Cardiomiopatia ipertrofica: nuove evidenze di terapia

Dott.ssa Simona De Vecchi
AOU Maggiore di Novara

7. Specific cardiomyopathy phenotypes

7.1. Hypertrophic cardiomyopathy

The *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy* provide detailed recommendations on the assessment and management of patients with HCM.[1] The aim in this guideline is to provide a focused update to the 2014 document, highlighting novel aspects and signposting the reader to the assessment and management of HCM in adults and children. Further details to support the recommendations are available in Supplementary data online, *Table S1*.

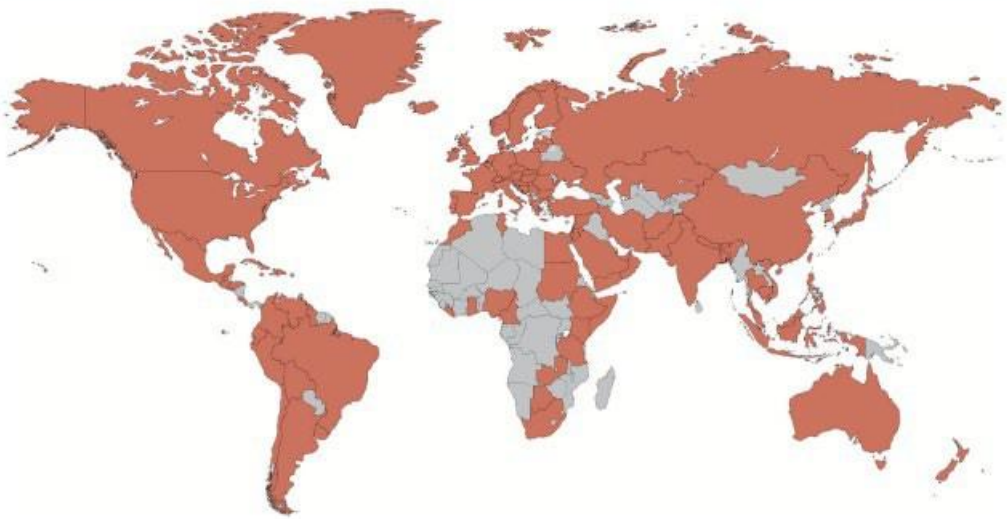
7.1.1. Diagnosis

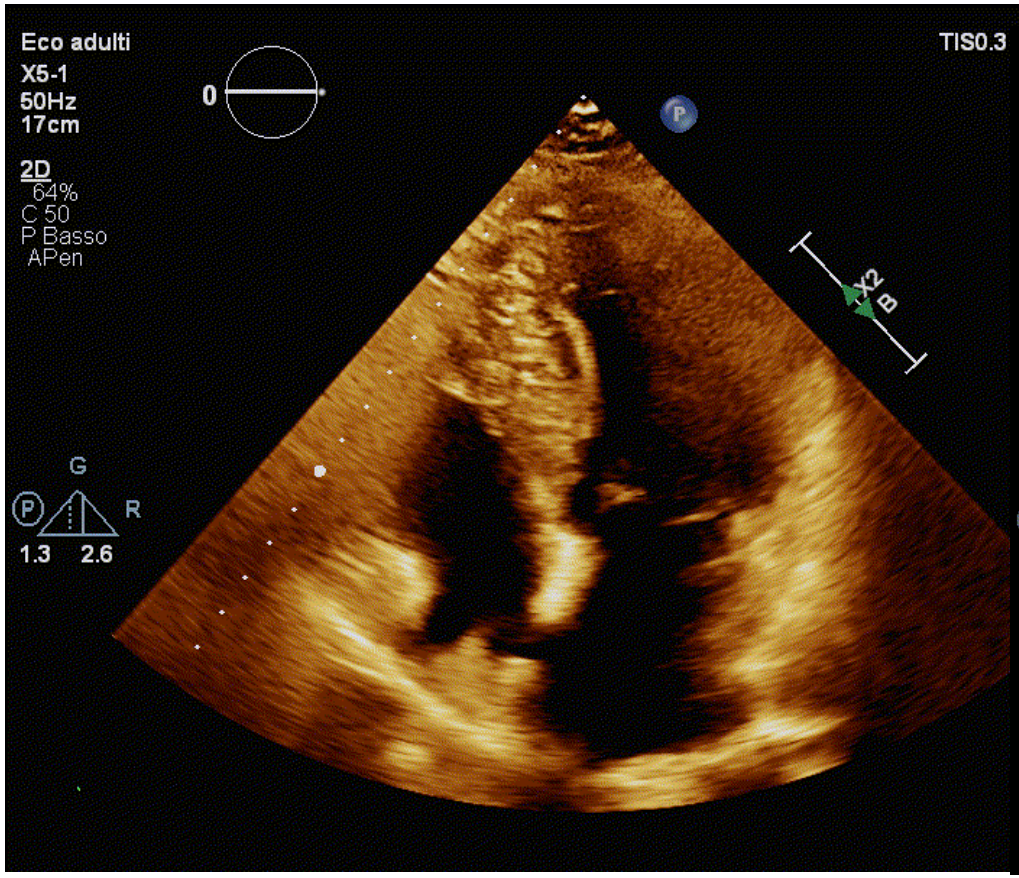
7.1.1.1. Diagnostic criteria

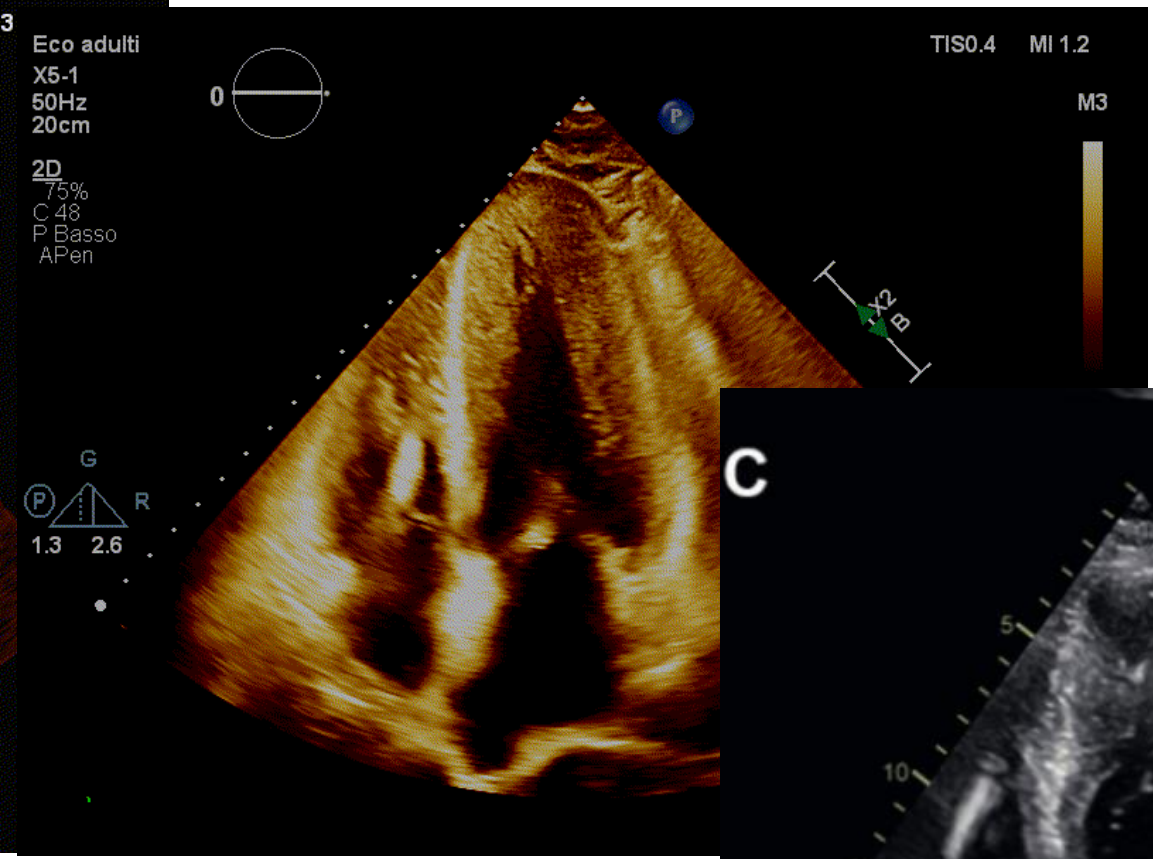
Adults: in an adult, HCM is defined by an LV wall thickness ≥15 mm in any myocardial segment that is not explained solely by loading conditions. Lesser degrees of wall thickening (13–14 mm) require evaluation of other features including family history, genetic findings, and ECG abnormalities.

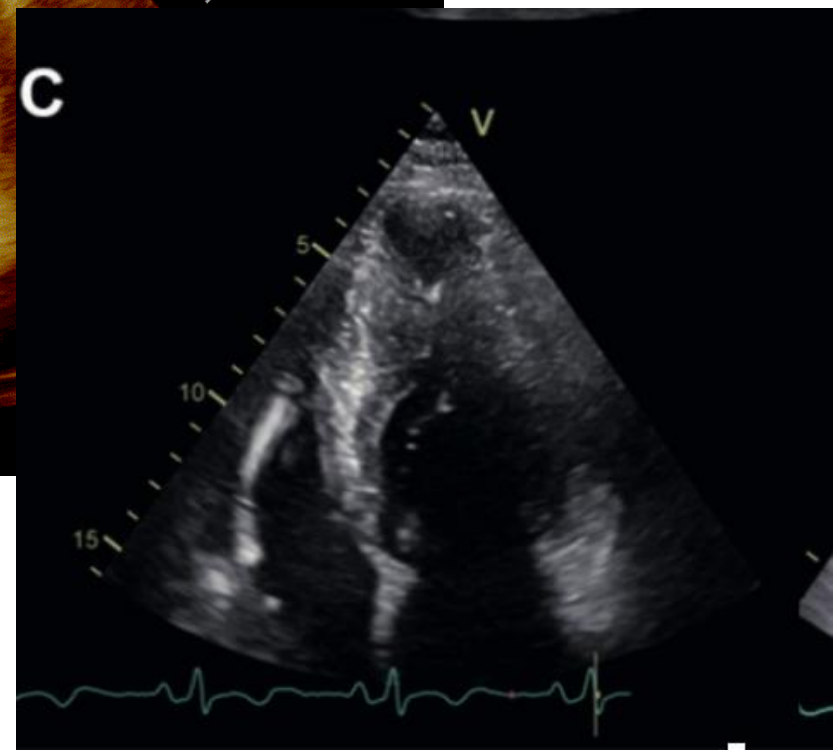
Children: the diagnosis of HCM requires an LV wall thickness more than 2 standard deviations greater than the predicted mean (z-score >2).[578]

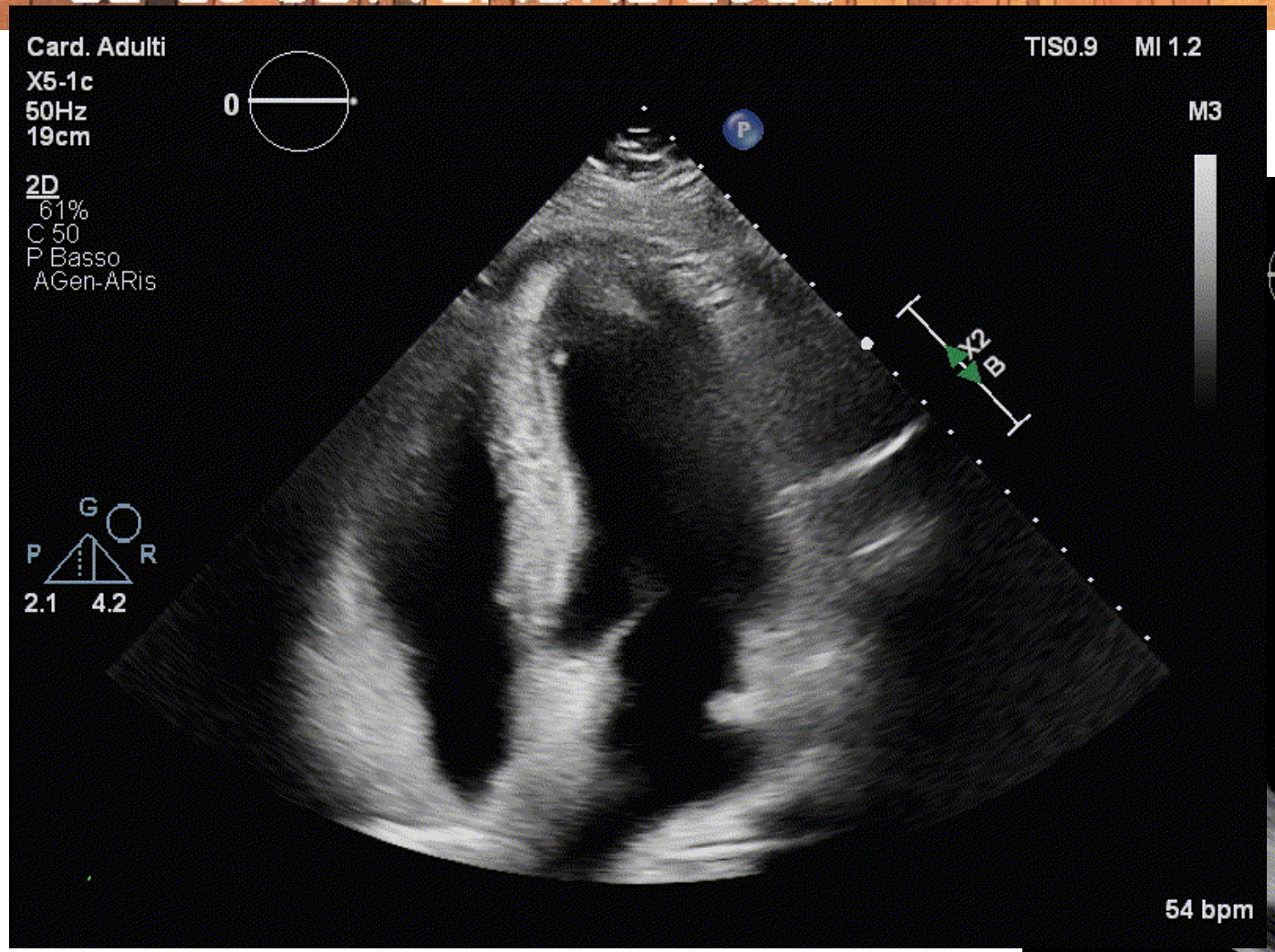
FIGURE 1 Global Distribution of HCM

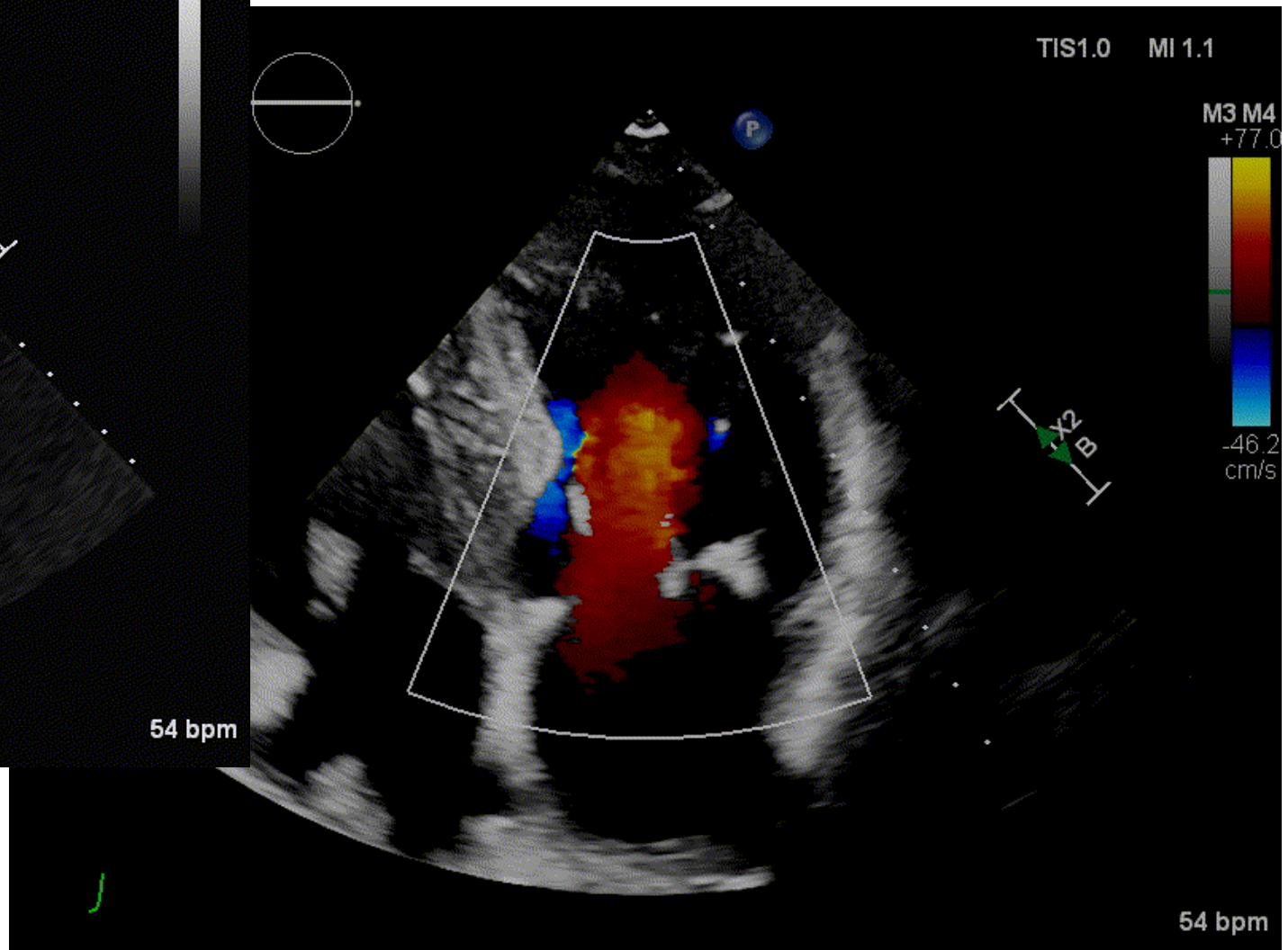



Eco adulti
X5-1
50Hz
17cm
2D
64%
C 50
P Basso
APen
TIS0.3
0
P
X2
B
G
P
R
1.3
2.6

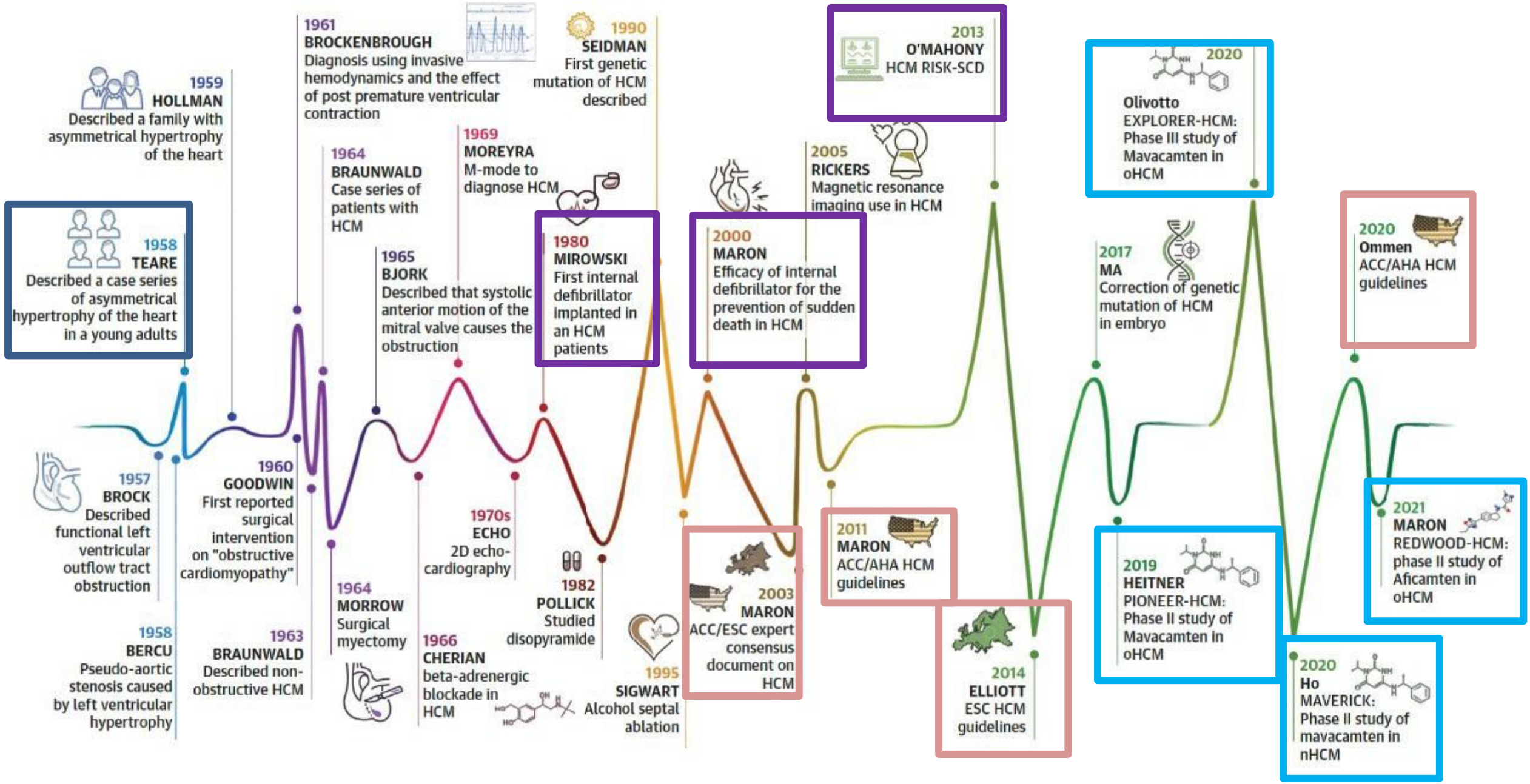

Eco adulti
X5-1
50Hz
20cm
2D
75%
C 48
P Basso
APen
TIS0.4
MI 1.2
M3
0
P
X2
B
G
P
R
1.3
2.6


C
V
5
10
15


Card. Adulti
X5-1c
50Hz
19cm
2D
61%
C 50
P Basso
AGen-ARis
TIS0.9
MI 1.2
M3
0
P
X2
B
G
P
R
2.1
4.2
54 bpm

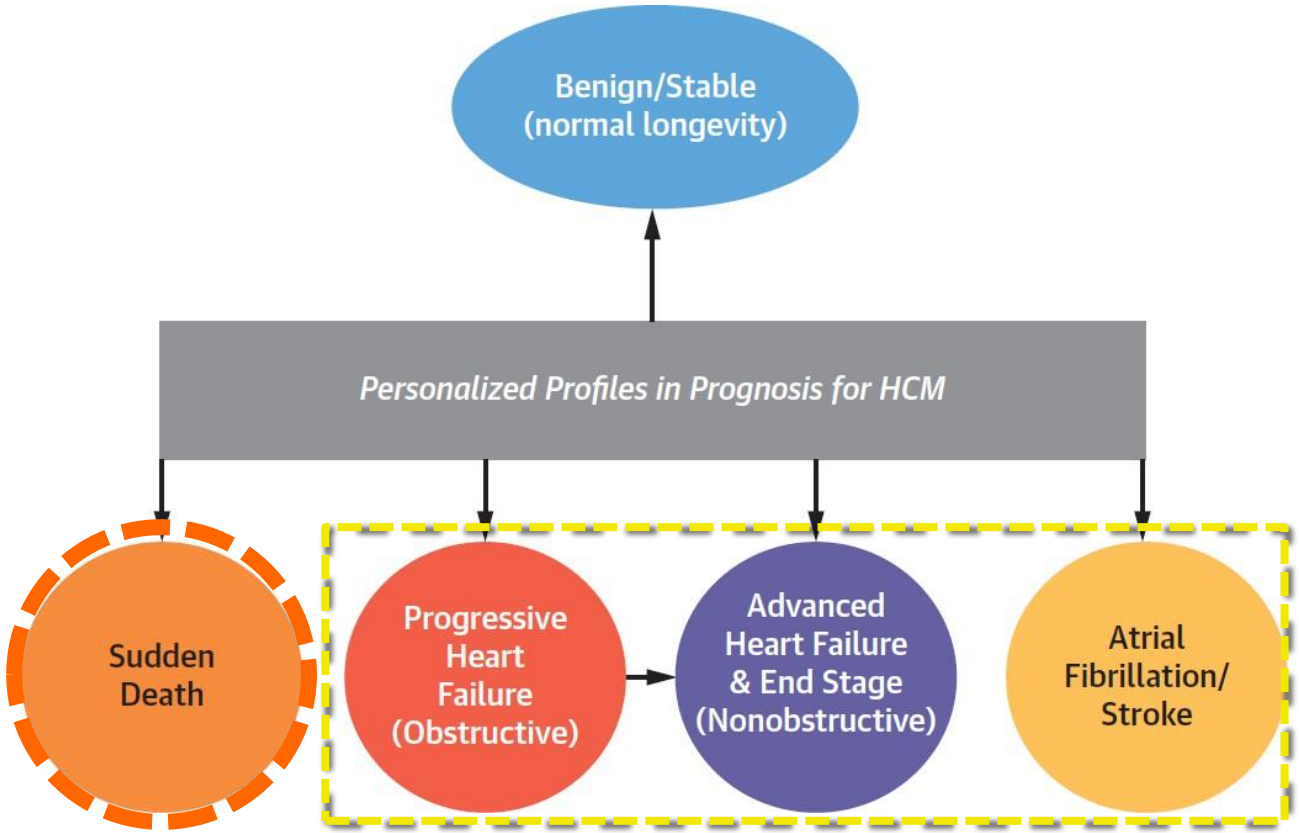

TIS1.0
MI 1.1
M3 M4
+77.0
-46.2
cm/s
P
X2
B
54 bpm

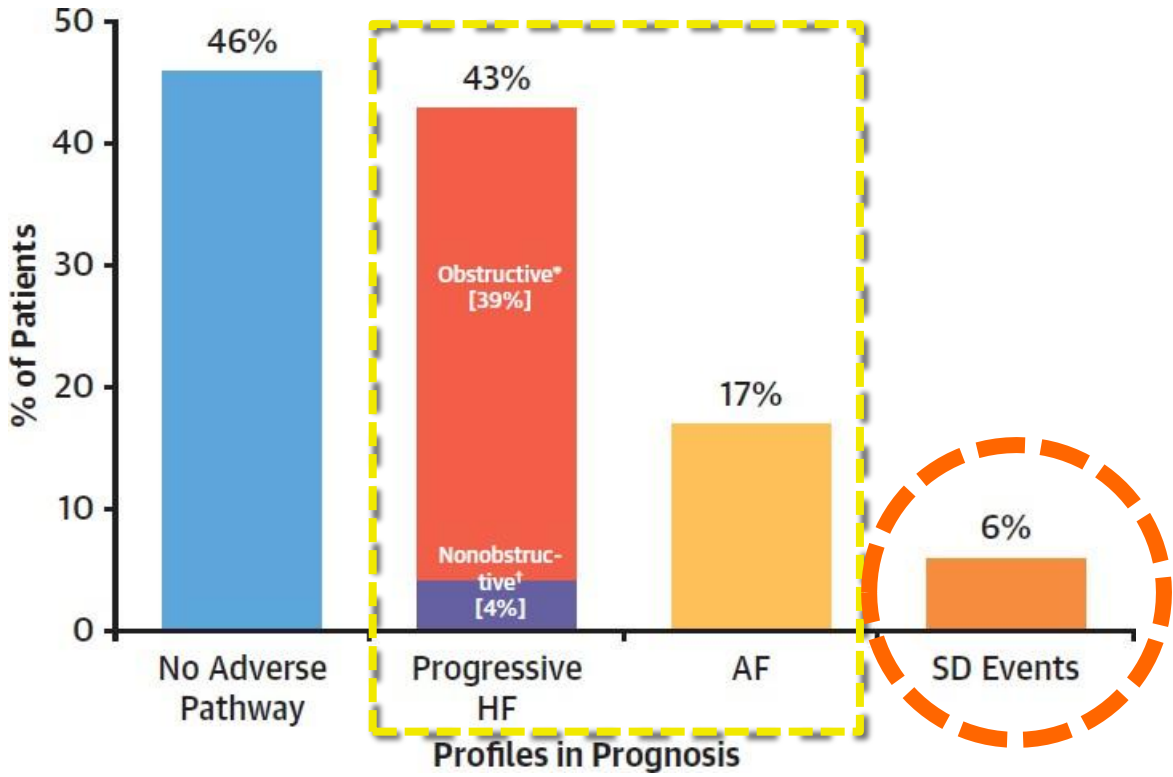
HCM timeline of the Major Advances and RCTs in HCM



Masri A. et al., Structutal Heart 2021

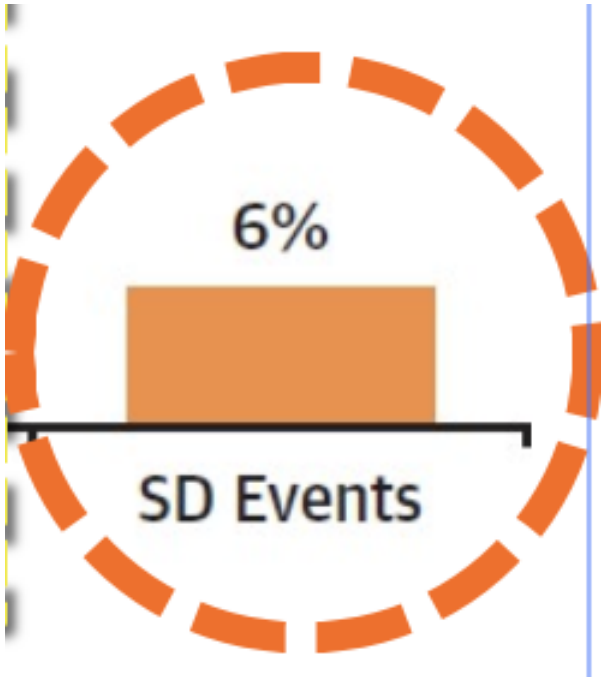
Prognostic profiles in HCM

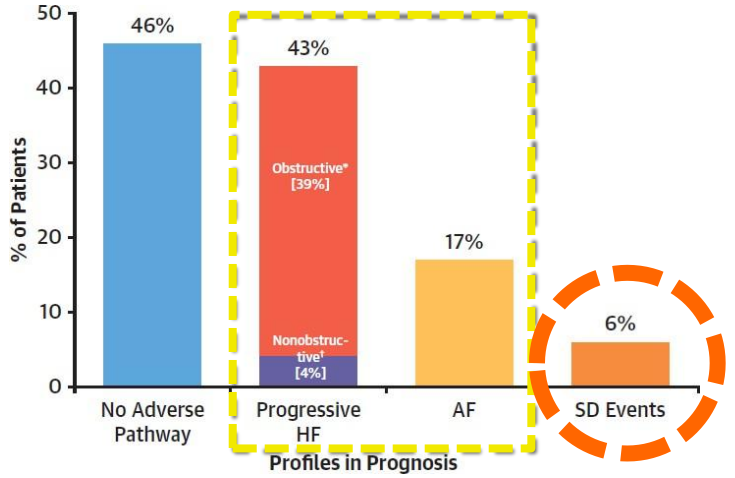




Maron et al. JACC 2022

Prognostic profiles in HCM





Rischio annuale specifico di morte cardiaca improvvisa è 0,8%

Maron et al. JACC 2022

The New England
Journal of Medicine

VOLUME 342 FEBRUARY 10, 2000 NUMBER 6

EFFICACY OF IMPLANTABLE CARDIOVERTER–DEFIBRILLATORS FOR THE PREVENTION OF SUDDEN DEATH IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

BARRY J. MARON, M.D., WIN-KUANG SHEN, M.D., MARK S. LINK, M.D., ANDREW E. EPSTEIN, M.D., ADRIAN K. ALMQUIST, M.D., JAMES P. DAUBERT, M.D., GUST H. BARDY, M.D., STEFANO FAVALE, M.D., ROBERT F. REA, M.D., GIUSEPPE BORIANI, M.D., N.A. MARK ESTES III, M.D., AND PAOLO SPIRITO, M.D.*

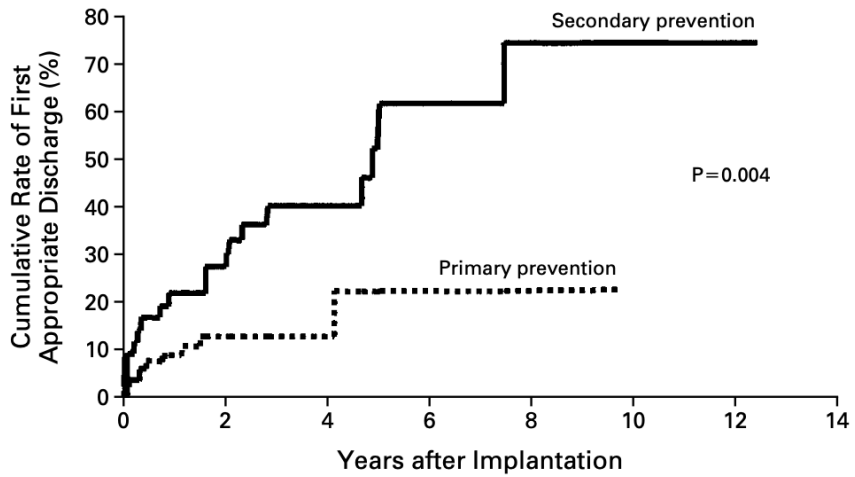


Figure 4. Estimated Cumulative Rates of First Appropriate Discharges, Calculated Separately for the 85 Patients with Defibrillators for Primary Prevention and the 43 Patients with Defibrillators for Secondary Prevention.

TABLE 1. CLINICAL AND ECHOCARDIOGRAPHIC DATA ON 128 PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY WHO RECEIVED IMPLANTABLE CARDIOVERTER–DEFIBRILLATORS.*

CHARACTERISTIC	VALUE
Mean age — yr	40±16
Male sex — no. (%)	88 (69)
NYHA class — no. (%)	
I	83 (65)
II	27 (21)
III or IV	18 (14)
Antiarrhythmic drugs — no.	
Amiodarone	
Before implantation	33
After implantation	22
Sotalol	
Before implantation	13
After implantation	11
Disopyramide	
Before implantation	7
After implantation	8
Maximal LV-wall thickness — mm†	
Mean	23±7
Range	14–60
LV end-diastolic cavity dimension — mm	
Mean	44±8
Range	23–61
Left atrial dimension — mm	
Mean	44±6
Range	26–62
LV outflow gradient — no. (%)	
≥30 mm Hg	23 (18)
<30 mm Hg‡	105 (82)
Electrophysiologic testing to induce VT or VF — no.	
Not inducible	12§
Inducible	79¶

studio retrospettivo di 128 pz con diagnosi di HCM sottoposti a AICD

EUROPEAN SOCIETY OF CARDIOLOGY®

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.*

Risk of SCD at 5 years (%):	
ESC recommendation:	

Reset

2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy (Eur Heart J 2014 – doi:10.1093/eurheartj/ehu284)

O'Mahony C et al Eur Heart J (2014) 35 (30): 2010-2020

Stima del rischio con HCM risk SCD

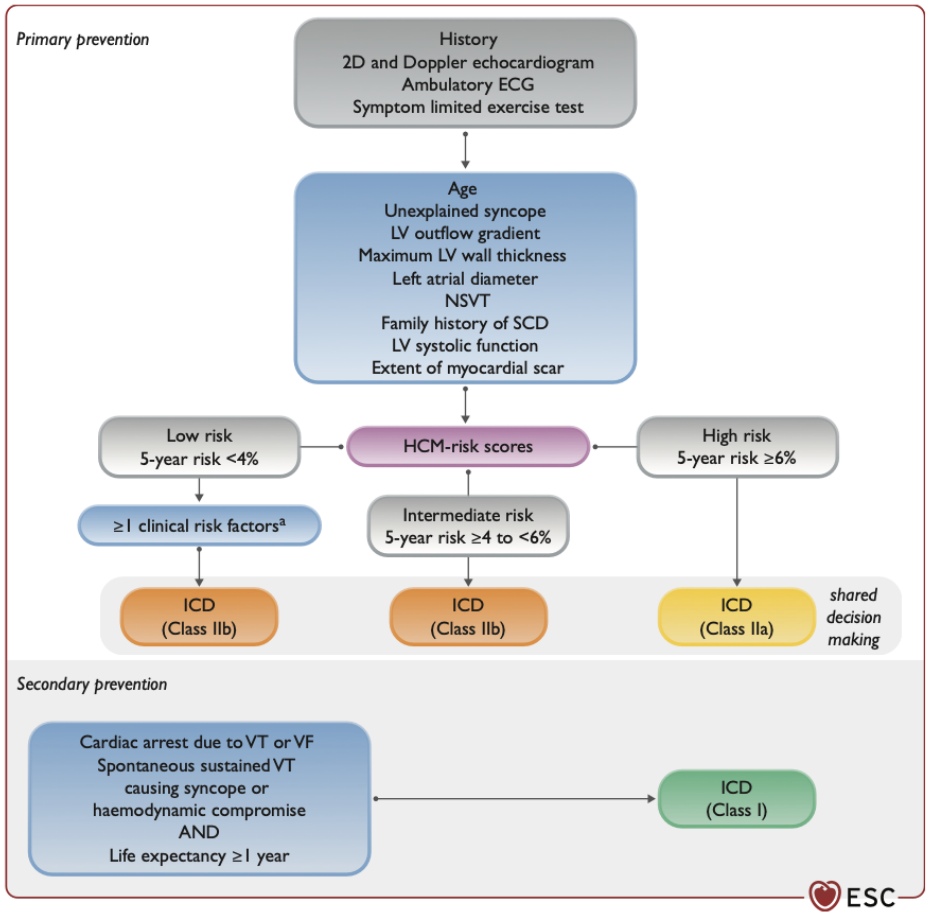
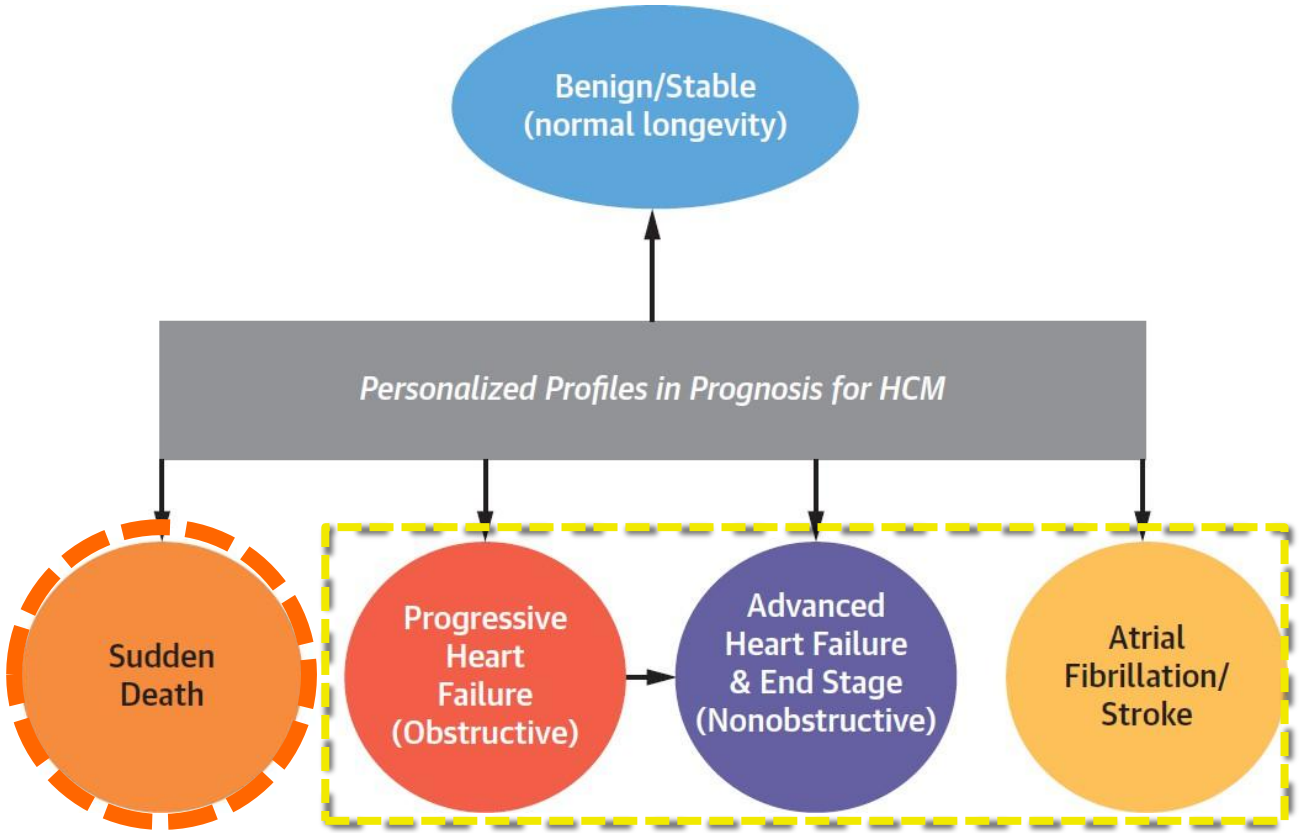
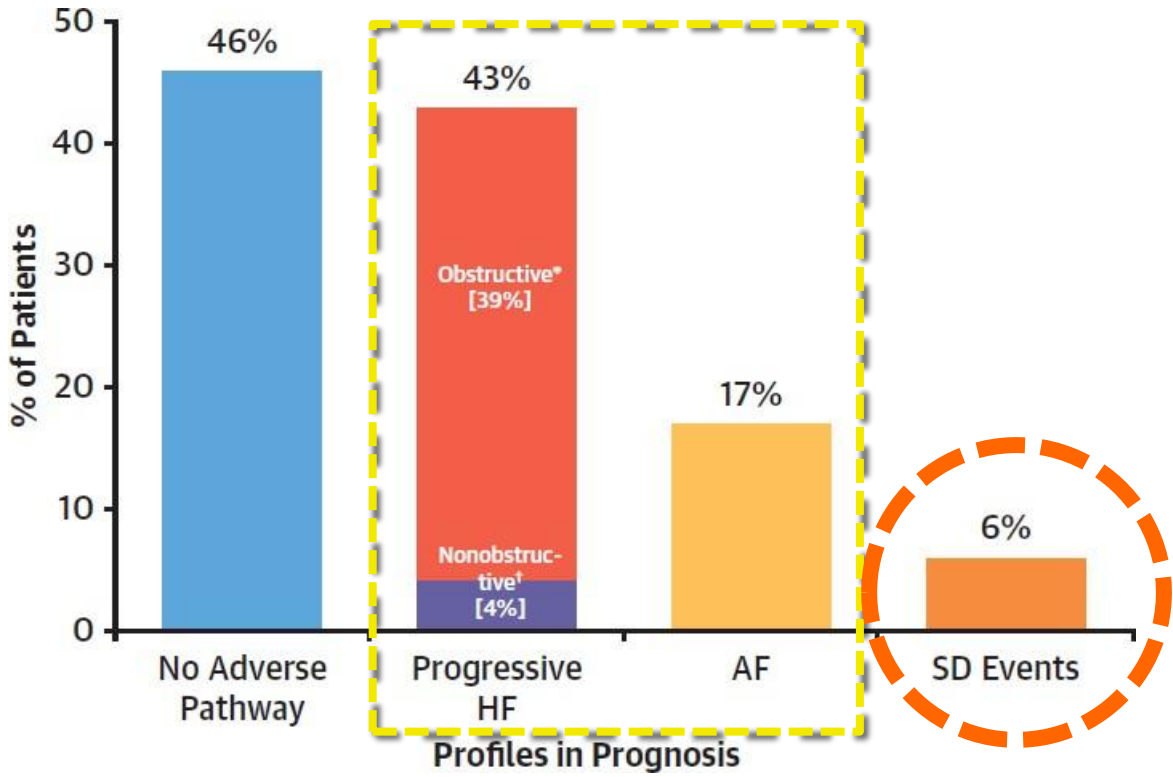


Figure 16 Flow chart for implantation of an implantable cardioverter defibrillator in patients with hypertrophic cardiomyopathy. 2D, two-dimensional; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia. [a]Clinical risk factors: extensive LGE (>15%) on CMR; LVEF <50%.

FE < 50%
LGE alla RMN > 15%

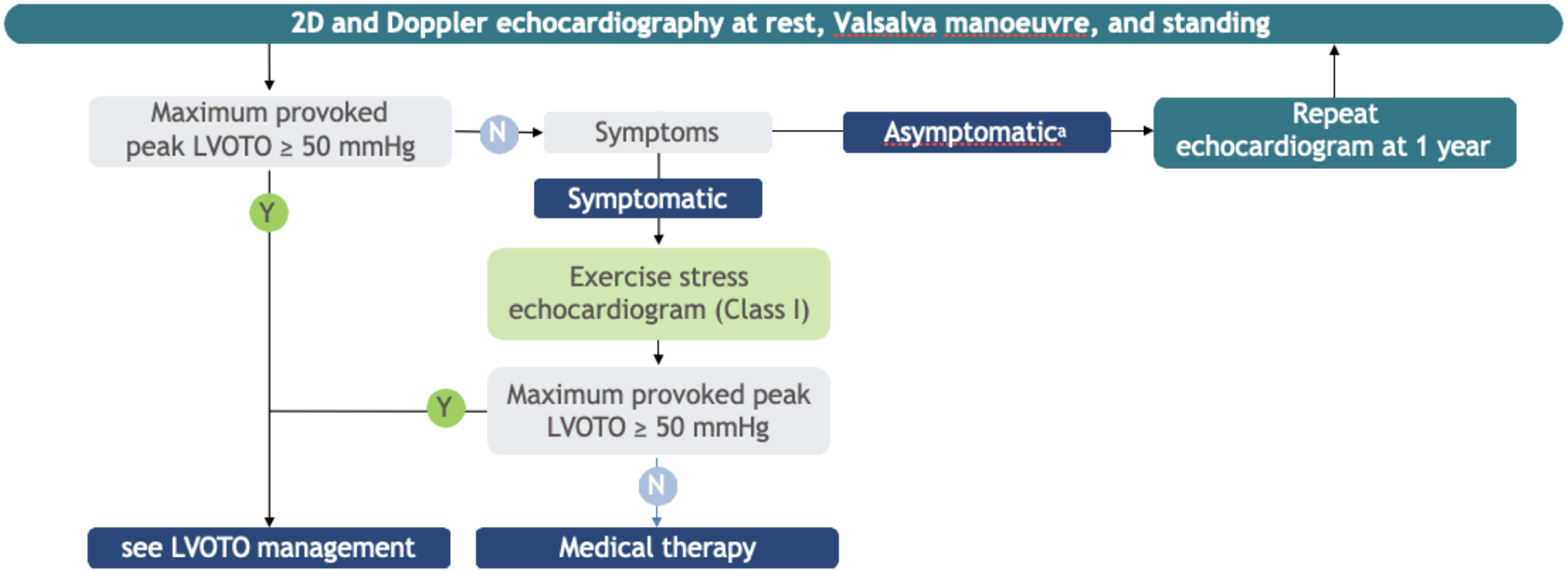
Prognostic profiles in HCM





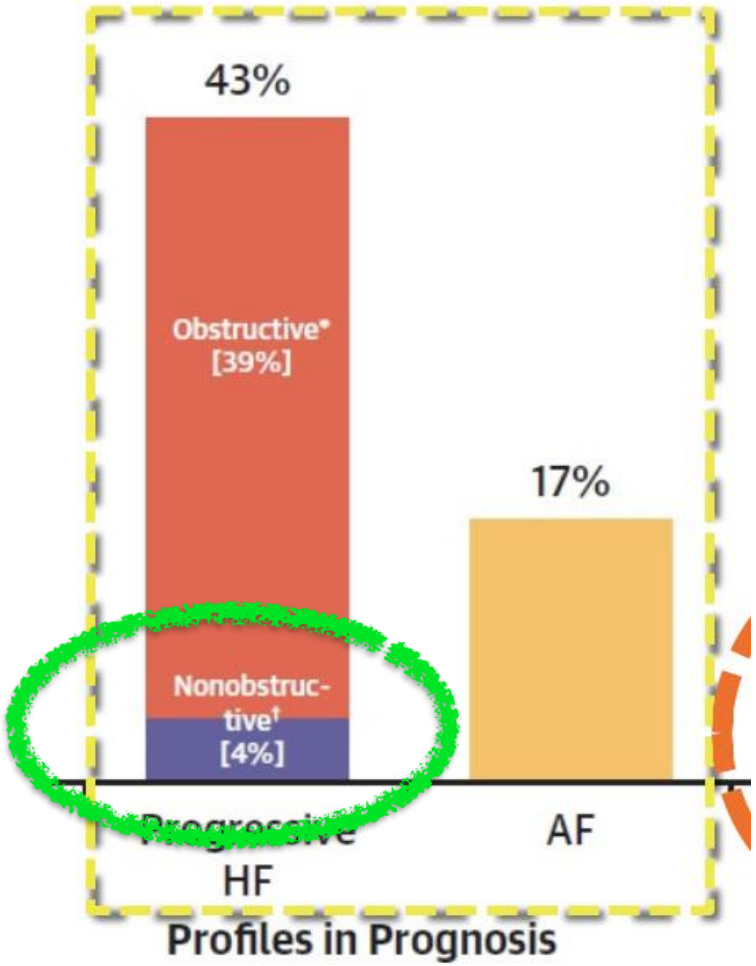
Maron et al. JACC 2022

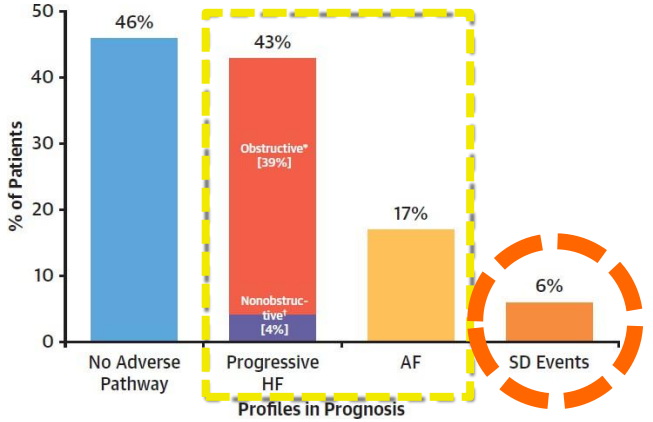
Assessment and treatment of left ventricular outflow tract obstruction



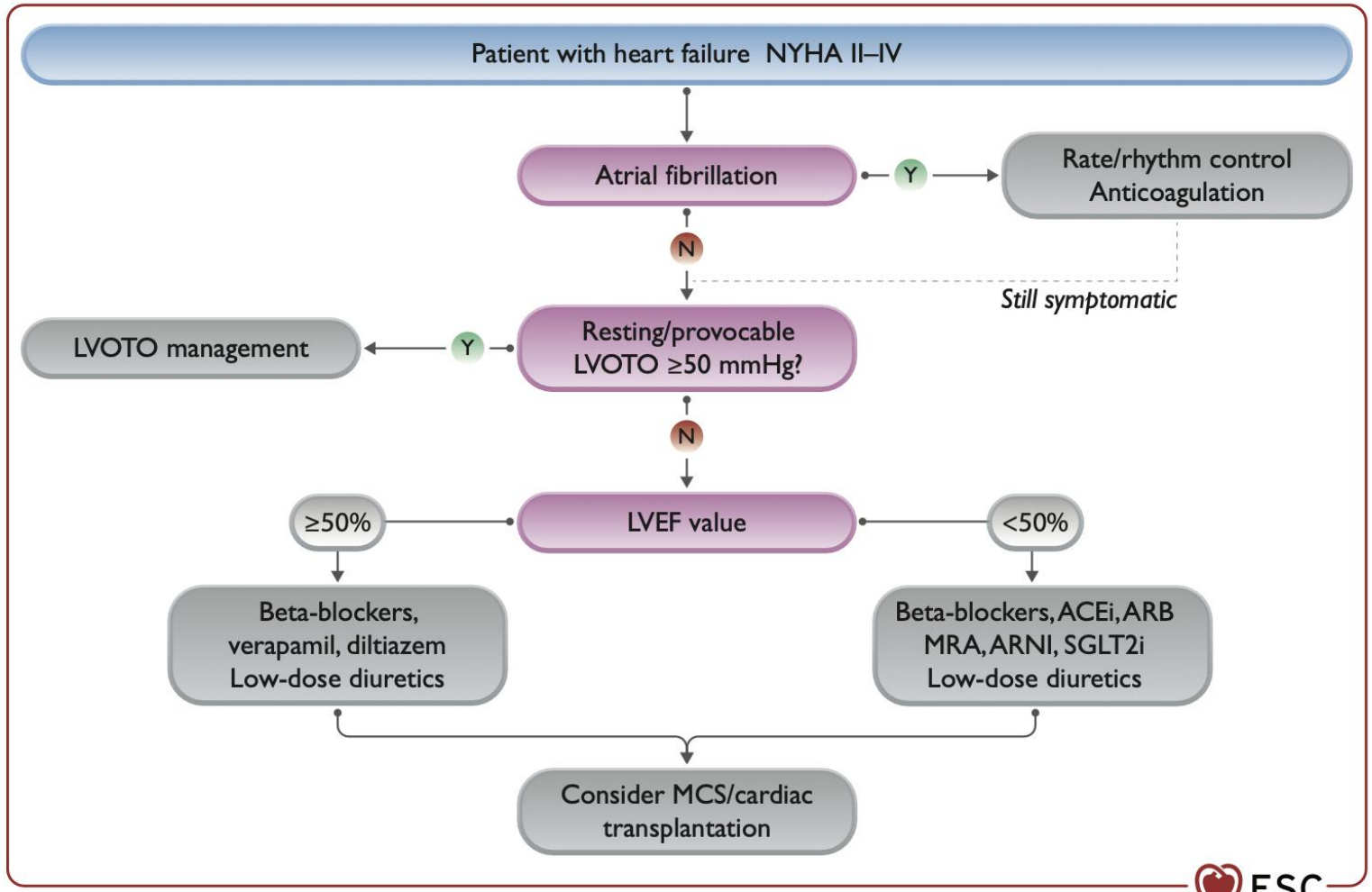
[a]Exercise echocardiography may be considered in individual patients when the presence of a left ventricular outflow tract gradient is relevant to lifestyle advice and decisions on medical treatment.
2D, two-dimensional; LVOTO, left ventricular outflow tract obstruction.
Adapted from Arbelo E, et al. Eur Heart J 2023; 10.1093/eurheartj/ehad194

Prognostic profiles in HCM
progressive HF in NON obstructive

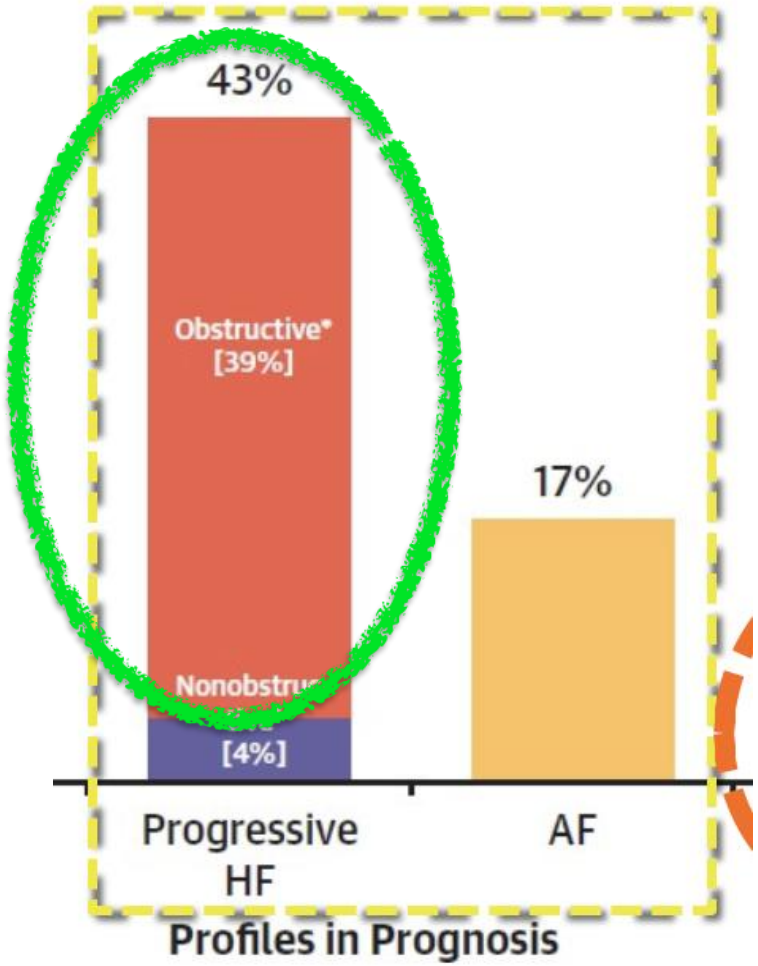




Maron et al. JACC 2022


Patient with heart failure NYHA II–IV
Atrial fibrillation
Y
Rate/rhythm control
Anticoagulation
N
Still symptomatic
LVOTO management
Y
Resting/provocable
LVOTO ≥50 mmHg?
N
≥50%
LVEF value
<50%
Beta-blockers,
verapamil, diltiazem
Low-dose diuretics
Beta-blockers, ACEi, ARB
MRA, ARNI, SGLT2i
Low-dose diuretics
Consider MCS/cardiac
transplantation
ESC

rognostic profiles in HCM progressive HF in obstructive



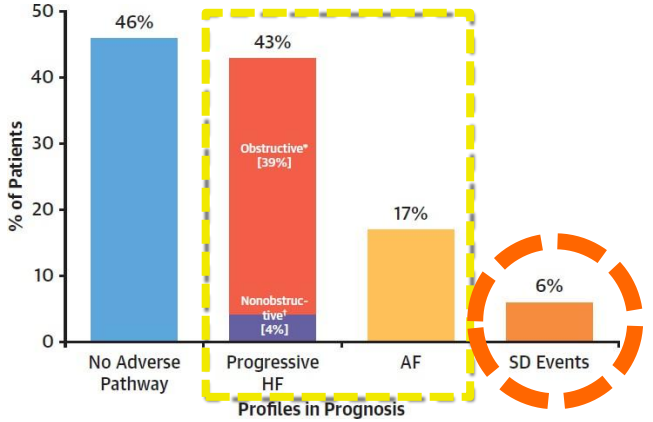
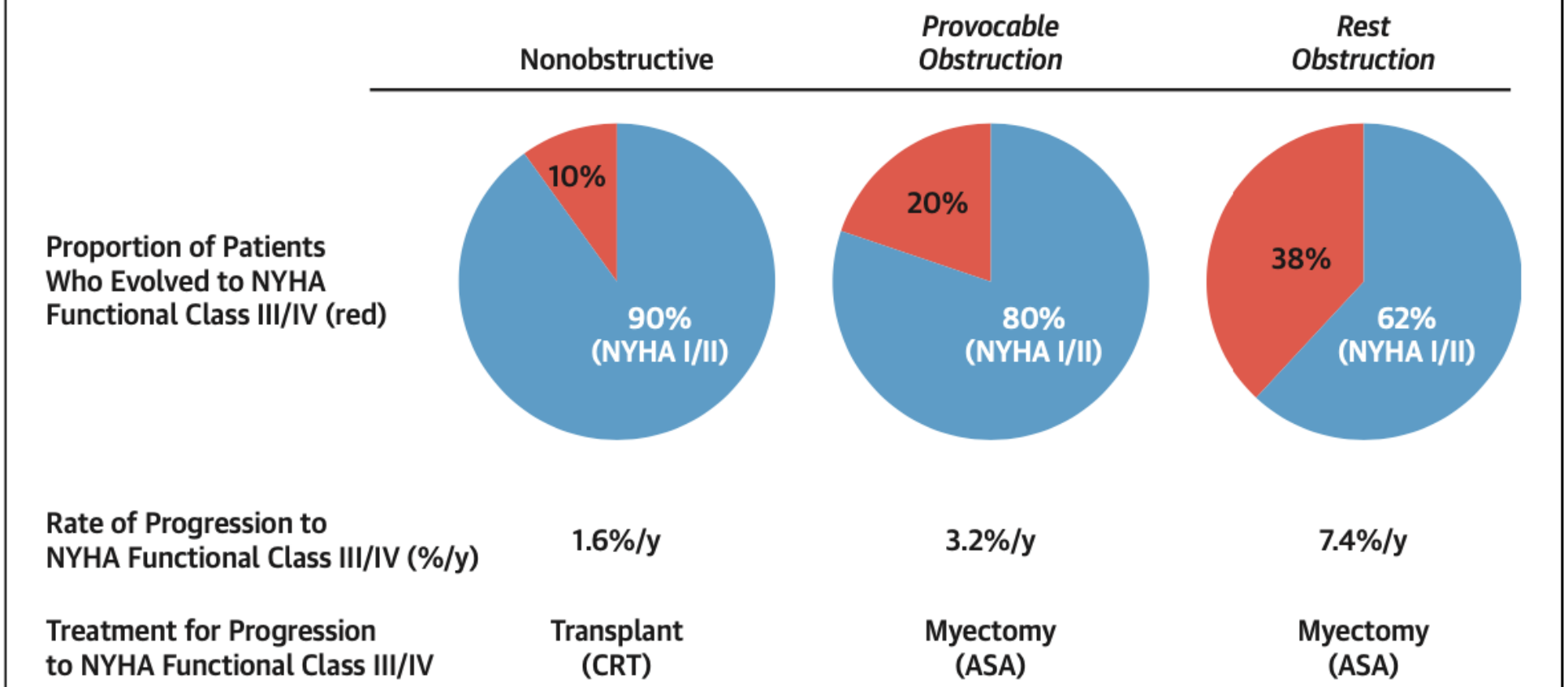


FIGURE 7 Progression of Severe Heart Failure Symptoms With Respect to Hemodynamic State in HCM



Demonstration that evolution to New York Heart Association (NYHA) functional class III symptoms are most common in obstructive patients (up to 38%) who may become candidates for surgical myectomy, and uncommon in nonobstructive patients (10%) who may become candidates for heart transplant. ASA = alcohol septal ablation; CRT = cardiac resynchronization therapy.

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

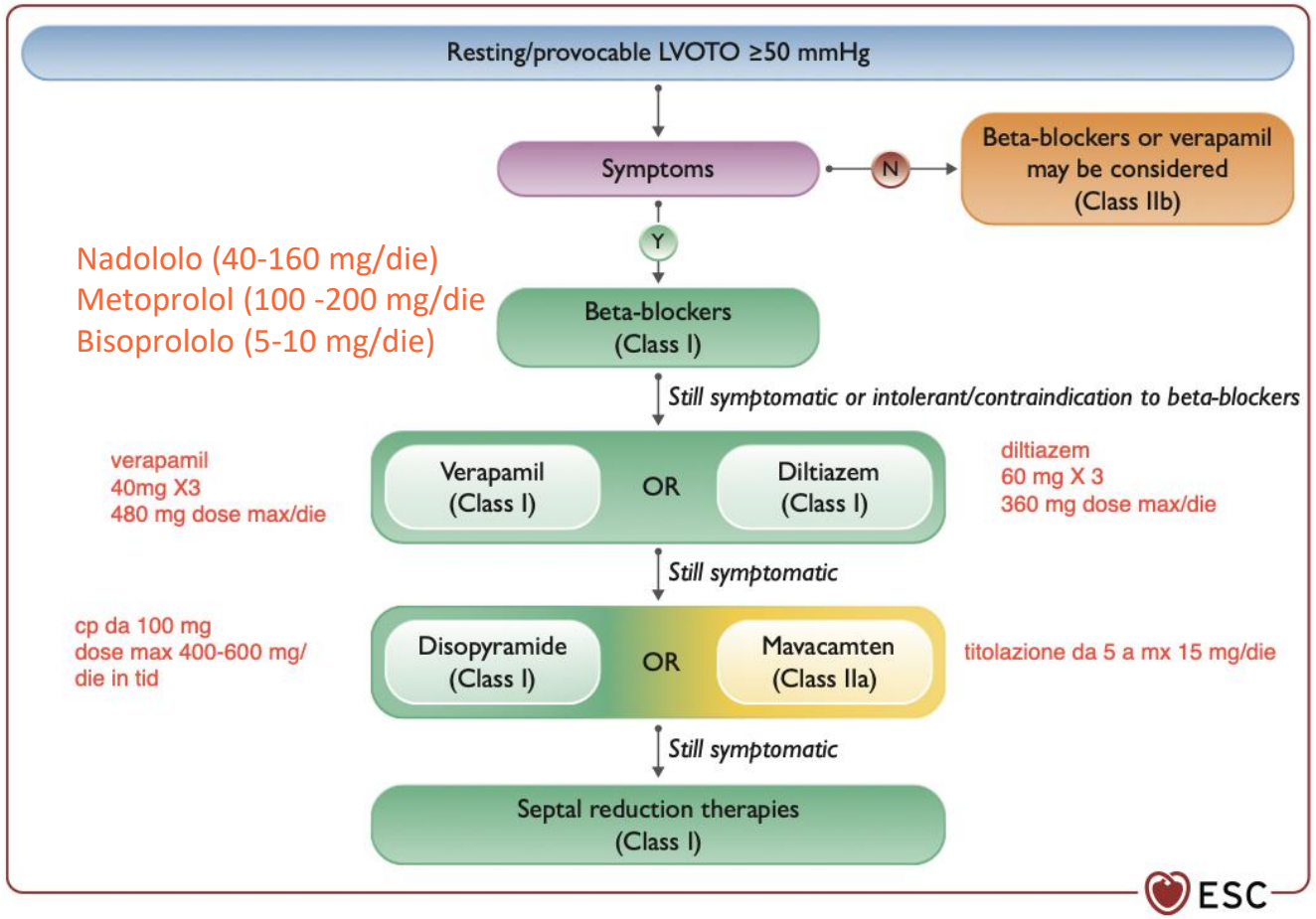
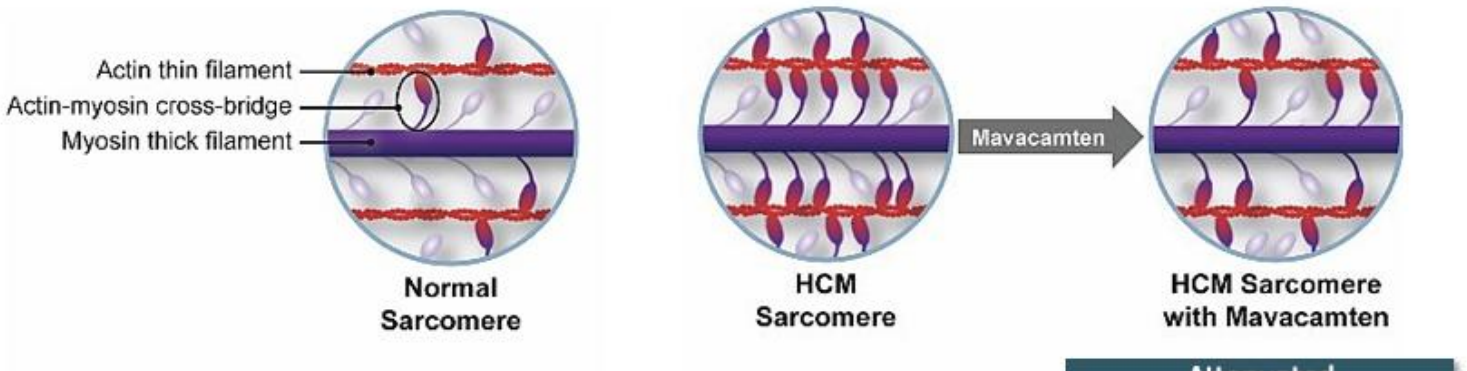


Figure 14 Flow chart on the management of left ventricular outflow tract obstruction. LVOTO, left ventricular outflow tract obstruction.

Mavacamten: Mechanism of Action

EXPLORER-HCM



- Attenuated hypercontractility
- Improved compliance
- Improved energetics

Mavacamten is a first-in-class, targeted inhibitor of cardiac myosin → It reduces the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

*Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ho, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators**

Summary

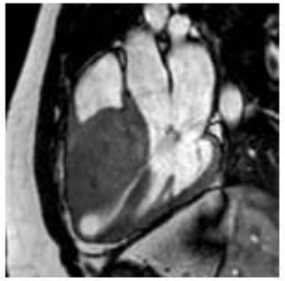
Background Cardiac muscle hypercontractility is a key pathophysiological abnormality in hypertrophic cardiomyopathy, and a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Available pharmacological options for hypertrophic cardiomyopathy are inadequate or poorly tolerated and are not disease-specific. We aimed to assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic obstructive hypertrophic cardiomyopathy.

Lancet 2020; 396: 759-69
Published Online
August 29, 2020
https://doi.org/10.1016/
S0140-6736(20)31792-X

Cardiac Myosin Inhibitors – A New Era in HCM?

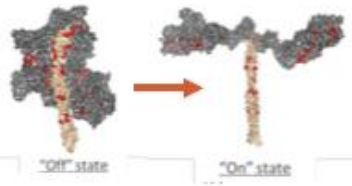
Clinical Studies

Hypercontractile LV
LVOT obstruction >> Symptoms



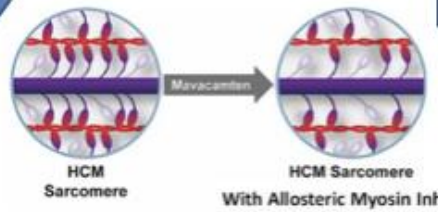
Basic Science

Gain of function MHY7 mutations



Targeted Molecular Approach

Myosin Inhibitors



Pre-clinical Data

↓ contractility
↑ compliance
↑ energetics
↓ LV hypertrophy
↓ disarray
↓ myocardial fibrosis

Phase 3 Clinical Trials

In Obstructive HCM

EXPLORER-HCM

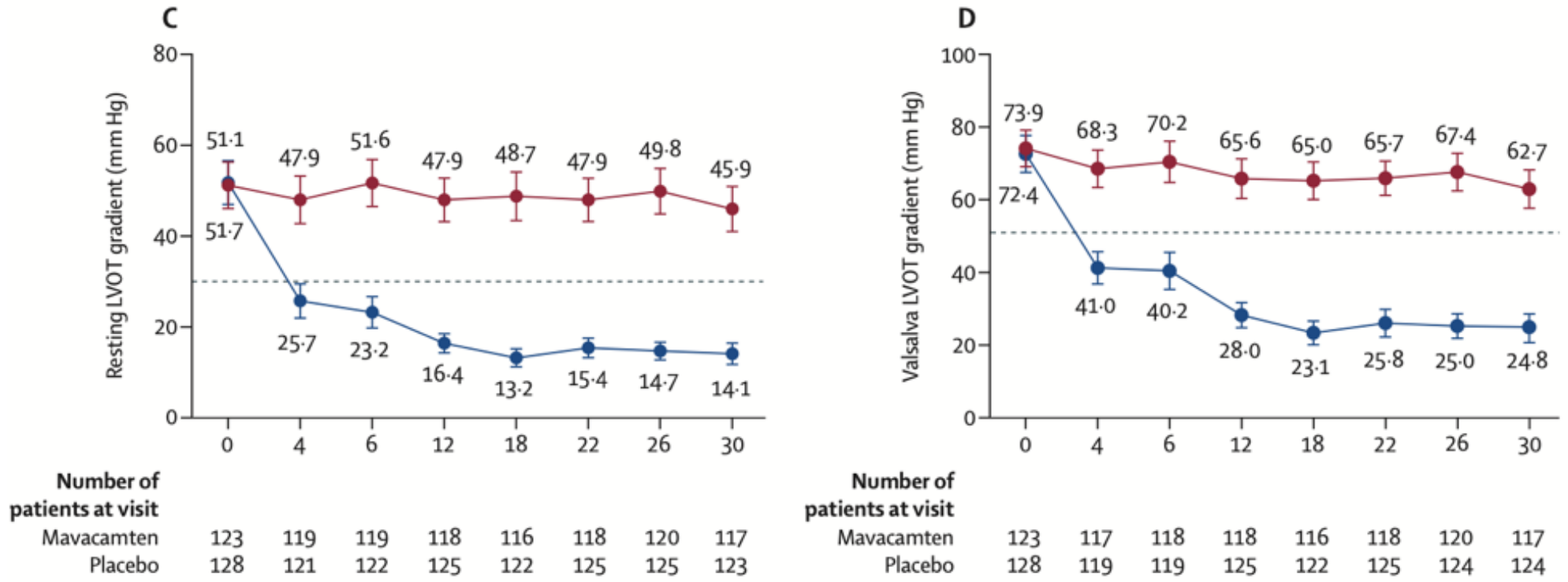
ValorHCM

Improved Symptoms and Exercise Performance
Relief of LVOT gradient
Improved QOL
↓ LA size
↓ E/e'
↑ LV cavity size
↓ NT ProBNP and HsTnT
Reduced need for Septal Reduction Therapies

In Nonobstructive HCM → ODYSSEY HCM (Ongoing)

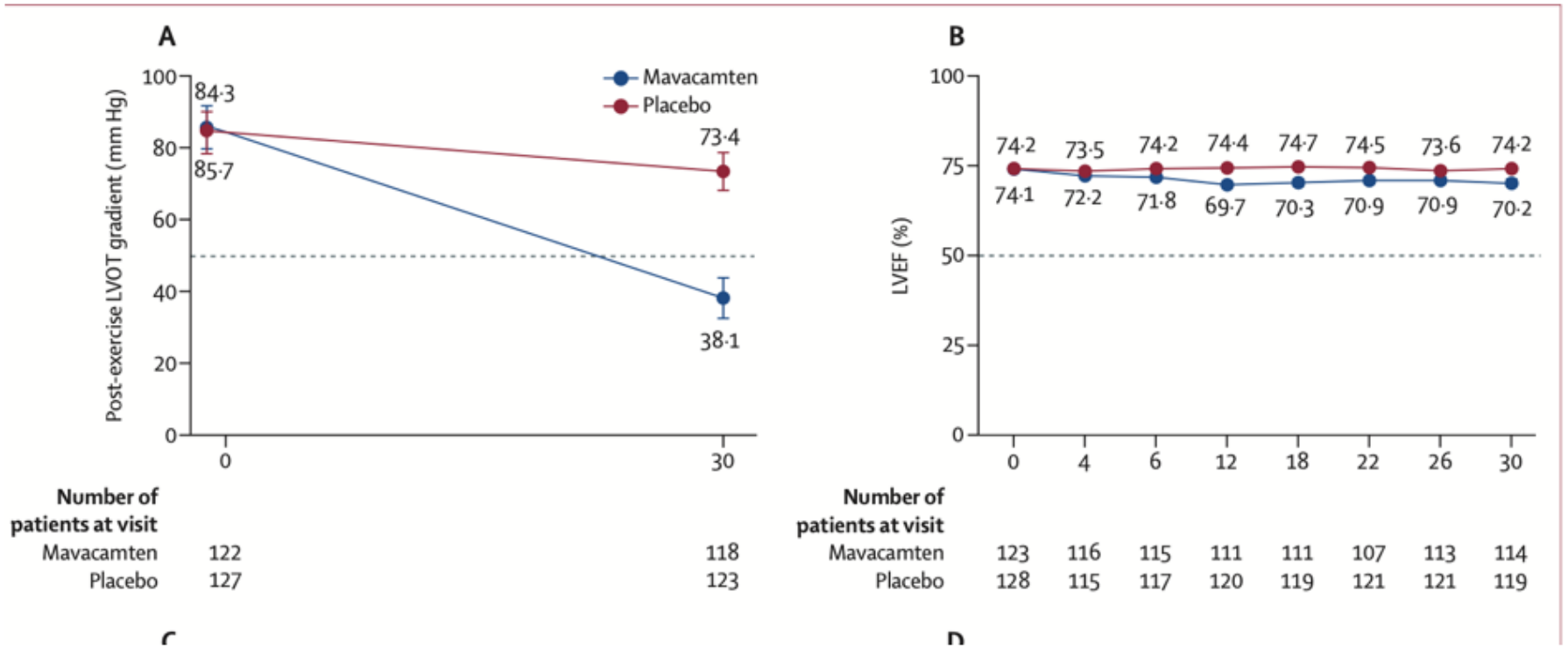
Braunwald E, Saberi S, Abraham TP, Elliott PM, Olivotto I, Eur Heart J, in press

LVOT Gradients



Olivotto et al, Lancet 2020

LVOT Gradients and LVEF

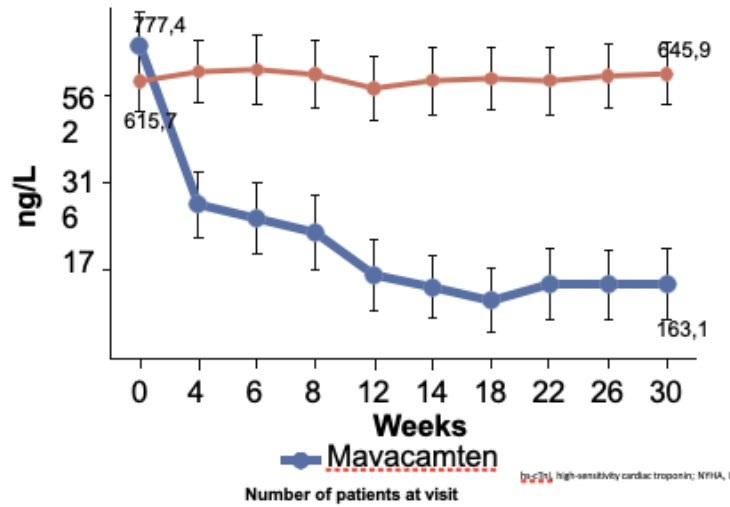


Olivotto et al, Lancet 2020

Cardiac Biomarkers

EXPLORER-HCM

Geometric mean (95% CI) NT-proBNP

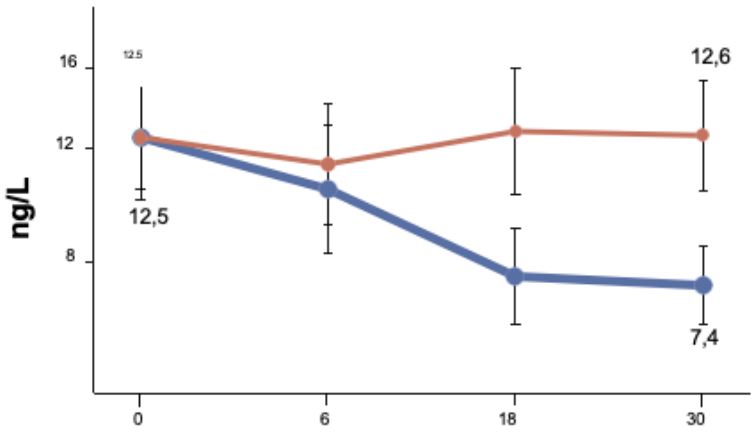


hs-TnI, high-sensitivity cardiac troponin; NYHA, New York Heart ,

Number of patients at visit

Mavacamten	120	115	114	115	114	109	115	115	117	119
Placebo	126	118	112	119	116	117	124	121	120	123

Geometric mean (95% CI) hs-cTnI



Number of patients at visit

Mavacamten	120	86	102	115
Placebo	119	84	104	115

Olivotto et al, Lancet 2020

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2024 VOL. 390 NO. 20

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*

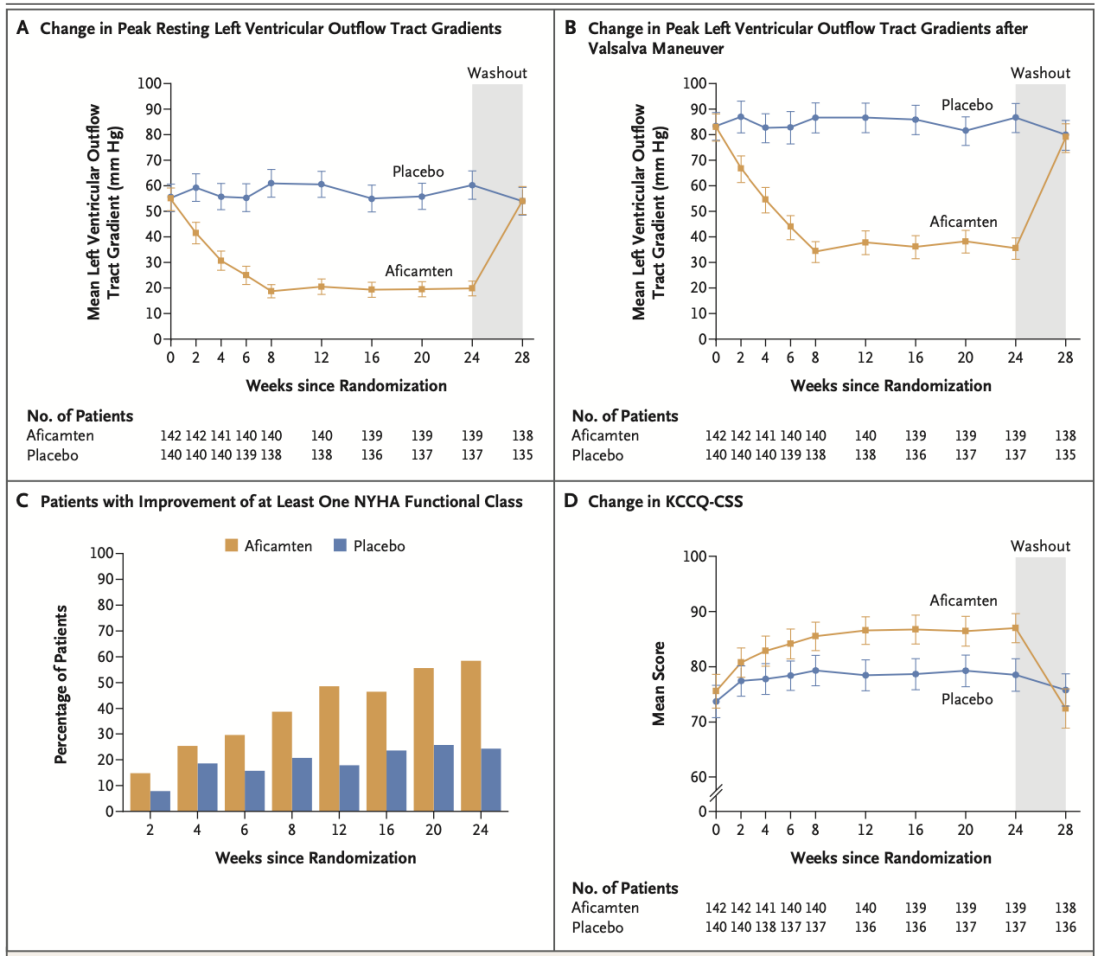


Figure 3. Key Secondary End Points and Other Outcomes.

Shown are the change from baseline in the mean peak resting left ventricular outflow tract gradient (Panel A), the change from baseline in the mean peak left ventricular outflow tract gradient after the Valsalva maneuver (Panel B), the percentage of patients with an improvement from baseline of at least one NYHA functional class (Panel C), and the change from baseline in the mean KCCQ-CSS (Panel D). The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

Septal Reduction therapy

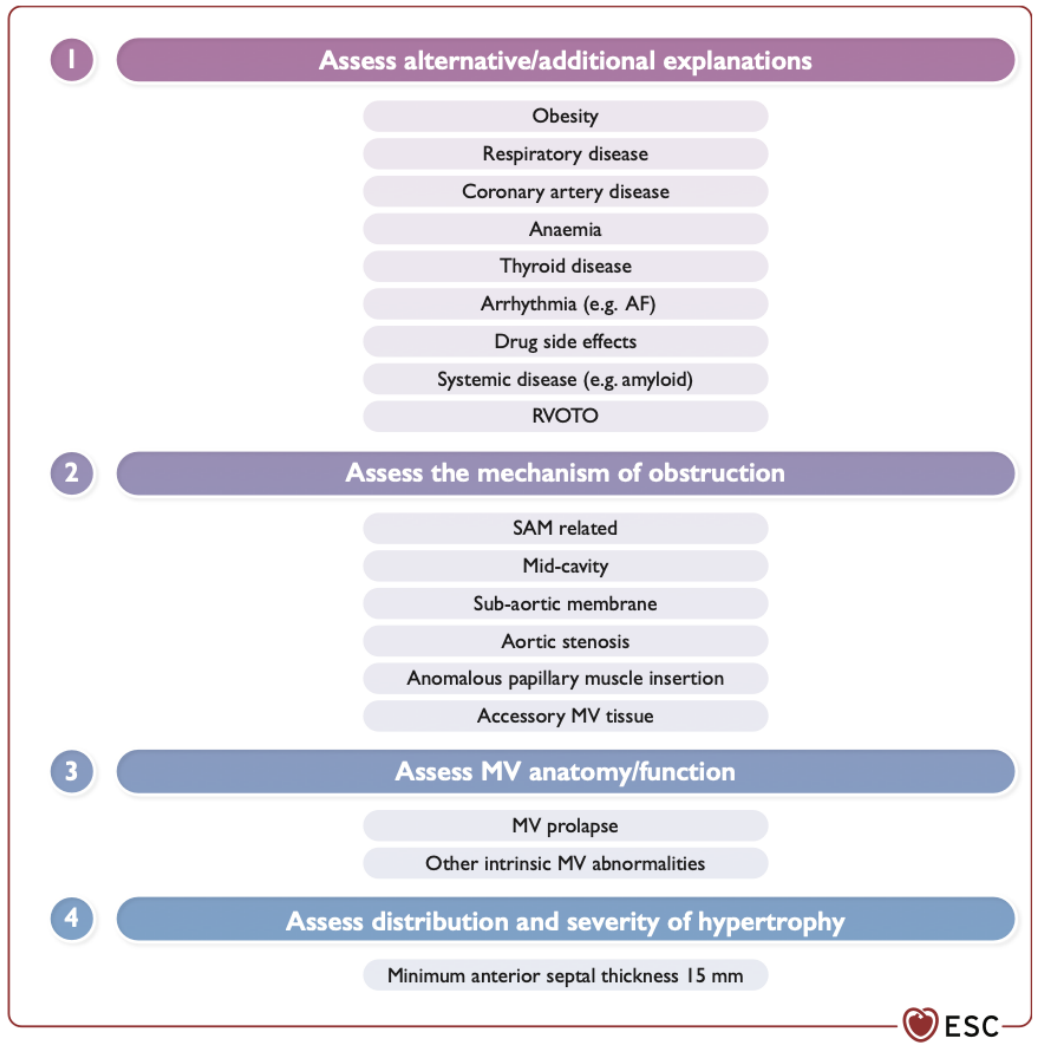


Figure 15 Pre-assessment checklist for patients being considered for invasive septal reduction therapies. AF, atrial fibrillation; MV, mitral valve; RVOTO, right ventricular outflow tract obstruction; SAM, systolic anterior motion.

Recommendation Table 20 — Recommendations for septal reduction therapy

Recommendations	Class[a]	Level[b]
It is recommended that SRT be performed by experienced operators working as part of a multidisciplinary team expert in the management of HCM.[664,665,687,695,696,708–710]	I	C
SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mmHg who are in NYHA/Ross functional class III–IV, despite maximum tolerated medical therapy.[697–702]	I	B
Septal myectomy, rather than ASA, is recommended in children with an indication for SRT, as well as in adult patients with an indication for SRT and other lesions requiring surgical intervention (e.g. mitral valve abnormalities).[673]	I	C
SRT should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mmHg despite optimal medical therapy.[686,711–713]	IIa	C
Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg and moderate-to-severe mitral regurgitation that cannot be corrected by SRT alone.[661,669–672,714]	IIa	C
Mitral valve repair should be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy.	IIa	C
SRT may be considered in expert centres with demonstrable low procedural complication rates in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked (exercise or Valsalva) gradient of ≥50 mmHg and: • moderate-to-severe SAM-related mitral regurgitation; or • AF; or • moderate-to-severe left atrial dilatation.[653,715]	IIb	C
Mitral valve replacement may be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy.[661,674,714,716]	IIb	C
Surgical AF ablation and/or left atrial appendage occlusion procedures during septal myectomy may be considered in patients with HCM and symptomatic AF.[717,718]	IIb	C

AF, atrial fibrillation; ASA, alcohol septal ablation; HCM, hypertrophic cardiomyopathy;

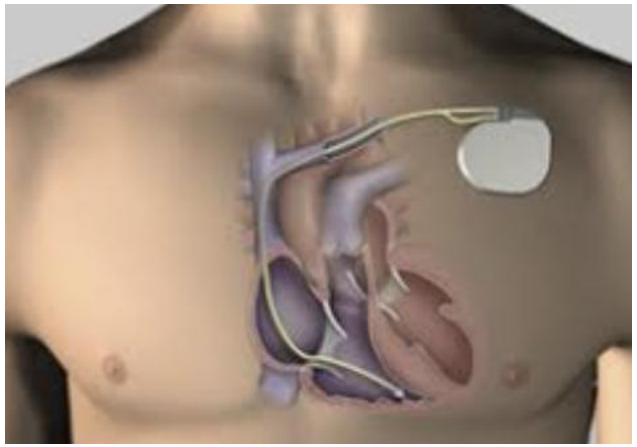
Septal Reduction therapy

Tabella 4. Confronto tra miectomia e ablazione alcolica del setto.

Caratteristica	Miectomia	ASA
Tipo di procedura	Chirurgia a cuore aperto	Cateterismo cardiaco
Invasività	Invasiva	Minimamente invasiva
Efficacia a lungo termine	Duratura	Buona, ma rischio di dilatazione VS
Mortalità operatoria	<1% nei centri esperti	1-3%
Complicanze maggiori	Sanguinamento, restenosi	Blocco AV, infarto settale
Selezione dei pazienti	Basso rischio chirurgico; IM severa da SAM	Pazienti anziani o con comorbilità

ASA, alcolizzazione settale; AV, atrioventricolare; IM, insufficienza mitralica; SAM, movimento anteriore sistolico; VS, ventricolare sinistra.

Indication for cardiac pacing



Recommendation Table 21 — Recommendations for indications for cardiac pacing in patients with obstruction

Recommendations	Class[a]	Level[b]
Sequential AV pacing, with optimal AV interval to reduce the LV outflow tract gradient or to facilitate medical treatment with beta-blockers and/or verapamil, may be considered in selected patients with resting or provocable LVOTO ≥50 mmHg, sinus rhythm, and drug-refractory symptoms, who have contraindications for ASA or septal myectomy or are at high risk of developing heart block following ASA or septal myectomy.[633,719–724]	IIb	C
In patients with resting or provocable LVOTO ≥50 mmHg, 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 beta-blockers and/or verapamil.[633,719–724,726]	IIb	C

ASA, alcohol septal ablation; AV, atrioventricular; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.

Canadian Journal of Cardiology 40 (2024) 326–328

Case Report

Transcatheter Edge to Edge Mitral Valve Repair for Mitra Regurgitation in Hypertrophic Cardiomyopathy: A Case Series

Shemy Carasso, MD, FESC, FASE,[a,b,c] David B. Marmor, MD,[a,b] and Mony Shuvy, MD, FESC

[a] Structural Interventional Program and Cardiomyopathy Service, Jesselson Integrated Heart Center, Shaare Zedek Medical Center, Jerusalem, Israel
[b] Hadassah Faculty of Medicine, Hebrew University, Jerusalem, Israel
[c] Azrieli Faculty of Medicine, Bar-Ilan University, Zefat, Isr

TEER and HCM

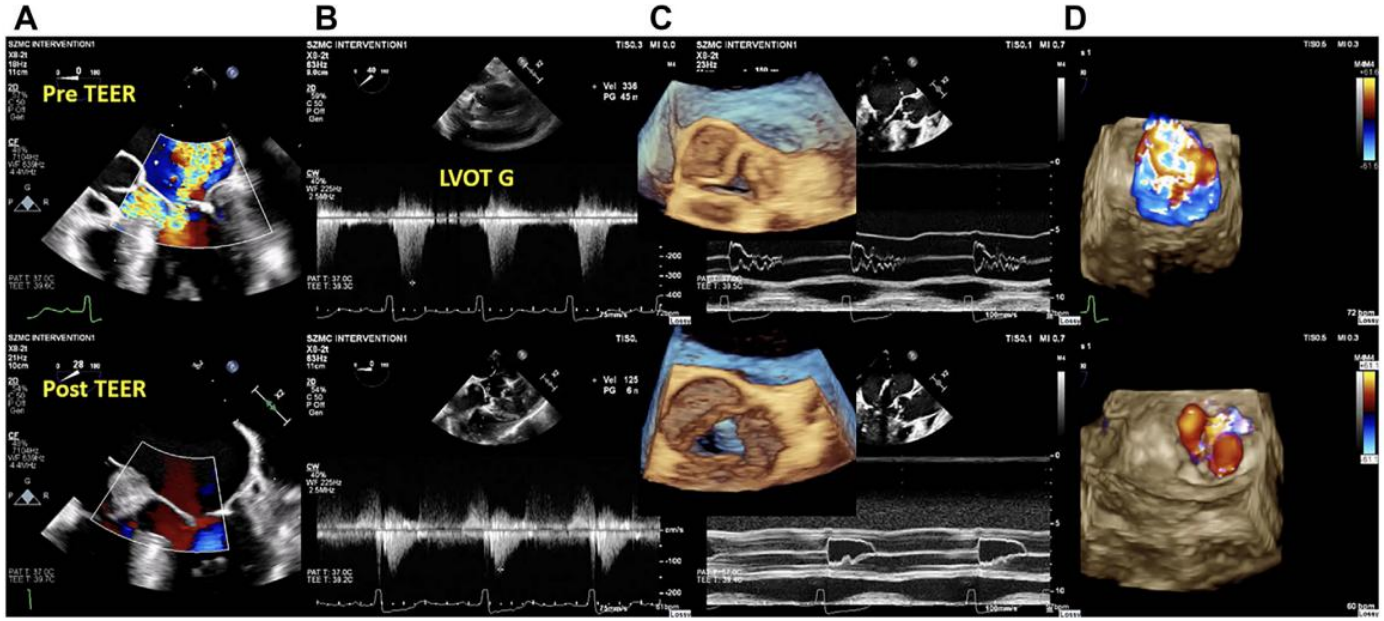
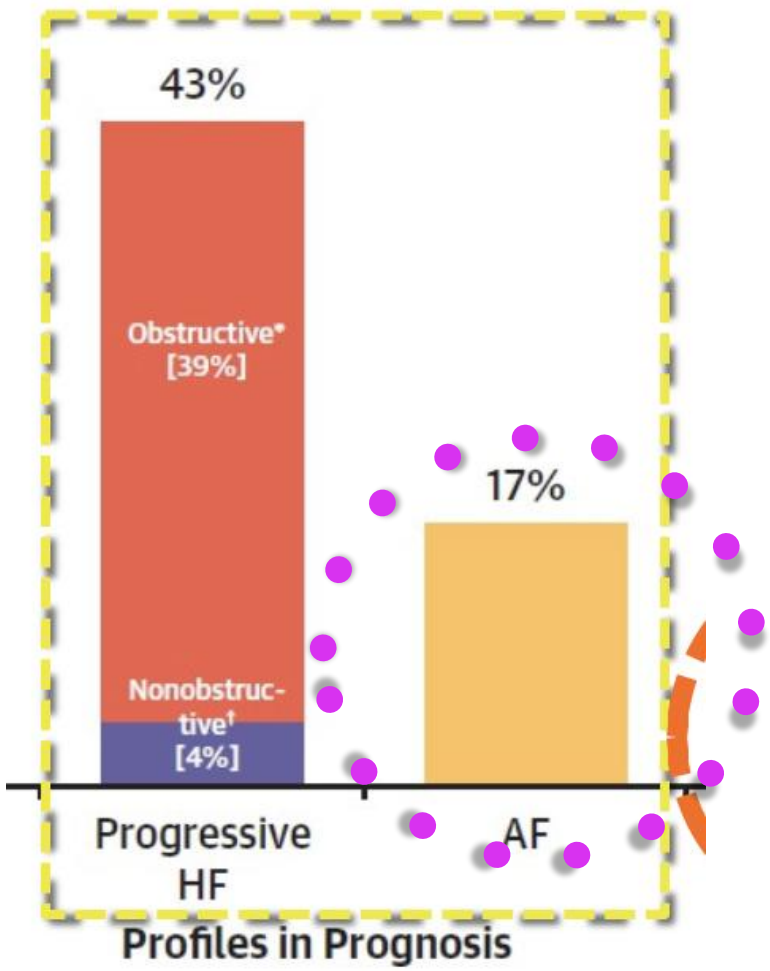
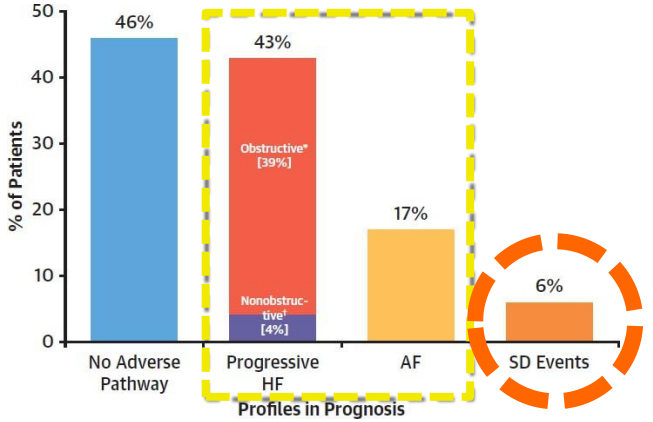


Figure 1. Transesophageal echocardiography assessment before (**top**) and after procedure (**bottom**). (**A**) Colour Doppler images of the mitral valve and left ventricular outflow tract (LVOT), (**B**) continuous-wave Doppler image of the LVOT velocity, (**C**) 3D images of the aortic valve near end-systole, M-mode images of the aortic valve, and (**D**) 3D colour images of the mitral valve. Postprocedural decrease in mitral regurgitation and LVOT flow velocities are shown, as well as an increase in aortic valve opening at end-systole. Elimination of aortic leaflet fluttering and premature closure also are demonstrated. LVOT G, left ventricular outflow tract gradient; TEER, transcatheter end-to-end repair.

Prognostic profiles in HCM and AF





or of 2 in women.[470–472]		
Control of symptoms and heart failure		
Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III AAD to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy.[335,397–399,412,415–420,430–435,447,451,473–498]	I	B
Atrial fibrillation catheter ablation is recommended to reverse LV dysfunction in AF patients with cardiomyopathy when tachycardia-induced component is highly probable, independent of their symptom status.[405,407,408,499–501]	I	B
Maintenance of sinus rhythm rather than rate control should be considered at an early stage for patients with a cardiomyopathy and AF without major risk factors for recurrence, regardless of symptoms.[402]	IIa	C
Atrial fibrillation catheter ablation should be considered as first-line rhythm control therapy to improve symptoms in selected patients with cardiomyopathy and paroxysmal or persistent AF without major risk factors for recurrences as an alternative to class I or III AADs, considering patient choice, benefit, and risk.[392,393,480,502–506]	IIa	C
Atrial fibrillation catheter ablation should be considered in selected patients with cardiomyopathy, AF, and heart failure and/or reduced LVEF to prevent AF recurrences and improve QoL, LVEF, and survival and reduce heart failure hospitalization.[399–401,403–408,499–501,507]	IIa	B

Antiarrythmic drug

Table 9. Antiarrhythmic Drug Therapy Options for Patients With HCM and AF

Antiarrhythmic Drug	Efficacy for AF	Adverse Effects	Toxicities	Use in HCM
Disopyramide	Modest	Anticholinergic HF	Prolonged QTc TdP	Particularly with early onset AF Generally used in conjunction with atrioventricular nodal blocking agents
Flecainide and propafenone	…	Prolonged QRS	Proarrhythmia Typical atrial flutter	Not generally recommended in the absence of an ICD
Sotalol	Modest	Fatigue Bradycardia	Prolonged QTc TdP	Reasonable
Dofetilide	Modest	Headache	Prolonged QTc TdP	Reasonable
Dronedarone	Low	HF	Prolonged QTc	…
Amiodarone	Modest-high	Bradycardia	Liver, lung, thyroid, skin, neurologic Prolonged QTc	Reasonable

AF indicates atrial fibrillation; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; and TdP, torsades de pointes.

Recommendation Table 6 — Recommendations to assess and manage thromboembolic risk in AF (see also Evidence Table 6)

Recommendations	Class[a]	Level[b]
Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.[239,240]	I	A
A CHA_2DS_2-VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decision [illegible] oral anticoagulation.	I	C
Oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA_2DS_2-VA score, to prevent ischaemic stroke and thromboembolism.[270–276]	I	B
Individualized [illegible] of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients.[277–280]	I	B

Continued


Grazie!


BIELLA CUORE
12-13 SETTEMBRE 2025

Recommendation Table 14 — Recommendations for family screening and follow-up evaluation of relatives

Recommendations	Class[a]	Level[b]
Following cascade genetic testing, clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging and long-term follow-up is recommended in first-degree relatives who have the same disease-causing variant as the proband.[178,544,547]	I	B
Following cascade genetic testing, it is recommended that first-degree relatives without a phenotype who do not have the same disease-causing variant as the proband are discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	I	C
It is recommended that when no P/LP variant is identified in the proband or genetic testing is not performed, an initial clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging is performed in first-degree relatives.	I	C
When no P/LP variant is identified in the proband or genetic testing is not performed, regular, long-term clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging should be considered in first-degree relatives.	IIa	C
During cascade screening, where a first-degree relative has died, clinical evaluation of close relatives of the deceased individual (i.e. second-degree relatives of the index patient) should be considered.	IIa	C

ECG, electrocardiogram; P/LP, pathogenic/likely pathogenic