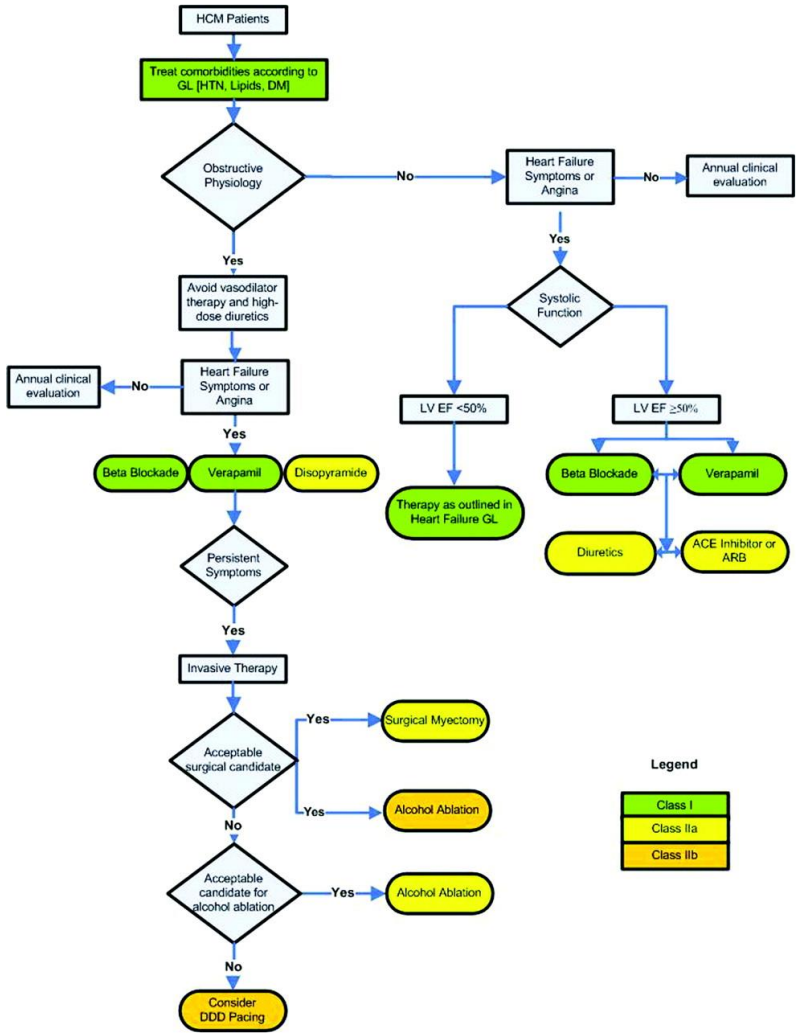


In patients with HCM with resting or provocable outflow tract obstruction, regardless of symptom status, pure vasodilators and high-dose diuretics are potentially harmful.

Management of HCM

Symptomatic Patients

Treatment algorithm.

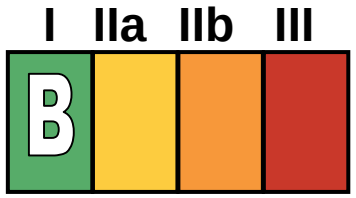


Writing Committee Members et al. Circulation. 2011;124:e783-e831

American Heart Association.

מר שמשון מועמד לניתוח כריתת כיס מרה בהרדמה מלאה- המלצות?

Pharmacologic Management



Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration.

Pharmacologic Management

Harm

The use of disopyramide alone without beta blockers or verapamil is potentially harmful in the treatment of symptoms (angina or dyspnea) in patients with HCM with AF because disopyramide may enhance atrioventricular conduction and increase the ventricular rate during episodes of AF.

Harm

Dopamine, dobutamine, norepinephrine, and other intravenous positive inotropic drugs are potentially harmful for the treatment of acute hypotension in patients with obstructive HCM.

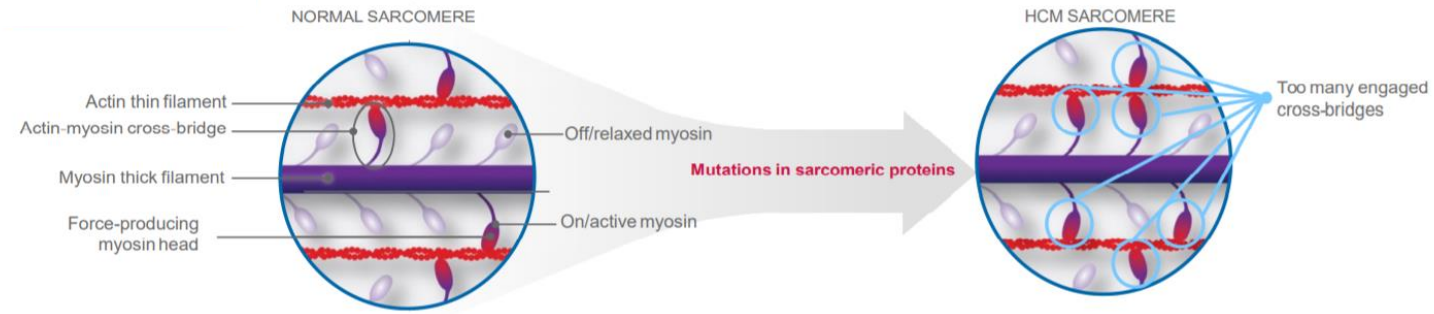
האם קיימים טיפולים חדשים
לטיפול ב-
HOCM?

האיגוד הקרדיולוגי בישראל
ISRAEL HEART SOCIETY
בשיתוף
עמותה לקרדיולוגיה בישראל (ע"ר)
ISRAEL CARDIOLOGY ASSOCIATION

כנס סיכום
HCM EXPLORER ESC 2020

Background

- **Hypertrophic Cardiomyopathy**= enhanced cardiac actin–myosin interactions =hypercontractility, diastolic abnormalities, and dynamic left ventricular outflow tract (LVOT) obstruction
- **Mavacamten** = a first-in-class, selective inhibitor of cardiac myosin ATPase that reduces actin–myosin cross-bridge formation reducing contractility and improving myocardial energetics



האיגוד הקרדיולוגי בישראל
ISRAEL HEART SOCIETY
בשיתוף
עמותה לקרדיולוגיה בישראל (ע"ר)
ISRAEL CARDIOLOGY ASSOCIATION

HCM EXPLORER ESC 2020 כנס סיכום

Background

- **PIONEER-HCM** study - phase 2, open-label mavacamten was well tolerated and significantly reduced post-exercise LVOT gradients in HOCM
- **EXPLORER-HCM** -to assess the efficacy and safety of mavacamten for targeted medical treatment of obstructive HCM

Methods

- 68 clinical cardiovascular centers in 13 countries
- Once-daily orally administered mavacamten (starting dose 5 mg) or placebo for 30 weeks (end of treatment)
- **Inclusion criteria**: age ≥18 years, with obstructive HCM, peak LVOT gradient at least 50 mmHg at rest, after Valsalva or exercise; LVEF at least 55%; NYHA class II–III
- **Exclusion criteria:** syncope or sustained ventricular tachyarrhythmia with exercise within 6 months before screening; QTc > 500 ms; PAF on screening ecg and persistent or permanent atrial fibrillation not on anticoagulation for 4 weeks or more

האיגוד הקרדיולוגי בישראל
ISRAEL HEART SOCIETY
בשיתוף
עמותה לקרדיולוגיה בישראל (ע"ר)
ISRAEL CARDIOLOGY ASSOCIATION

HCM EXPLORER ESC 2020 כנס סיכום

- **<u>Conclusion</u>: mavacamten treatment improved functional capacity, LVOT gradient, symptoms, and key aspects of health status in patient with HOCM**

Do I need Defibrillator?

Mortality in HCM

Studied 744 consecutive patients from Tuscany and Midwest
HCM related deaths in 86 (12%) over mean follow up of 8 years

Mode of Death	Percent	Mean age
Sudden Death (only 16% during mod-severe exercise)	51%	45
CHF	36%	56
CVA (91% hadAF) (64% had LVOTO)	13%	73

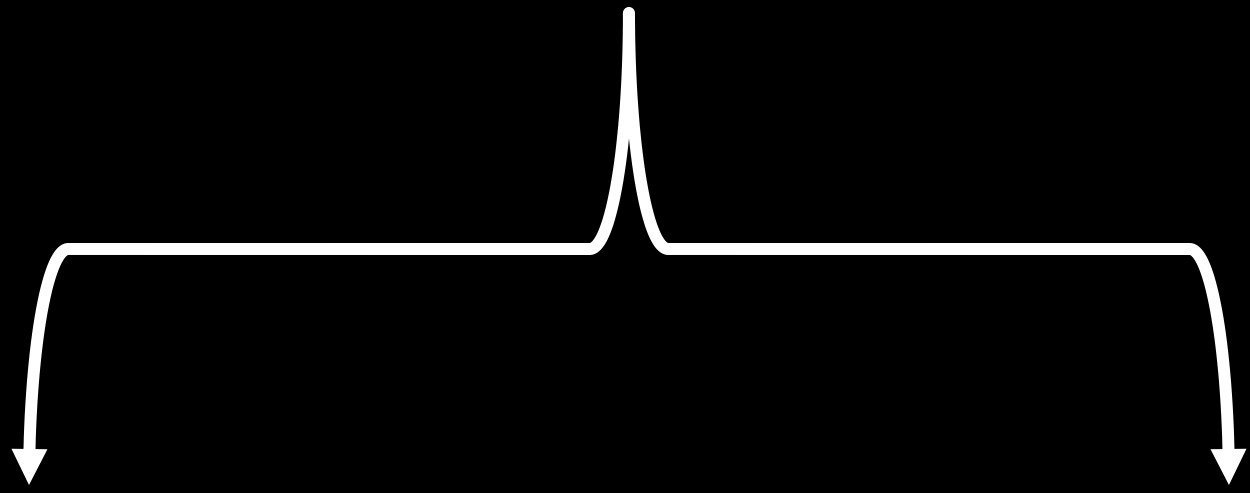
Maron et al Circ 2000

- Sudden Death has been the most visible and feared consequence of HCM for both physicians and patients

- For 20 years there has been a way to actually prevent these deaths…ie., prophylactic ICD

- Now, the controversy that has emerged is the best way to identify patients who deserve ICD

Strategies for Identification of High-Risk HCM Patients



ACC/AHA
Individual
Risk Factors

ESC
Risk Score

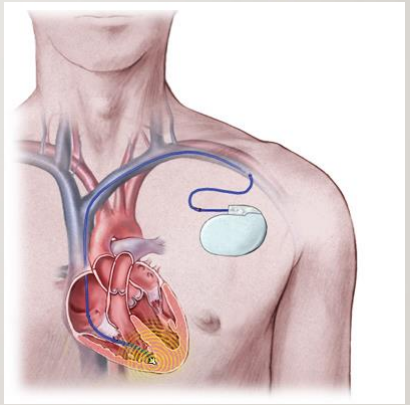
Risk Factors for Sudden Death: ICD Criteria

Primary Indications For ICD

Major Risk Factors

Minor Risk Factors

Likely Risk Factors



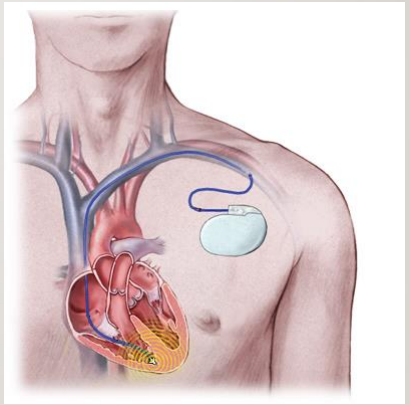
Risk Factors for Sudden Death: ICD Criteria

Primary Indications For ICD

- Aborted sudden death
- Sustained VT

Major Risk Factors

- Septum 30mm or greater
- First degree family member SD
- Syncope (non hemodynamic)



Minor Risk Factors

- Abn BP response to exercise
- SD in non first degree relative?
- Non sustained VT on Holter
- Septum 25-29mm?

Likely Risk Factors

- Mod or > delayed enhancement
- LVOT obstruction?
- Abnormal LV ejection fraction
- Apical LV aneurysm

- 47 y old male with HOCM
- NYHA class II
- Treatment?
- AICD?

ECHO

- EF=65%
- IVS-33 mm; PW-15mm
- LVOT gradient:

Rest- 48mmHg;

Post valsalva- 80mmHg

LA- 47mm

- SAM with mod MR

IVS- 33 mm

Family history- yes

Syncope- 2 y ago

Holter- NSR 55-110/MIN; 1500 VPBS

; 5 COUPLETS; 2 NSVT- 4 beats

Stress test- 9 min; STT changes;

CMR-LGE

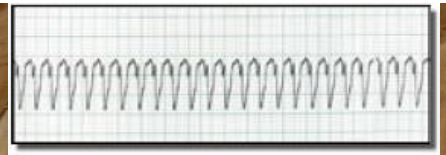
- IVS- 33 mm
- Family history- cousin with scd (age 45)
- Syncope- 2 y ago (m/p post micturation)
- Holter- NSR 55-110/MIN; 1500 VPBS

; 5 COUPLETS; 2 NSVT- 4 beats HR- 115

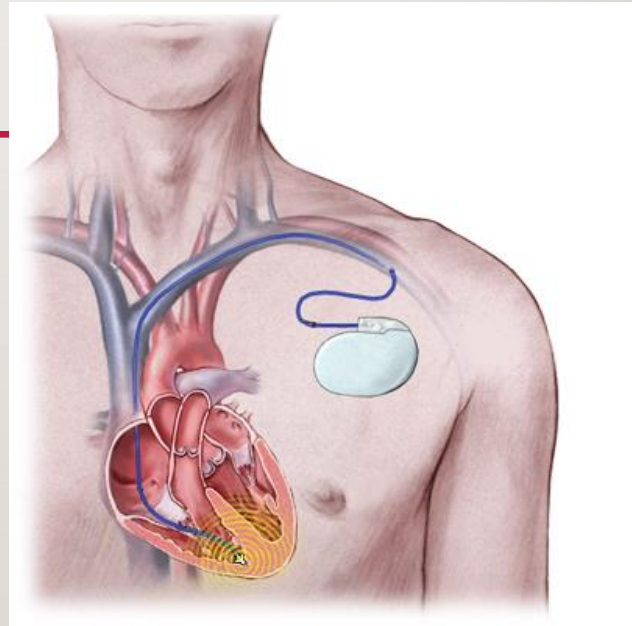
- Stress test- 9 min; STT changes;
  BP- 110/70-→ 130/70
- CMR-LGE – 15% of myocard

IMPLANTABLE DEFIBRILLATOR INDICATED BY GUIDELINES?

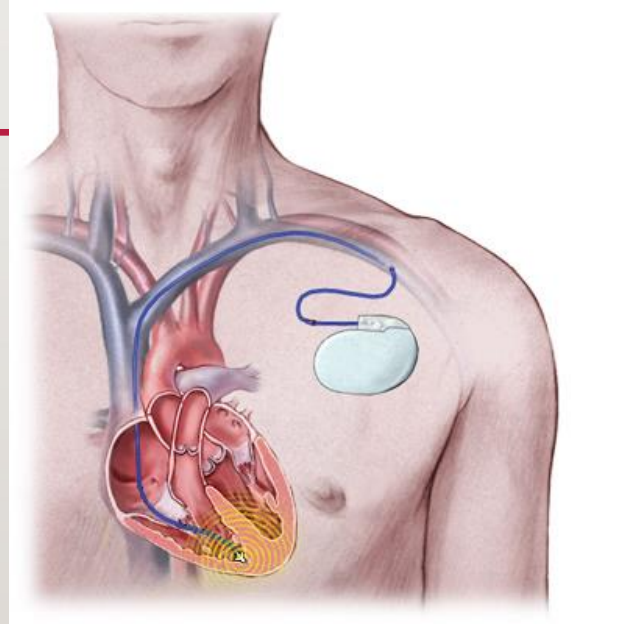
Risk Factor	Positive/Negative
Survived SCD, relevant VT	-
Family history of premature SD	+/-
Maximal wall thickness ≥ 30mm	+ (33)
Syncope	+ but no
Abnormal exercise BP response	-
Non sustained VT	+ but no
LVOT obstruction	+
LV systolic function < 45%	-
Late gadolinium enhancement	+ but …
Apical aneurysm	-



BENEFITS AND RISK OF ICD



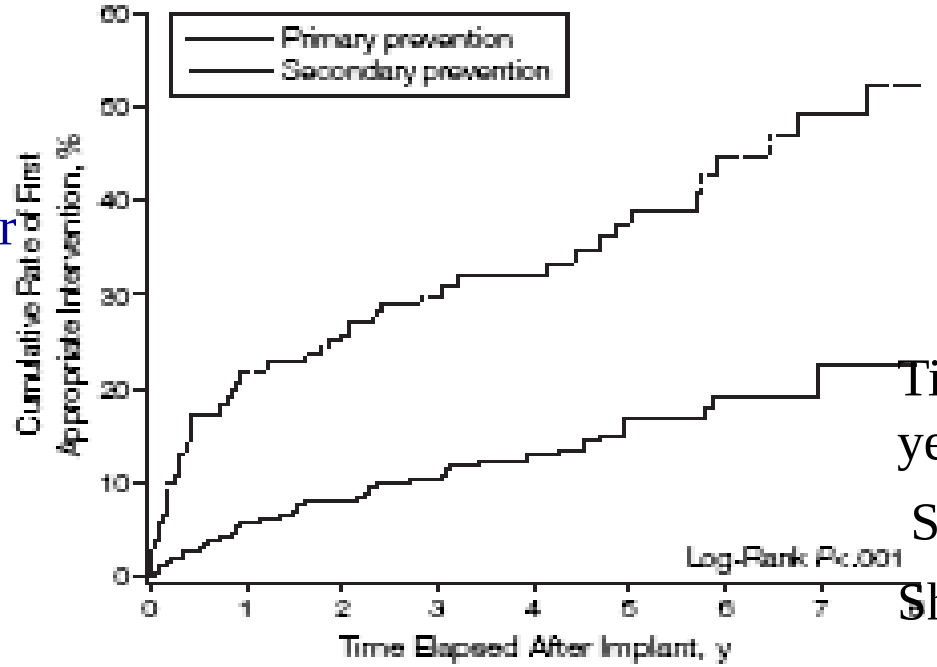
BENEFITS AND RISK OF ICD



- Rate of appropriate shocks
  - Primary prevention
  - Secondary prevention
- Complications
  - Inappropriate shocks
  - Early (Infection, hematoma, lead dislocation, pneumothorax)
  - Intermediate (Lead infection/endocarditis, lead changes, lead failure

RATE OF APPROPRIATE SHOCKS

Figure 1. Cumulative Rates for First Appropriate Implantable Defibrillator Intervention in Patients Who Had Received Devices for Primary (n=383) or Secondary Prevention (n=123)



No. at risk									
Primary prevention	383	332	256	205	148	96	70	43	28
Secondary prevention	123	95	65	70	51	39	28	18	16

Primary4%/yr

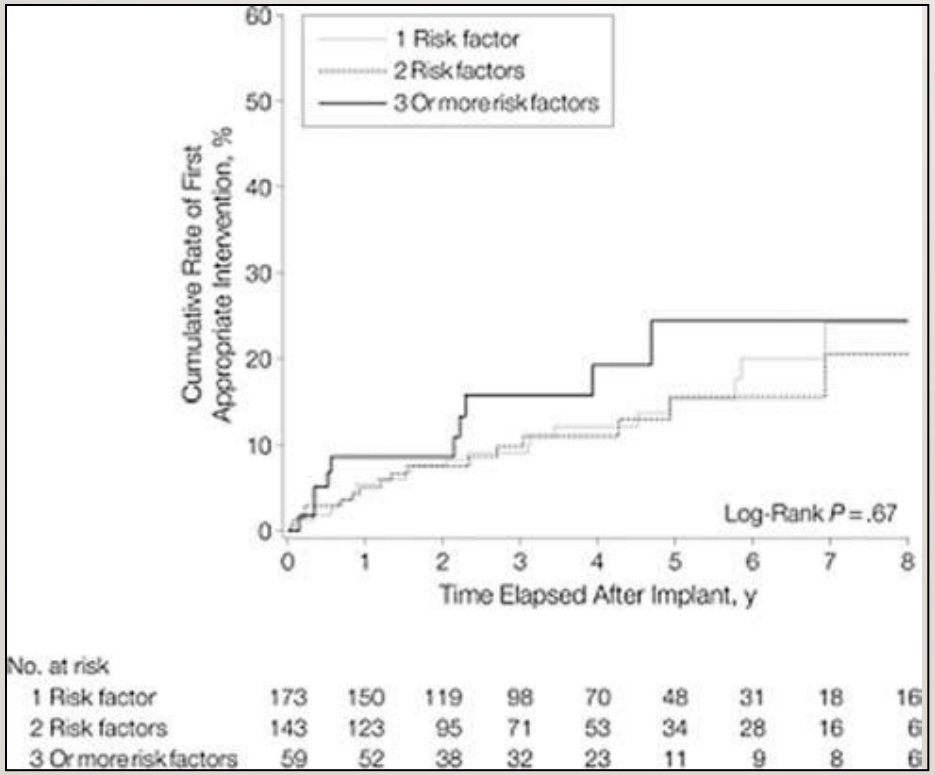
Secondary 11%/yr

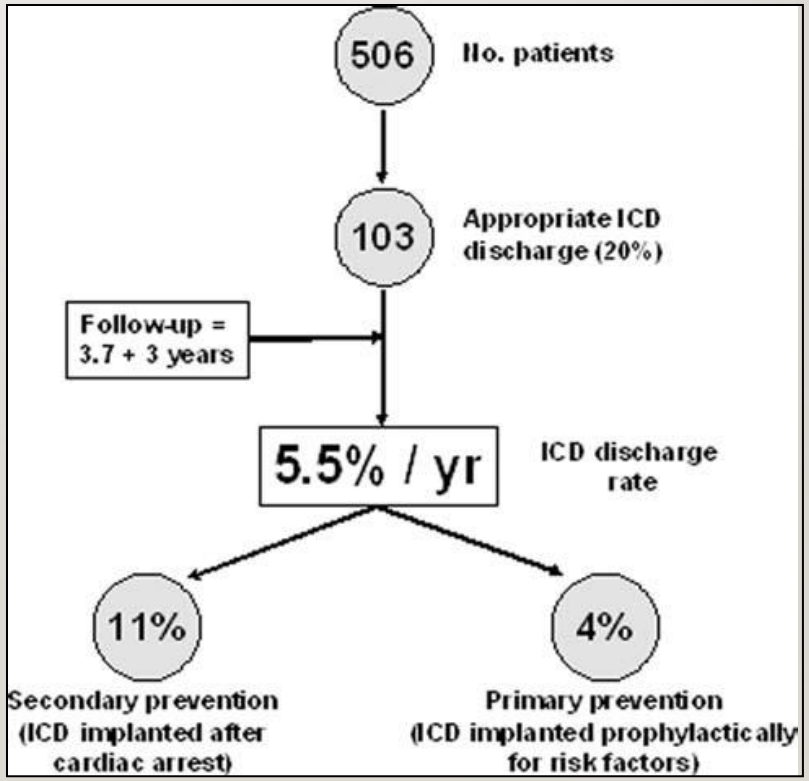
Time to first appropriate discharge was up to 10 years.

Shocks occurred 5-10yrs post implant in 16 pts

Shocks independent of # of risk factors

Maron et al JAMA 2007





JAMA. 2007;298(4): 405-12.

J Cardiovasc Electrophysiol 2008;19(10).

ICD in HCM: Risks

	Toronto General Hospital	Mayo Clinic	Warsaw	MCR 2000	MCR 2007
Number of Patients	61	181	104	128	506
Length of Follow-up	40 ± 27	59 ± 42	54 ± 31	38	44 ± 34
Inappropriate shocks	20 (33%)	42 (23%)	35 (34%)	32 (25%)	136 (27%)
Device complications	8 (13%)	Overall (23%) Infection (5%) Lead (13%)	Overall (17.3%) Infection (4.8%) Lead (12.5%)	18 (14%)	Overall (12%) Infection (3.8%) Lead (6.7%)

Beadle et al. 2010, Expert Rev Cardiovasc Ther

ICD IN HCM: PREDICTORS OF INAPPROPRIATE SHOCKS

INAPPROPRIATE SHOCKS

- **Age < 35yrs**
- **Hx of Atrial Fibrillation**
- ***B Blocker use and dual-chamber ICD had no impact***

(Lin* et al *Heart 2009)

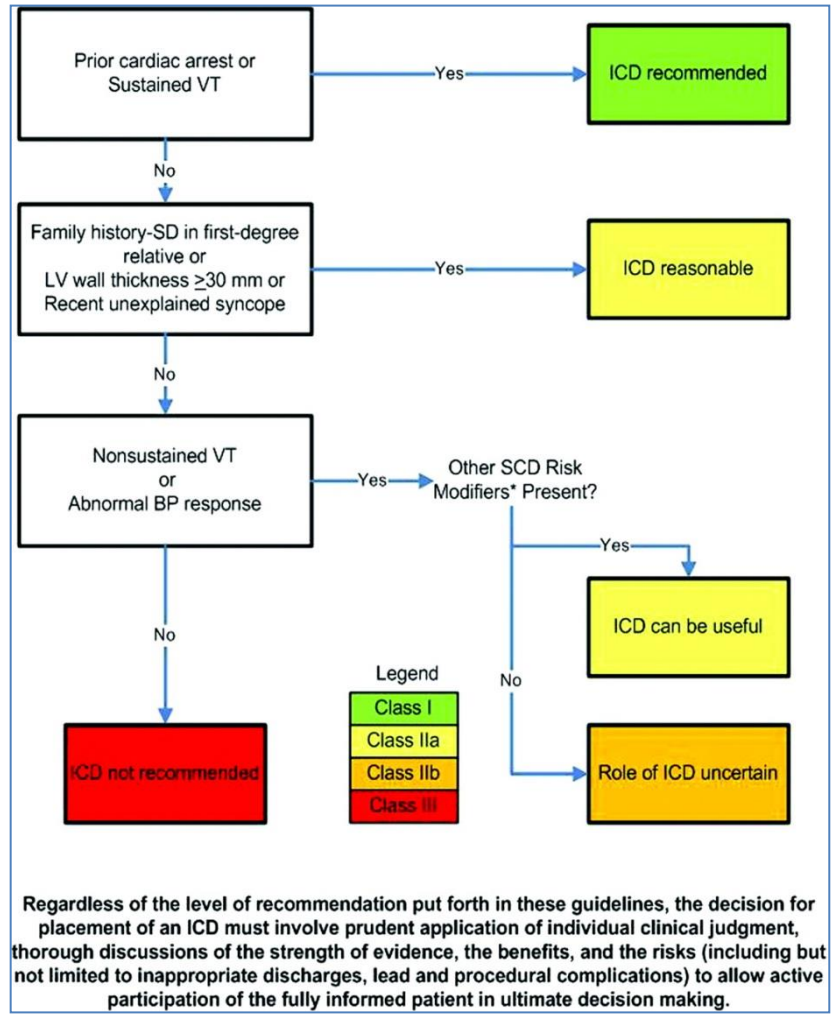
(Syska* et al *J Cardiovasc Elect 2010)

EUROPE

Variable	ESC guidelines	ACCF/AHA guidelines
Age (years)		
Maximum LV wall thickness (mm		
LVOT gradient (mmHg)		
LA size (mm)		
NSVT		
Family history of SCD		
Unexplained syncope		
Blood pressure response to exercise		
Risk modifiers (LGE on CMR, large-sized LV apical aneurysm)		

Variable	ESC guidelines	ACCF/AHA guidelines
Age (years)	Age at evaluation	Not incorporated into the risk stratification algorithm (notably, the guidelines address age <30 in patients with NSVT)
Maximum LV wall thickness (mm)	Used as a continuous variable. In the HCM risk-SCD, there was a non-linear relationship between the risk of SCD and maximum LV wall thickness. This is accounted for in the risk prediction model by the inclusion of a quadratic term for maximum LV wall thickness	Used as a binary variable where LV wall thickness >30 mm considered a major risk factor for SCD
LVOT gradient (mmHg)	The maximum gradient measured at rest or on Valsava, irrespective of concurrent medical therapy	Not incorporated into the risk stratification algorithm
LA size (mm)	LA diameter determined by 2D echocardiography or M-mode	Not incorporated into the risk stratification algorithm
NSVT	Binary variable (yes = 1, no = 0)	Minor risk factor, which constitutes an indication for an ICD in the presence of other SCD risk modifier
Family history of SCD	Binary variable (yes = 1, no = 0)	Major risk factor, which constitutes an indication for ICD as a sole risk factor
Unexplained syncope	Binary variable (yes = 1, no = 0), history of syncope irrespective of the time of occurrence	Recent unexplained syncope is a major risk factor, which constitutes an indication for an ICD as a sole risk factor
Blood pressure response to exercise	Not incorporated in the risk prediction model	Minor risk factor, which constitutes an indication for an ICD in the presence of other SCD risk modifier
Risk modifiers (LGE on CMR, large-sized LV apical aneurysm)	Not incorporated in the risk prediction model	Support ICD implantation in borderline cases

USA



Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

5-year risk of SCD using the HCM Risk-SCD model

Probability $_{\text{SCD at 5 years}}$ **= 1-0.998** $^{\exp(\text{Progostic index})}$

where Prognostic index = [0.15939858 x maximal wall thickness (mm)] – [0.00294271 x maximal wall thickness^2 (mm^2)] + [0.0259082 x left atrial diameter (mm)] + [0.00446131 x maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)] + [0.4583082 x family history SCD] + [0.82639195 x NSVT] + [0.71650361 x unexplained syncope] – [0.01799934 x age at clinical evaluation (years)].

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Prevention of sudden cardiac death

Recommendations	Class	Level
Avoidance of competitive sports is recommended in patients with HCM.	I	C
ICD implantation is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT causing syncope or haemodynamic compromise, and have a life expectancy of >1 year.	I	B
HCM Risk-SCD is recommended as a method of estimating risk of sudden death at 5 years in patients aged ≥16 years without a history of resuscitated VT/VF or spontaneous sustained VT causing syncope or haemodynamic compromise.	I	B
It is recommended that the 5-year risk of SCD be assessed at first evaluation and re-evaluated at 1–2 yearly intervals or whenever there is a change in clinical status.	I	B
ICD implantation should be considered in patients with an estimated 5-year risk of sudden death of ≥6% and a life expectancy of >1 year, following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status and psychological health.	IIa	B

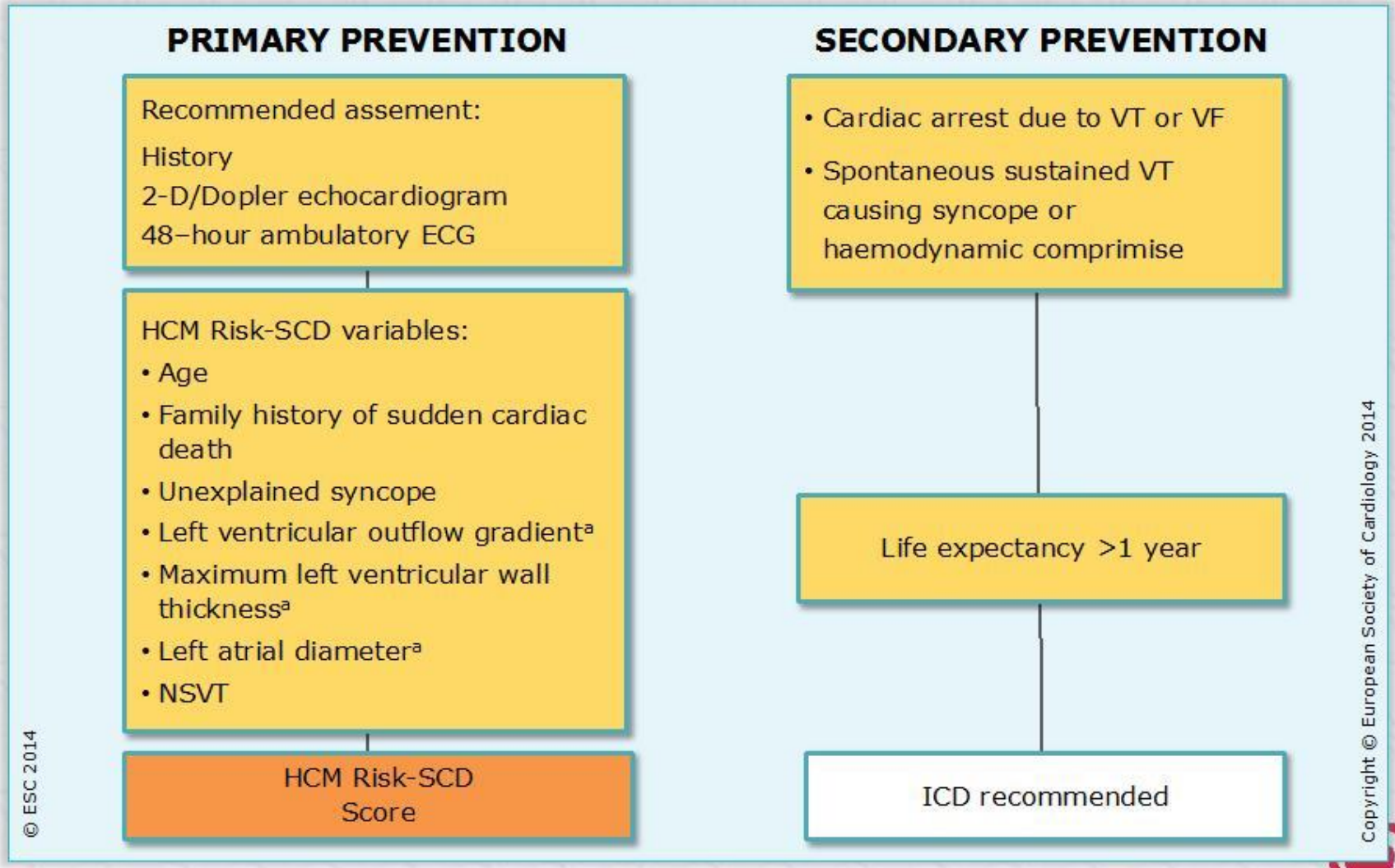
European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Prevention of sudden cardiac death *(Cont.)*

Recommendations	Class	Level
ICD implantation may be considered in individual patients with an estimated 5–year risk of SCD of between ≥4% and <6% and a life expectancy of >1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status and psychological health.	**IIb**	**B**
ICD implantation may be considered in individual patients with an estimated 5–year risk of SCD of <4% only when they have clinical features that are of proven prognostic importance, and when an assessment of the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status and psychological health suggests a net benefit from ICD therapy.	**IIb**	**B**
ICD implantation is not recommended in patients with an estimated 5–year risk of SCD of <4% and no other clinical features that are of proven prognostic importance.	**III**	**B**

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Flow chart for ICD implantation

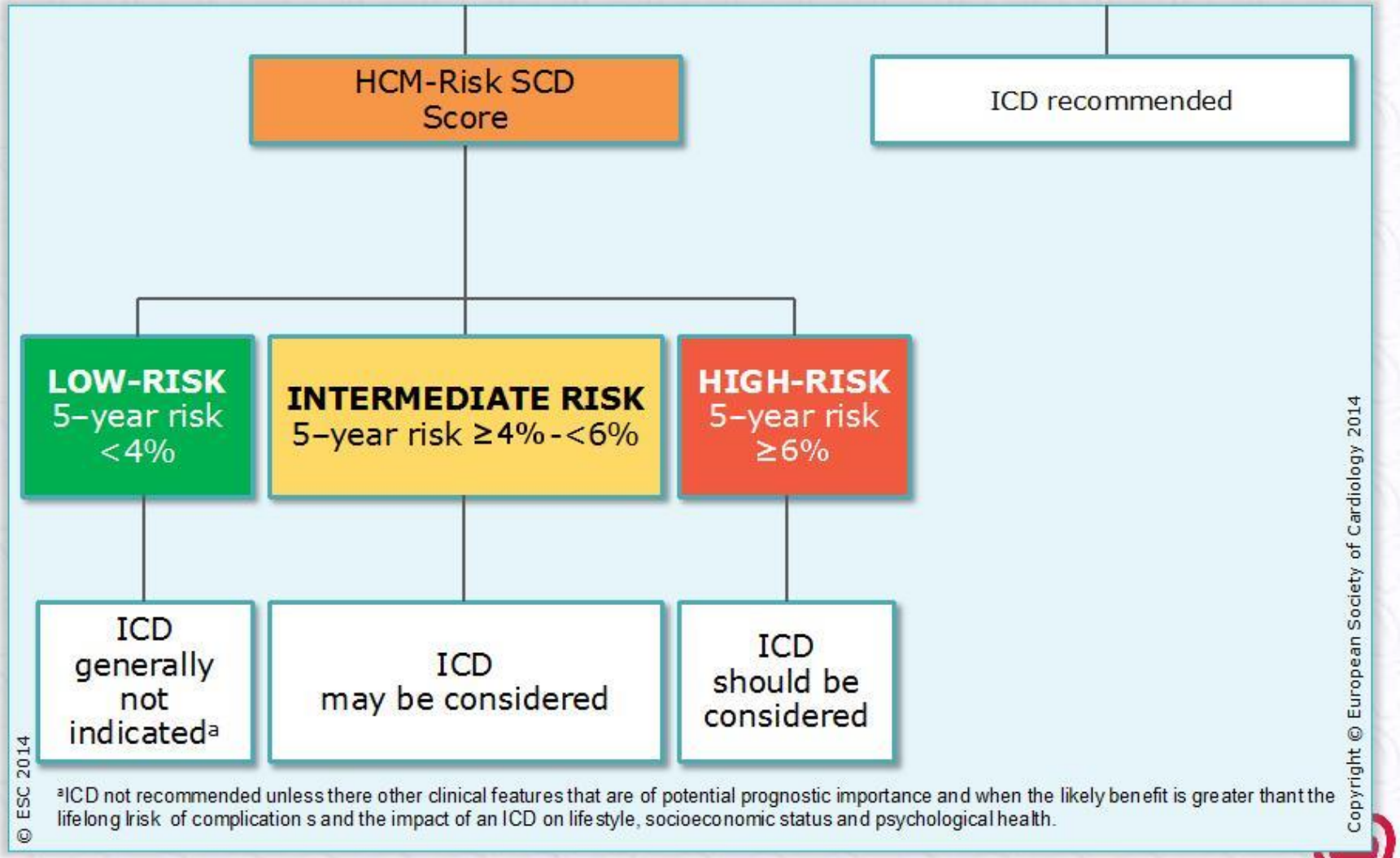


[a]Use absolute values for LVOT gradient, MLVWT and left atrial dimension.

www.escardio.org/guidelines European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

EUROPEAN SOCIETY OF CARDIOLOGY®

Flow chart for ICD implantation



European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

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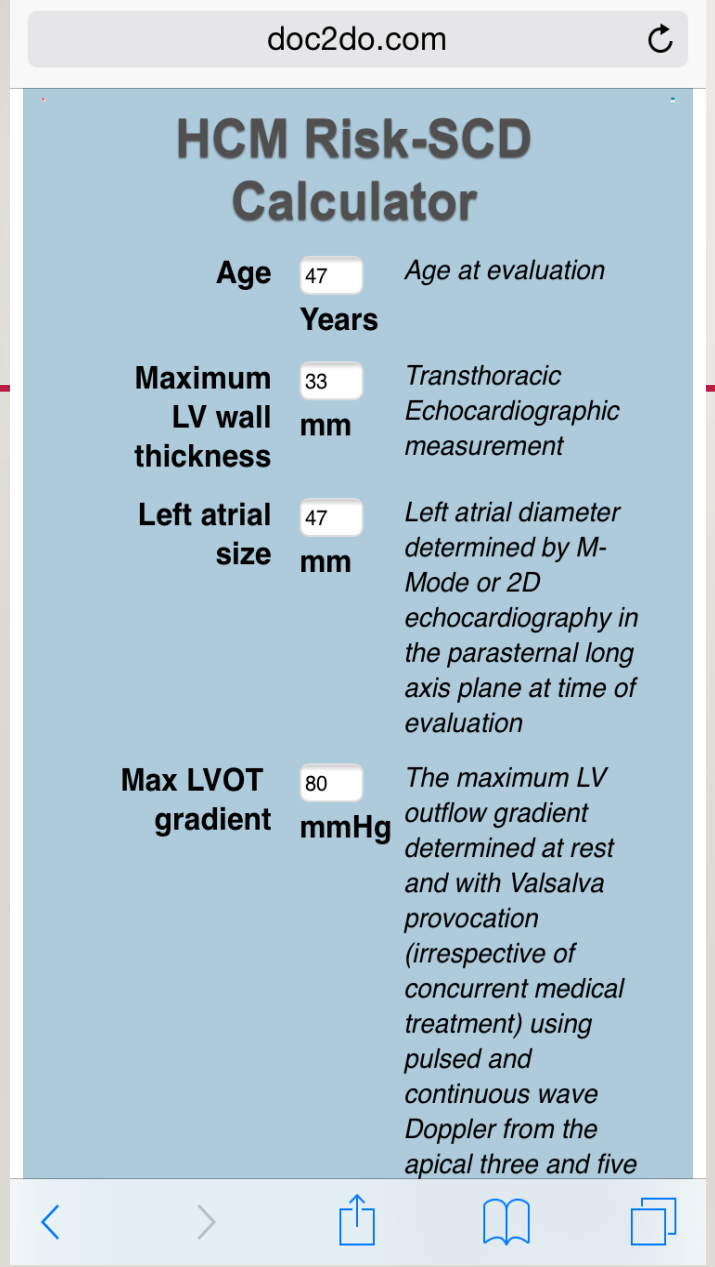
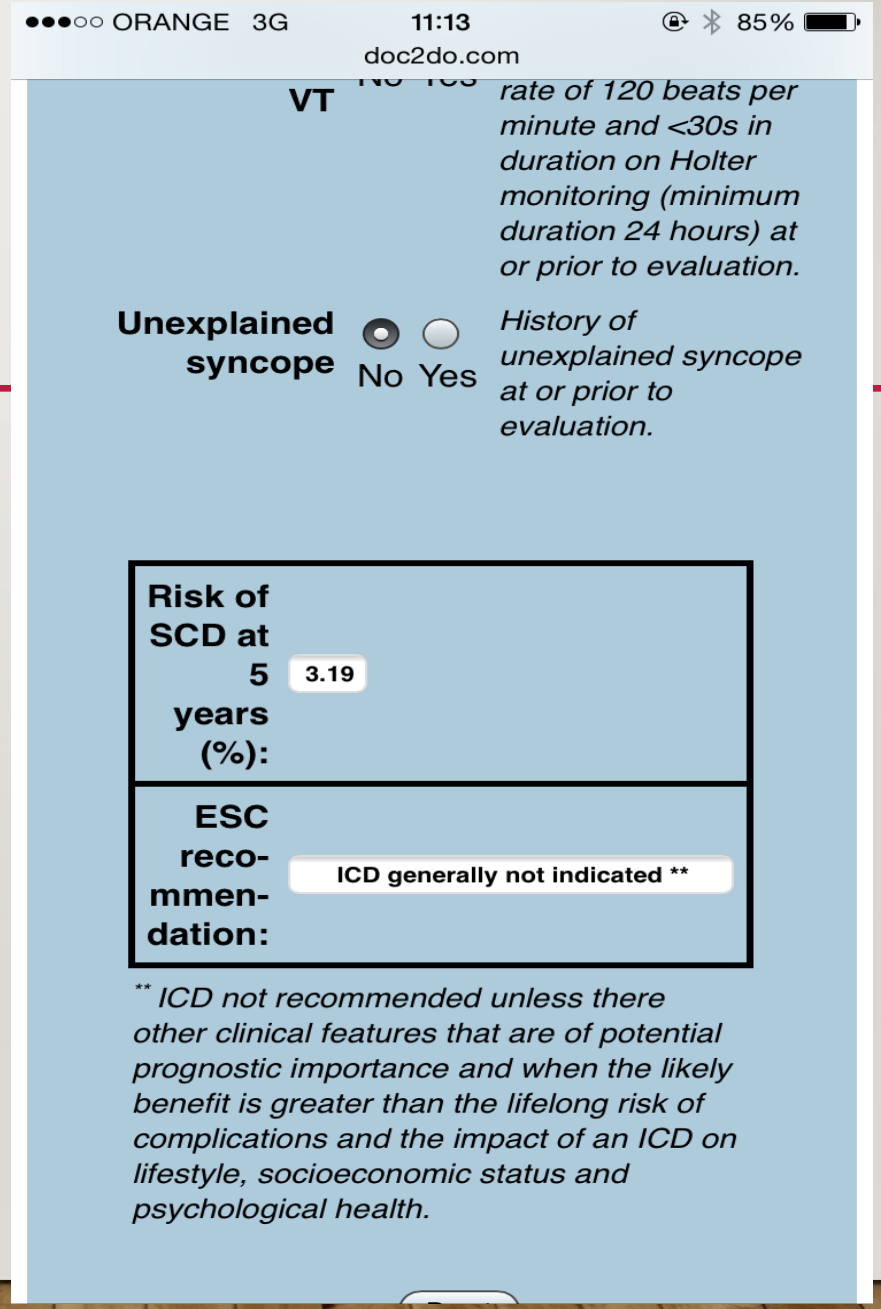
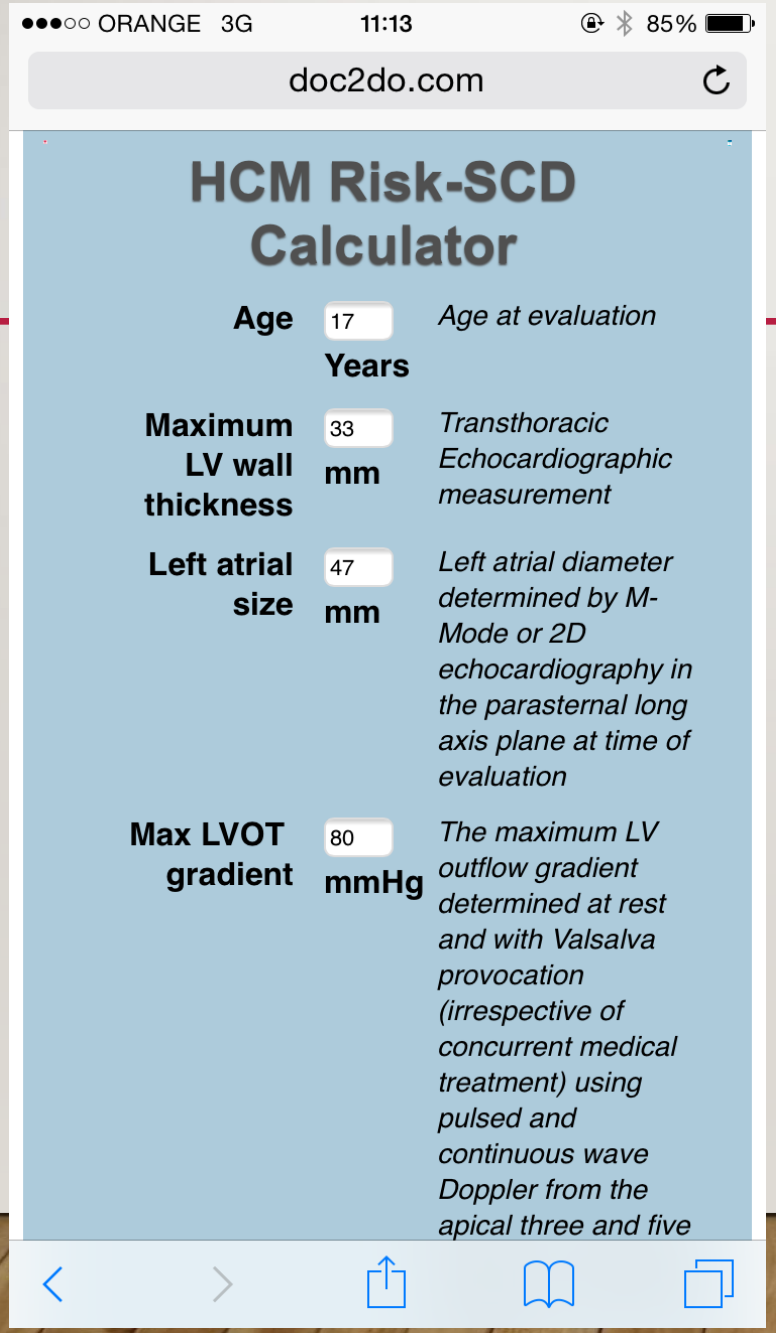

doc2do.com
HCM Risk-SCD Calculator
Age
47
Years
Age at evaluation
Maximum LV wall thickness
33
mm
Transthoracic Echocardiographic measurement
Left atrial size
47
mm
Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
Max LVOT gradient
80
mmHg
The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five


ORANGE 3G
11:13
85%
doc2do.com
VT
rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.
Unexplained syncope
No Yes
History of unexplained syncope at or prior to evaluation.
Risk of SCD at 5 years (%):
3.19
ESC recommendation:
ICD generally not indicated **
** ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.


●●●○○ ORANGE 3G
11:13
85%
doc2do.com
HCM Risk-SCD Calculator
Age
17
Years
Age at evaluation
Maximum LV wall thickness
33
mm
Transthoracic Echocardiographic measurement
Left atrial size
47
mm
Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
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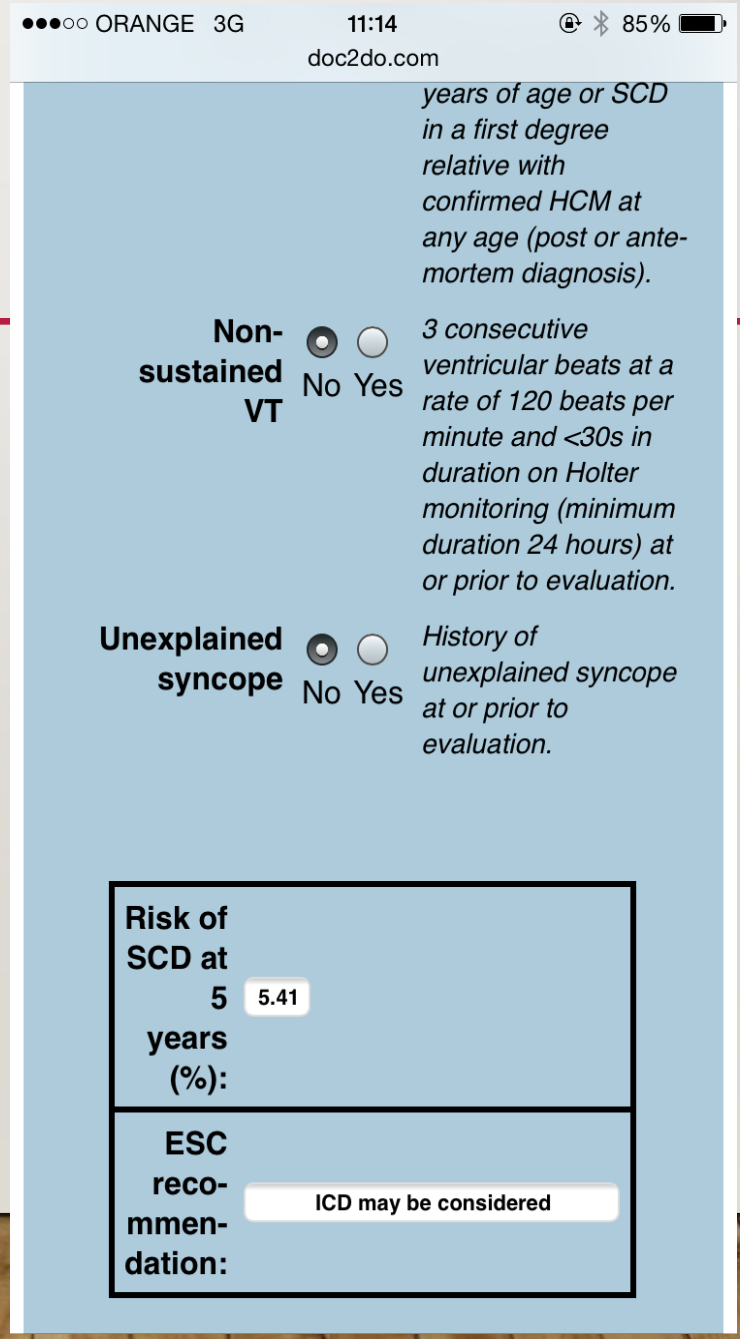

●●●○○ ORANGE 3G
11:14
85%
doc2do.com
years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).
Non-sustained VT
No Yes
3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.
Unexplained syncope
No Yes
History of unexplained syncope at or prior to evaluation.
Risk of SCD at 5 years (%):
5.41
ESC recommendation:
ICD may be considered

HCM Risk-SCD

- **HCM Risk-SCD** is a clinical risk prediction model that uses readily available clinical parameters to estimate the individualised probability of SCD at 5 years.
- The model was developed and validated in 3675 HCM patients and is an alternative approach to the 2011 ACCF/AHA and 2003 ACC/ESC guidelines on the management of patients with HCM.
- HCM Risk-SCD was peered reviewed and published in the European Heart Journal.

Eur Heart J. 2014 Aug 7;35(30):2010-20

HCM Risk-SCD

- The **2014 ESC Guidelines on the diagnosis and management of hypertrophic cardiomyopathy** have recommended HCM Risk-SCD as the preferred method of estimating the risk of sudden death in patients aged ≥16 years without a history of resuscitated VT/VF or spontaneous sustained VT causing syncope or haemodynamic compromise

An international external validation study of the 2014 ESC guideline on SCD prevention in HCM [EVIDENCE-HCM]

Dr Costas O'Mahony
Consultant Cardiologist, St. Bartholomew's Centre for Inherited Cardiovascular Disease & Honorary Senior Lecturer, University College London Centre for Heart Muscle Disease United Kingdom

Results

- Overall, the analysis showed that the tool could distinguish well between high- and low-risk patients, with good agreement between what it predicted and their actual 5-year SCD rates.

- Specifically, patients classified as low risk (predicted to have a SCD incidence of <4% at 5 years) , had a 5-year SCD incidence of 1.4%, while those classified as high risk (predicted to have a SCD incidence ≥6% at 5 years) had an incidence of 8.9%

Conclusion

- “We calculated that for every 13 high-risk patients who receive an ICD as recommended by ESC guidelines, one patient could potentially be saved from SCD,”
- “The study also shows that the HCM Risk-SCD calculator can be used to avoid unnecessary ICD implants in low risk patients, supporting the 2014 ESC recommendation not to implant ICDs in these individuals.”


CRITICISM
IMAGERY
PUBLIC
POLITICS
PLAN
AUTHOR
TRIBE
REMARK
THINK
APPRAISAL
KNOWLEDGE

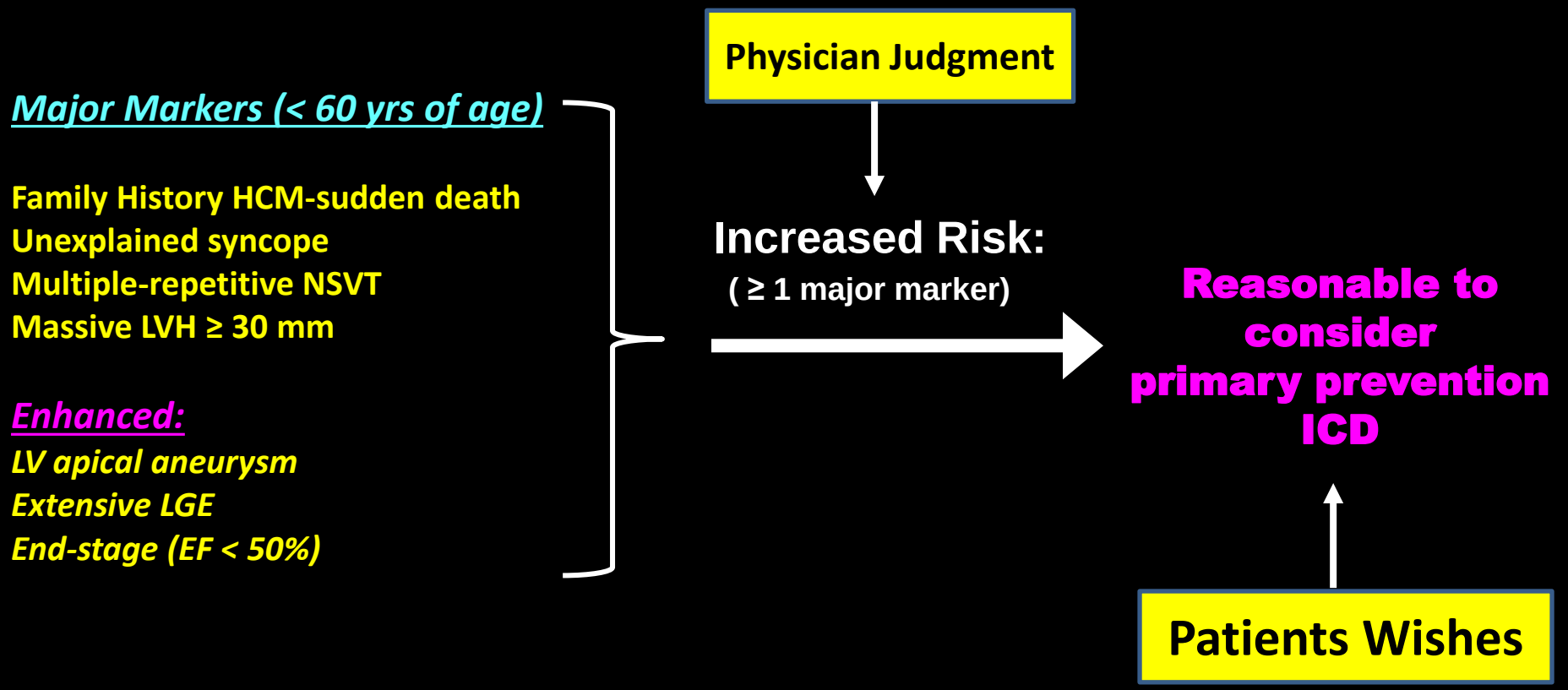
MISSING FROM ESC RISK MODEL:

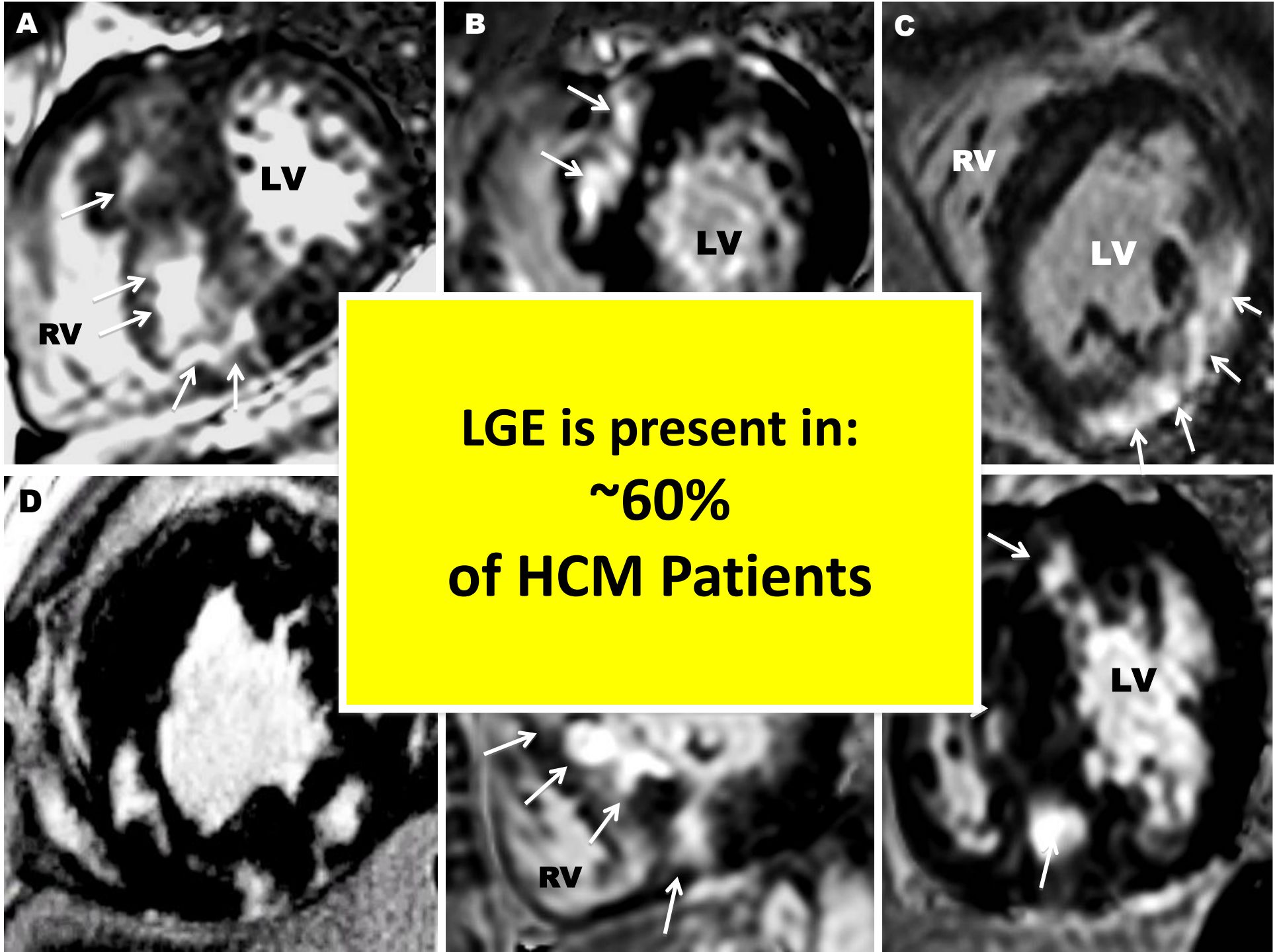
- CMR - LGE
- LV apical aneurysm
- End stage HCM(EF <50%)

QUESTIONABLE ADDITIONS TO ESC RISK MODEL:

- Left atrial size
- LV outflow gradient
- Remote syncope

ACC/AHA Individual Risk Markers




A
LV
RV
B
LV
C
RV
LV
D
RV
LV
LGE is present in:
~60%
of HCM Patients

Ischemic

A **Subendocardial Infarct**

B **Transmural Infarct**

Nonischemic

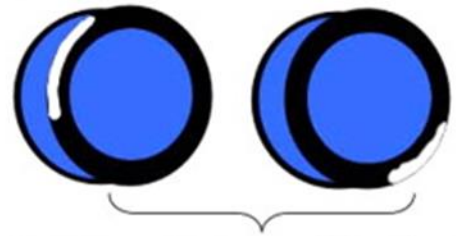
A **Mid-wall HE**

- Idiopathic Dilated Cardiomyopathy
- Myocarditis

- Hypertrophic Cardiomyopathy
- Right ventricular pressure overload (e.g. congenital heart disease, pulmonary HTN)

- Sarcoidosis
- Myocarditis
- Anderson-Fabry
- Chagas Disease

B **Epicardial HE**

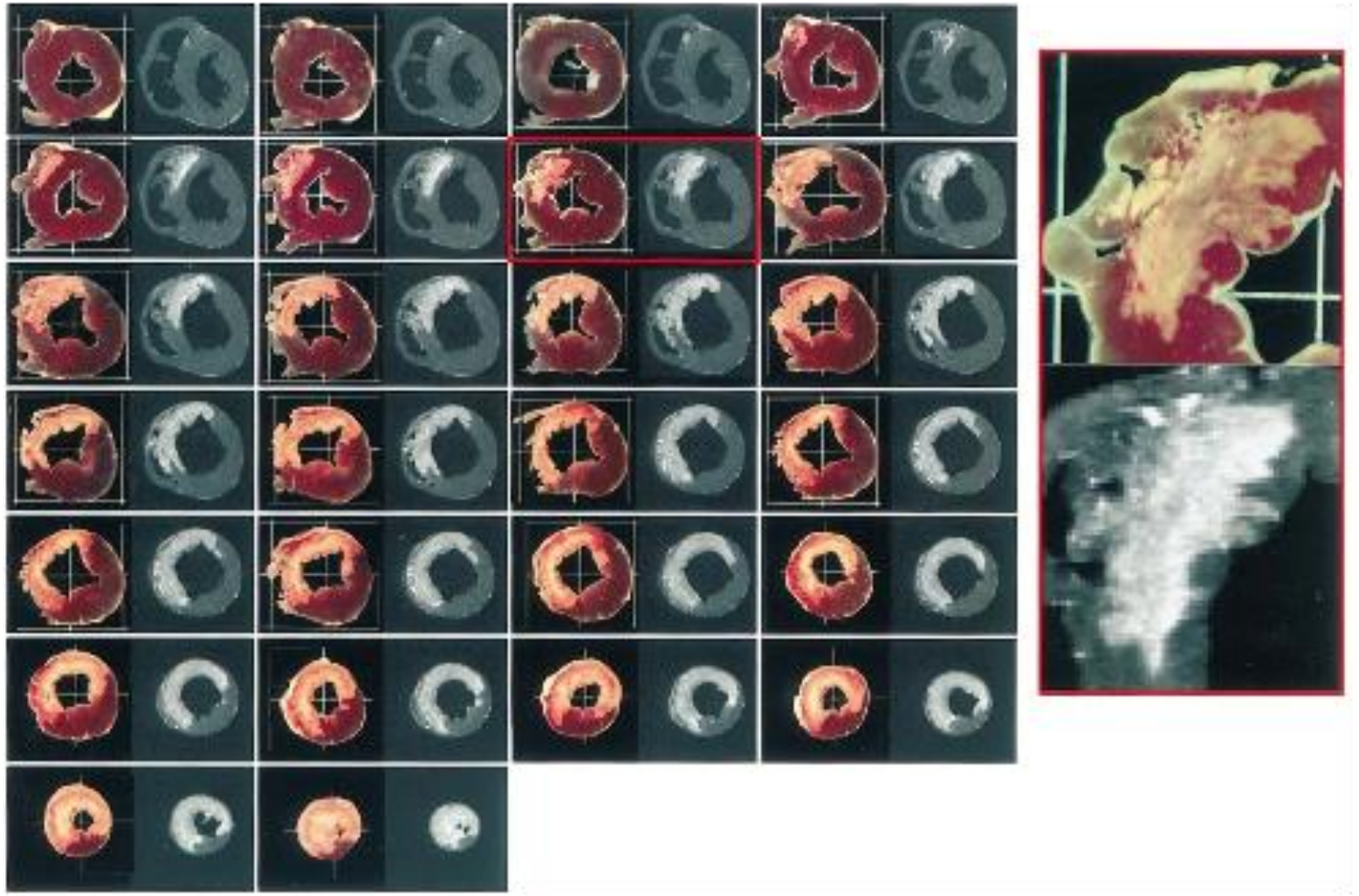


- Sarcoidosis, Myocarditis, Anderson-Fabry, Chagas Disease

C **Global Endocardial HE**

- Amyloidosis, Systemic Sclerosis, Post cardiac transplantation

Role of Cardiac MRI:Late Gadolinium Enhancement (LGE)

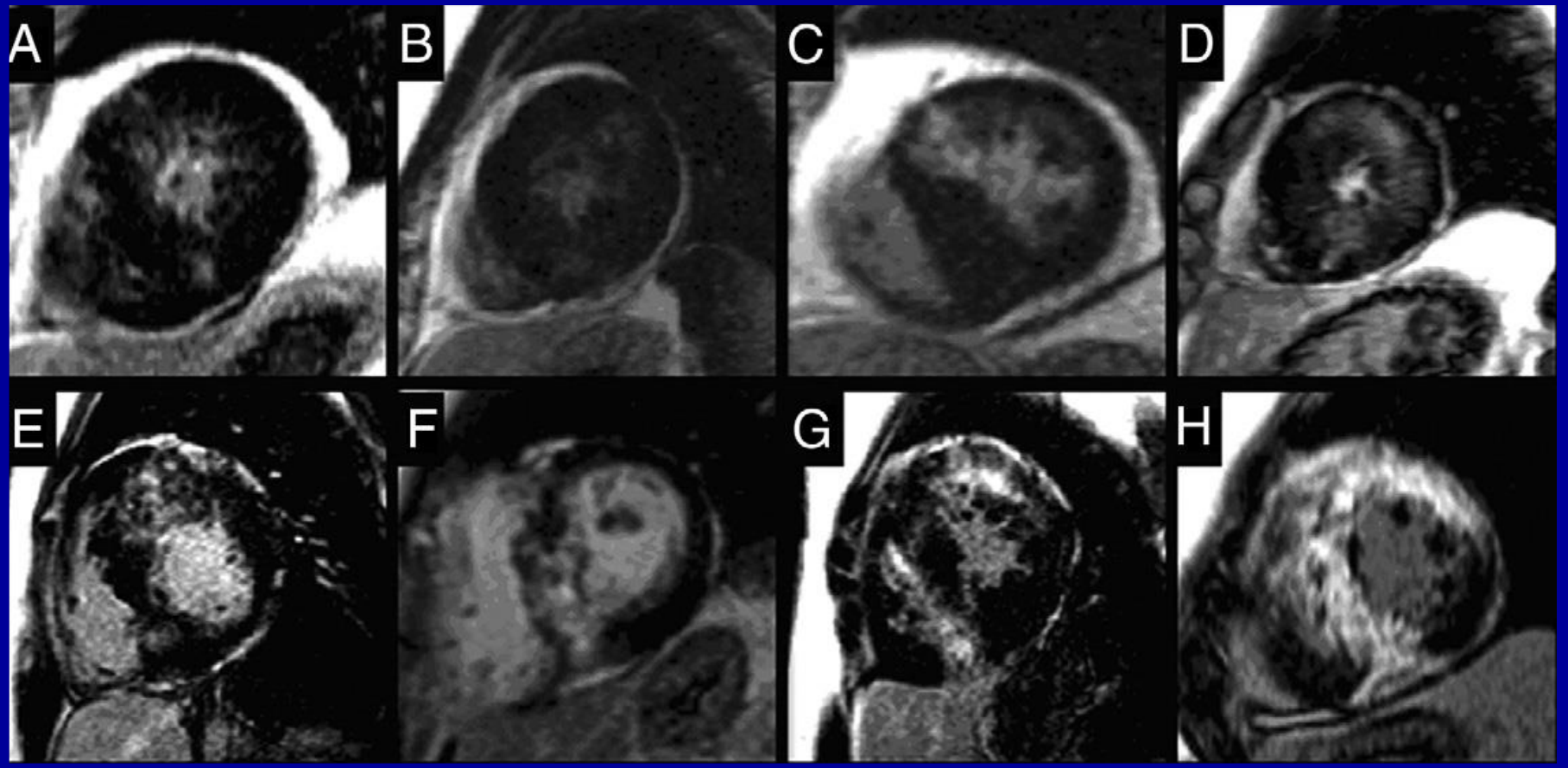


Kim et al Circulation. 1999;100:1992-2002.

CMR advantages in HCM

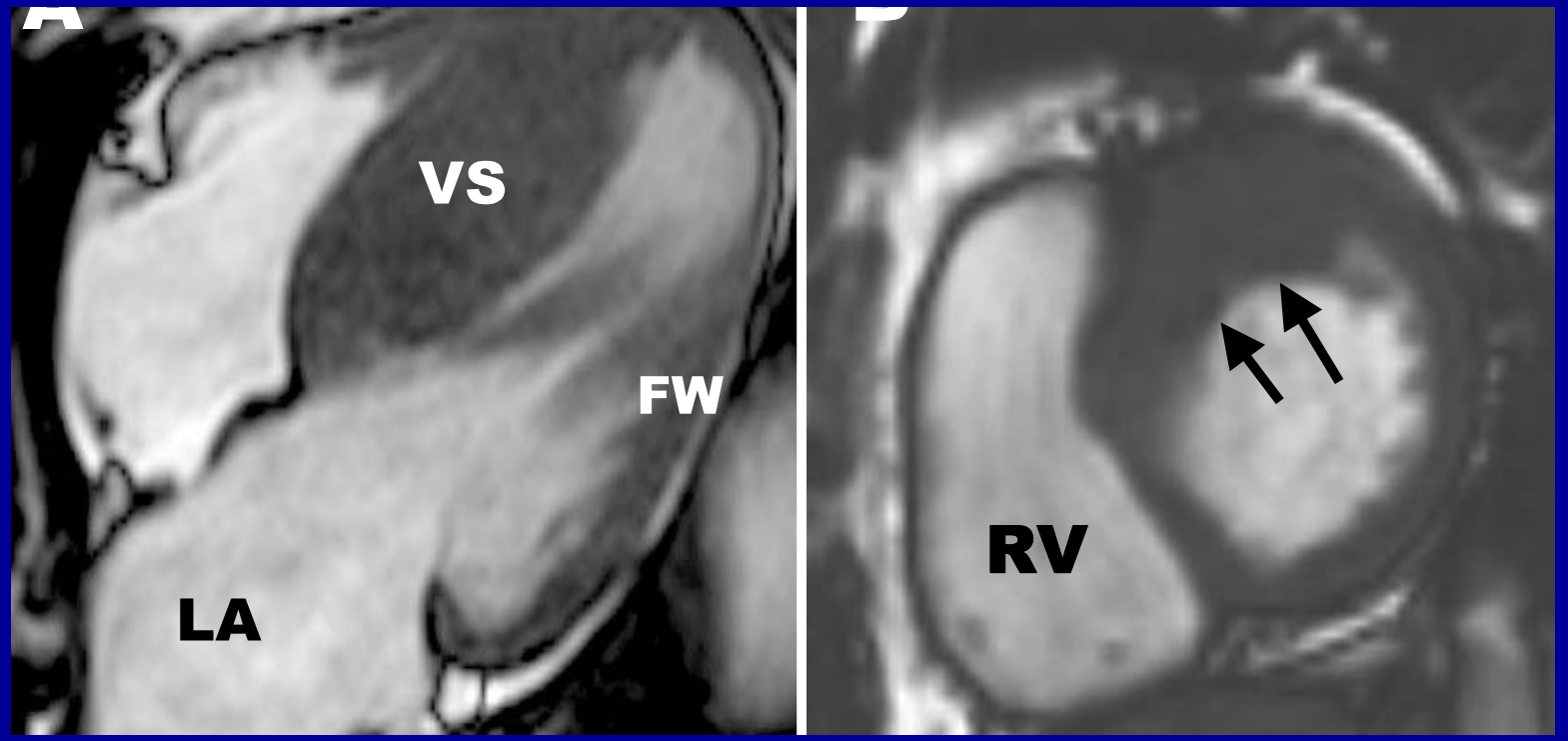
- CMR is capable of identifying regions of LV hypertrophy not readily recognized by echocardiography
- Better for Apical CMP diagnosis -including apical infarct.
- Better for LV mass assessment.
- Delayed enhancement (=Fibrosis) assessment.

Representative patterns of LGE in HCM



O'Hanlon et al JACC Vol. 56, No. 11, 2010

Various phenotypes of HCM by MRI

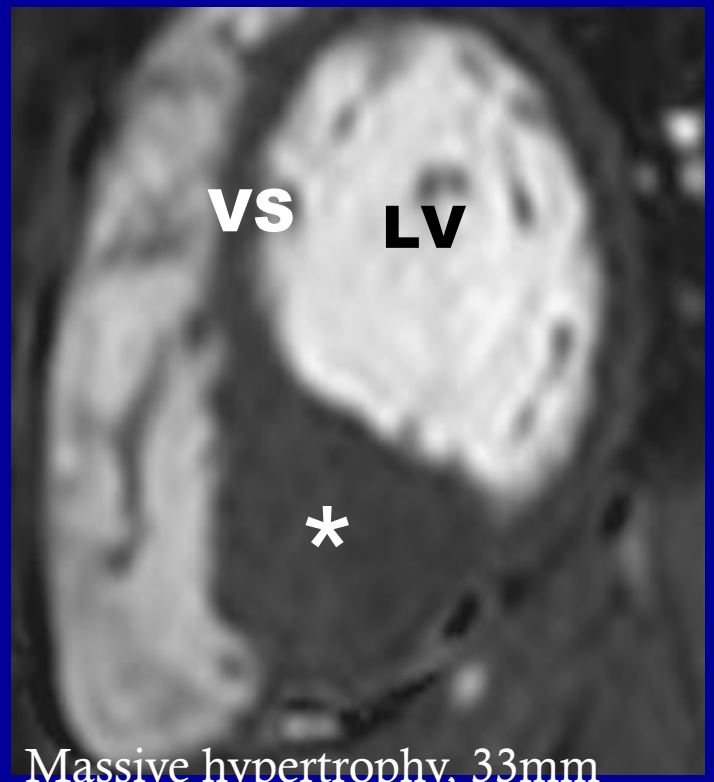


Ventricular septum, sparing LV free wall

Basal anterior free wall and anterior septum

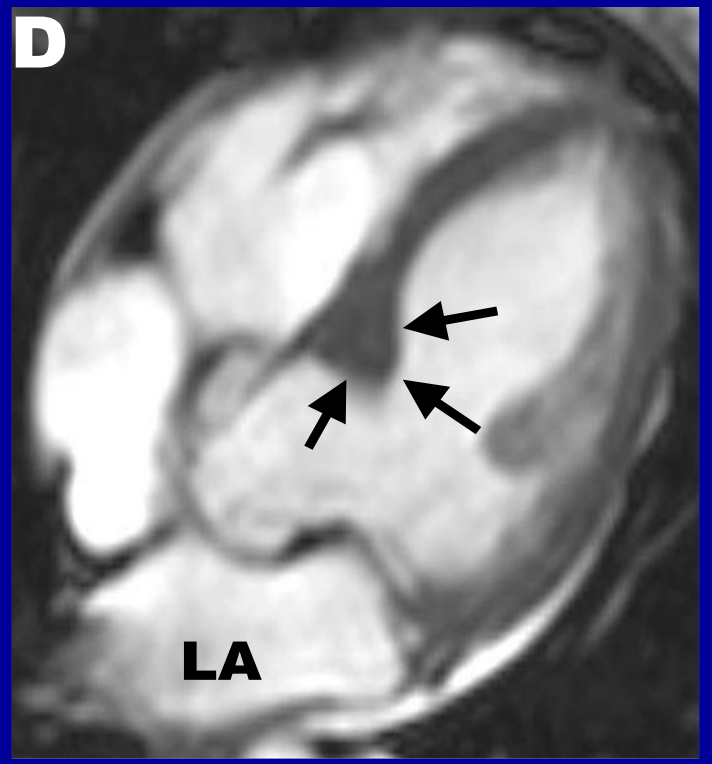
Maron J. Cardiovas MR 2012, 14: 13

Various phenotypes of HCM by MRI



Massive hypertrophy, 33mm

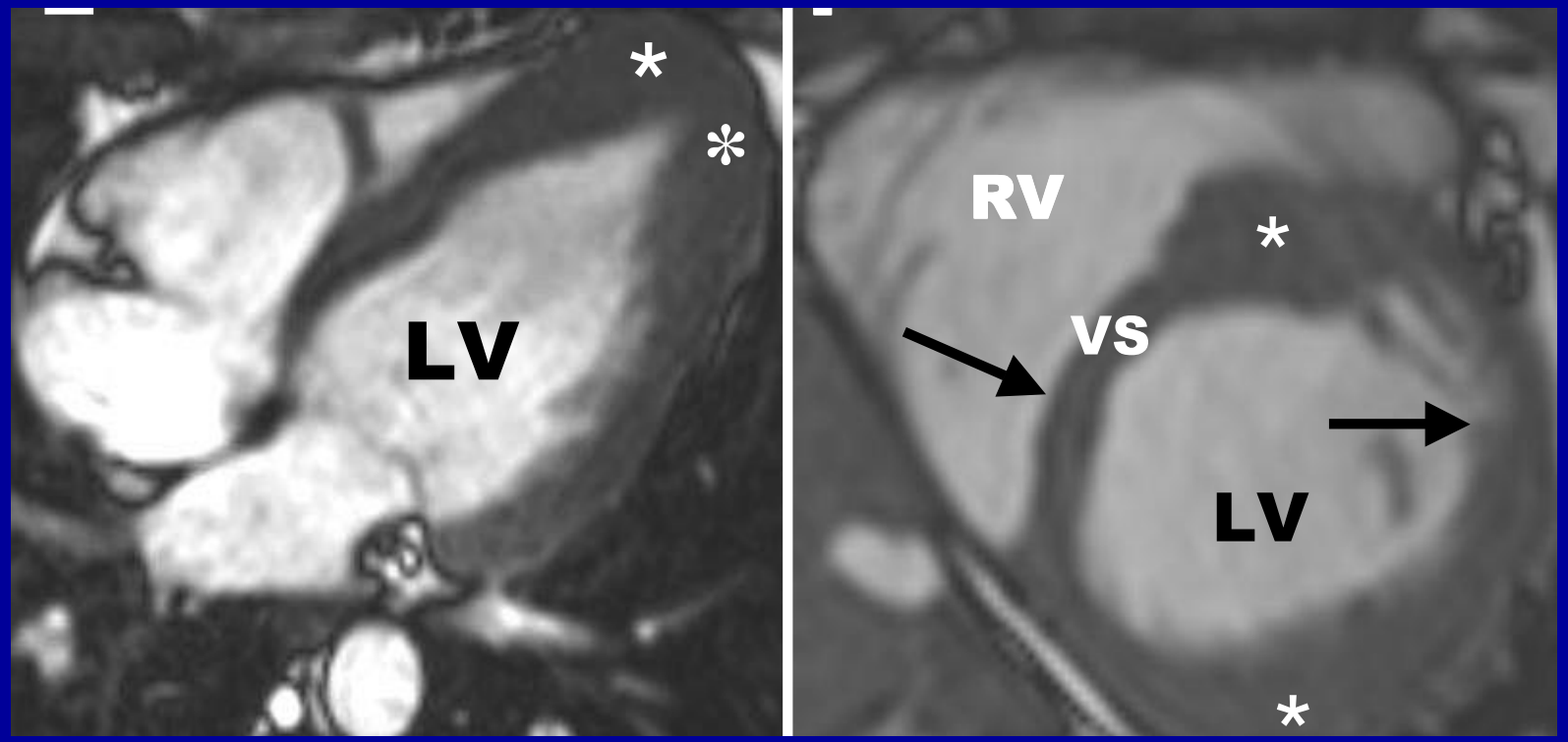
Basal posterior septum



Focal basal anterior septum

Maron J. Cardiovas MR 2012, 14: 13

Various phenotypes of HCM by MRI



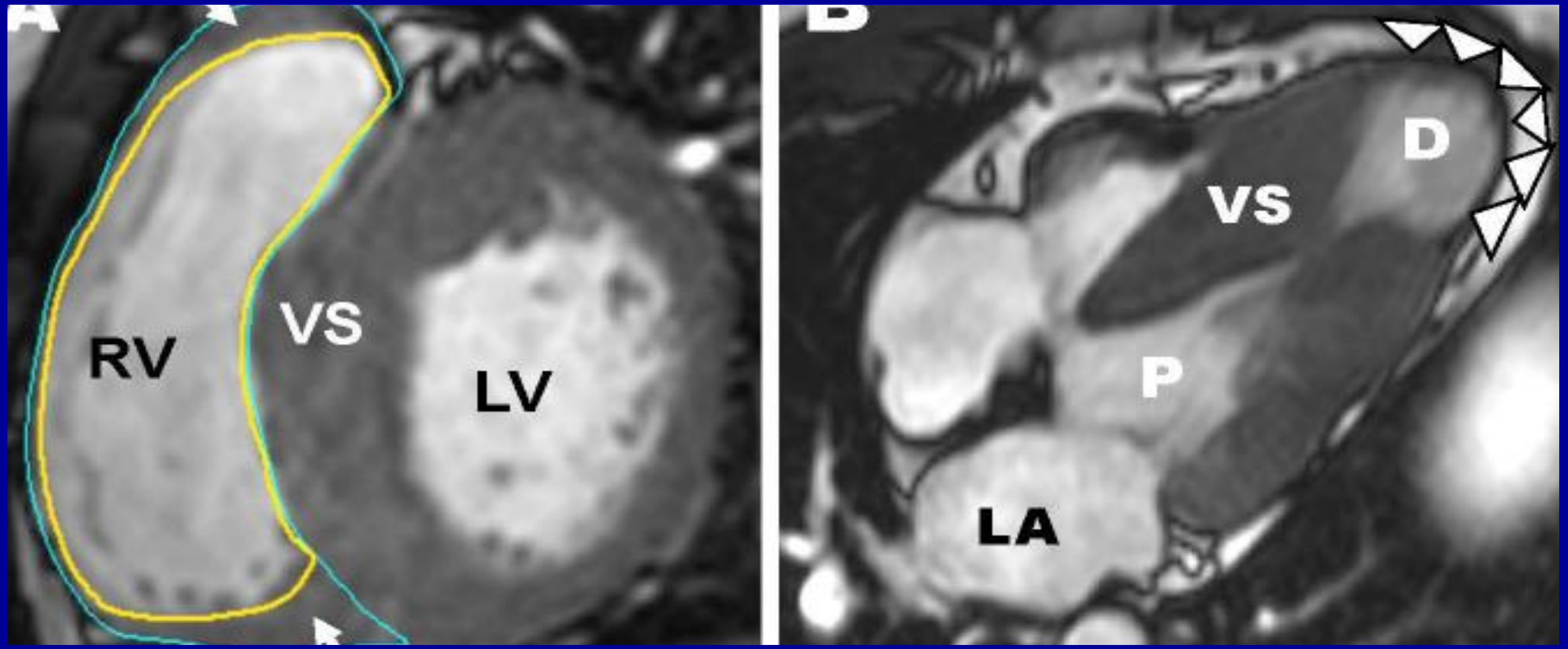
Apical hypertrophy

Noncontiguous hypertrophy of basal

Anterior septum and anterolateral wall

Maron J. Cardiovas MR 2012, 14: 13

Various phenotypes of HCM by MRI

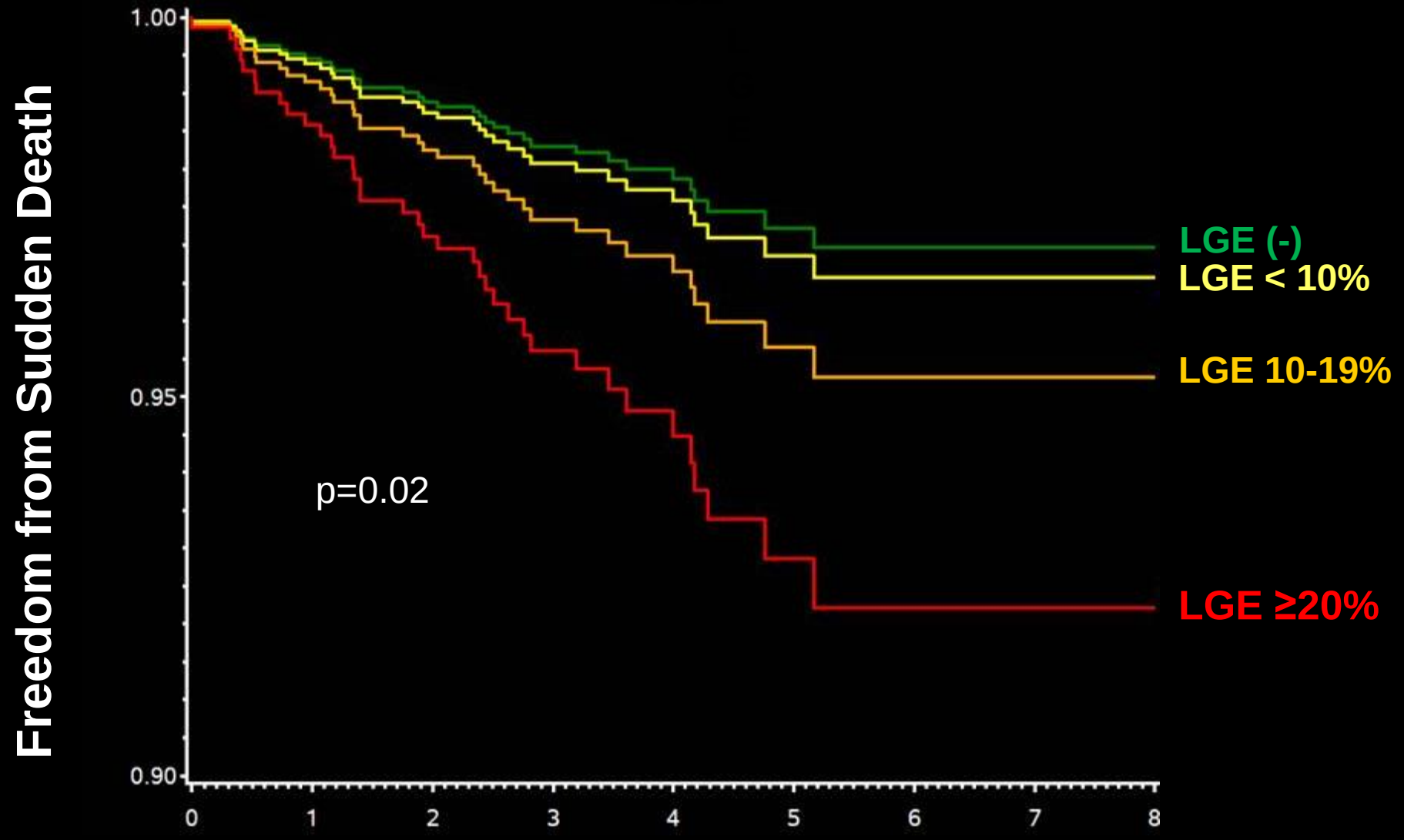


RV hypertrophy

Maron et al. JACC 2009, 54: 220-8

Apical aneurysm with mid-ventricular muscular apposition

Relation Between Sudden Death and Extent of LGE in 1293 HCM Patients



Chan R, Maron MS et al. *Circulation 2014*

Meta-analysis:

Extent of LGE in HCM:

Increased Risk of ***All-Cause Mortality*** (HR1.3/10% LGE)

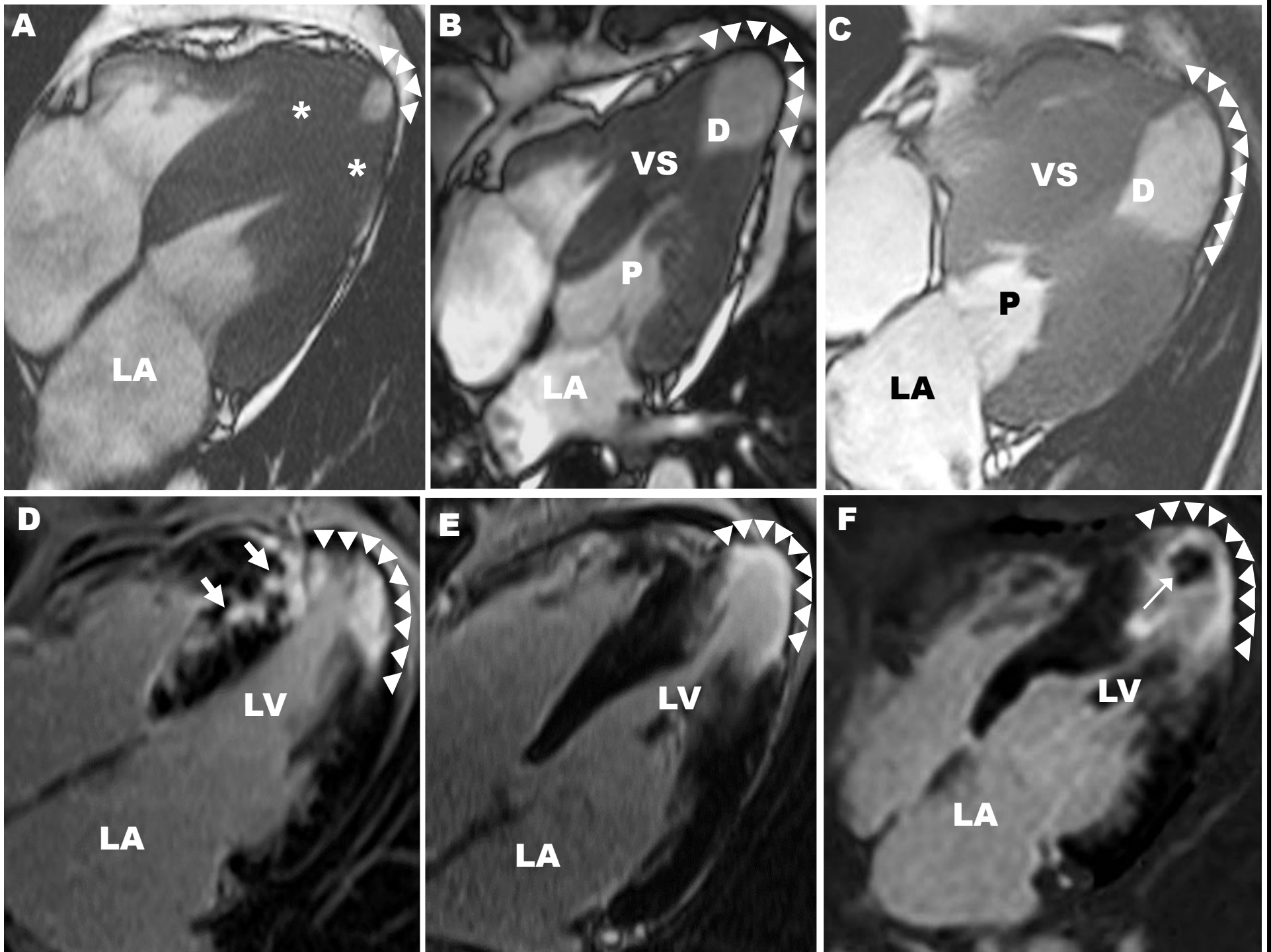
Increased Risk of ***Cardiovascular Mortality*** (HR 1.6/10%LGE)

Increased Risk of ***Heart Failure Death*** (HR1.6/10% LGE)

Increased Risk of ***Sudden Death Events*** (HR 1.6/10% LGE)

Extent of LGE is a strong prognostic marker in HCM

Weng et al., JACC: CV Imaging *2016*


A
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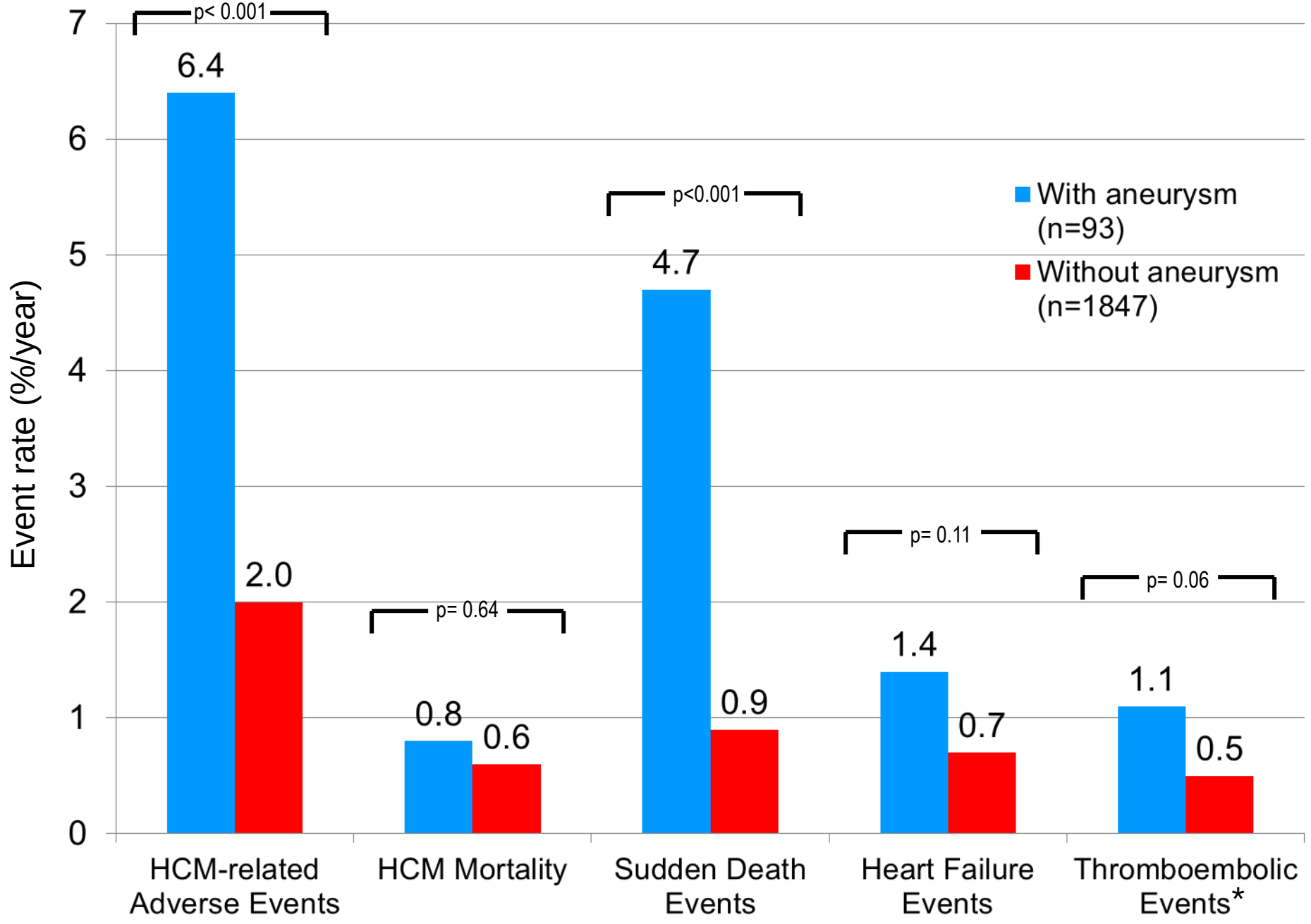
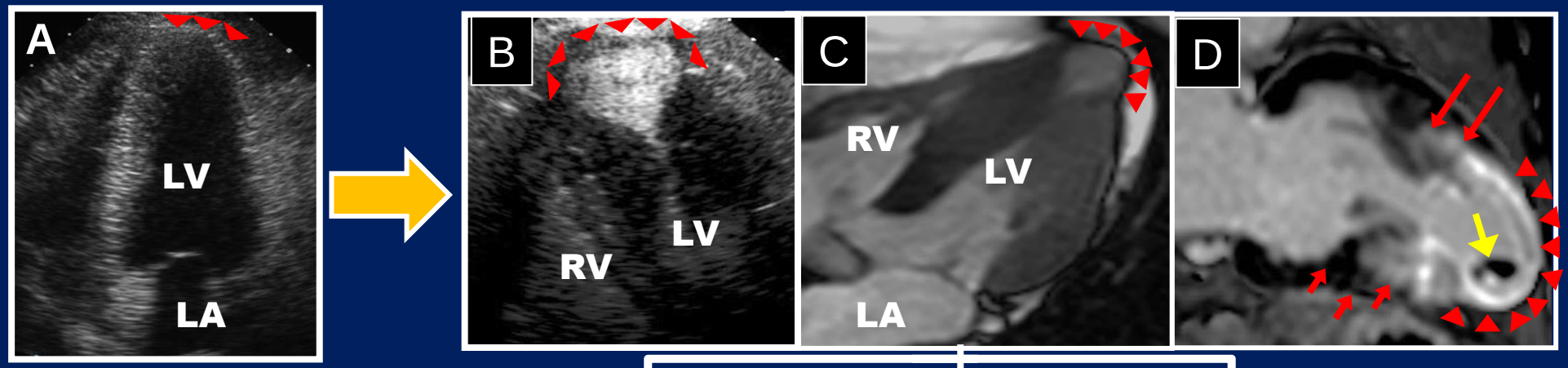
Rowin E et al JACC, 2017



ECHO without contrast

ECHO with contrast

CMR



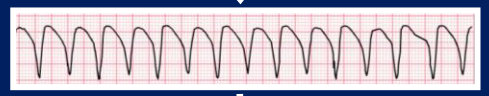
Sudden Death Events (4.7%/yr)

ICD
Primary Prevention of SD

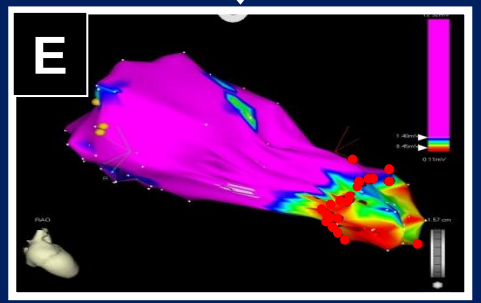
Thromboembolic Events (1.1%/yr)

Anti-coagulation

Recurrent Monomorphic VT

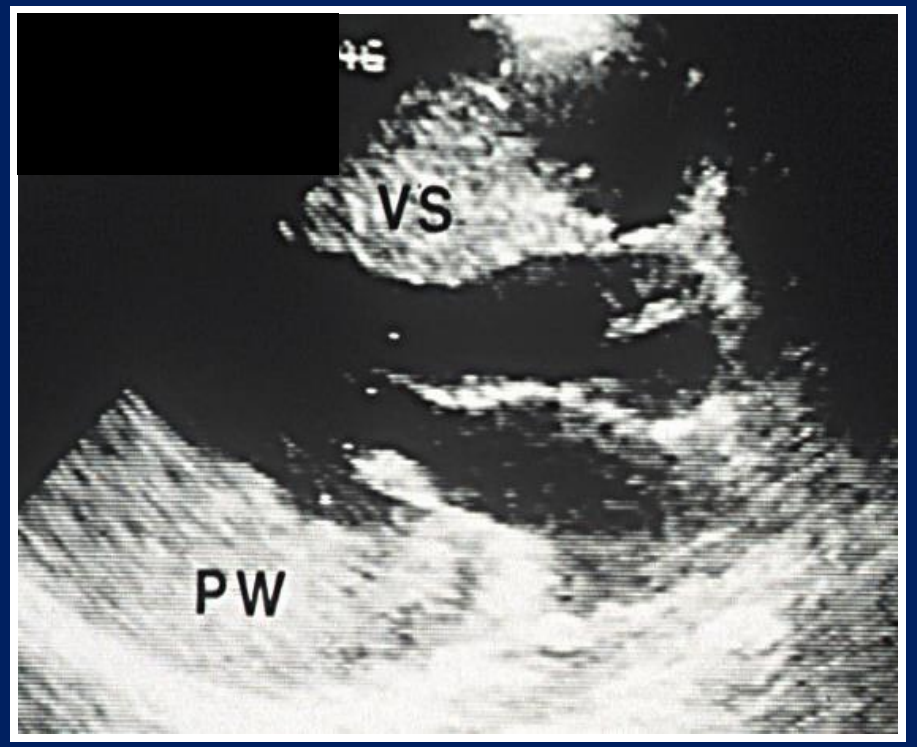


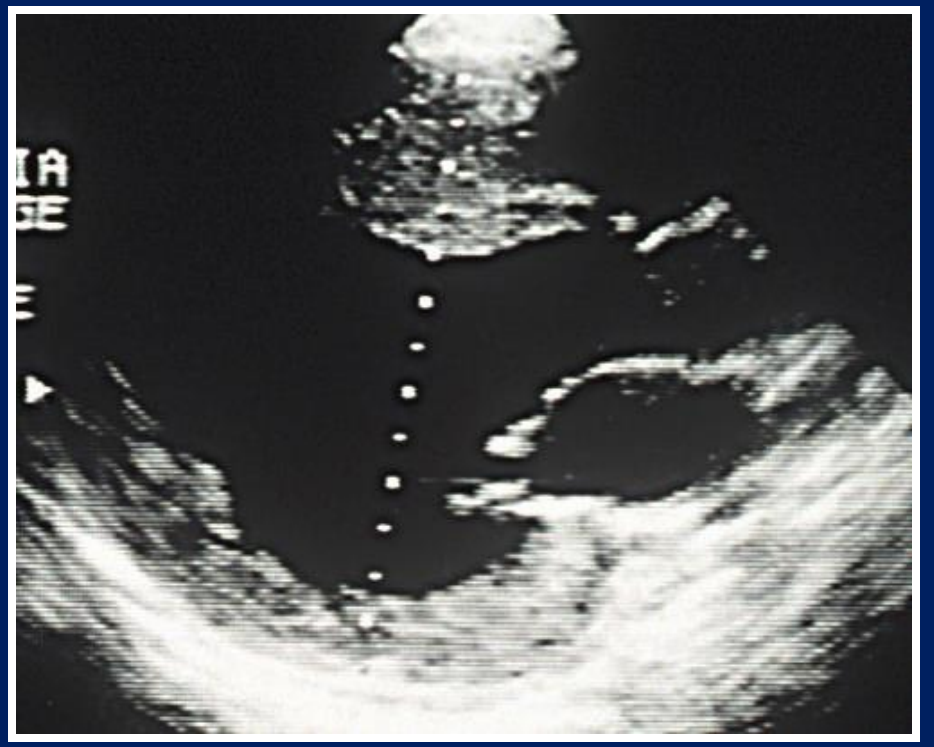
Radiofrequency VT Ablation



Rowin E et al JACC, 2017

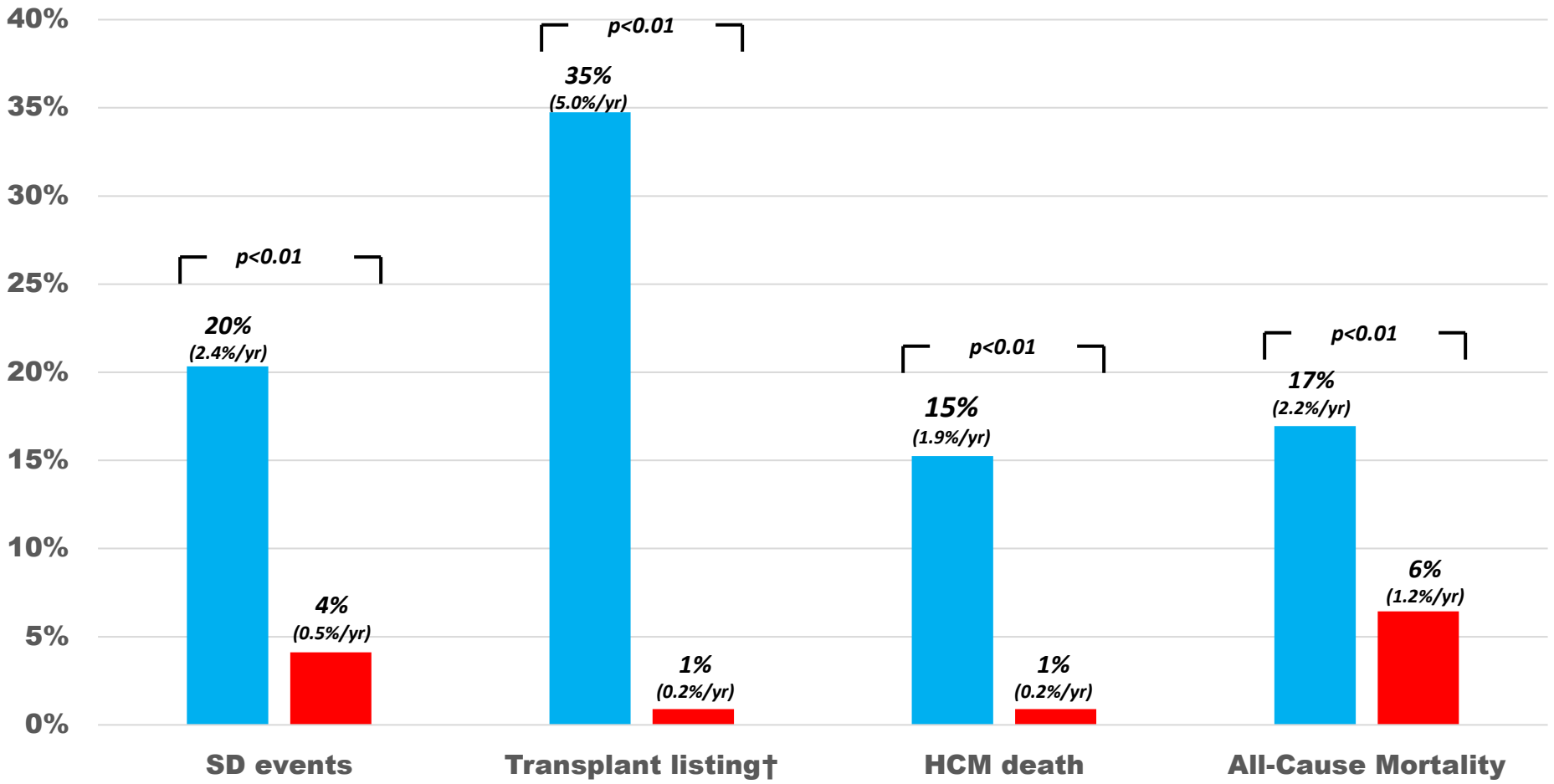
“End-stage” Hypertrophic Cardiomyopathy





EF <50%

Rate of Adverse Events in End-Stage (EF<50%) HCM Patients



Rowin et al JACC *2020*

ACC/AHA Individual Risk Markers

Major Markers (< 60 yrs of age)

Family History HCM-sudden death
Unexplained syncope
Multiple-repetitive NSVT
Massive LVH ≥ 30 mm

Enhanced:
LV apical aneurysm
Extensive LGE
End-stage (EF < 50%)

Increased Risk:
(≥ 1 major marker alone or with arbitrator)

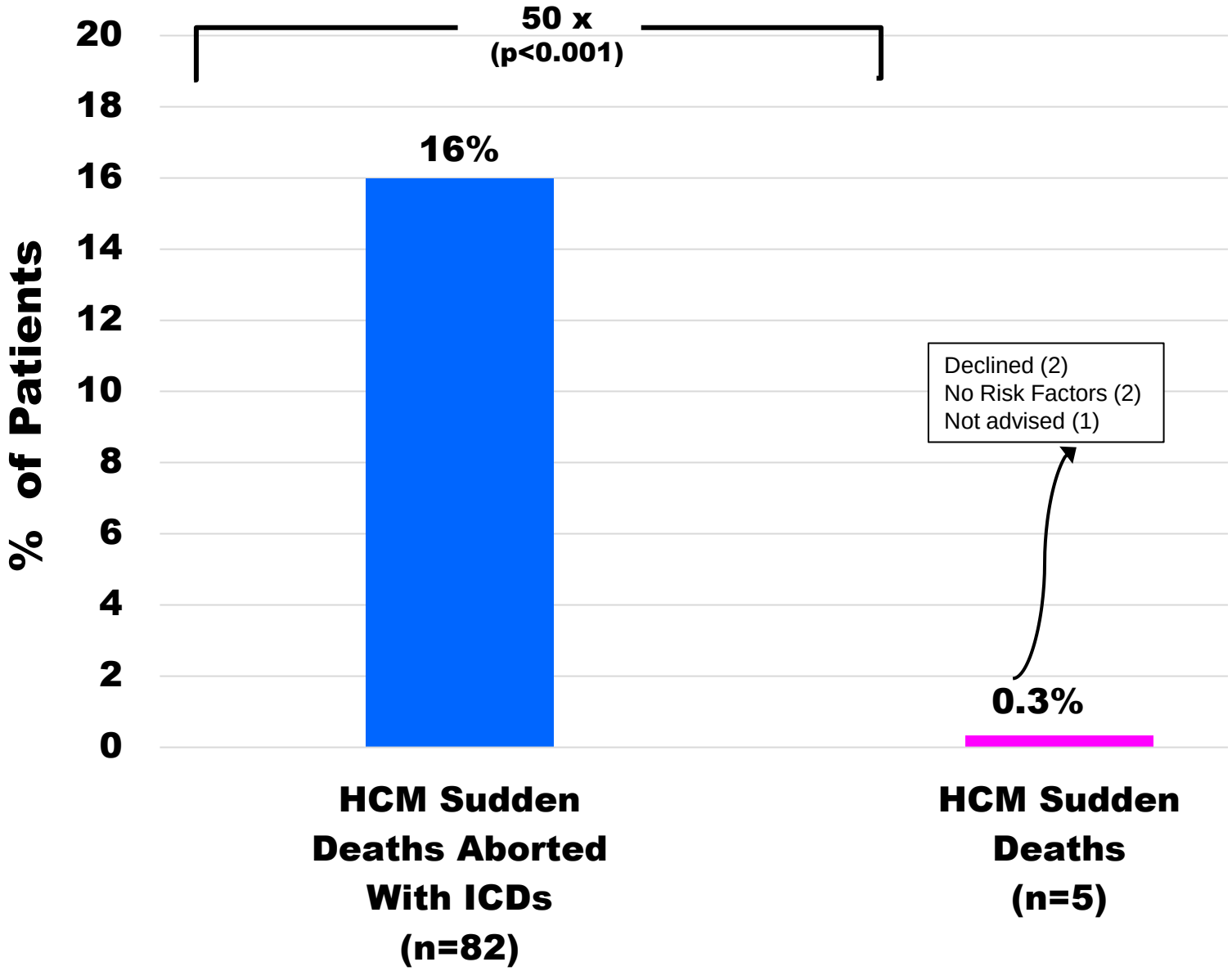
Reasonable to consider primary prevention ICD

Prevention of Sudden Death in HCM
With Prospective Decision-Making: *Tufts HCM Center*

- **17 years**
- **2094 Consecutive HCM Patients**
- **5 ± 3 year follow-up**
- **Primary Prevention: 527 ICDs**
- **Age: 51 ± 17 (Range: 12 to 70 years)**

Maron et al JAMA Cardiology *2019*

17-year Tufts SD Prevention Experience (Enhanced ACC/AHA Markers)



Maron et al JAMA Cardiology *2019*

Using enhanced risk markers, along with shared decision-making and good clinical judgment, over a 17-year period we were able to identify nearly all at-risk HCM patients….

Sudden death prevention in HCM is a reality

How Does the ESC Risk Score Compare to ACC/AHA?...

Low Predictive Value for ESC SCD Risk Score: *Tufts Study*

Risk category	ACC/AHA Risk Factors	ESC Risk Score
Sensitivity (prevent SD)	**95%** (Intention to treat)	**34%**

Maron et al JAMA Cardiology *2019*

Low Predictive Value for ESC SCD Risk Score: Global Experience

Study	Cohort Size	SCD events	SCD Events (ESC score <6%)	Sensitivity
O'Mahony, et al. 2014	2597	84	41	51%
Maron, et al. 2015	1497	81	65	20%
Zhu, et al 2017	165	5	4	20%
Leong, et al 2018	260	14	7	50%
Nakag				32%
O'Ma				52%
Desai et al. 2018	1495	171	149	13%
Choi et al 2019	730	16	10	38%
Freitas et al 2019	493	23	18	22%
Rowin et al 2019	92	16	10	37%
Maron et al 2019	2019	91	60	34%

Avg. Sensitivity for ESC: 34%

Why is sensitivity of ESC score low?

MISSING FROM ESC RISK MODEL:

- *CMR and LGE*
- LV apical aneurysm
- End stage (EF <50%)

} 20% of Appropriate ICD Therapy

QUESTIONABLE ADDITIONS TO ESC RISK MODEL:

- LA size
- LV outflow gradient
- Remote syncope

→ *Little relation to SD risk*

Restrictive for Decision-Making

Is There A "Cost" to Higher Sensitivity?

Risk category	Enhanced ACC/AHA Risk Factors	ESC Risk Score
Sensitivity (prevent SD)	95% (Intention to treat)	34%
Specificity (detecting pts not at risk)	78%	92%
Number Needed To Treat	6.6	7.2

Maron et al JAMA Cardiology *2019*

CONCLUSIONS

ACC/AHA risk factor strategy incorporates physician judgement and shared-decision making, along with flexibility to incorporate novel sudden death risk markers….
LV Apical Aneurysm, extensive LGE and systolic dysfunction

ACC/AHA Individual Risk Factor Strategy associated with higher *sensitivity* for predicting sudden death events in HCM Patients compared to ESC risk score…the opportunity to identify nearly all at risk HCM patients for sudden death prevention with ICD

The "cost" of greater sensitivity is some degree of overtreatment (specificity) with ACC/AHA Strategy vs. ESC risks core…but NNT is equal.

Should Use Both Strategies Together….

Can You Really Combine Them?

Table 2 Simulated hypertrophic cardiomyopathy patients scenarios

Case	Age	IVS thickness (mm)	LA diameter (mm)	LVOT gradient (mmHg)	Family history of SCD	NSVT	Syncope	LGE on CMR	Apical aneurysm	BP response
1	30	31	35	7	No	No	No	<5%	No	Normal
2	30	31	35	7	Yes	No	No	<5%	No	Normal
3	30	31	35	7	No	No	No	20%	No	Normal
4	60	20	47	2	No	No	Yes	17%	Yes	Abnormal
5	25	20	55	100	No	No	No	<5%	No	Normal
6	45	15	50	20	No	Yes	No	<5%	No	Normal
7	45	27	50	20	No	Yes	No	<5%	No	Normal
8	25	20	47	2	No	No	Yes	17%	Yes	Abnormal
9	45	28	50	20	No	Yes	No	20%	No	Normal

Weissler-Snir A et al. Eur Heart J. 2017

Table 3 The recommendations of the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines and hypertrophic cardiomyopathy experts from Europe and North America participating in our survey on the simulated patients' scenarios presented in Table 2

Case	ESC risk calculator	Calculated 5-year risk of SCD by the ESC risk calculator	ACCF/AHA guidelines	No. of HCM experts in Europe recommending ICD	No. of HCM experts in North America recommending ICD
1	ICD not recommended	2.44	ICD is reasonable	1/8	10/13
2	ICD not recommended	3.83	ICD is reasonable	5/8	12/13
3	ICD not recommended	2.44	ICD is reasonable	4/8	12/13
4	ICD not recommended	3.48	ICD is reasonable	5/8	9/13
5	ICD should be considered	6.01	ICD not recommended	0/7	0/13
6	ICD should be considered	6.42	ICD not recommended	2/8	2/13
7	ICD should be considered	6.79	ICD not recommended	4/8	5/13
8	ICD should be considered	6.44	ICD is reasonable	7/8	13/13
9	ICD should be considered	6.78	ICD is reasonable	8/8	12/13

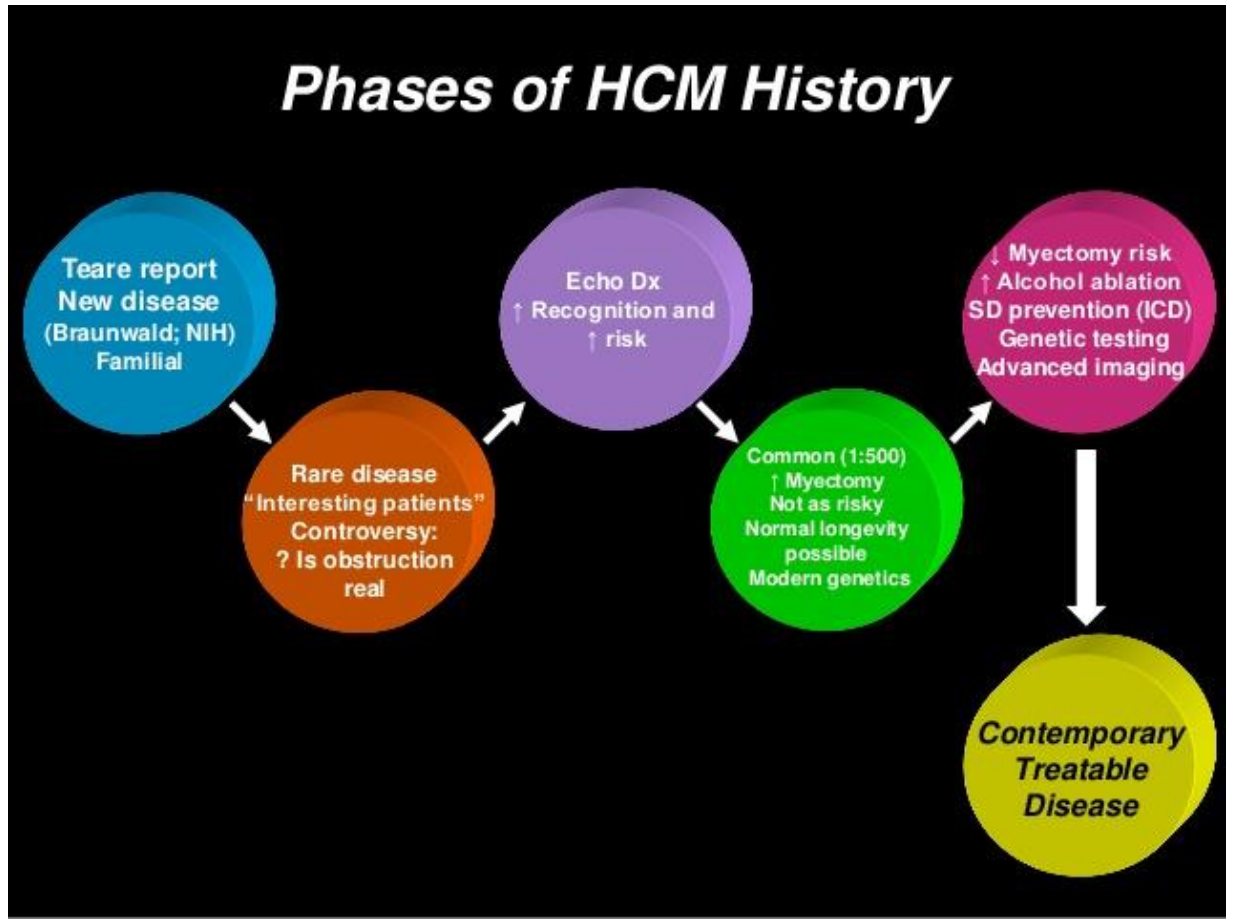
Weissler-Snir A et al. Eur Heart J. 2017

Do I need Defibrillator?

- IVS- 33 mm
- Family history- cousin with scd (age 45)
- Syncope- 2 y ago (m/p post micturation)
- Holter- NSR 55-110/MIN; 1500 VPBS

; 5 COUPLETS; 2 NSVT- 4 beats HR- 115

- Stress test- 9 min; STT changes;
  BP- 110/70-→ 130/70
- CMR-LGE – 15% of myocard


Phases of HCM History
Teare report
New disease
(Braunwald; NIH)
Familial
Rare disease
"Interesting patients"
Controversy:
? Is obstruction
real
Echo Dx
↑ Recognition and
↑ risk
Common (1:500)
↑ Myectomy
Not as risky
Normal longevity
possible
Modern genetics
↓ Myectomy risk
↑ Alcohol ablation
SD prevention (ICD)
Genetic testing
Advanced imaging
Contemporary
Treatable
Disease

What about sport?

Recommendations	Class[a]	Level[b]
Exercise recommendations		
Participation in high-intensity exercise/competitive sports, if desired (with the exception of those where occurrence of syncope may be associated with harm or death), may be considered for individuals who do not have any markers of increased risk[c] following expert assessment.	IIb	C
Participation in low- or moderate-intensity recreational exercise, if desired, may be considered for individuals who have any markers of increased risk[c] following expert assessment .	IIb	C
Participation in all competitive sports, if desired, may be considered for individuals who are gene positive for HCM but phenotype negative.	IIb	C
Participation in high-intensity exercise (including recreational and competitive sports) is not recommended for individuals who have ANY markers of increased risk[c].	III	C
Follow-up and further considerations relating to risk		
Annual follow-up is recommended for individuals who exercise on a regular basis.	I	C
Six-monthly follow-up should be considered in adolescent individuals and young adults who are more vulnerable to exercise-related SCD.	IIa	C
Annual assessment should be considered for genotype-positive/phenotype-negative individuals for phenotypic features and risk stratification purposes.	IIa	C

Routine flollow-up

Recommendations	Class	Level
A clinical evaluation, including 12-lead ECG and TTE, is recommended every 12–24 months in clinically stable patients.	I	C
A clinical evaluation, including 12-lead ECG and TTE, is recommended whenever there is a change in symptoms.	I	C
48-Hour ambulatory ECG is recommended every 12–24 months in clinically stable patients, every 6–12 months in patients in sinus rhythm with left atrial dimension ≥45 mm, and whenever patients complain of new palpitations.	I	C
CMR may be considered every 5 years in clinically stable patients, or every 2–3 years in patients with progressive disease.	IIb	C
Symptom-limited exercise testing should be considered every 2–3 years in clinically stable patients, or every year in patients with progressive symptoms.	IIa	C
Cardiopulmonary exercise testing (when available) may be considered every 2–3 years in clinically stable patients, or every year in patients with progressive symptoms.	IIb	C

European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284


Thank
you !!!