CARDIOMIOPATIA IPERTROFICA: NOVITÀ

- Rischio di Morte Improvvisa
- dalla Genetica ai Markers di Imaging

(diagnosi differenziale, malattia di Fabry, percorsi decisionali)

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HCM is a global now treatable disease (prevalence : 2 per 1000)

50 countries….all continents

Courtesy of Maron B, mod.

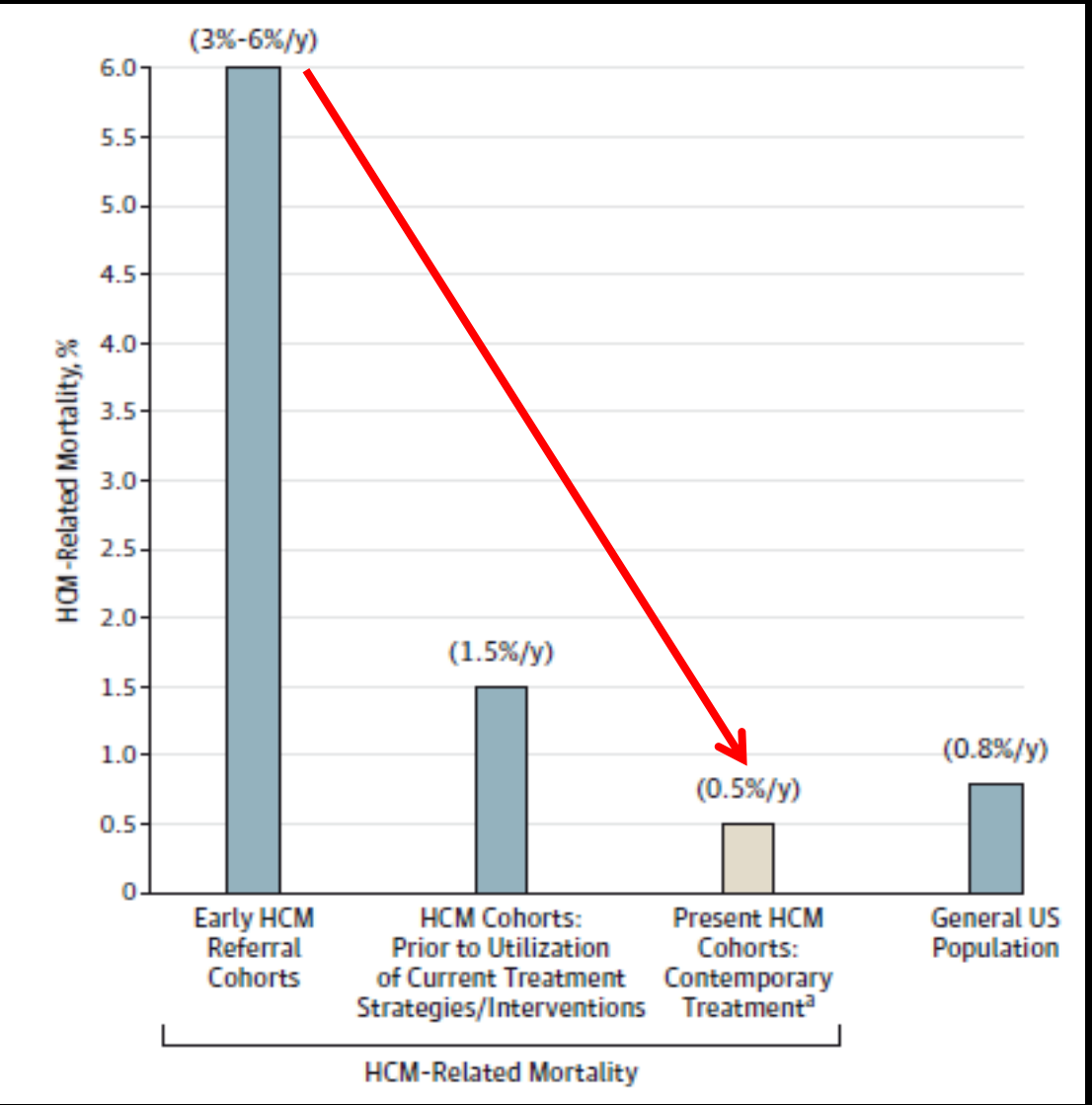
Review

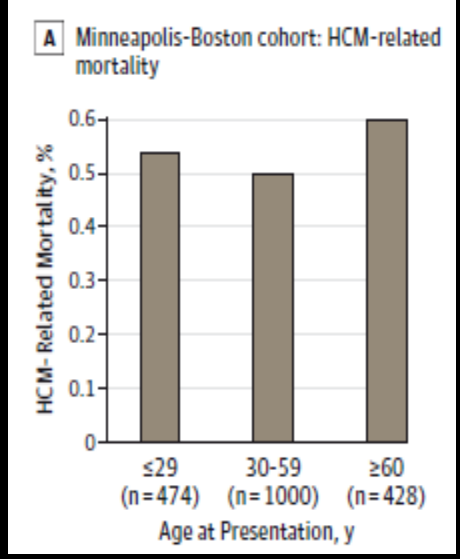
How Hypertrophic Cardiomyopathy Became a Contemporary Treatable Genetic Disease With Low Mortality

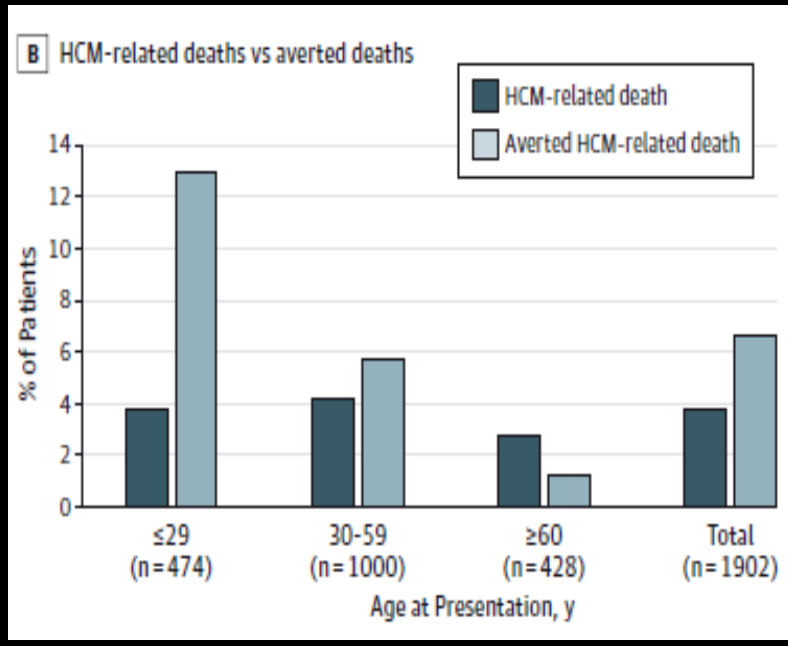
Shaped by 50 Years of Clinical Research and Practice

Barry J. Maron, MD; Ethan J. Rowin, MD; Susan A. Casey, RN; Martin S. Maron, MD

JAMA Cardiol. doi:10.1001/jamacardio.2015.0354
Published online March 2, 2016.







2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy
European Heart Journal
doi:10.1093/eurheartj/ehu284

1. Diagnosi e diagnosi differenziale

   (Segni clinici, ECG, ECO, test genetici, screening familiare)

2. Valutazione e trattamento dell'ostruzione VS ± VDx

   (Tratto d'efflusso, medioventricolare)

3. Gestione clinica dello scompenso cardiaco

4. Valutazione del rischio individuale di morte improvvisa

5. Prevenzione della morte improvvisa

   (Terapia medica e/o chirurgica, indicazione ad ICD o S-ICD)

6. Altro (Follow up, Stile di vita , gravidanza , sport , etc)

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC)

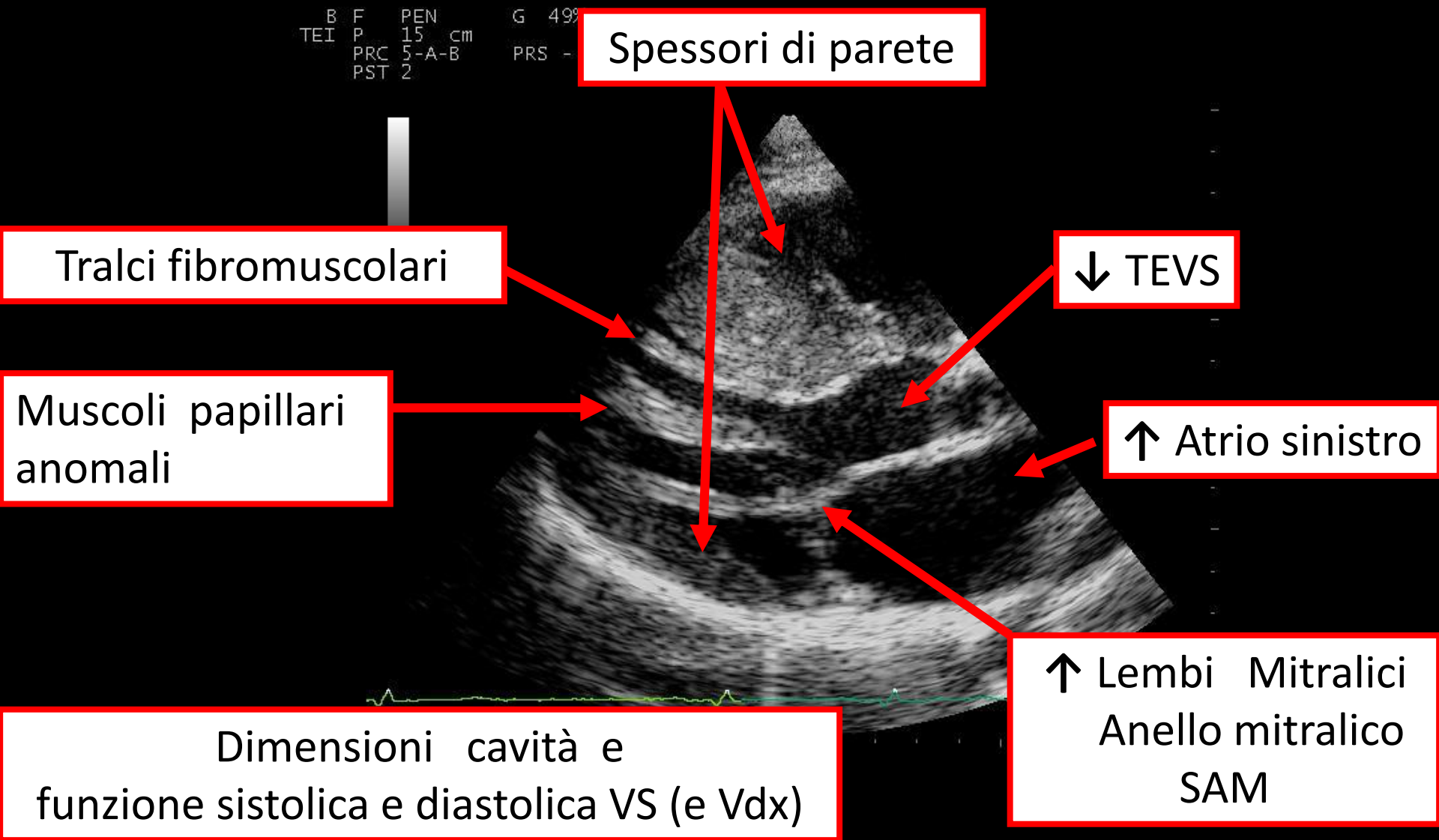
European Heart Journal
doi:10.1093/eurheartj/ehu284

Negli adolescenti ed adulti con spessore > 15 mm (CMI)

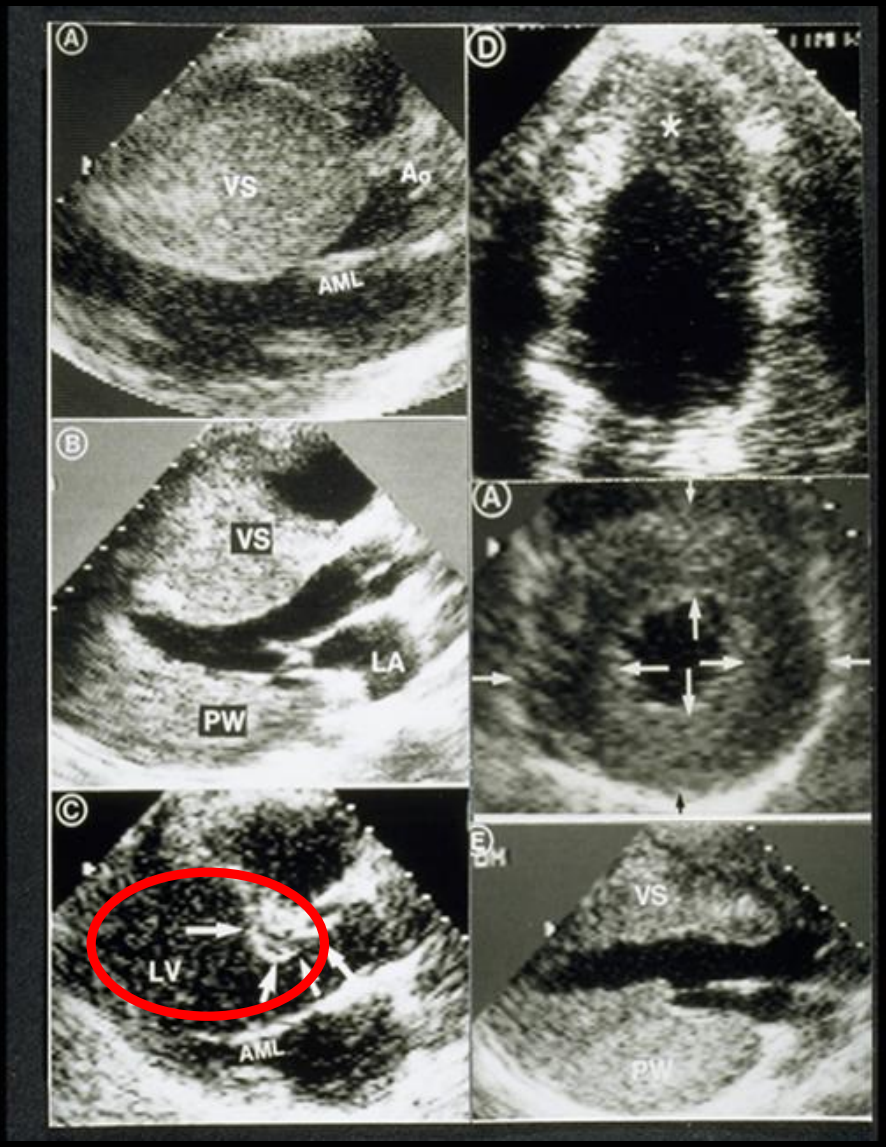
la valutazione clinica dovrebbe comprendere (classe I):

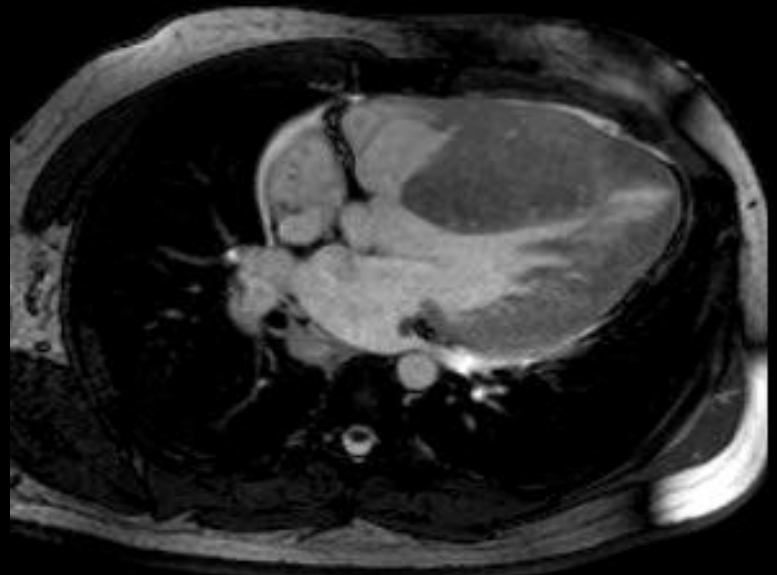
- storia clinica e familiare,
- Ecocolordoppler TT (± Eco da sforzo)
- ECG dinamico **48 ore**
- RMN cardiaca con mdc
- Test da sforzo (cardiopolmonare , se possibile)
- Analisi genetica (12 geni: 8 sarcomerici + GLA, TTR, PRKAG2, LAMP2)
- Screening familiari I grado

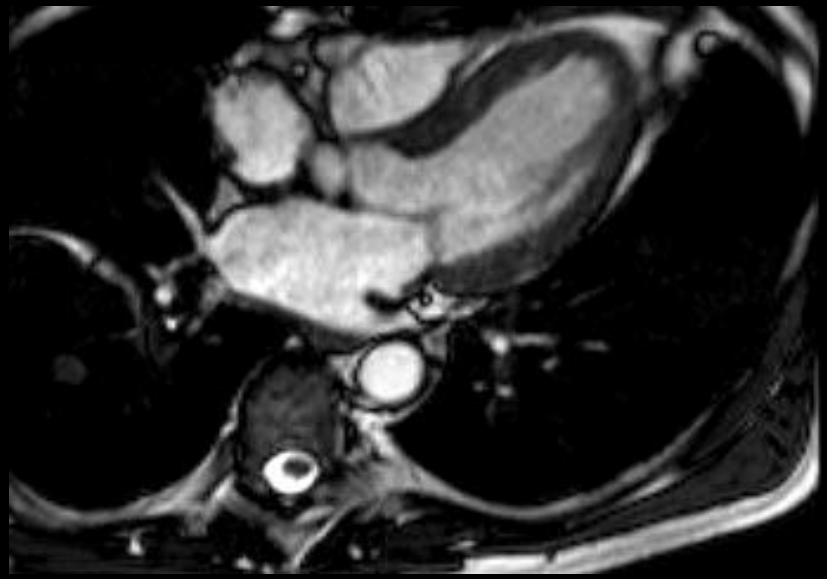
CMI: una miriade di anomalie da valutare



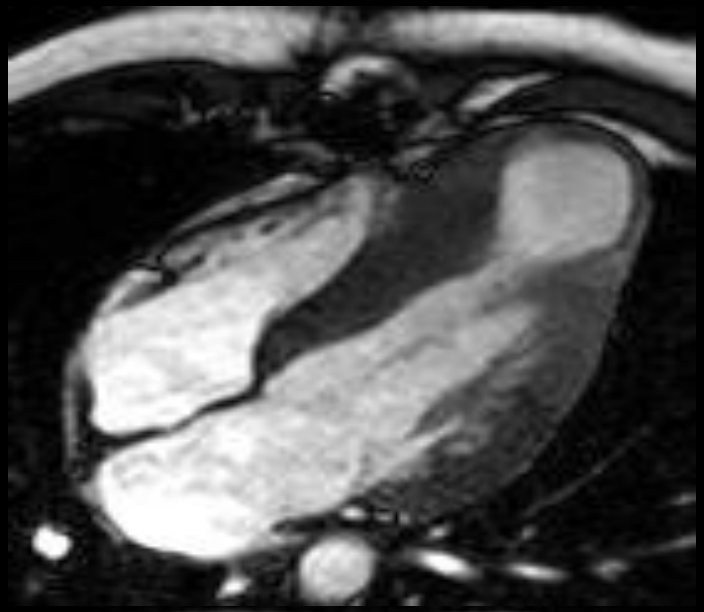
L’importanza del MULTIIMAGING nella diagnosi e valutazione del paziente

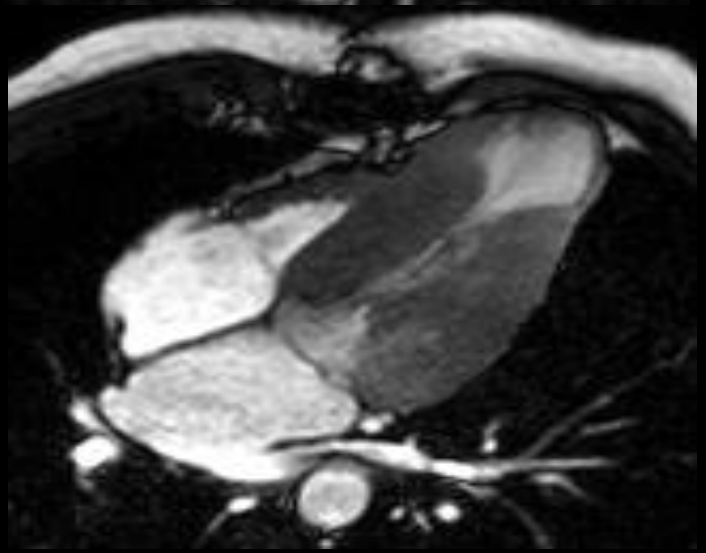


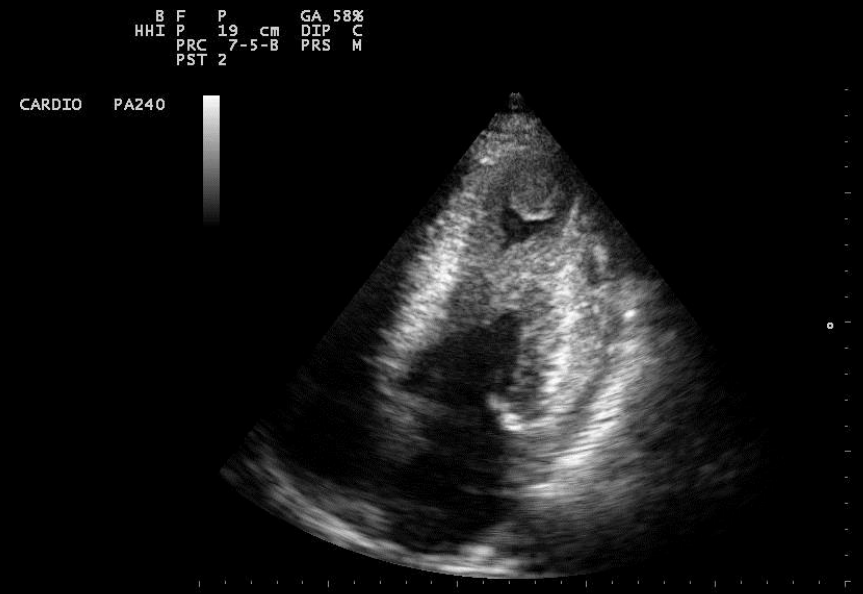


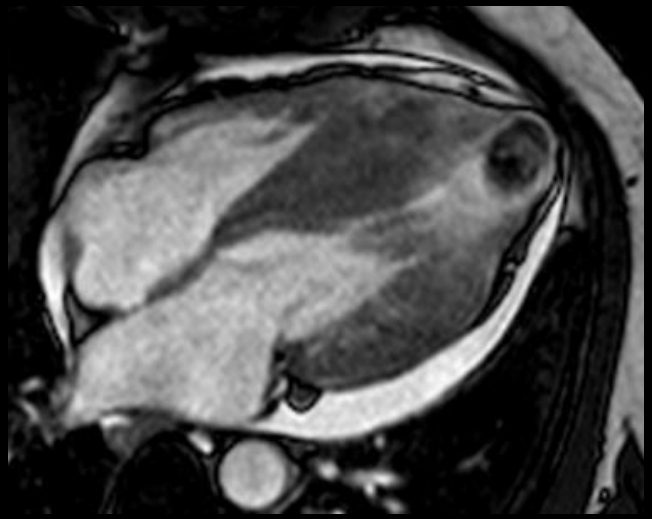


Ostruzione medioventricolare + aneurismi apicali (~5-10%)





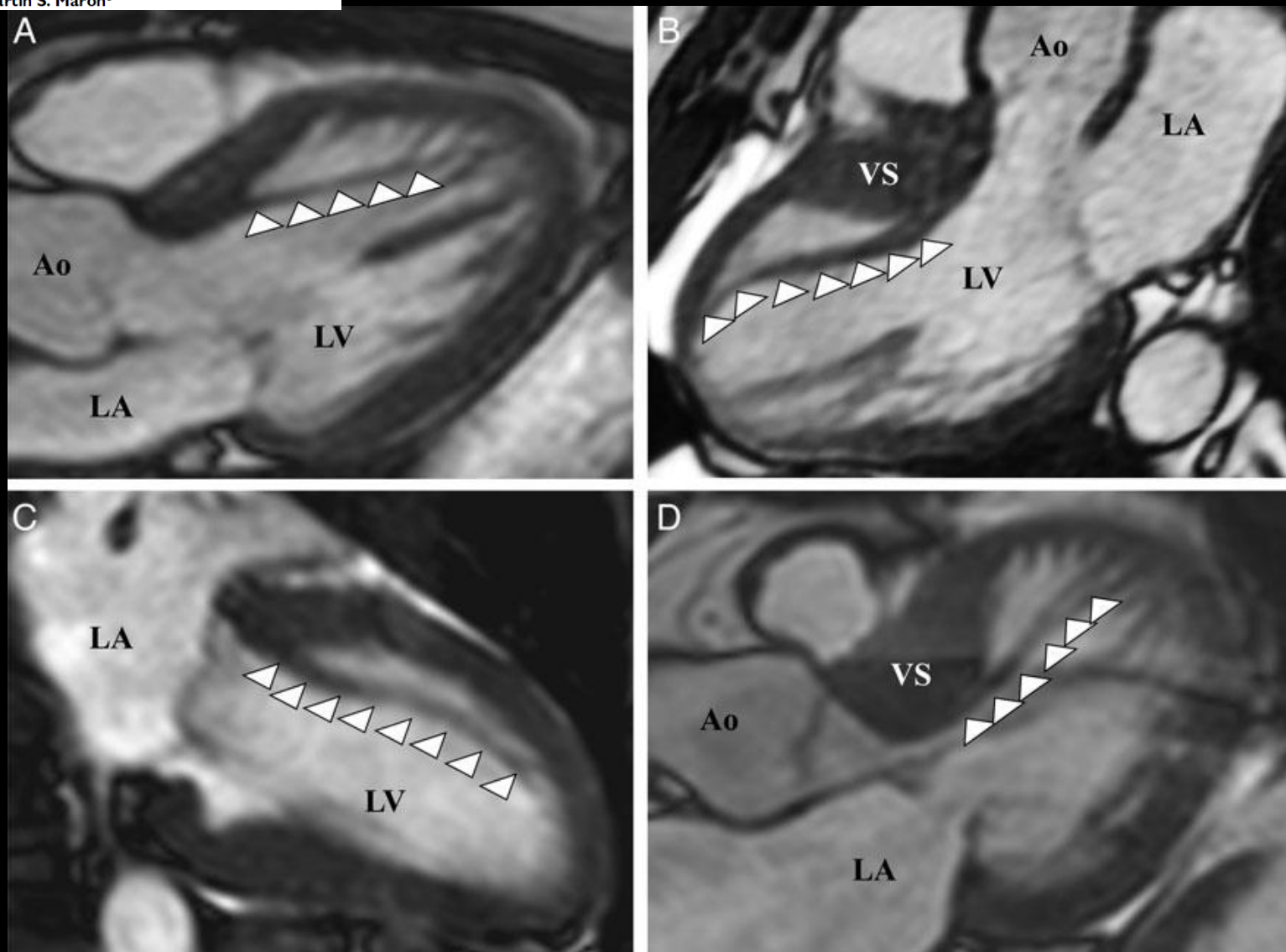




Significance of left ventricular apical–basal muscle bundle identified by cardiovascular magnetic resonance imaging in patients with hypertrophic cardiomyopathy

Christiane Gruner[1,2*], Raymond H. Chan[3,4], Andrew Crean[1], Harry Rakowski[1], Ethan J. Rowin[5], Melanie Care[6,7], Djeven Deva[1], Lynne Williams[1], Evan Appelbaum[3,4], C. Michael Gibson[3,4], John R. Lesser[8], Tammy S. Haas[8], James E. Udelson[5], Warren J. Manning[3,4], Katherine Siminovitch[6,7], Anthony C. Ralph-Edwards[1], Hassan Rastegar[5], Barry J. Maron[8], and Martin S. Maron[5]

European Heart Journal (2014)

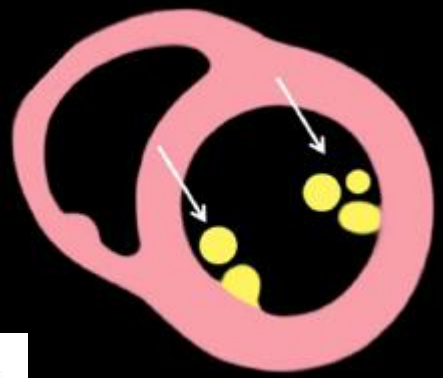


Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy Patients Without Severe Septal Hypertrophy

Implications of Mitral Valve and Papillary Muscle Abnormalities Assessed Using Cardiac Magnetic Resonance and Echocardiography

Parag Patel, MD; Ashwat Dhillon, MD; Zoran B. Popovic, MD, PhD; Nicholas G. Smedira, MD; Jessica Rizzo, RDCS; Maran Thamilarasan, MD; Deborah Agler, RDCS; Bruce W. Lytle, MD; Harry M. Lever, MD; Milind Y. Desai, MD

Circ Cardiovasc Imaging 2015



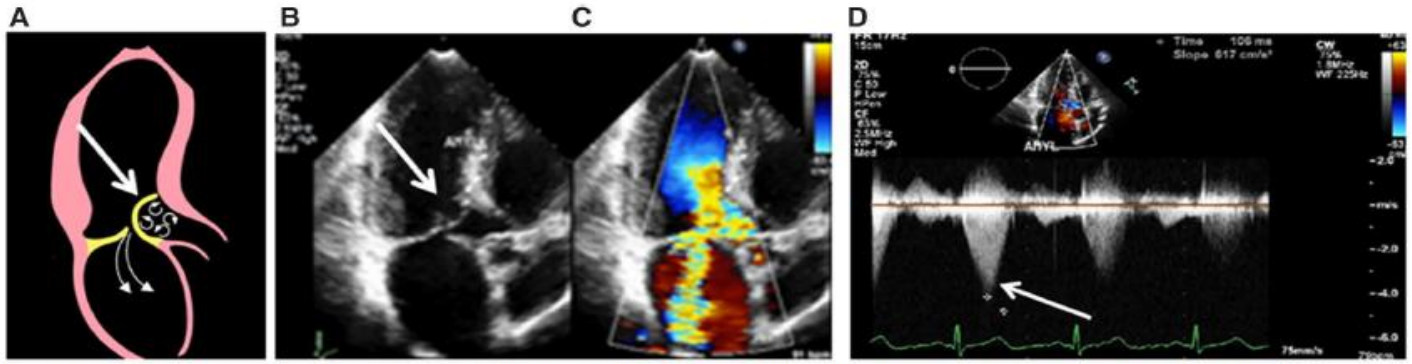


Figure 1. A symptomatic patient with no significant left ventricular hypertrophy but with severe provocable left ventricular outflow tract (LVOT) obstruction. **A**, Illustration shows elongated anterior mitral leaflet (yellow color, arrow) with severe systolic anterior motion (SAM). **B** and **C**, Echocardiogram shows elongated anterior mitral leaflet (arrow) with severe SAM, septal contact, and significant posteriorly directed mitral regurgitation, after administration of amyl nitrite. **D**, Spectral Doppler across LVOT with severe late peaking dynamic LVOT obstruction (arrow).

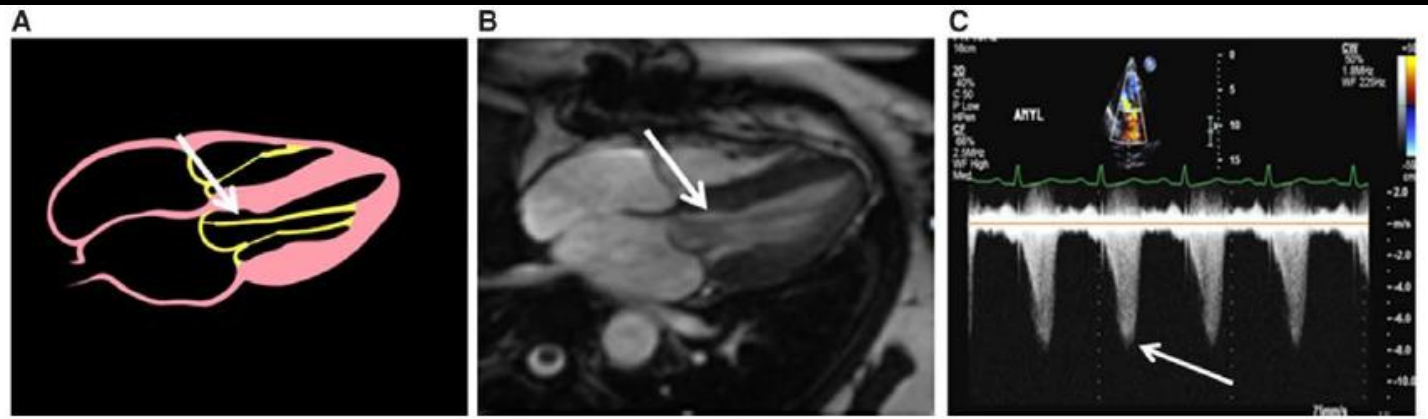


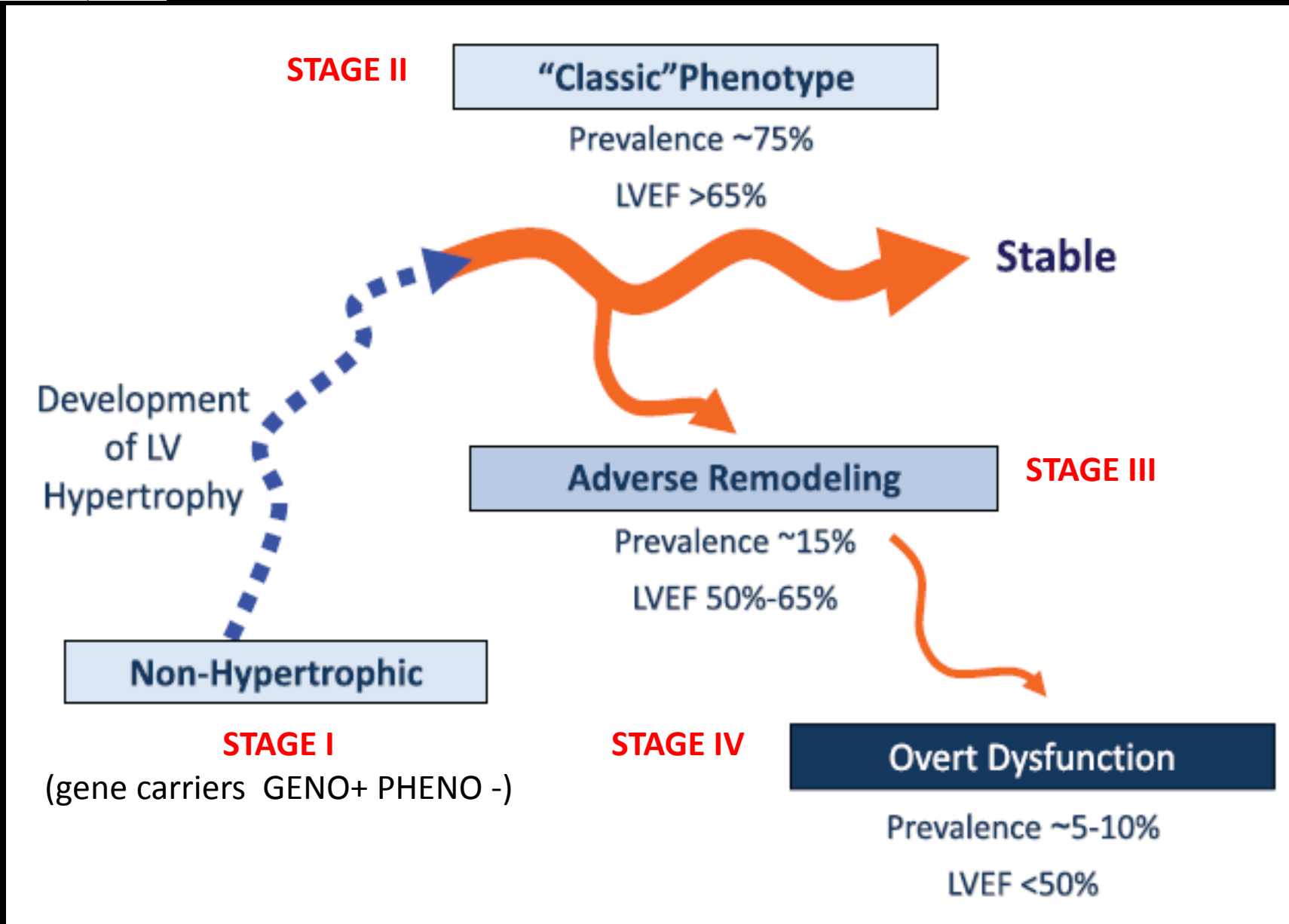
Figure 2. A symptomatic patient with no significant left ventricular hypertrophy but with severe provocable left ventricular outflow tract (LVOT) obstruction. **A**, Illustration shows abnormal chordal attachment to the base of the anterior mitral leaflet (yellow color, arrow). **B**, Echocardiogram shows abnormal chordal attachment to the base of the anterior mitral leaflet (arrow). **C**, Spectral Doppler across LVOT with severe late peaking dynamic LVOT obstruction (arrow).

Patterns of Disease Progression in Hypertrophic Cardiomyopathy

An Individualized Approach to Clinical Staging

Iacopo Olivotto, MD; Franco Cecchi, MD; Corrado Poggesi, MD; Magdi H. Yacoub, MD, FRS

Circ Heart Fail. 2012;5:535-546



Diagnosi differenziale

CMI sarcomerica e non sarcomerica

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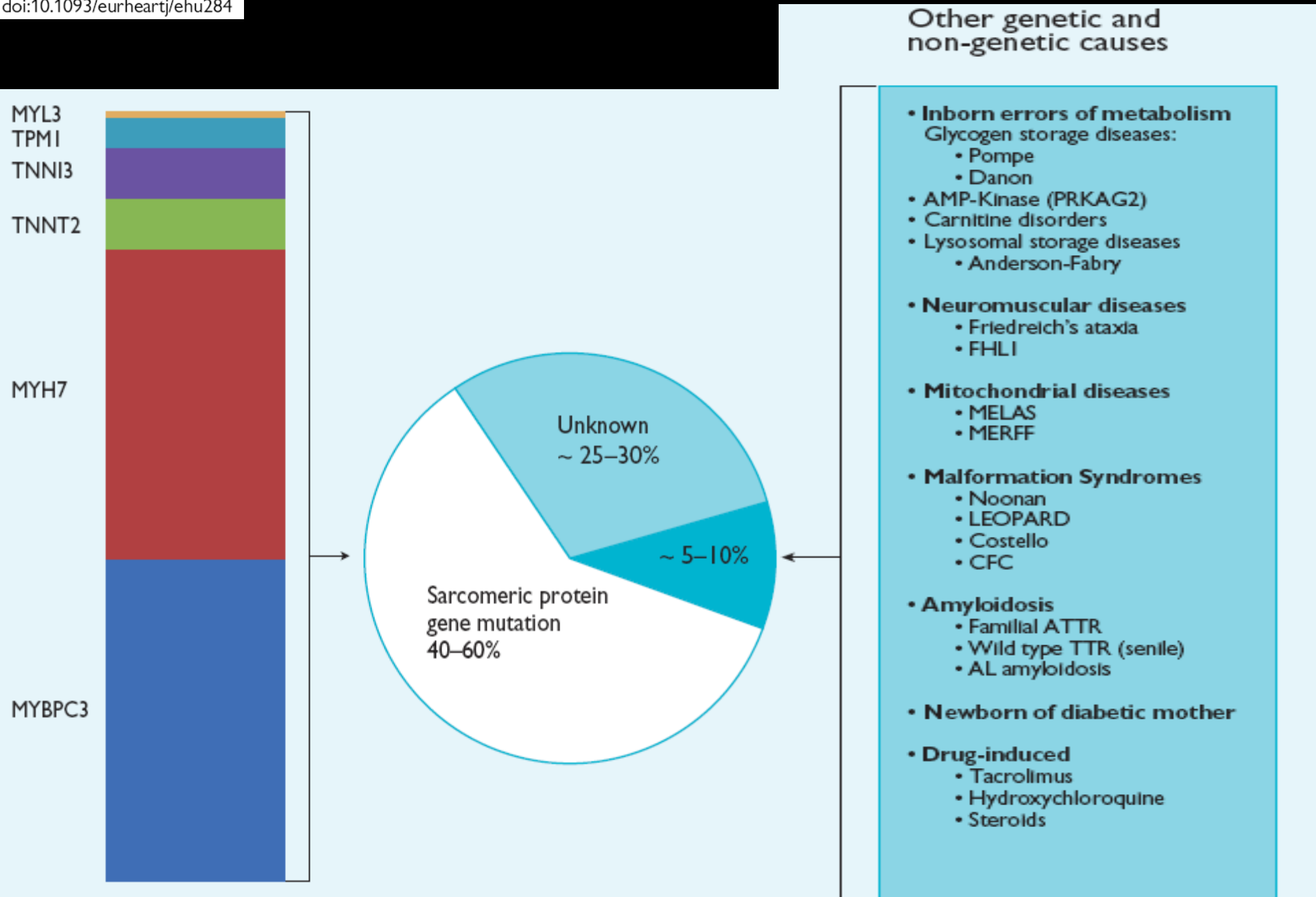

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SEGNI & SINTOMI

Symptom/sign	Diagnosis
Learning difficulties, mental retardation	• Mitochondrial diseases • Noonan/LEOPARD/Costello syndrome • Danon disease
Sensorineural deafness	• Mitochondrial diseases (particularly with diabetes) • Anderson-Fabry disease • LEOPARD syndrome
Visual impairment	• Mitochondrial diseases (retinal disease, optic nerve atrophy) • TTR-related amyloidosis (cotton wool type vitreous opacities) • Danon disease (retinitis pigmentosa) • Anderson-Fabry disease (cataracts, corneal opacities)
Gait disturbance	• Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	• Amyloidosis • Anderson-Fabry disease
Carpal tunnel syndrome	• TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	• Mitochondrial diseases • Glycogen storage disorders • FHL1 mutations • Friedreich's ataxia
Palpebral ptosis	• Mitochondrial diseases • Noonan/LEOPARD syndrome • Myotonic dystrophy
Lentigines/café au lait spots	• LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	• Anderson-Fabry disease

ECG

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.
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 elevation in the lateral chest leads.

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Eco : Diagnosi Differenziale

Echocardiographic features that suggest specific aetiologies[a]	
Finding	**Specific diseases to be considered**
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2-D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

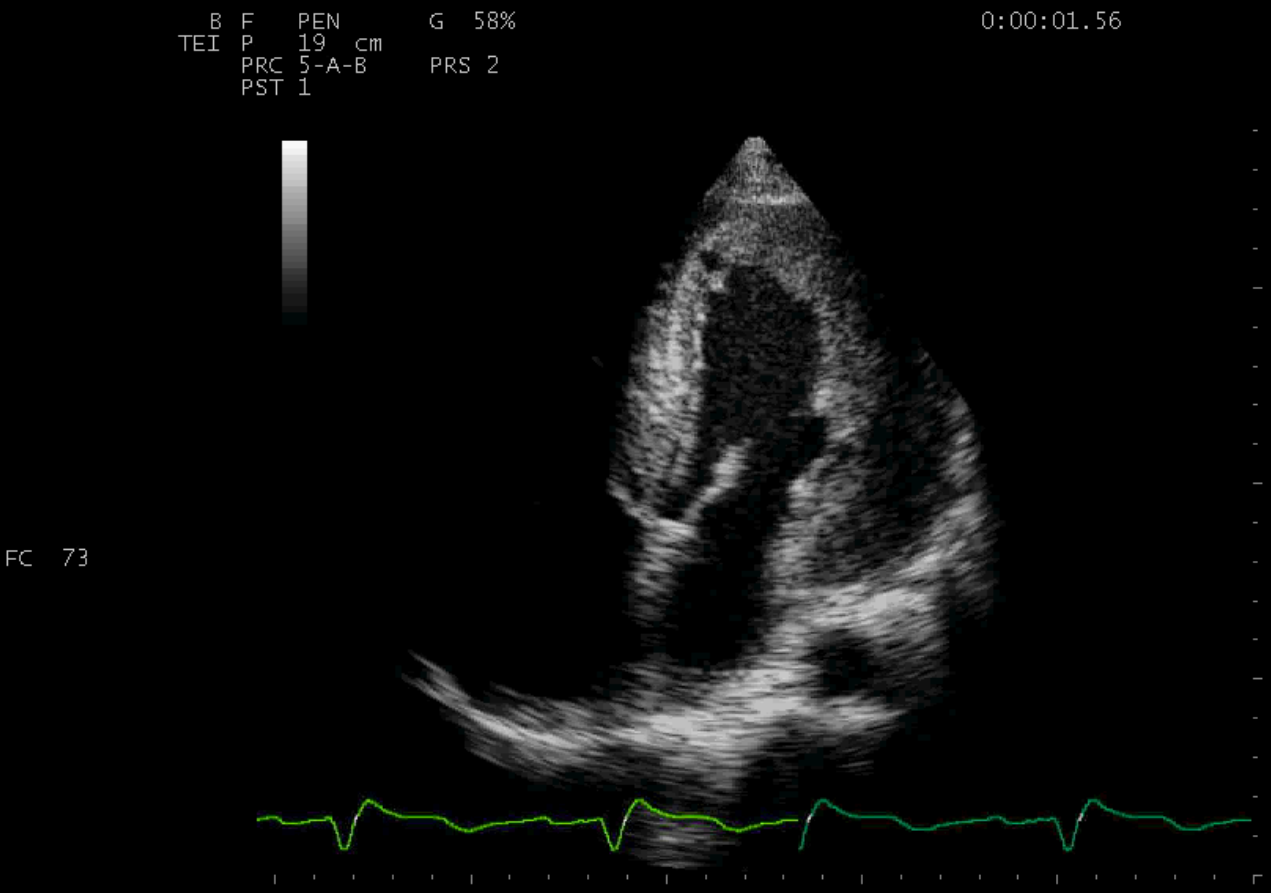
MM 46 y male

His sister died suddenly 7 days ago at age 46. His mother died suddenly at age 52

His wife wants to know whether he has heart disease. He claims no symptoms. FC I

Abnormal ECG

ECHO LVH EF 44%

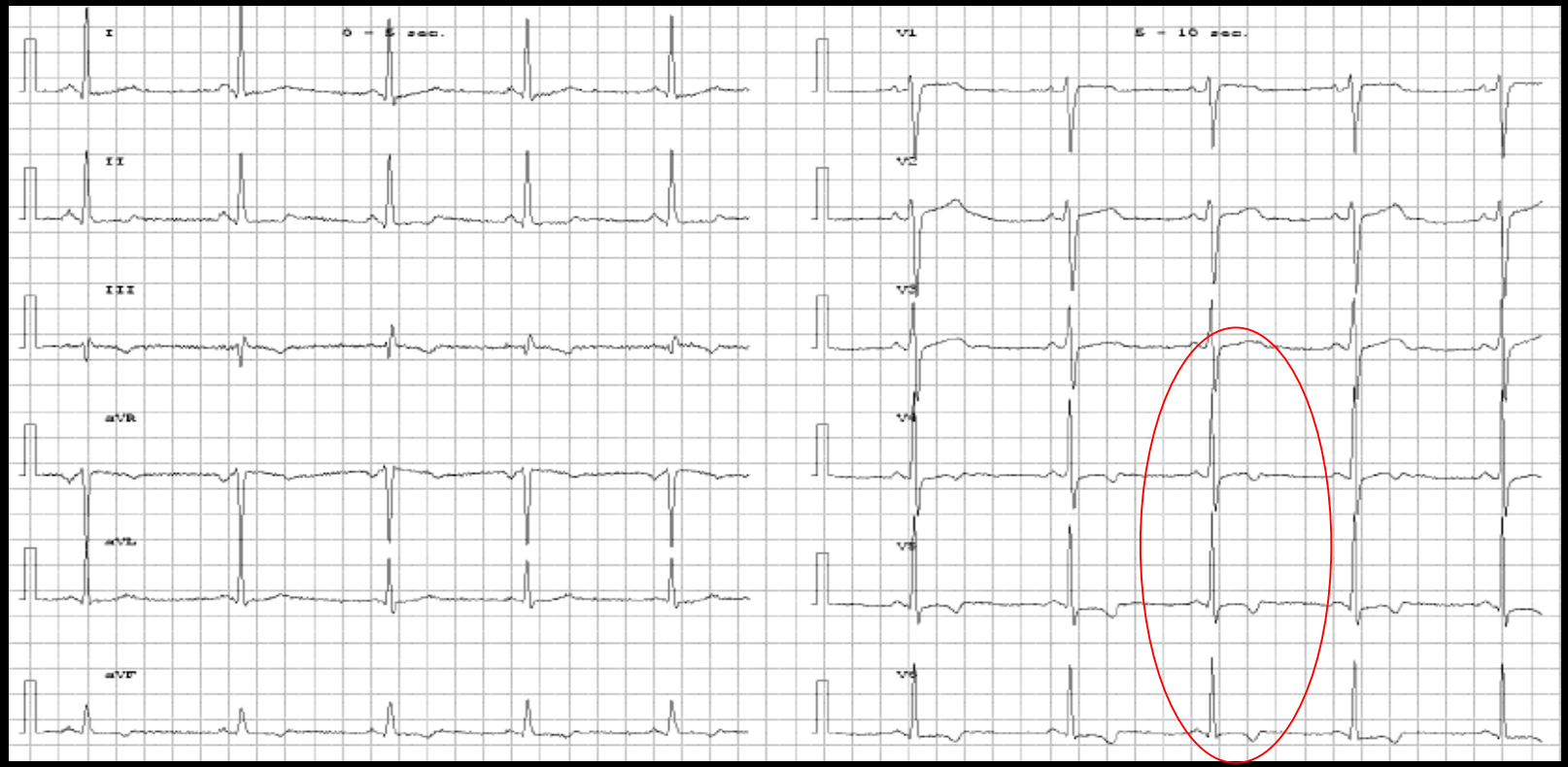


FAMILIAL TTR AMYLOIDOSIS

HEART AND LIVER TRANSPLANT

B MG, female, age 48, referred to ED for severe angina

- No family history
- At age 40 she was diagnosed with depression
- At age 45 she started to complain of fatigue, palpitations and angina
- No significant clinical signs; BP 120/80. Normal enzymes



B MG, female, age 48

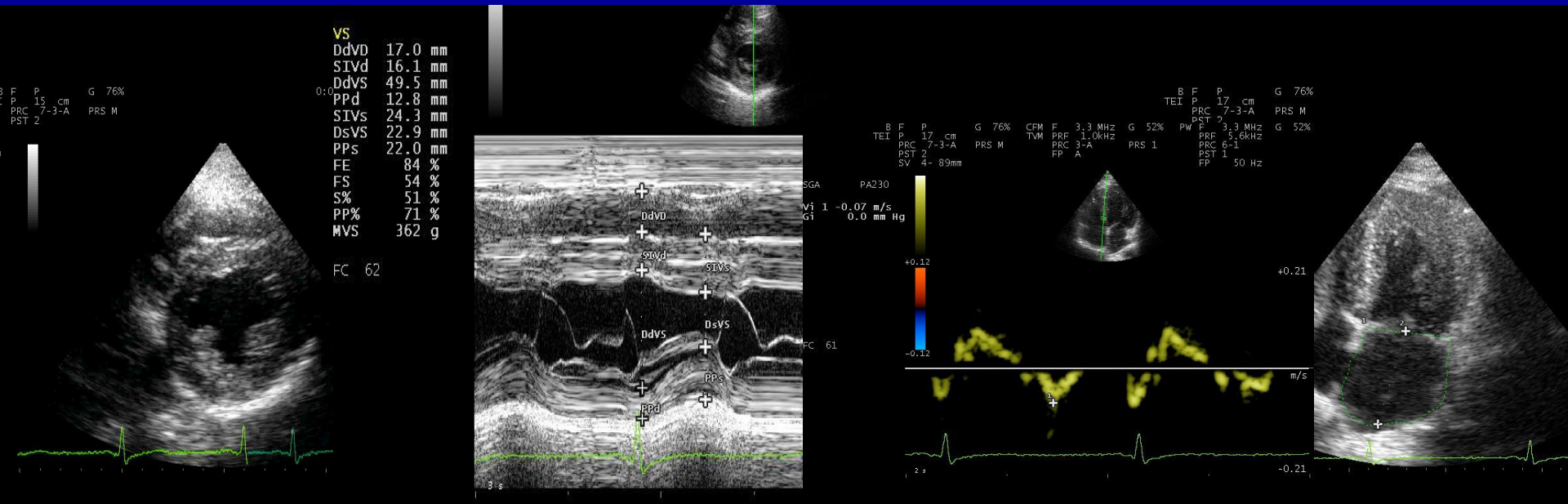
- No Coronary artery disease at coronary angio

- Unexplained LVH at echo (16 mm) LV EF 65%
- Diastolic dysfunction (TDI septal e' 7 cm/sec) + Mild LA dilatation

Anderson Fabry HCM

α-Gal leucocyte activity 46.02 nmol/mg/h

GLA c.1 A>G (p.Met 1 Val)



Prevenzione morte improvvisa

RISK STRATIFICATION: RISK FACTORS

(ICD Guidelines for HCM AHA/ESC 2003 & AHA 2011)

RISK FACTOR	Sensitivity	Specificity	PPV	NPV
Family history of SD	42	79	28	88
Max LV thickness >30 mm	26	88	13	95
NSVT run > 120’	69	80	22	97
Abnormal pressure response at exercise test age < 45	75	66	15	97
Syncope	29	83	25	86

Elliot P, W.McKenna, 2003

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The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC)

http://www.escardio.org/Guidelines-&-Education/

http://doc2do.com/hcm/webHCM.html

Risk of SCD at 5 years (%):

Valutazione del rischio individuale di morte improvvisa a 5 anni

(da fare alla prima visita,

poi ogni 1-2 anni oppure

se cambia la Classe funzionale)

HCM Risk-SCD Calculator

Age	Years	*Age at evaluation*
Maximum LV wall thickness	mm	*Transthoracic Echocardiographic measurement*
Left atrial size	mm	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	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 chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	No Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 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.*

Indicazione clinica ad ICD

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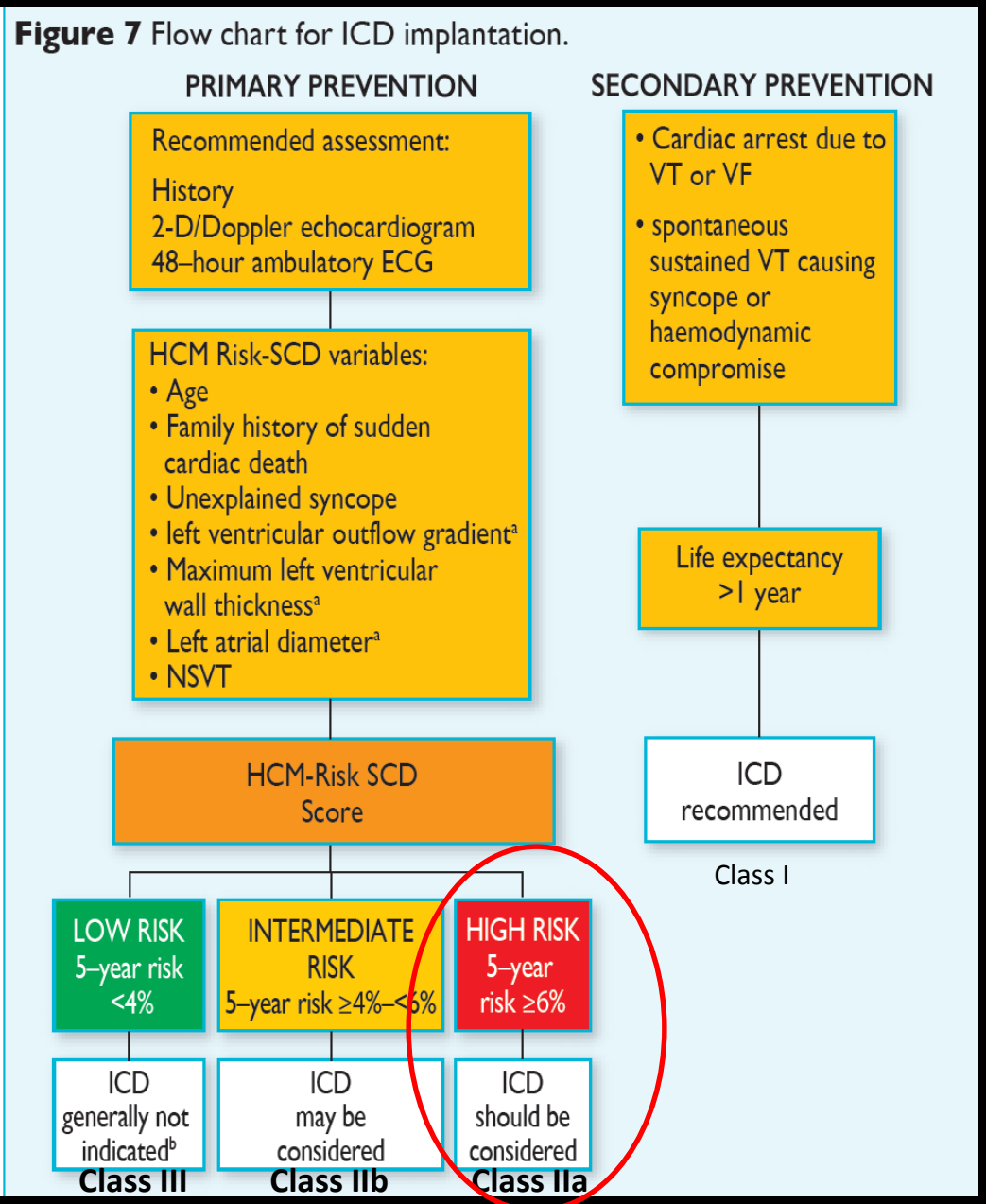


Figure 7 Flow chart for ICD implantation.

Occorre tenere conto non solo del rischio individuale a 5 anni, ma anche:

- Età del paziente
- Condizioni generali salute
- Fattori socio-economici
- Impatto psicologico

Additional Risk Factors for SCD risk stratification

- CHF, end stage /overt dysfunction disease (Stage III-IV EF < 50%)
- Abn BP response / Ventricular arrhythmias (NSVT /VF) on Ex test
- Extent of LGE by CMR (>15%)
- Bizarre ECG (pseudo STEMI pattern; low QRS voltages; QRS > 120)
- VE/VCO2 > 31 at cardiopulmonary test

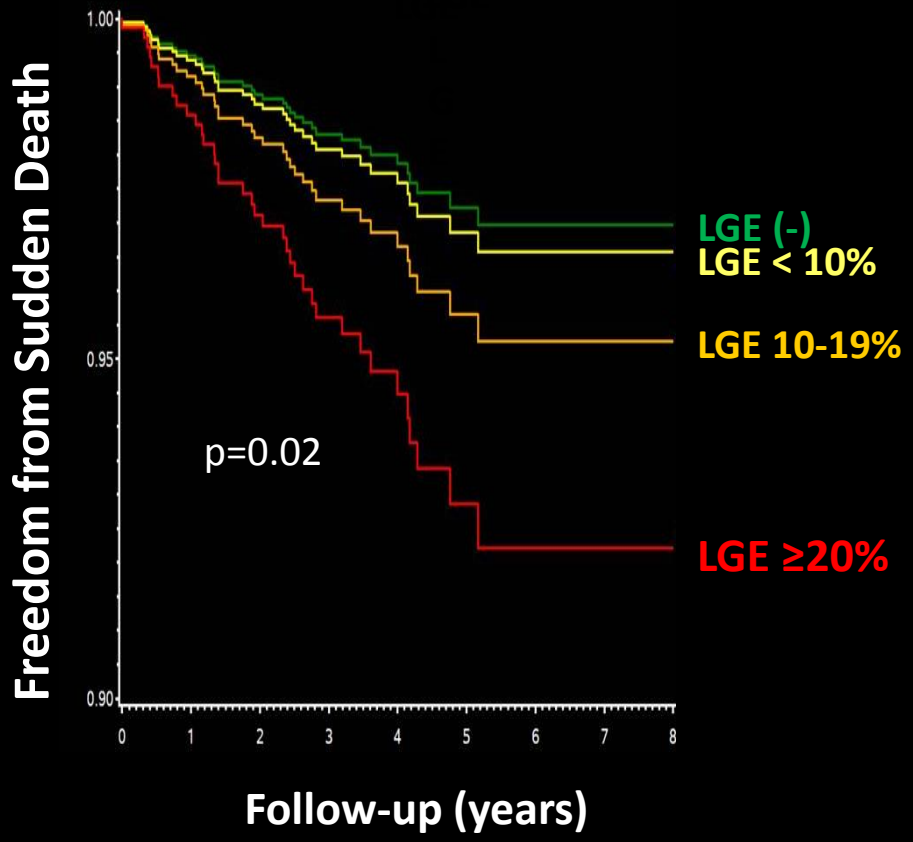
Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients With Hypertrophic Cardiomyopathy

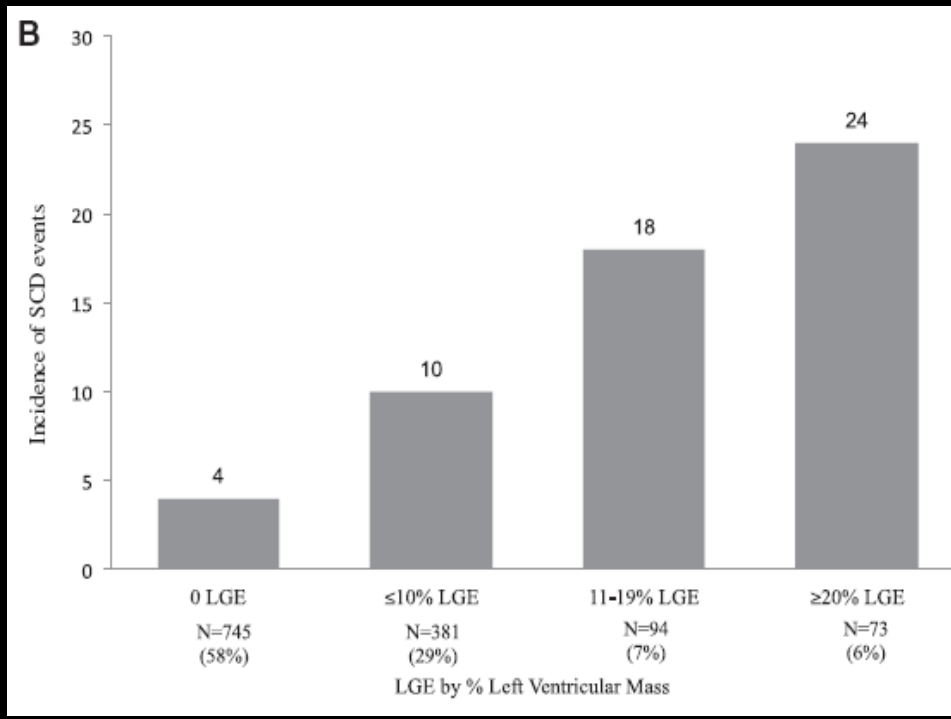
Raymond H. Chan, MD, MPH; Barry J. Maron, MD; Iacopo Olivotto, MD; Michael J. Pencina, PhD; Gabriele Egidy Assenza, MD; Tammy Haas, RN; John R. Lesser, MD; Christiane Gruner, MD; Andrew M. Crean, MD; Harry Rakowski, MD; James E. Udelson, MD; Ethan Rowin, MD; Massimo Lombardi, MD; Franco Cecchi, MD; Benedetta Tomberli, MD; Paolo Spirito, MD; Francesco Formisano, MD; Elena Biagini, MD; Claudio Rapezzi, MD; Carlo Nicola De Cecco, MD; Camillo Autore, MD; E. Francis Cook, PhD; Susie N. Hong, MD; C. Michael Gibson, MD, MS; Warren J. Manning, MD; Evan Appelbaum, MD; Martin S. Maron, MD

Circulation 2014

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

Extent of LGE (> 15%)
is an additional risk factor in pts considered at low risk



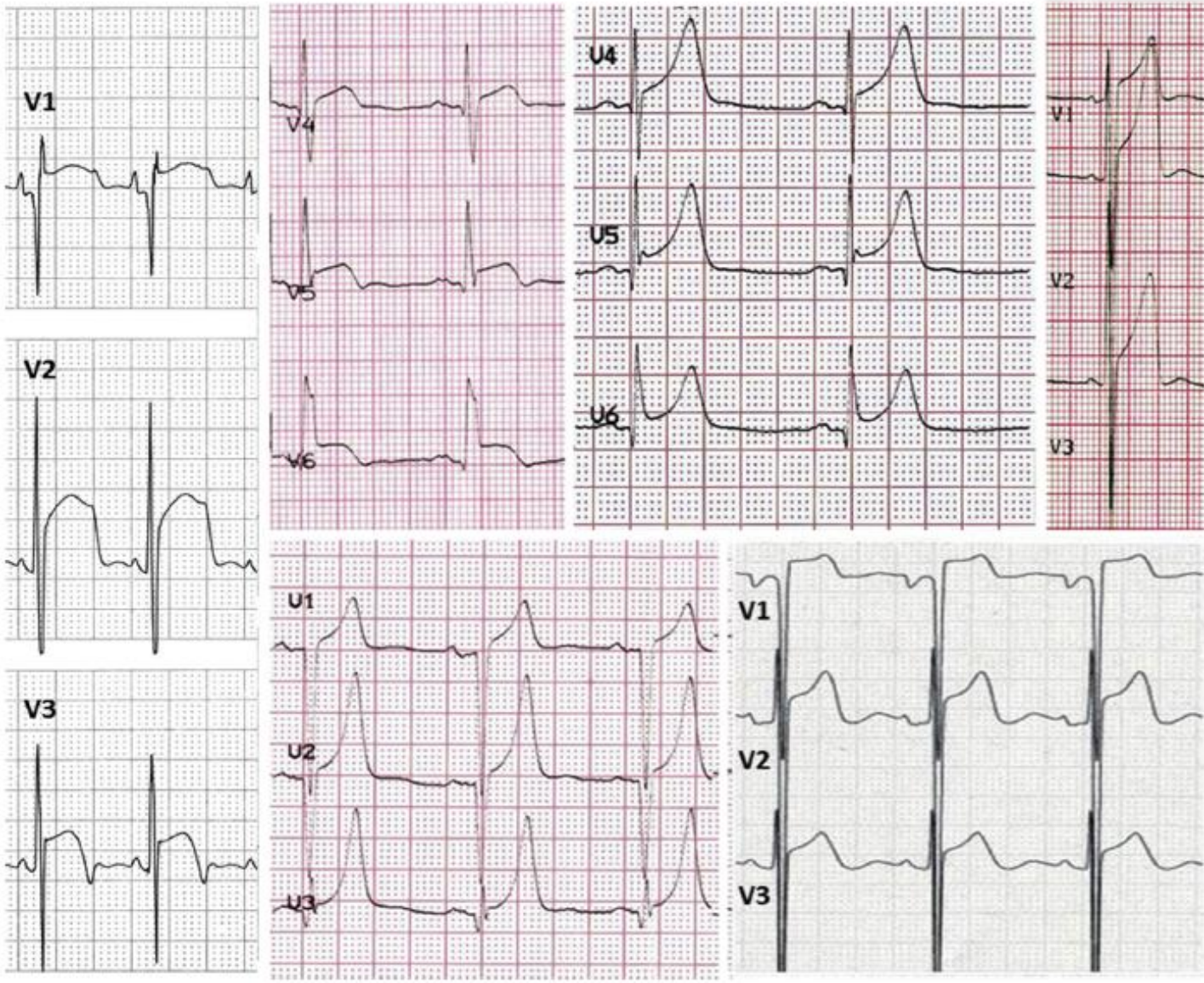


PSEUDOSTEMI PATTERN (17%)

Usefulness of Electrocardiographic Patterns at Presentation to Predict Long-term Risk of Cardiac Death in Patients With Hypertrophic Cardiomyopathy

Elena Biagini, MD, PhD[a], Chiara Pazzi, MD[a], Iacopo Olivotto, MD[b], Beatrice Musumeci, MD[c], Giuseppe Limongelli, MD[d], Giuseppe Boriani, MD, PhD[a], Giuseppe Pacileo, MD[d], Vittoria Mastromarino, MD[c], Maria Letizia Bacchi Reggiani, BSc[a], Massimiliano Lorenzini, MD[a], Francesco Lai, MD[a], Alessandra Berardini, MD[a], Francesca Mingardi, MD[a], Stefania Rosmini, MD, PhD[a], Elvira Resciniti, MD[a], Claudia Borghi, MD, PhD[a], Camillo Autore, MD[c], Franco Cecchi, MD[b], and Claudio Rapezzi, MD[a,*]

Am J Cardiol 2016

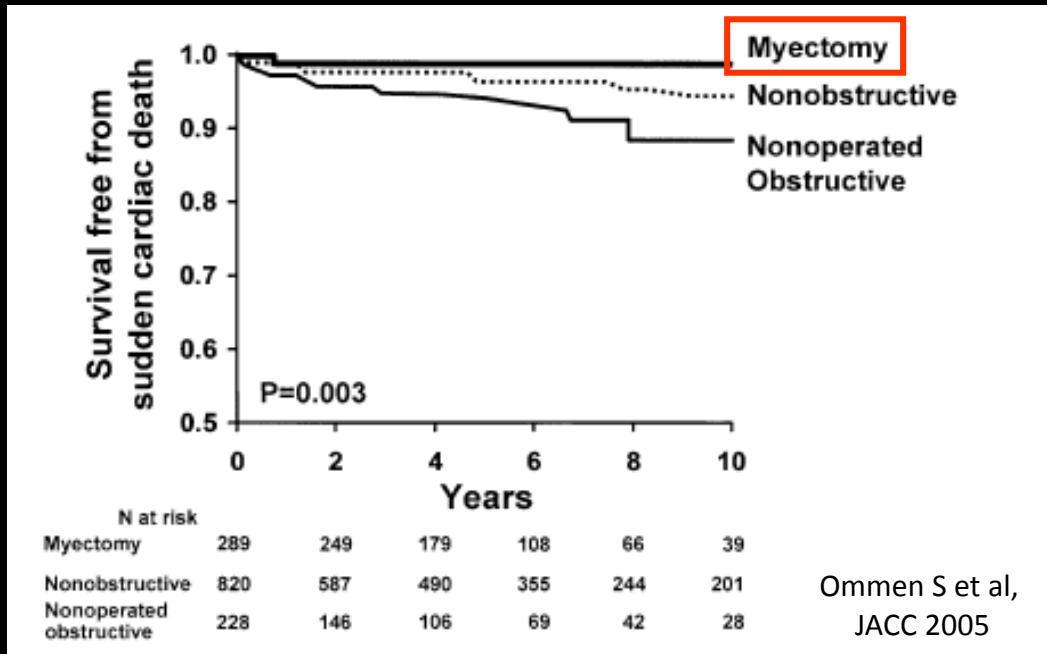


Lifestyle and treatment options for SCD risk reduction

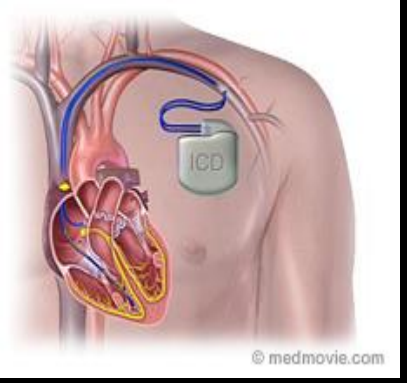
- Avoidance of competitive sports is recommended (Class I)
- AF ablation for AF with rapid ventricular response
- CAD treatment
- Myectomy reduces SD risk in HOCM pts

SURVIVAL FREE OF SUDDEN DEATH

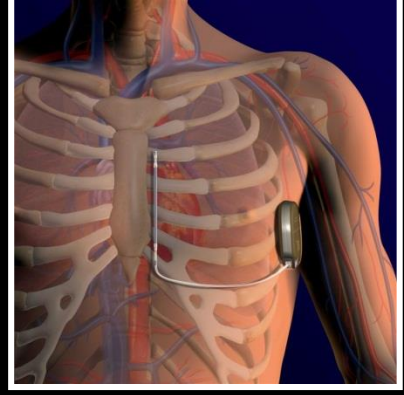
(Rochester Mayo Clinic, versus Minneapolis + Florence)



Ommen S et al, JACC 2005



CHOICE BETWEEN STANDARD VERSUS SUBCUTANEOUS ICD (S-ICD)



S-ICD may :

- avoid lead fracture and reduce sepsis management
- reduce inappropriate discharges due to SV arrhythmias
- improve LONG TERM RISK/BENEFIT RATIO + QOL
- increase acceptance by children and adolescents

S-ICD is not recommended when pacing is required

High Risk HCM patients

Favour S-ICD		*Favour Transvenous ICD*
+	Young Age	-
-	Atrial Fibrillation	+
+	Prior Lead Related Complication	-
-	Indication for Pacing	+
-	Sustained VT amenable to ATP	+
-	Planned Myectomy/Alcohol ablation	+
+/-	QRS/T< 1.36	+/-
-	TWIs in more than two leads	+

Thanks !!

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