Role of echocardiography in risk stratification and treatment decision-making

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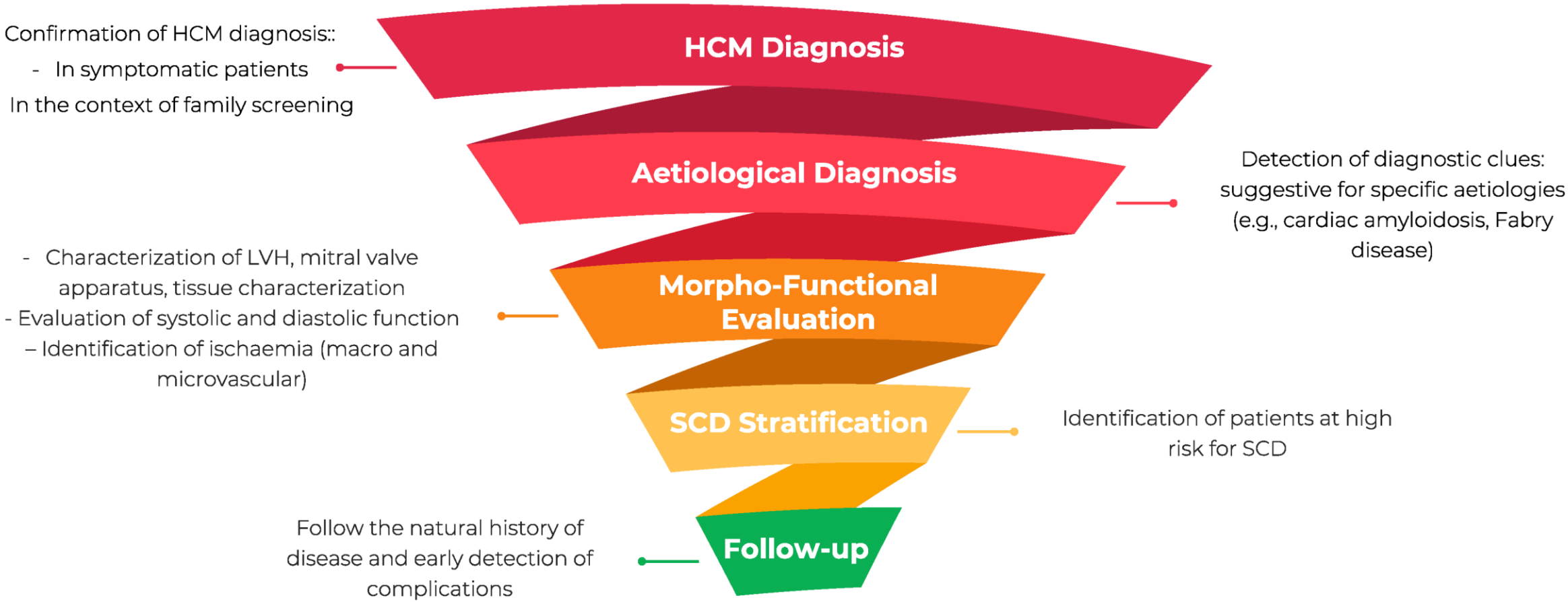
Disclosure

- Advisory board and speaker fees from:
  - Sanofi
  - Amicus therapeutics
  - Chiesi Pharma
  - Pfizer
  - Bristol Myers Squibb
  - Cytokinetics

Multimodality Imaging in HCM



Monda E. et al. JCM 2022

The Role of Echocardiography in Hypertrophic Cardiomyopathy

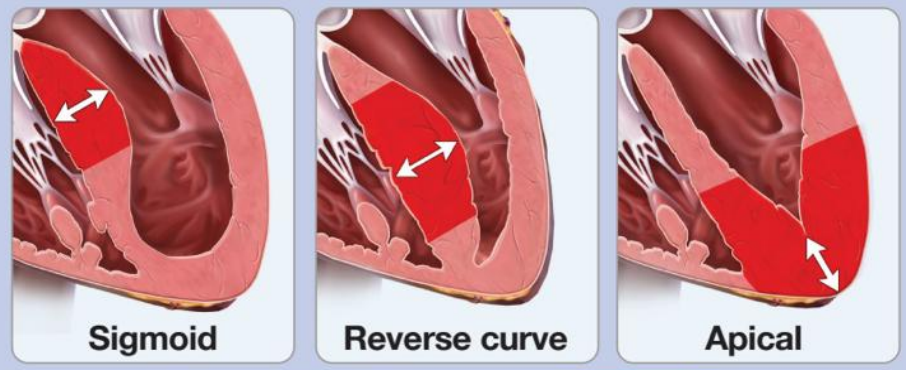
Goals of Echocardiographic Assessment in Hypertrophic Cardiomyopathy (HCM)

Establish diagnosis & determine pattern of hypertrophy

Clinical diagnosis should be suspected with imaging evidence of a maximal end-diastolic wall thickness of >15 mm anywhere in the left ventricle, absent another cause of hypertrophy in adults

Differentiate sigmoid septum (with ovoid cavity) versus reverse curve (with crescent cavity) versus apical hypertrophic phenotypes

Massive left ventricular hypertrophy >30 mm in any left ventricular segment is a risk factor for sudden cardiac death (SCD)



Evaluate global myocardial function

Systolic dysfunction defined as LVEF <50%

Strain abnormalities correlate with increased wall thickness & delayed gadolinium enhancement by MRI

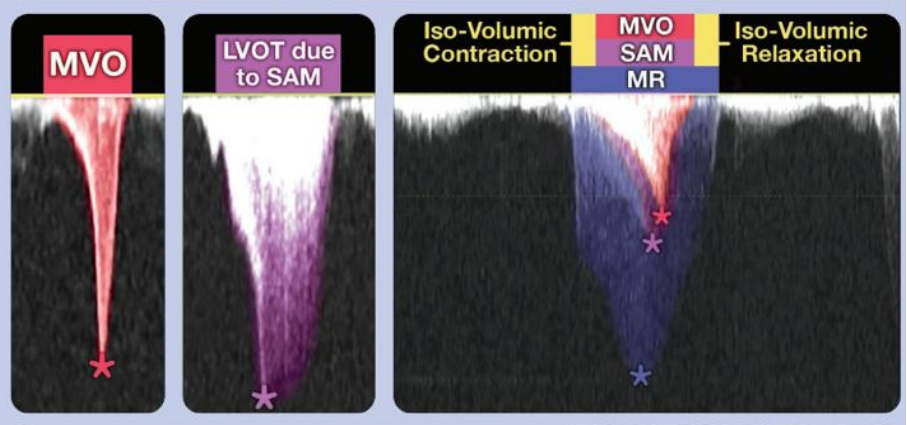
Establish presence & severity of LVOT obstruction

Peak LVOT gradient of ≥50 mmHg at rest or with provocation or exercise indicates obstruction

Differentiate SAM-mediated LVOT obstruction from mid-ventricular obstruction (MVO; "dagger" shaped)

Caution with contamination of LVOT signal with MR. MR velocity is higher & signal is of longer duration (spanning isovolumic contraction & relaxation) vs LVOT signal. MR contour may be incomplete if Doppler signal not optimally aligned

Estimated LVOT gradient from MR signal calculated as: LV Pressure - Systolic BP, where



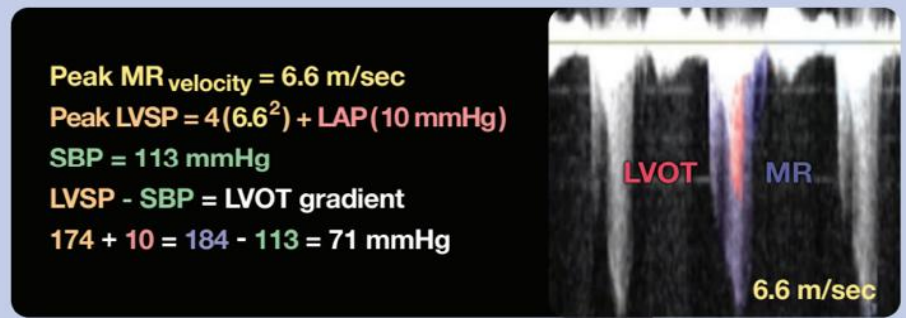


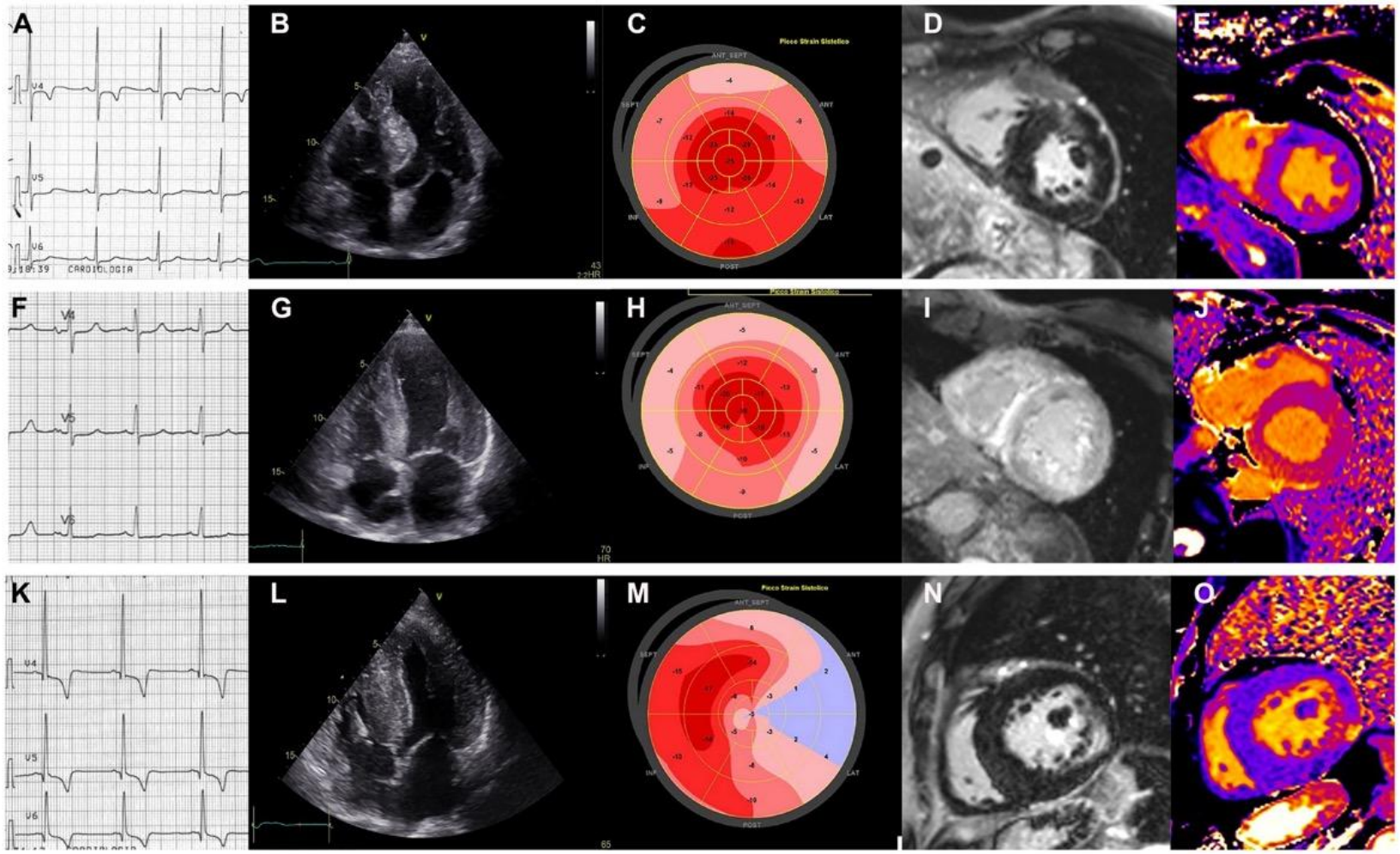
Table 17 Imaging evaluation in hypertrophic cardiomyopathy

Item to assess	Primary imaging modality	Comments
LV wall thickness	ECHO/CMR	• All LV segments from base to apex examined in end-diastole, preferably in the 2D short-axis view, ensuring that the wall thickness is recorded at mitral, mid-LV, and apical levels. • CMR is superior in the detection of LV apical and anterolateral hypertrophy, aneurysms,[580] and thrombi,[581] and is more sensitive in the detection of subtle markers of disease in patients with sarcomeric protein gene variants (e.g. myocardial crypts, papillary muscle abnormalities).[159,582,583]
Systolic function (global and regional)	ECHO/CMR	• Ejection fraction is a suboptimal measure of LV systolic performance when hypertrophy is present. • Doppler myocardial velocities and deformation parameters (strain and strain rate) are typically reduced at the site of hypertrophy despite a normal EF and may be abnormal before the development of increased wall thickness in genetically affected patients.
Diastolic function	ECHO	• Routine examination should include mitral inflow assessment, tissue Doppler imaging, pulmonary vein flow velocities, pulmonary artery systolic pressure, and LA size/volume.
Mitral valve	ECHO	• Assess presence and degree of SAM and mitral regurgitation. The presence of a central- or anteriorly directed jet of mitral regurgitation should raise suspicion of an intrinsic/primary mitral valve abnormality and prompt further assessment.
LVOT	ECHO	• See *Figure 12*.
LA dimensions	ECHO/CMR	• Provides important prognostic information.[365,525,584] • Most common mechanisms of LA enlargement are SAM-related mitral regurgitation and elevated LV filling pressures.
Myocardial fibrosis/LGE	CMR	• The distribution and severity of interstitial expansion can suggest specific diagnoses. Anderson–Fabry disease is characterized by a reduction in non-contrast T1 signal and the presence of posterolateral LGE.[134,155] In cardiac amyloidosis, there is often global, subendocardial or segmental LGE and a highly specific pattern of myocardial and blood-pool gadolinium kinetics caused by similar myocardial and blood T1 signals.[585,586]

2D, two-dimensional; CMR, cardiac magnetic resonance; ECHO, echocardiogram; EF, ejection fraction; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow tract; SAM, systolic anterior motion; SCD, sudden cardiac death.

Arbelo E et al. Eur Heart J 2023;44(37):3503–3626.

HCM phenocopies differential diagnosis

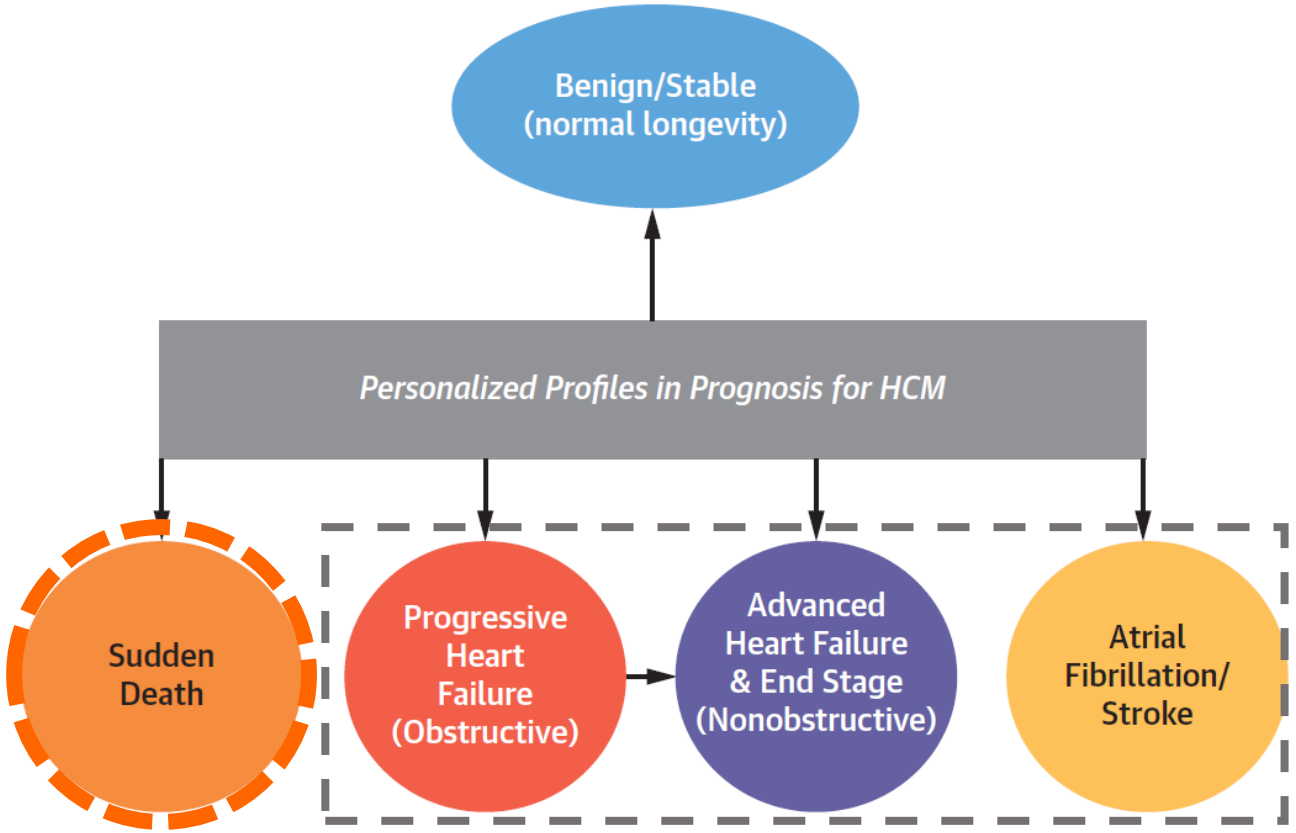


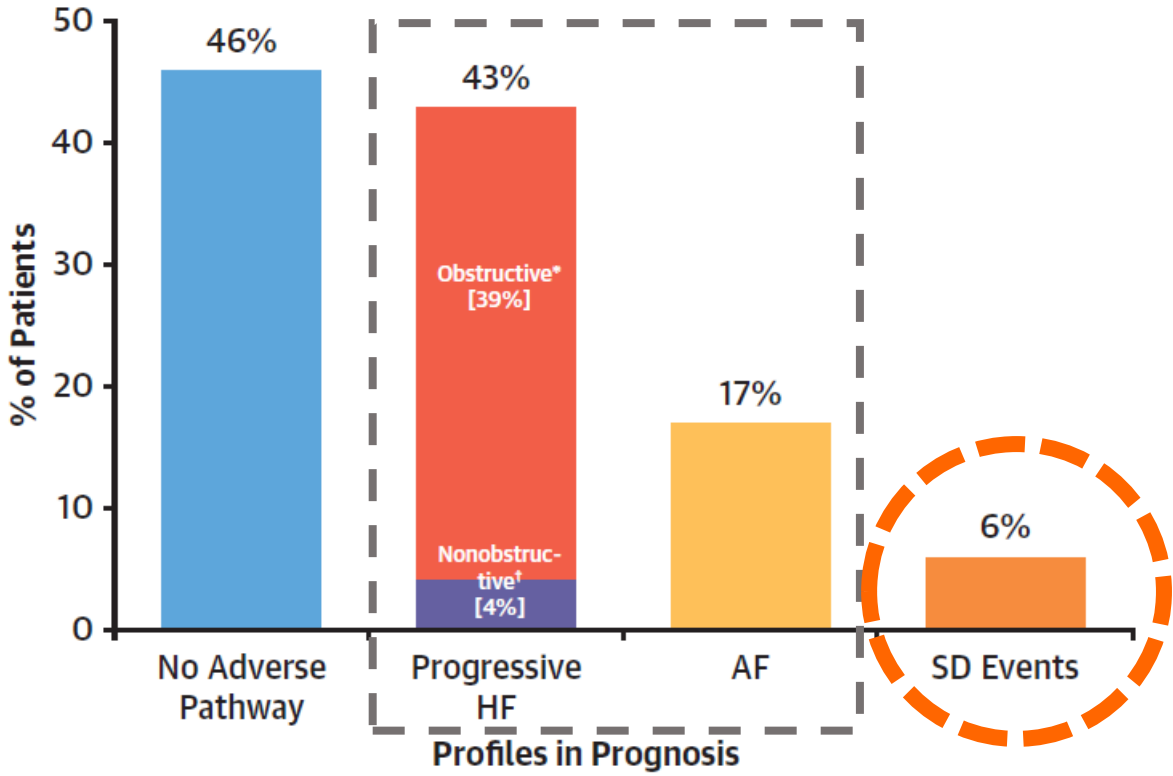
HCM

ATTR Amyloidosis

Fabry disease

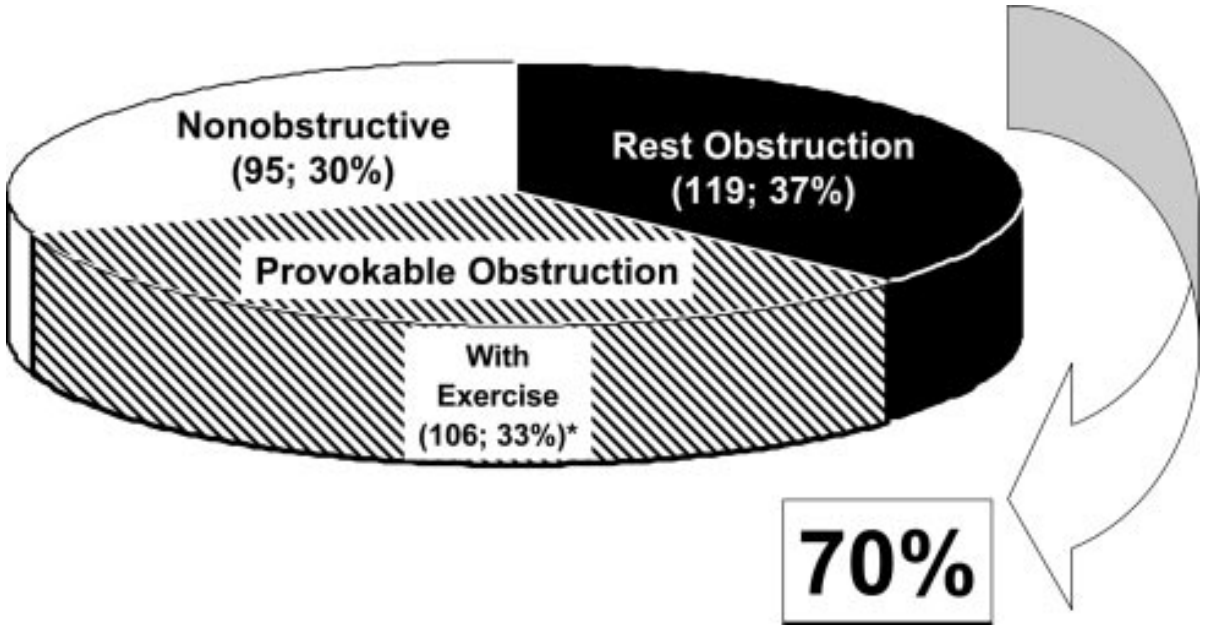
Prognostic profiles in HCM

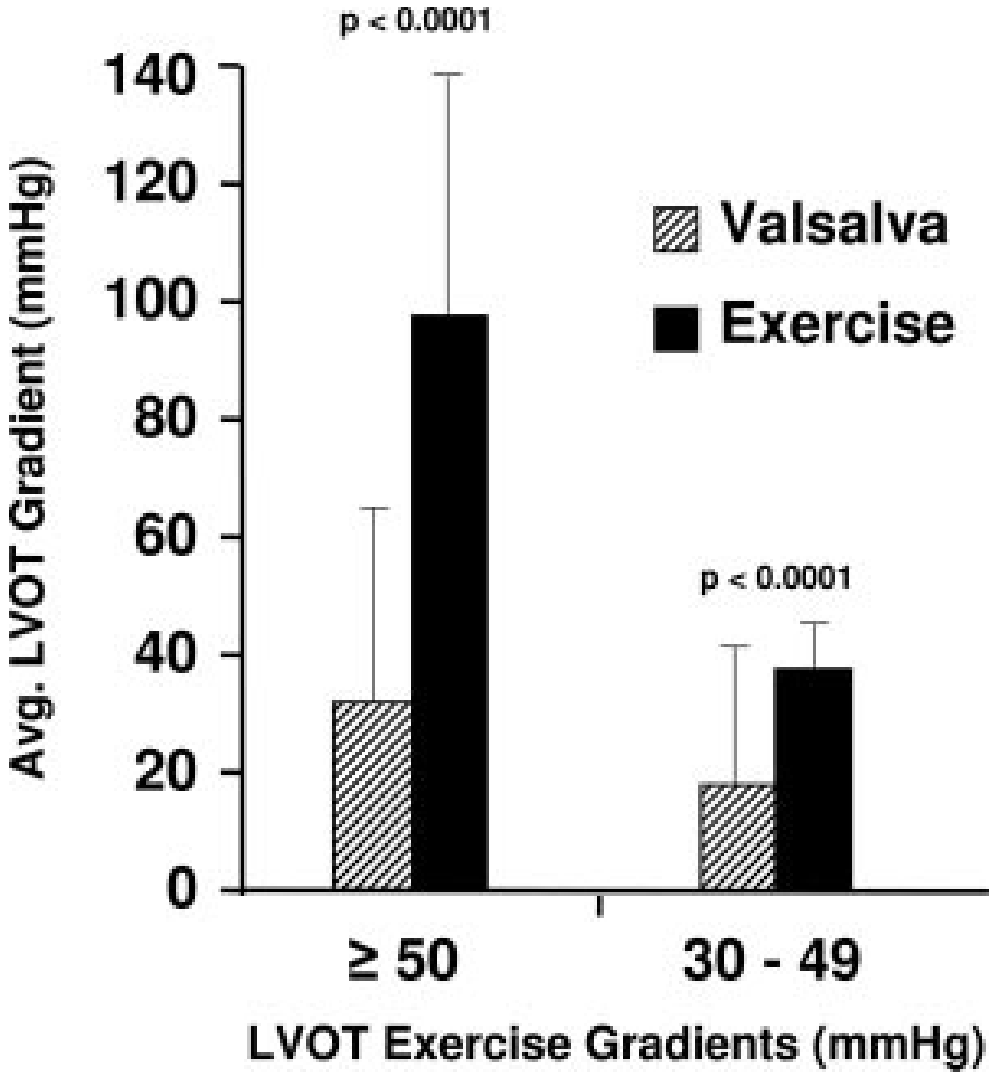




Maron BJ et al. J Am Coll Cardiol 2022

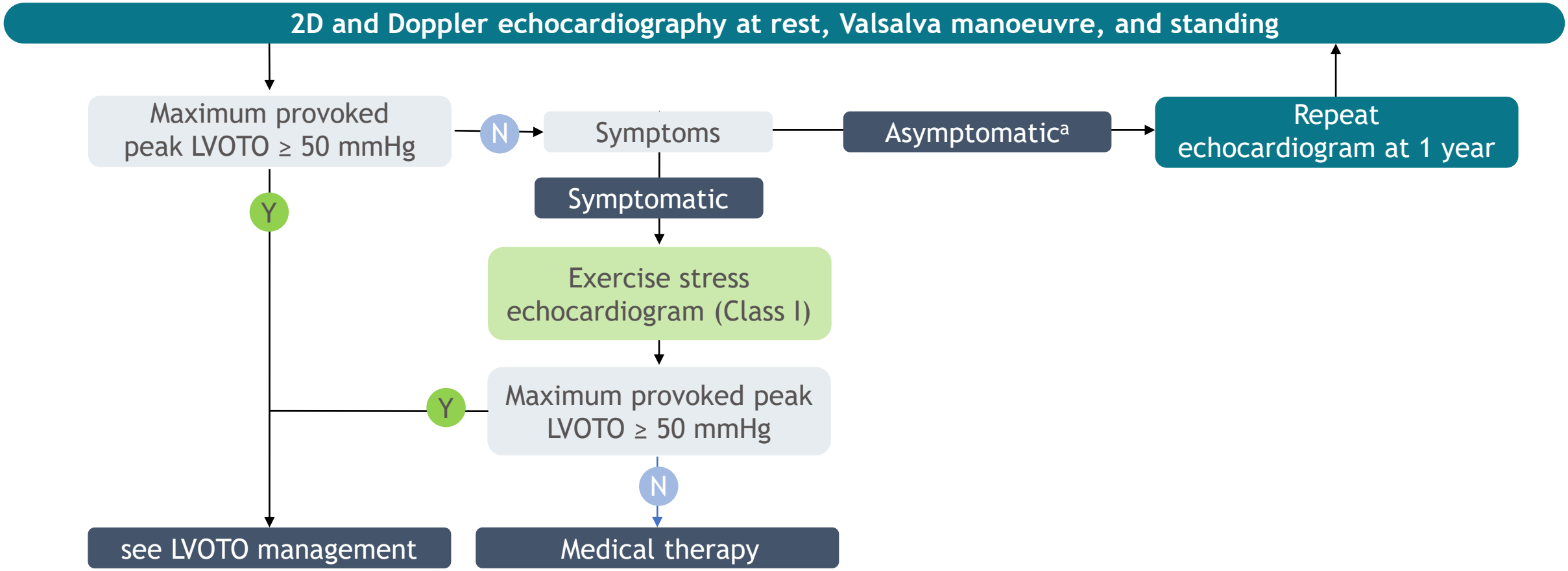
Provokable LVOTO





Maron et al Circulation 2006.

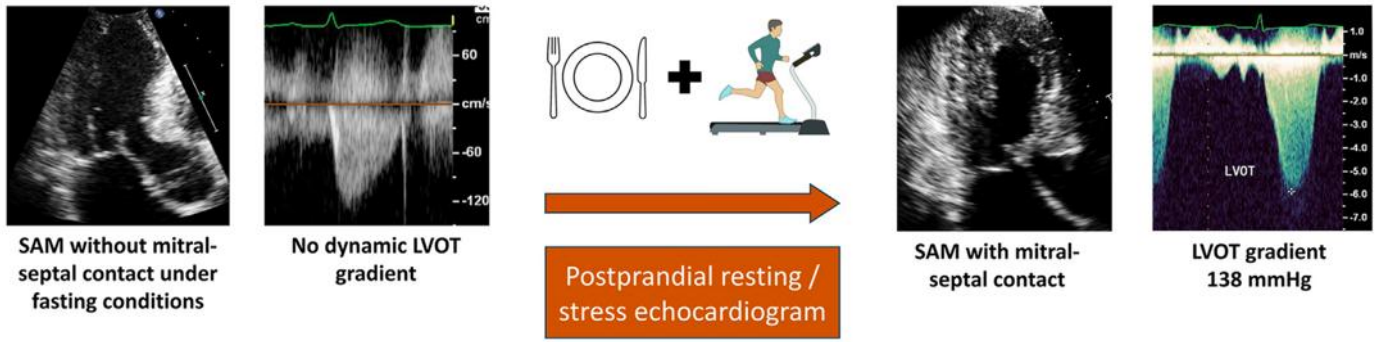
Assessment and treatment of left ventricular outflow tract obstruction

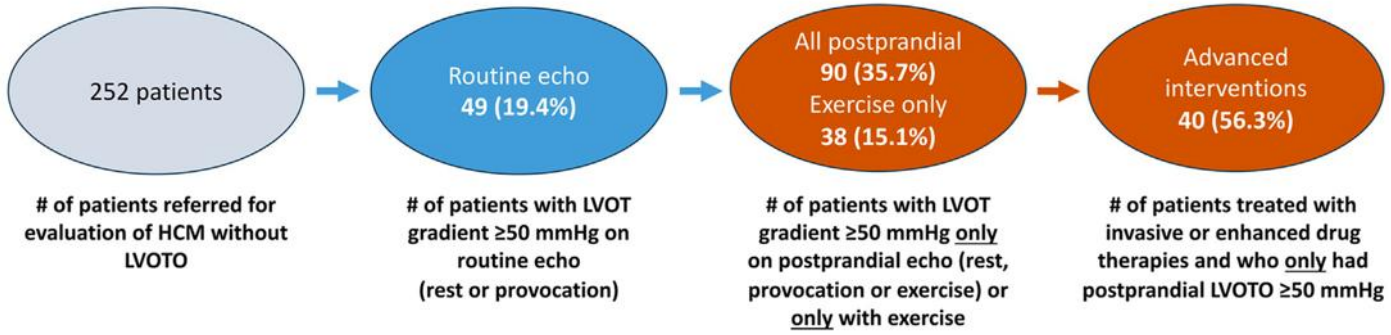


[a]Exercise echocardiography may be considered in individual patients when the presence of a left ventricular outflow tract gradient is relevant to lifestyle advice and decisions on medical treatment. 2D, two-dimensional; LVOTO, left ventricular outflow tract obstruction. Adapted from Arbelo E, et al.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

Unmasking Obstruction in Hypertrophic Cardiomyopathy With Postprandial Resting and Treadmill Stress Echocardiography

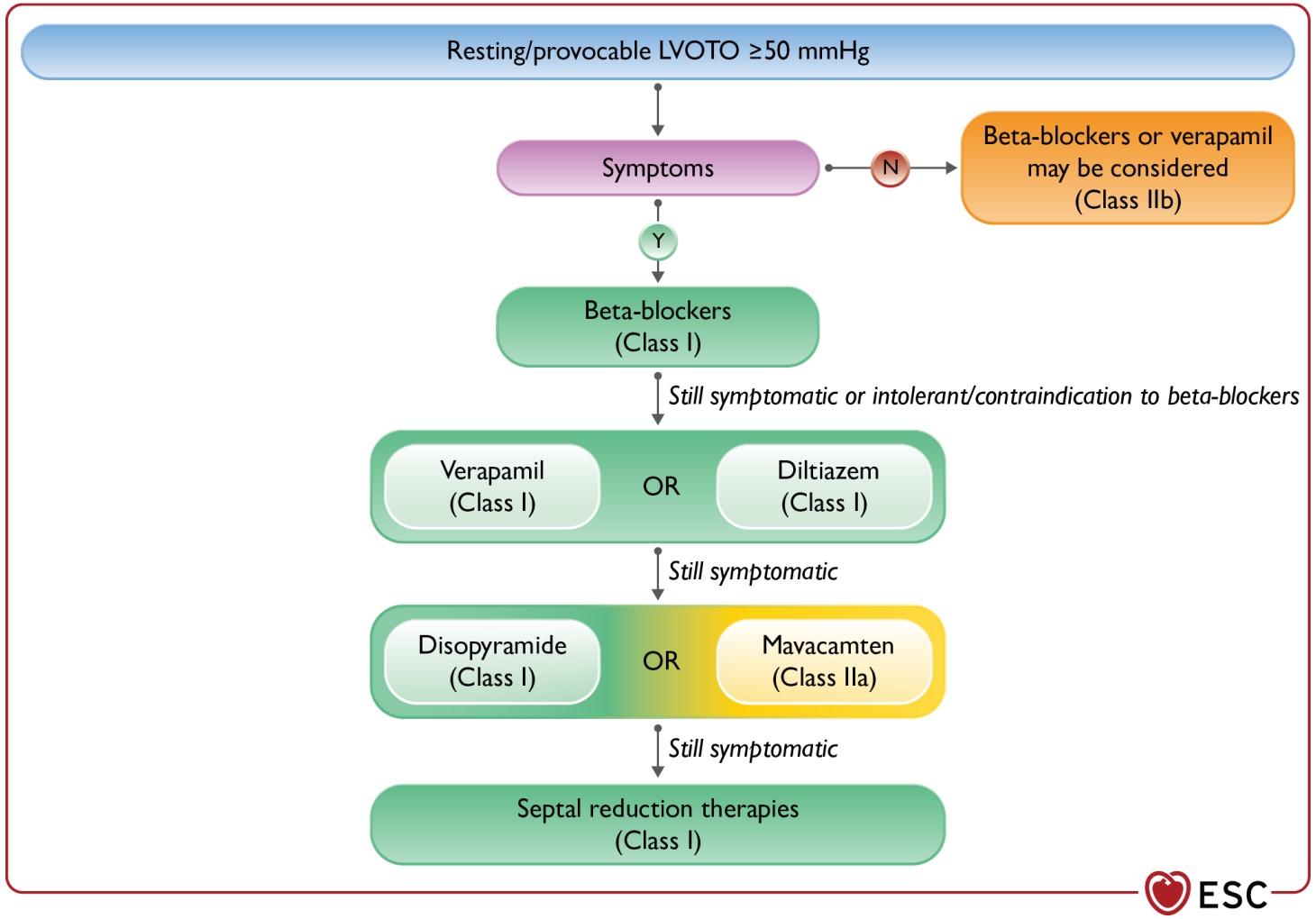
Daniele Massera, MD, MSc, Clarine Long, MD, Yuhe Xia, MS, Les James, MD, MPH, Elizabeth Adlestein, BA, Isabel C. Alvarez, BS, MPH, Woon Y. Wu, FNP, Maria C. Reuter, AGACNP, Milla Arabadjian, PhD, Eugene A. Grossi, MD, Muhamed Saric, MD, PhD, and Mark V. Sherrid, MD, *New York and Mineola, New York*





Massera et al. J Am Soc Echocardiogr. 2024

Management of left ventricular outflow tract obstruction

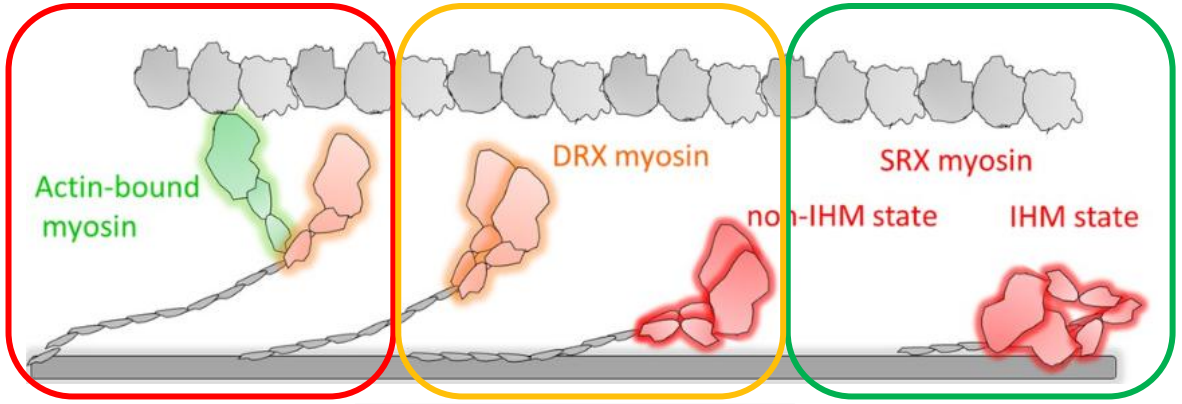


Arbelo E et al. Eur Heart J 2023;44(37):3503–3626.

Myosin states

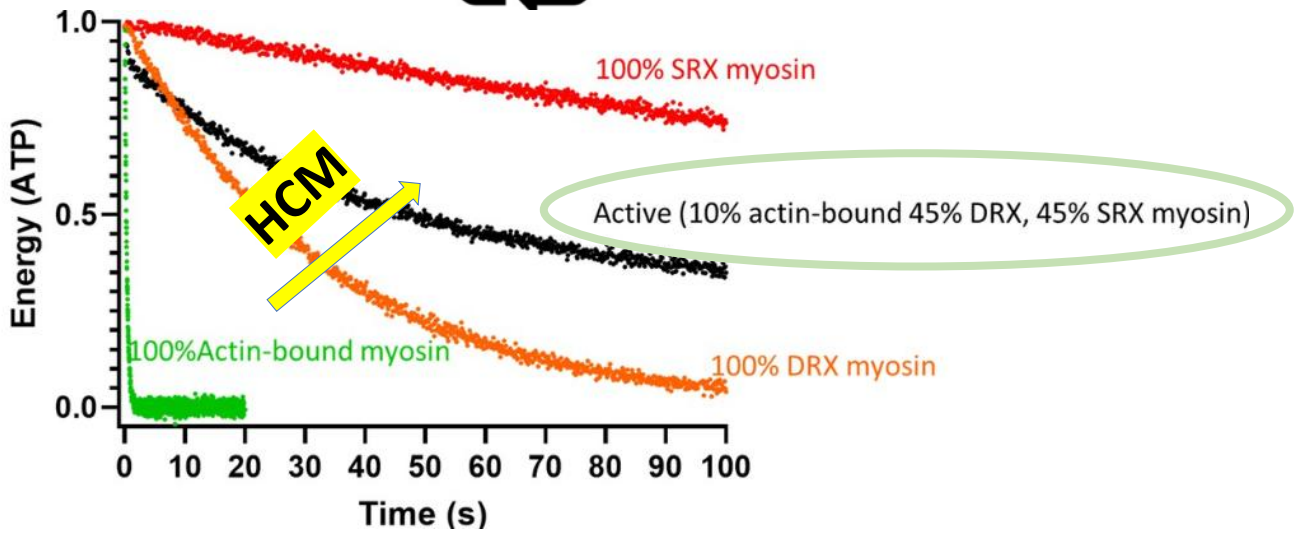
[1]

Calcium-mediated actin-myosin interaction



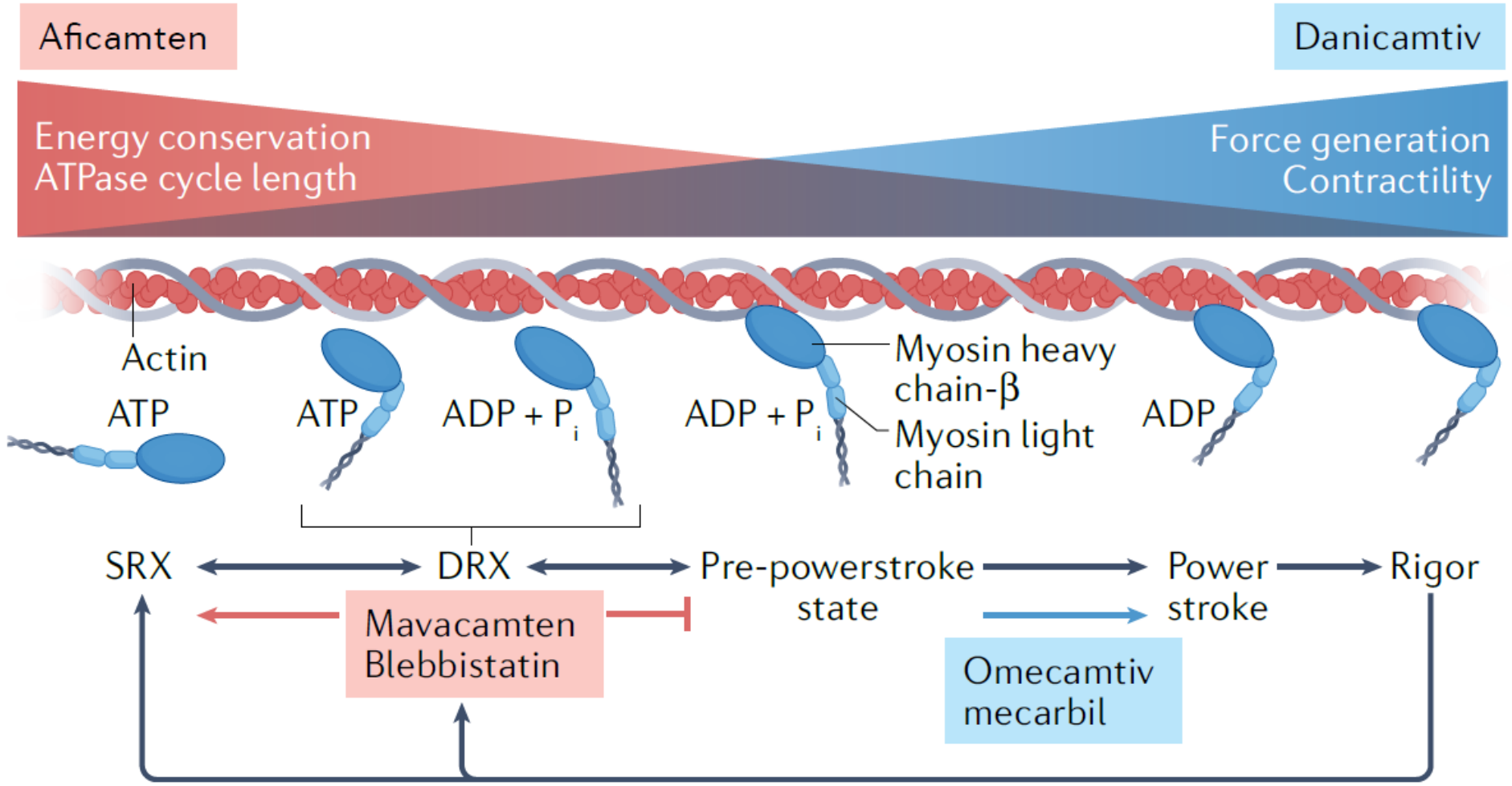
"A new state of cardiac myosin with very slow ATP turnover" (interacting heads motif)[2]

Energy Cycling



1. Nag S, Trivedi DV. *eLife* 2021;10:e63703; 2. Hooijman P, et al. *Biophys J* 2011;100:1969–1976.

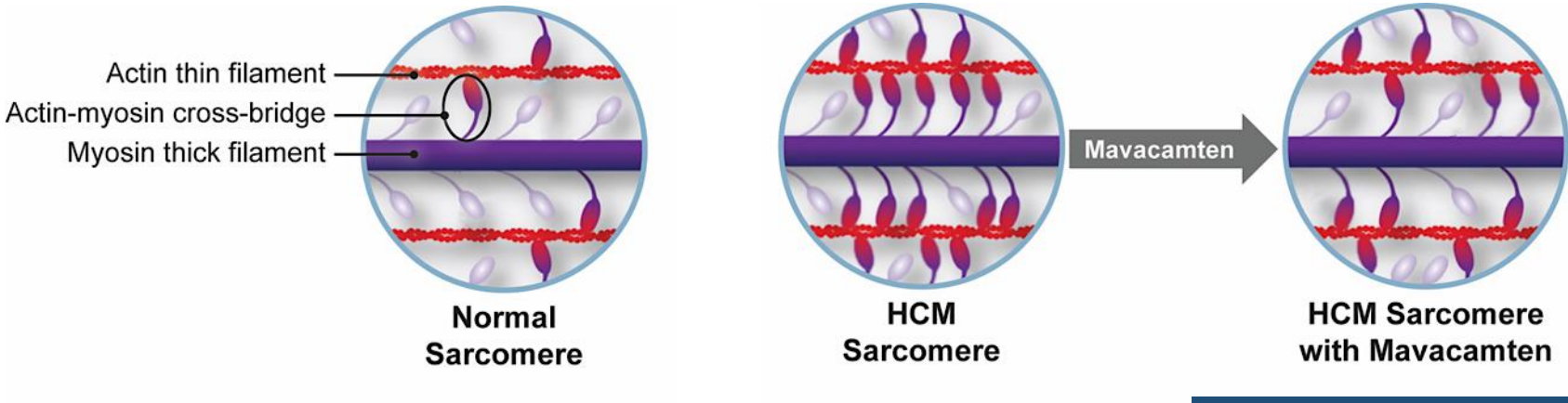
The Molecular Mechanisms of Myosin Modulation by Targeted Small Molecules



Lehman, Crocini and Leinwand, Nat Cardiol Rev 2022

Mavacamten: Mechanism of Action

EXPLORER-HCM



- Attenuated hypercontractility
- Improved compliance
- Improved energetics

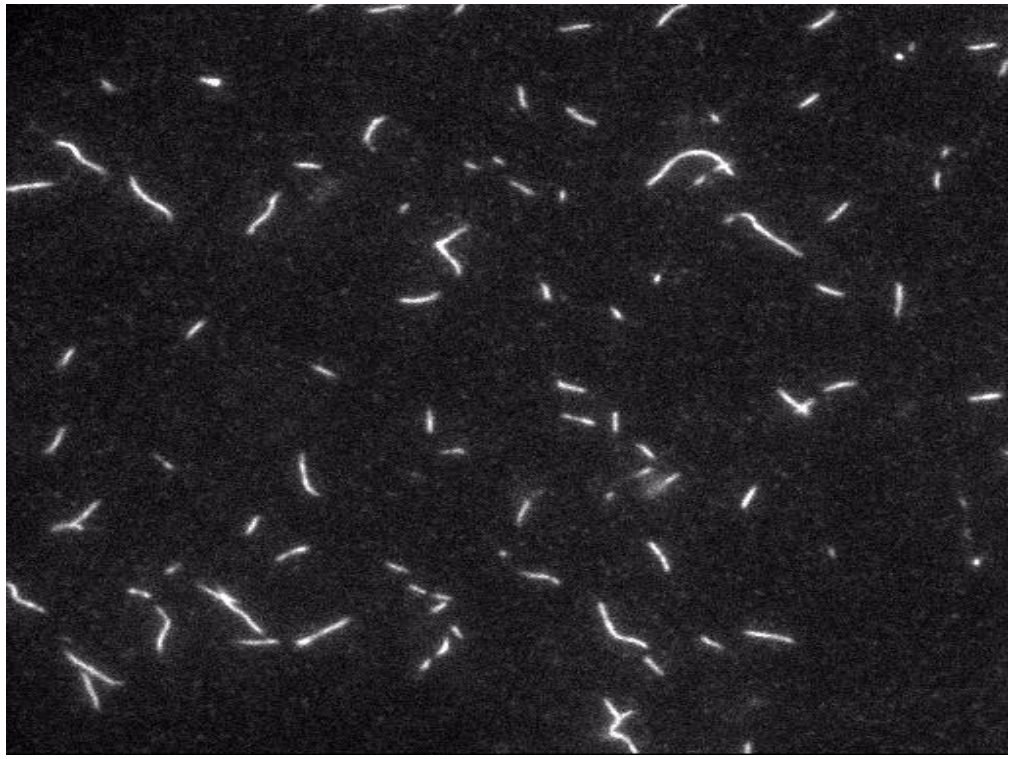
Mavacamten is a first-in-class, targeted inhibitor of cardiac myosin

→ It reduces the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM

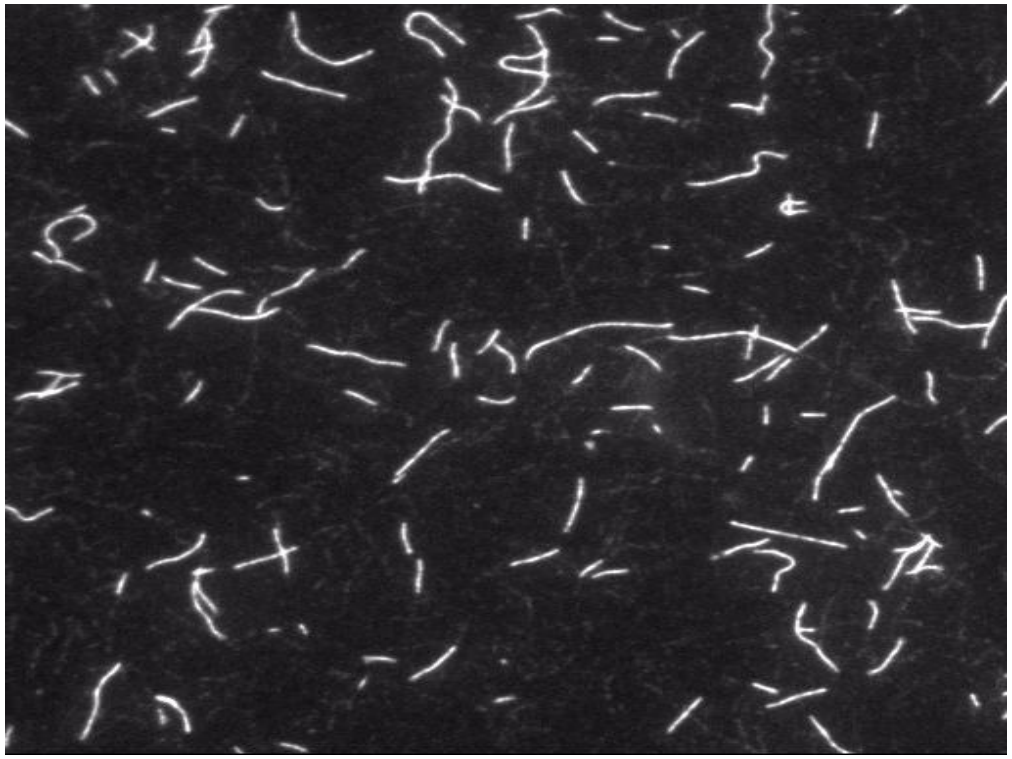
Proprietary Assays Measuring Changes in Velocity and Force of Contraction

Fluorescently-labeled actin being moved by myosin “motor” fixed to well

Control



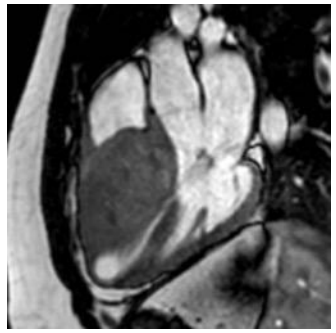
Mavacamten Reduces Contraction



Courtesy of Prof. Olivotto

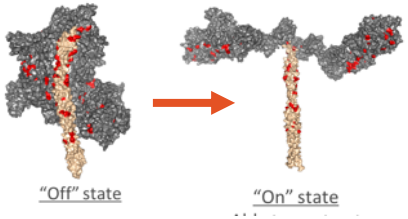
Clinical Studies

Hypercontractile LV
LVOT obstruction >>
Symptoms



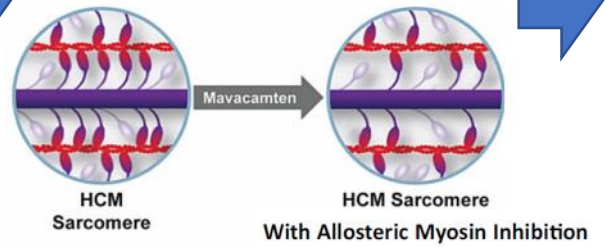
Basic Science

Gain of function MHY7 mutations



Targeted Molecular Approach

Mavacamten



Pre-clinical Data

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

Phase 3 Clinical Trials

In Obstructive HCM

EXPLORER-HCM

ValorHCM

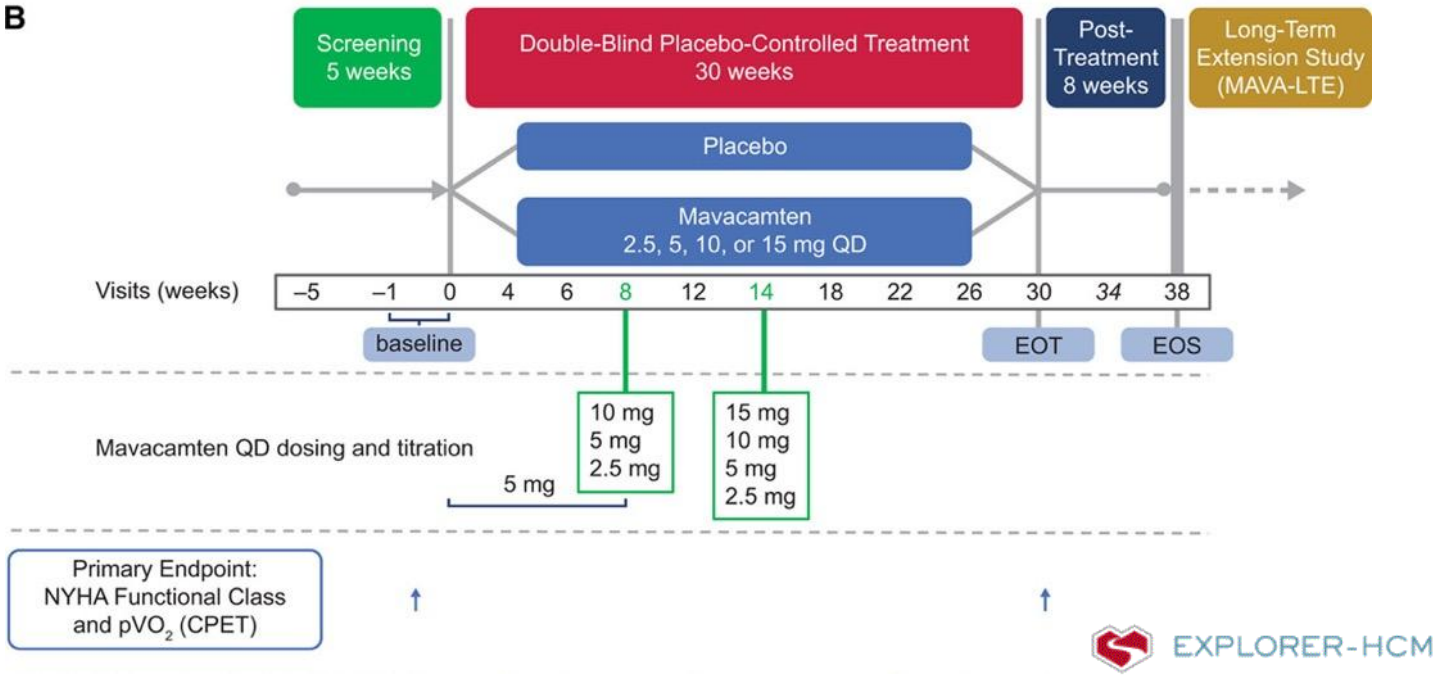
Improved Symptoms and Exercise Performance
Relief of LVOT gradient
Improved QOL
↓ LA size
↓ E/e'
↑ LV cavity size
↓ NT ProBNP and HsTnT
Reduced need for Septal Reduction Therapies

In Nonobstructive HCM → ODYSSEY HCM (Ongoing)

For Obstructive HCM: FDA Approval April 2022, **EC Approval** June 2023

Braunwald E, Saberi S, Abraham TP, Elliott PM, Olivotto I, Eur Heart J, 2023

Explorer-HCM

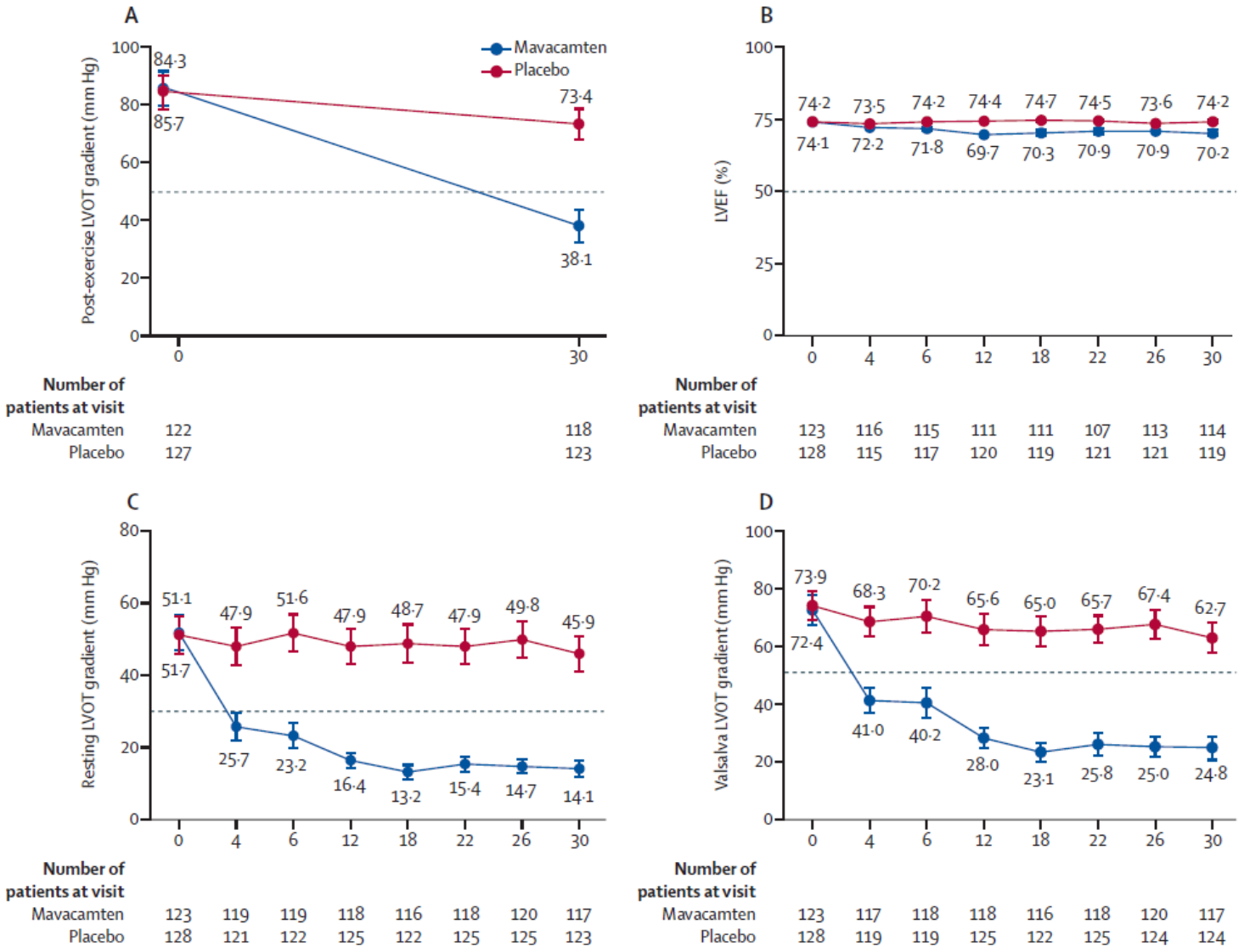


	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Difference (95% CI) P value
EITHER ≥1.5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement **OR** ≥3.0 ml/kg/min increase in pVO_2 with no worsening of NYHA class	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1) 0.0005
BOTH ≥3.0 ml/kg/min increase in pVO_2 **AND** ≥1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.0, 21.0) 0.0005*

Olivotto et al, Lancet 2020

*P value not alpha-controlled
NYHA, New York Heart Association; pVO_2, peak oxygen consumption.

LVOT Gradients and LVEF



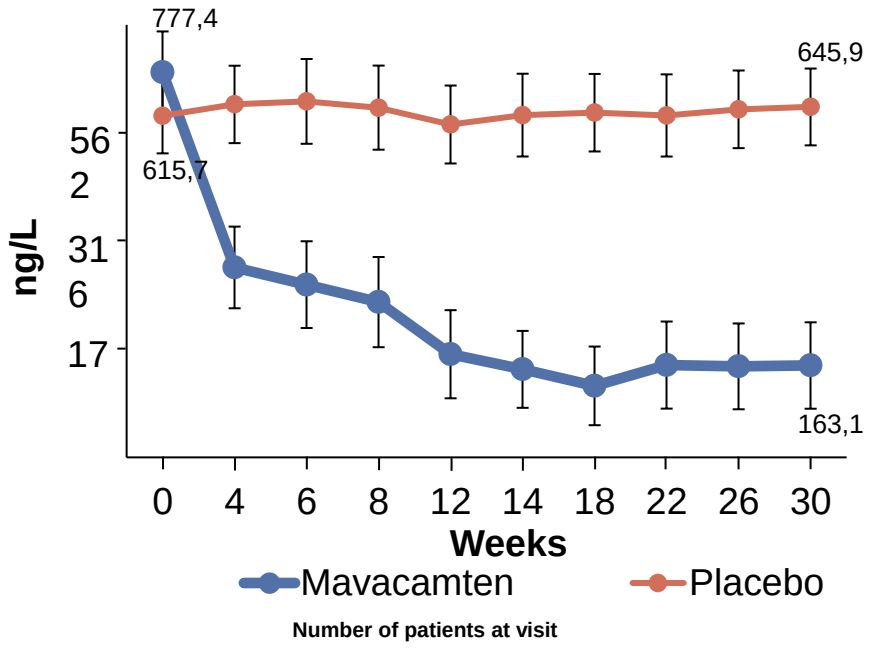
EXPLORER-HCM

Olivotto et al, Lancet 2020

Cardiac Biomarkers

EXPLORER-HCM

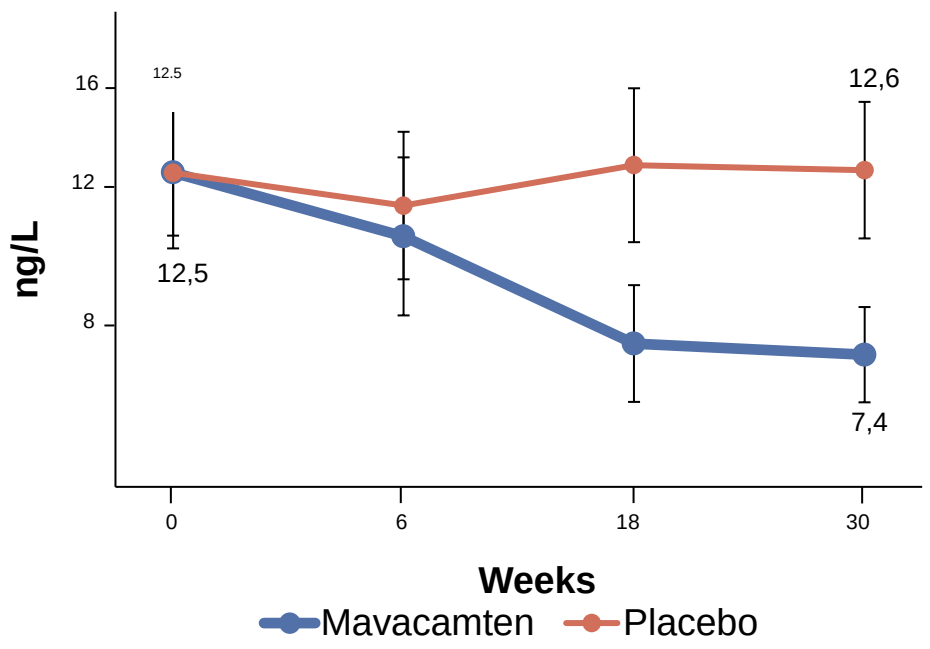
Geometric mean (95% CI) NT-proBNP



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



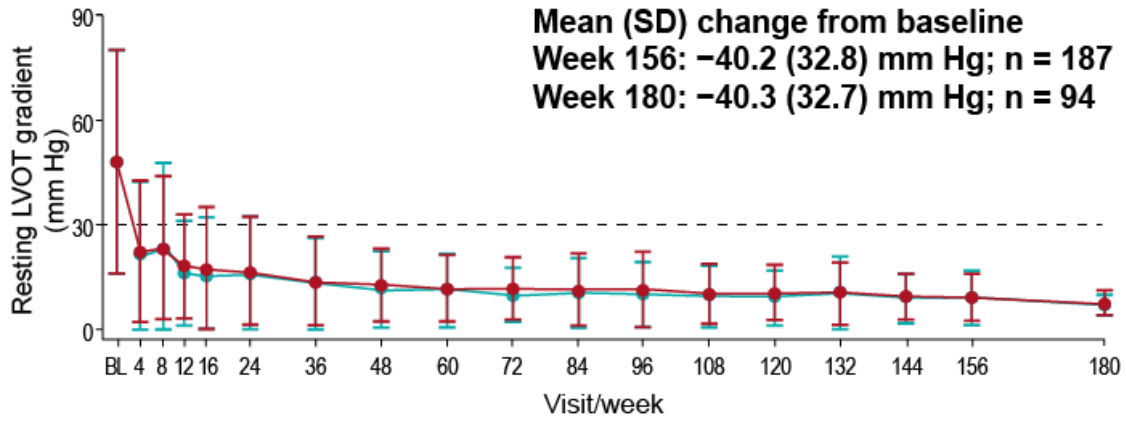
Number of patients at visit

Mavacamten	120	86	102	115
Placebo	119	84	104	115

Olivotto et al, Lancet 2020

Sustained improvements in LVOT gradients over 3.5 years of treatment

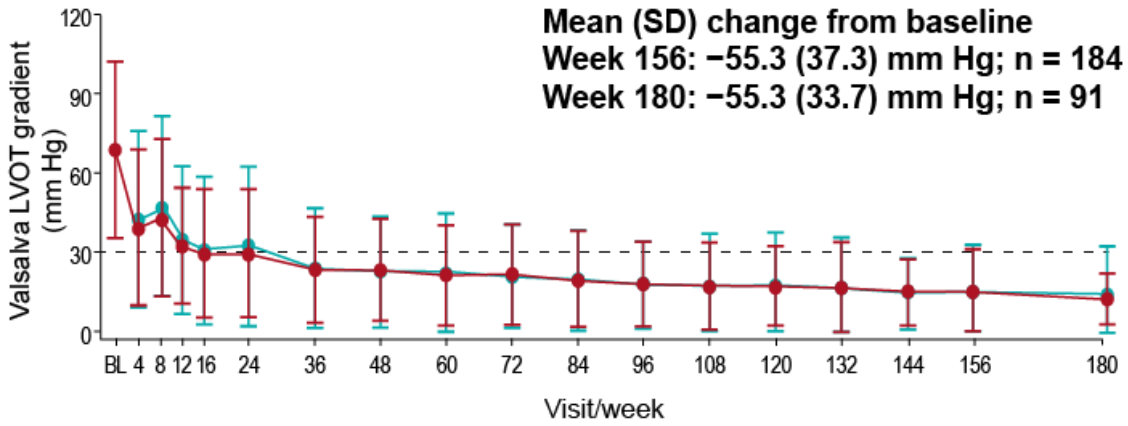
Resting LVOT gradient



Number of patients at visit

	BL	4	8	12	16	24	36	48	60	72	84	96	108	120	132	144	156	180
Central-read LVOT	231	220	223	199	220	224	225	224	220	218	215	213	208	209	206	201	187	94
Site-read LVOT		221	225	199	219	224	225	223	218	217	213	214	210	210	205	200	186	94

Valsalva LVOT gradient



Number of patients at visit

	BL	4	8	12	16	24	36	48	60	72	84	96	108	120	132	144	156	180
Central-read LVOT	229	218	223	199	220	224	224	224	220	218	215	215	209	208	206	198	186	93
Site-read LVOT		221	225	199	218	224	225	223	218	217	213	213	210	210	204	199	185	94

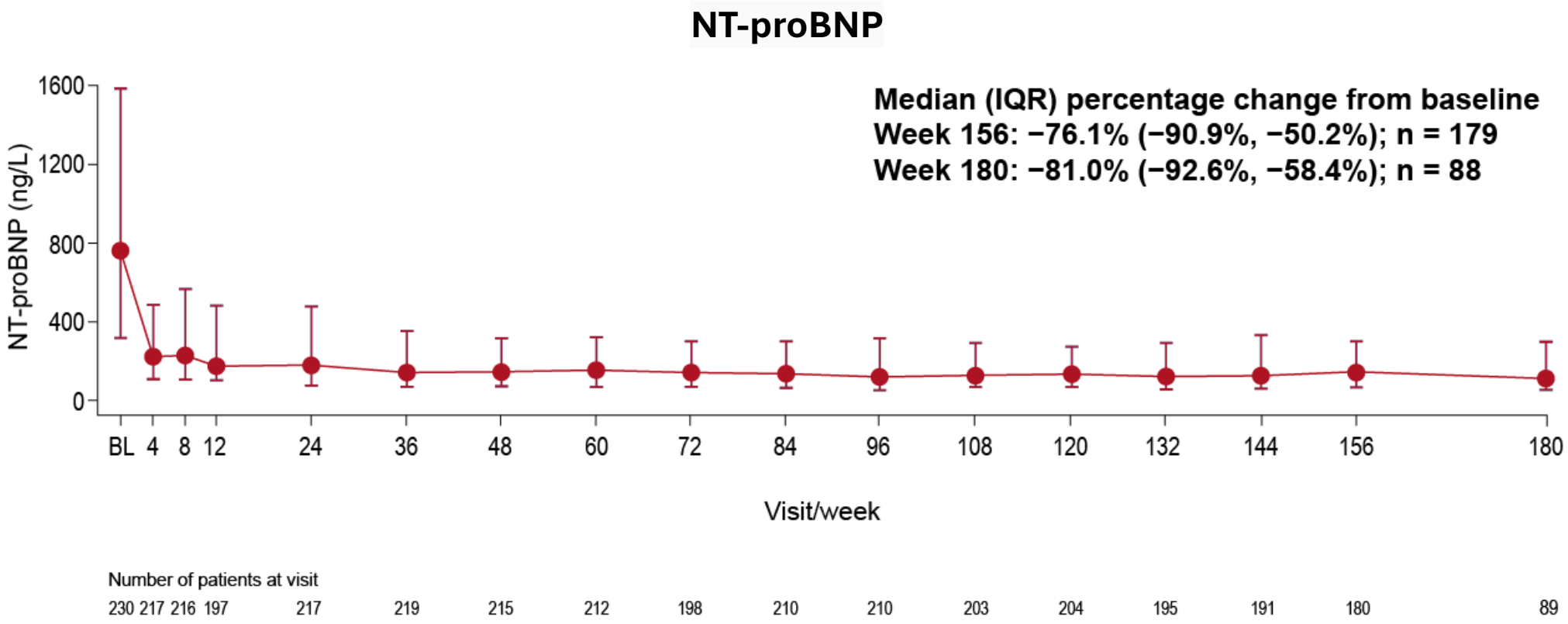
Central-read LVOT Site-read LVOT

- Improvements in resting and Valsalva LVOT gradients with mavacamten treatment were sustained through weeks 156 and 180, as confirmed by both site-read and central-read echocardiograms
- Overall, 191 patients (82.7%) achieved a central-read Valsalva LVOT gradient of ≤ 30 mm Hg – indicative of nonobstruction – during the study and remained at or below the 30 mm Hg threshold until the data cutoff

Baseline is defined as the last nonmissing measurement before the first dose of mavacamten in MAVA-LTE. The dotted lines represent the threshold for nonobstruction
BL, baseline; LTE, Long-Term Extension; LVOT, left ventricular outflow tract; SD, standard deviation

Garcia-Pavia et al, Eur Heart J. 2024

Sustained improvements in NT-proBNP over 3.5 years of treatment

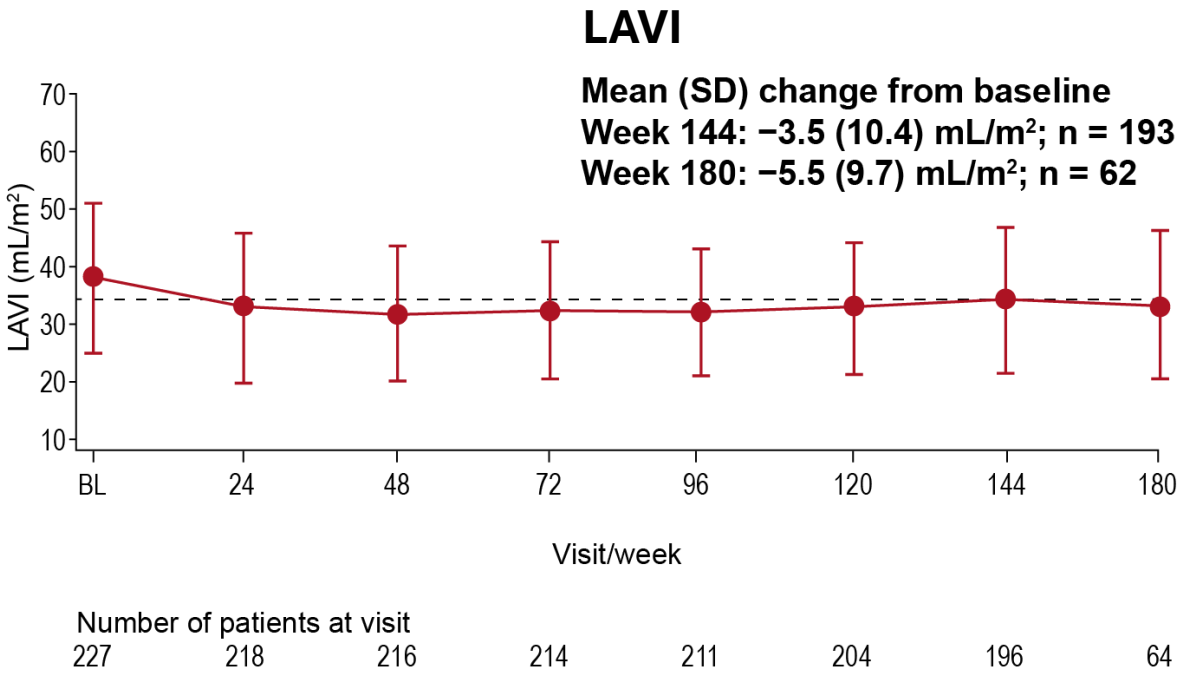


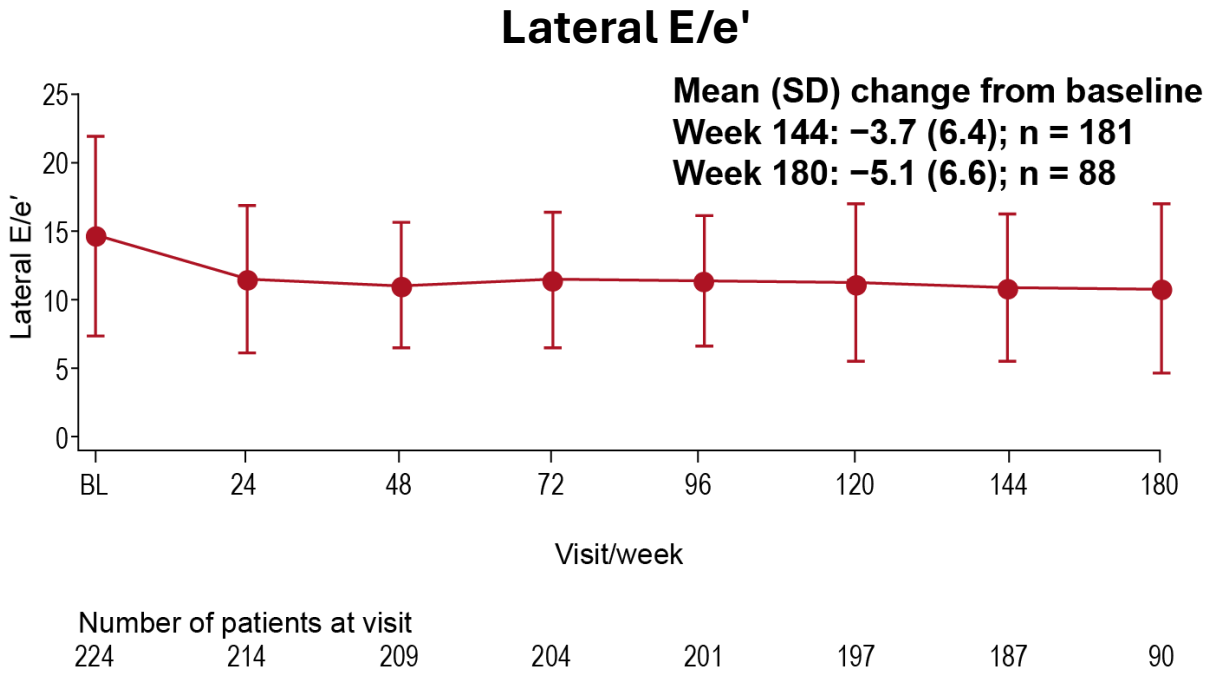
- The proportion of patients with a NT-proBNP concentration of < 124 ng/L – indicative of normal range – increased from 9.6% at baseline to 43.2% at week 156 and 53.8% at week 180

Baseline is defined as the last nonmissing measurement before the first dose of mavacamten in MAVA-LTE
BL, baseline; IQR, interquartile range; LTE, Long-term Extension; NT-proBNP, N-terminal pro B-type natriuretic peptide

Garcia-Pavia et al, Eur Heart J. 2024

Sustained improvements in LAVI and lateral E/e' over 3.5 years of treatment





- Clinically meaningful improvements with mavacamten treatment in mean LAVI and lateral E/e' values were sustained through weeks 144 and 180

Baseline is defined as the last nonmissing measurement before the first dose of mavacamten in MAVA-LTE. LAVI and lateral E/e' were not scheduled measurements at week 156. The dotted line on the LAVI figure represents the threshold for normal LAVI[1]

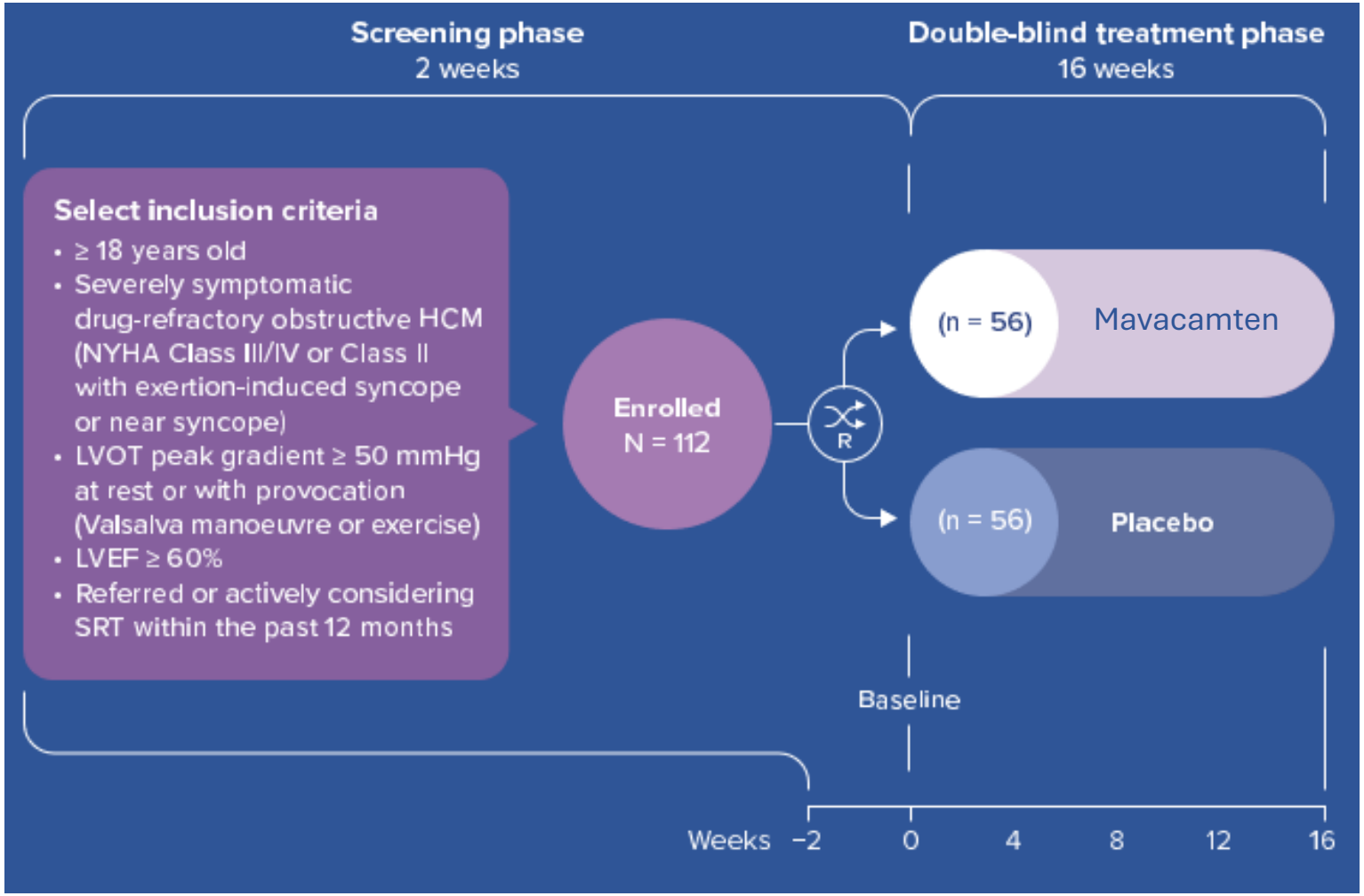
BL, baseline; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LAVI, left atrial volume index; LTE, Long-Term Extension; SD, standard deviation

1. Lang RM, et al. *J Am Soc Echocardiogr* 2015;28:1–39.e14

Garcia-Pavia et al, Eur Heart J. 2024

VALOR-HCM

A phase 3 trial in SRT-eligible patients with symptomatic obstructive HCM in the US



5 mg starting dose mavacamten was taken orally QD. The dose was periodically adjusted to optimize patient response.

Desai MY et al. J AM Coll Cardiol. 2022

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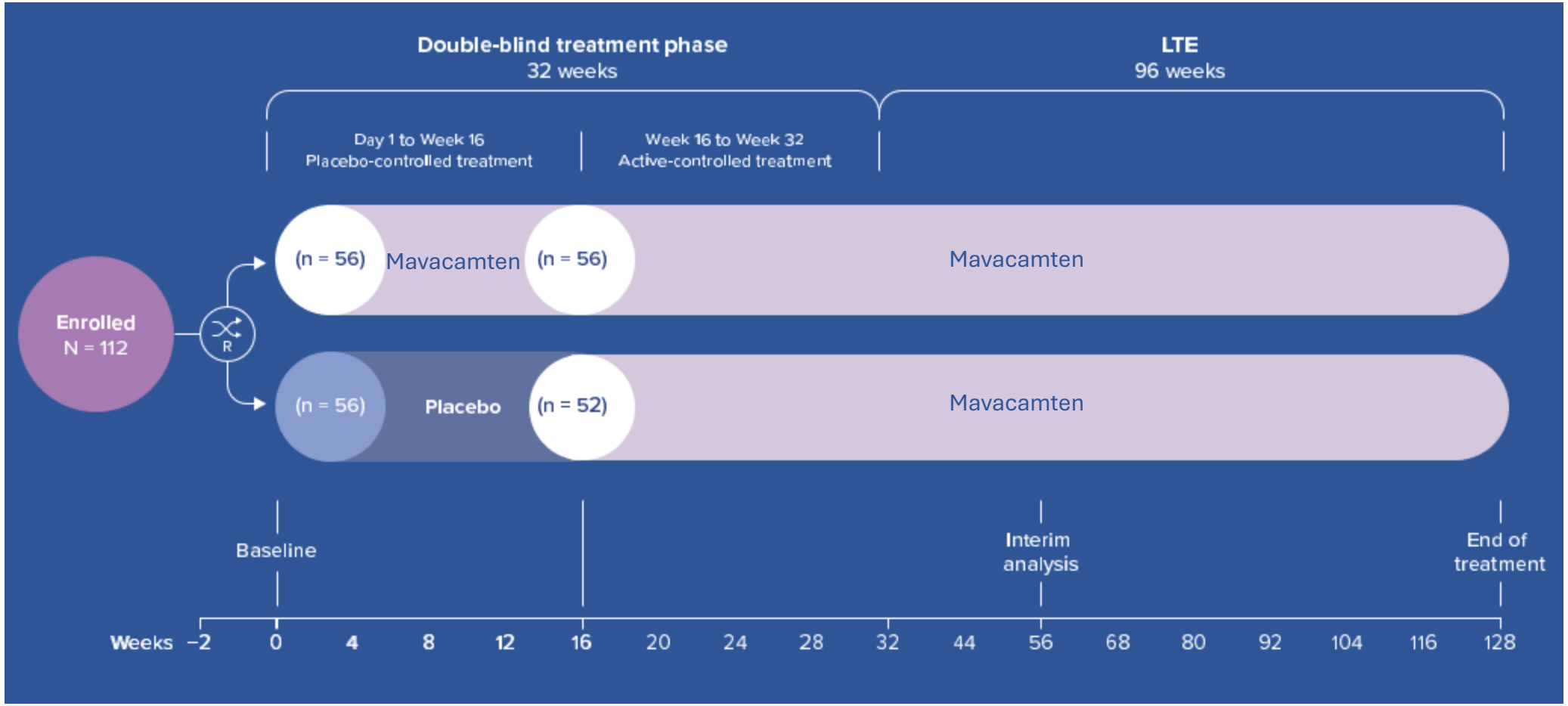

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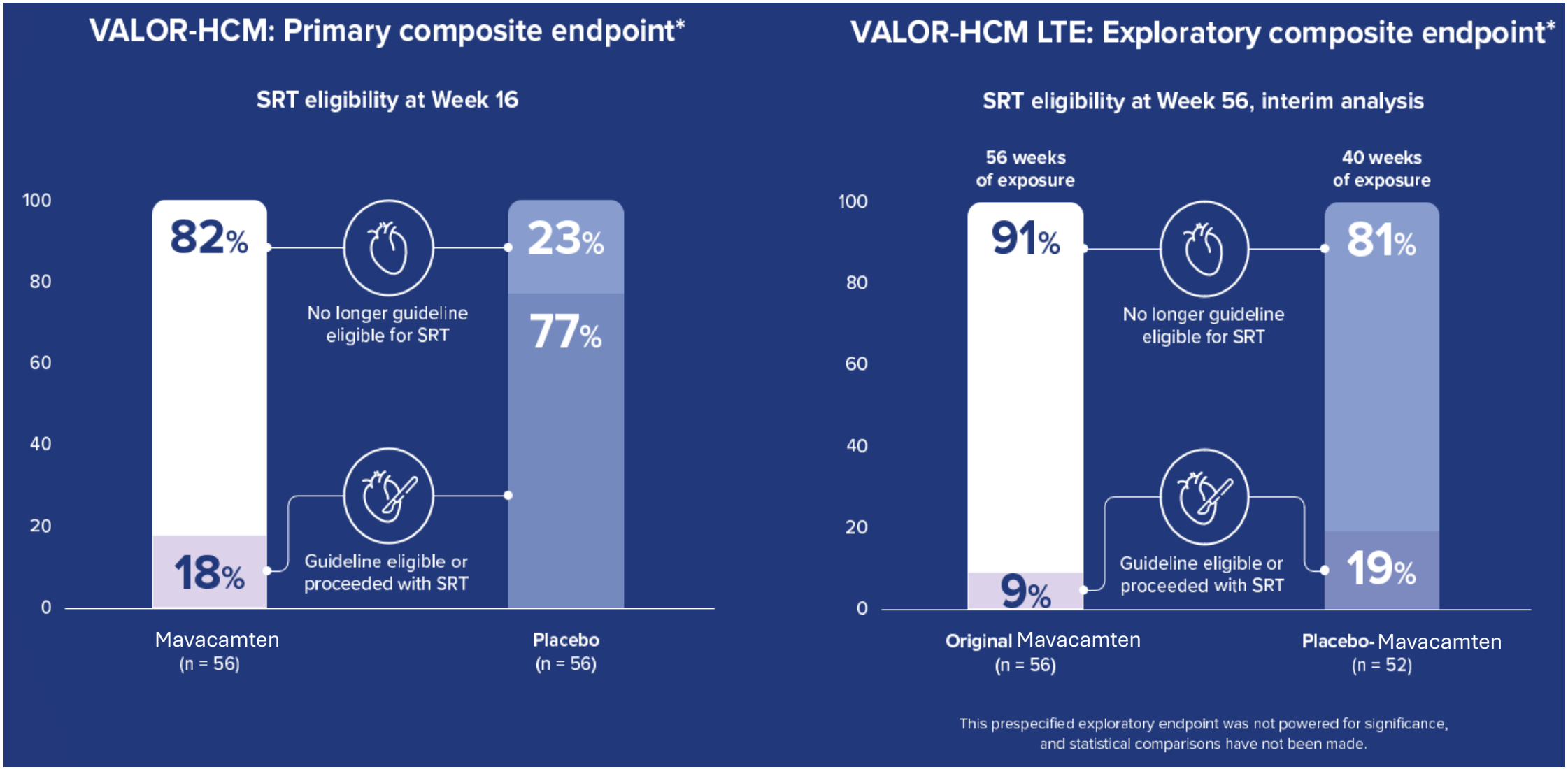

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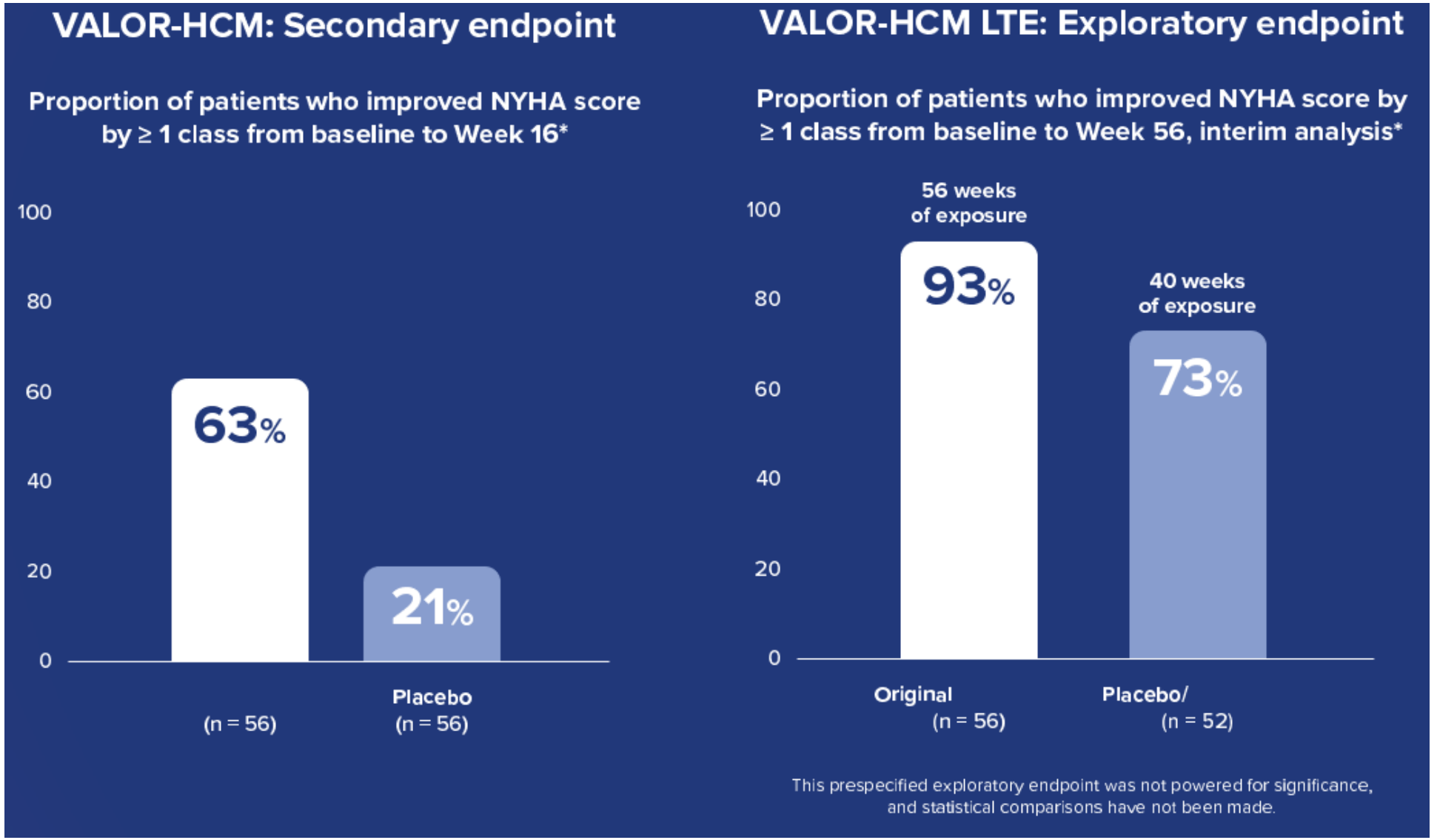
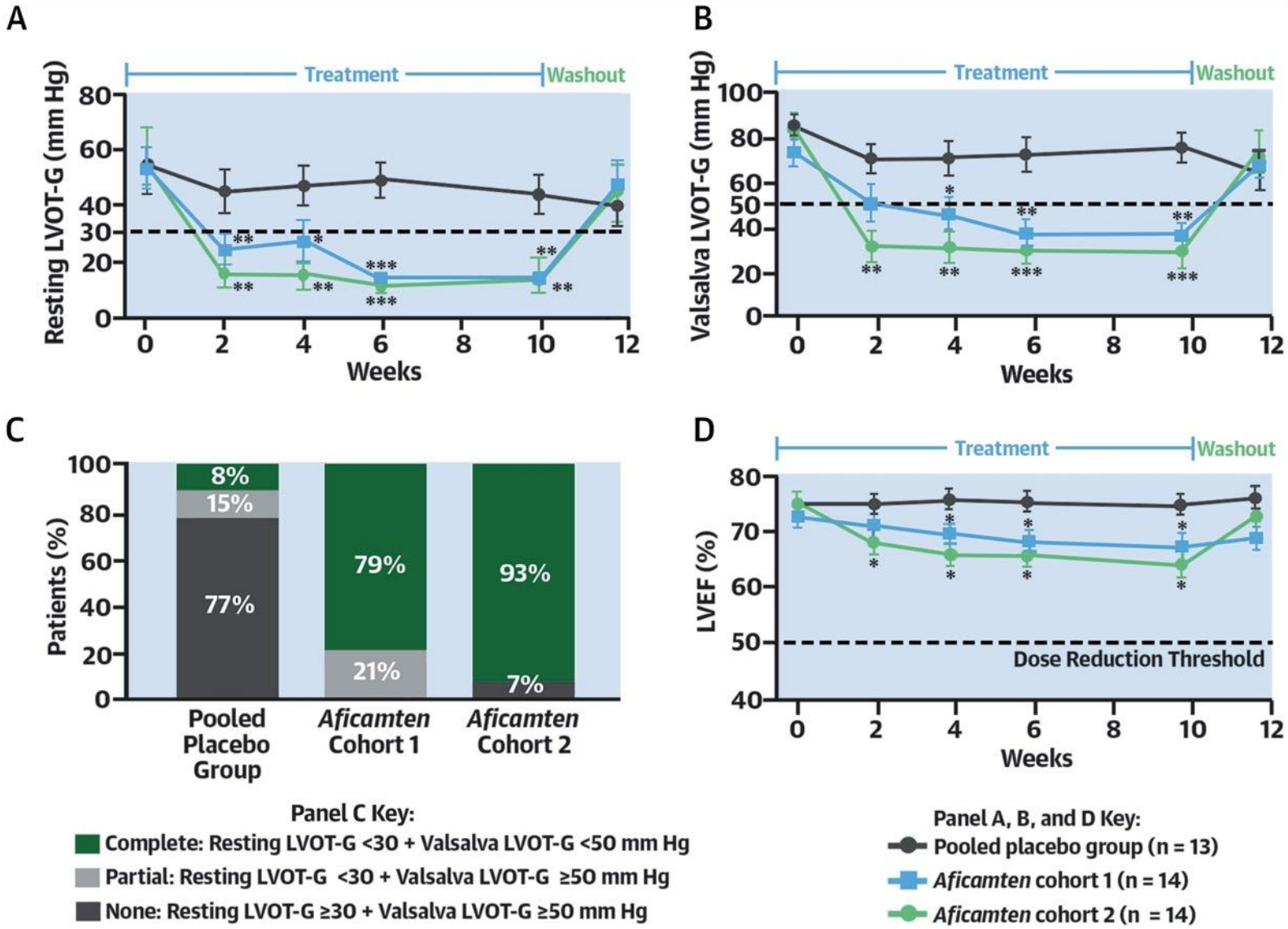


Desai MY et al. J AM Coll Cardiol. 2022

REDWOOD-HCM Cohort 1 and 2:

Phase II, Randomized (2:1), Placebo-Controlled Study of *Aficamten* in Symptomatic oHCM



Maron MS, et al. J Am Coll Cardiol. 2023;81(1):34–45.

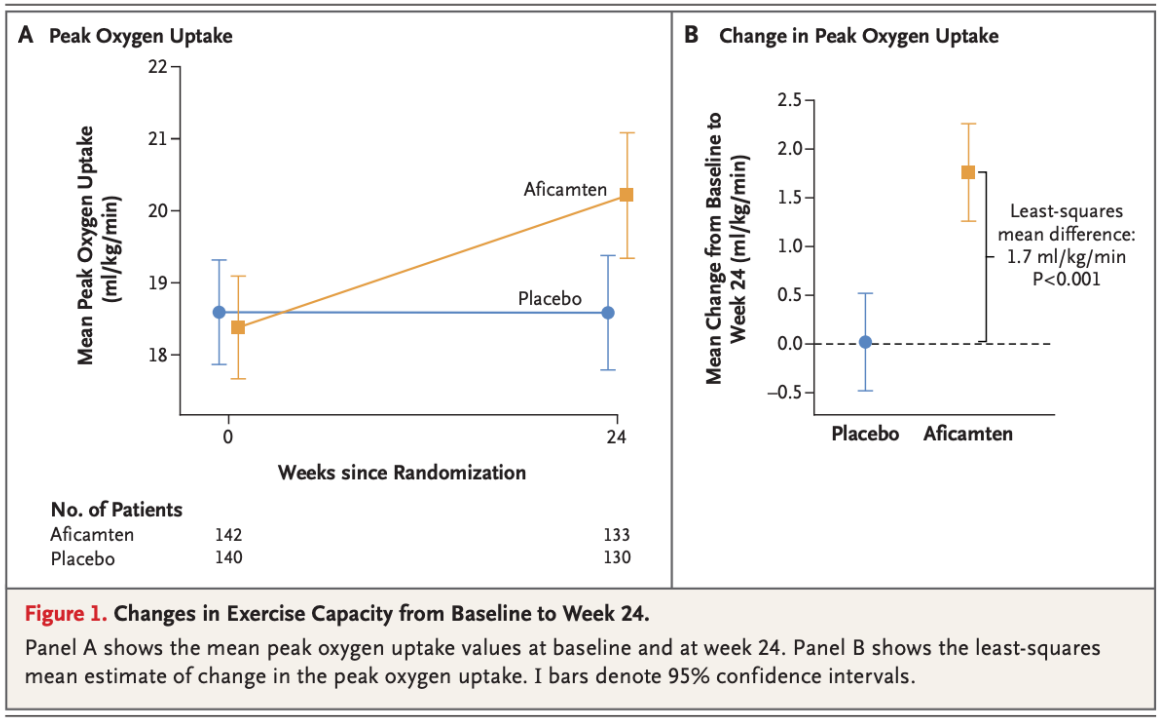
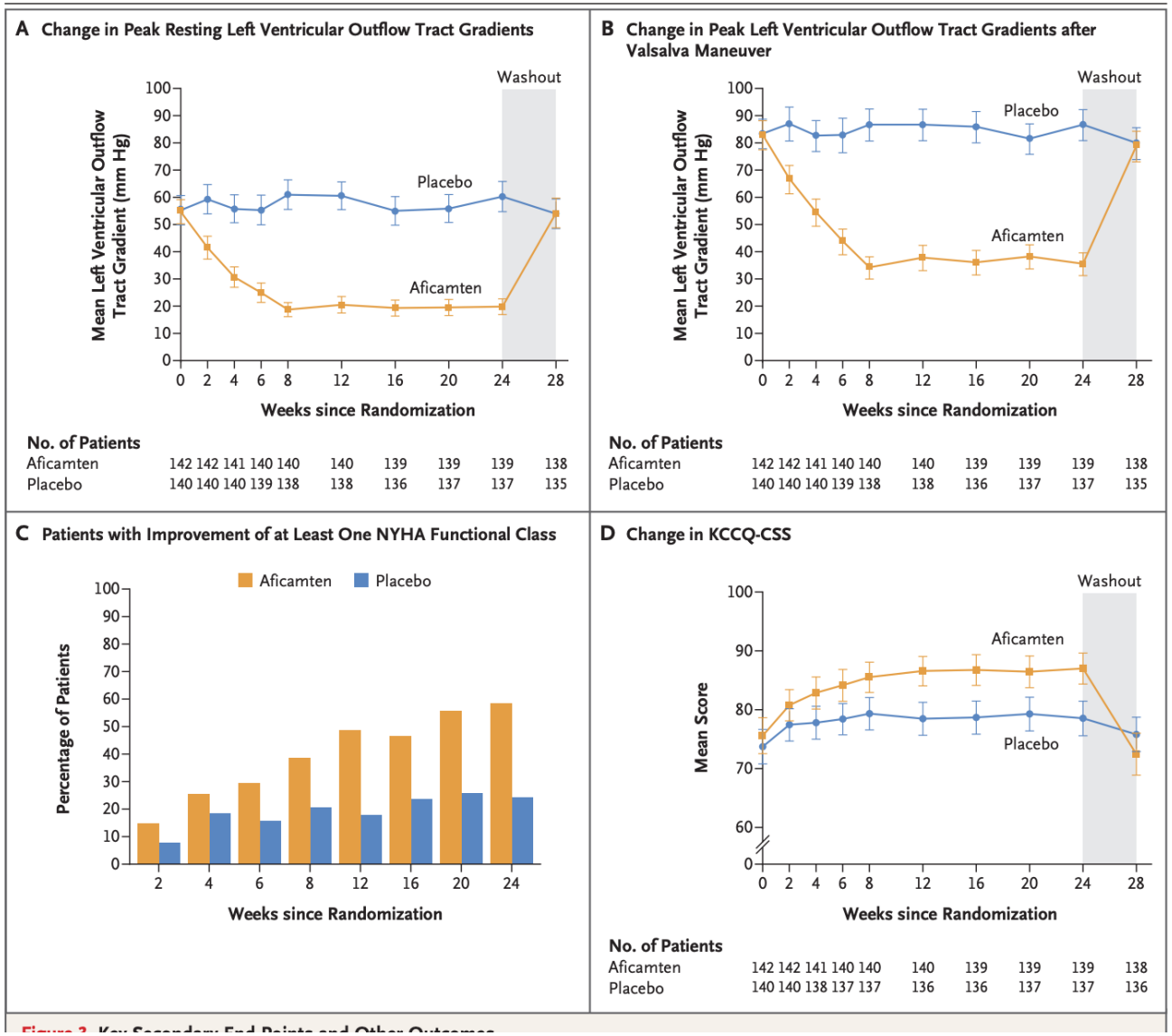
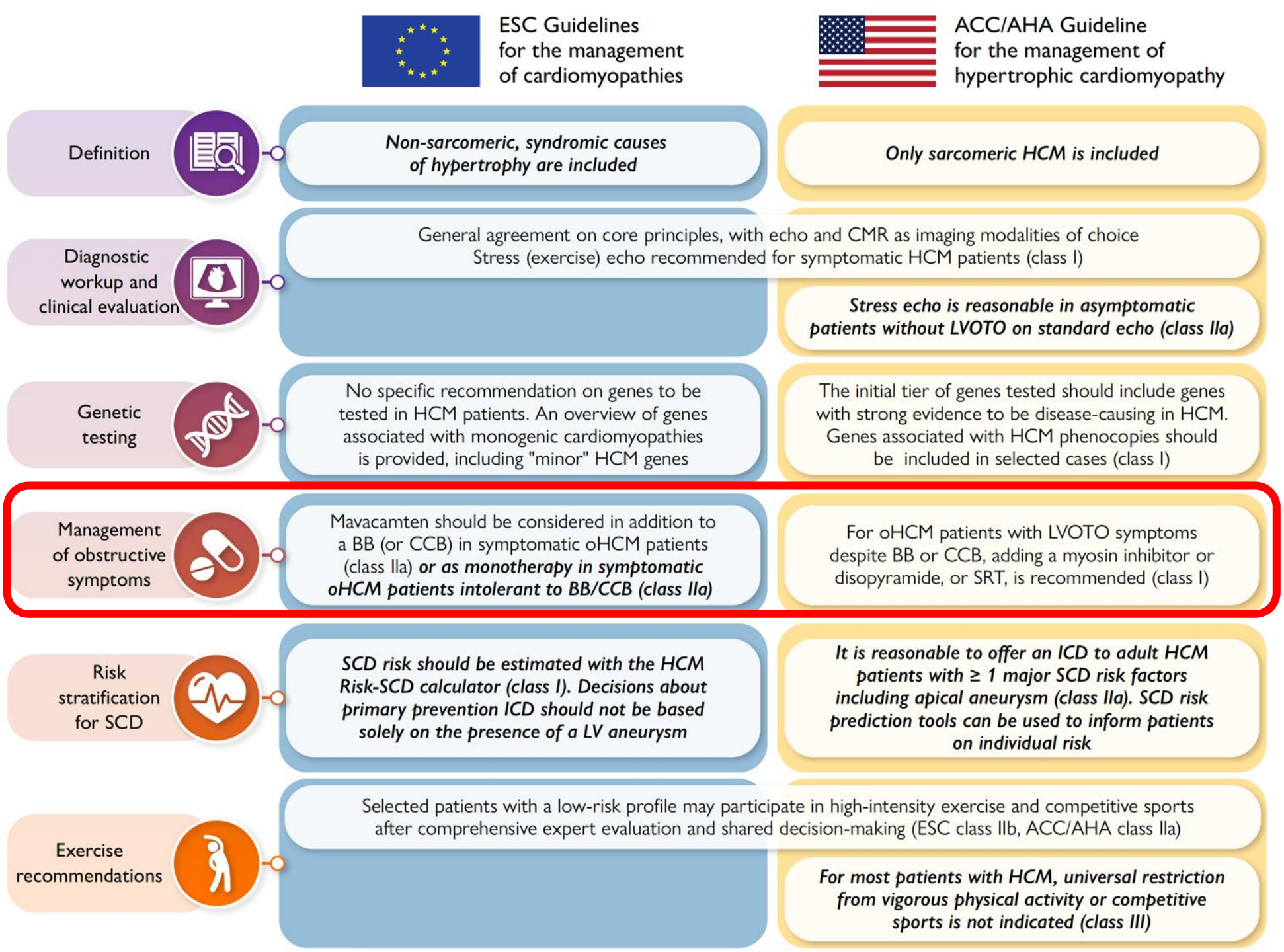


Figure 1. Changes in Exercise Capacity from Baseline to Week 24.

Panel A shows the mean peak oxygen uptake values at baseline and at week 24. Panel B shows the least-squares mean estimate of change in the peak oxygen uptake. I bars denote 95% confidence intervals.



Maron MS et al N Engl J Med 2024



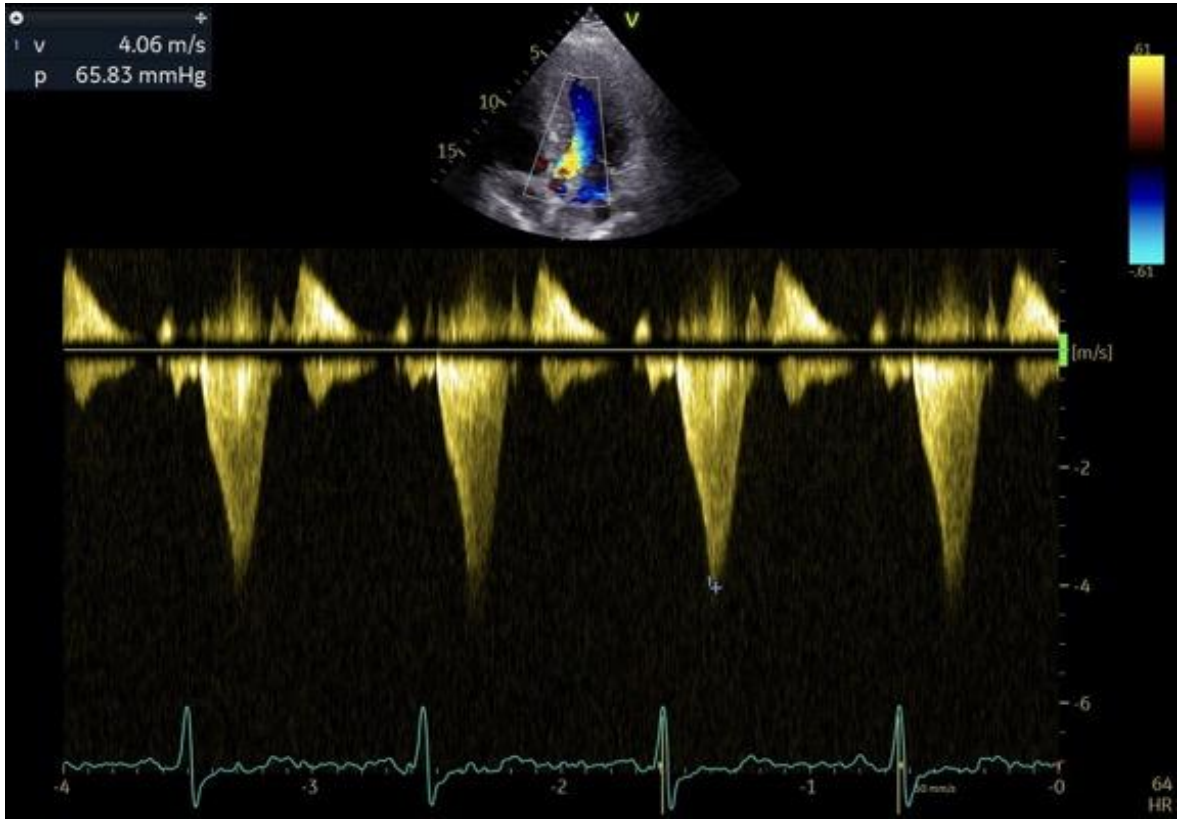
The Evolving Landscape of Hypertrophic Cardiomyopathy Management: A Comparison of ACC/AHA and ESC Guidelines

Bertero E, Canepa M, Olivotto I *(EHJ Accepted)*

Clinical Case

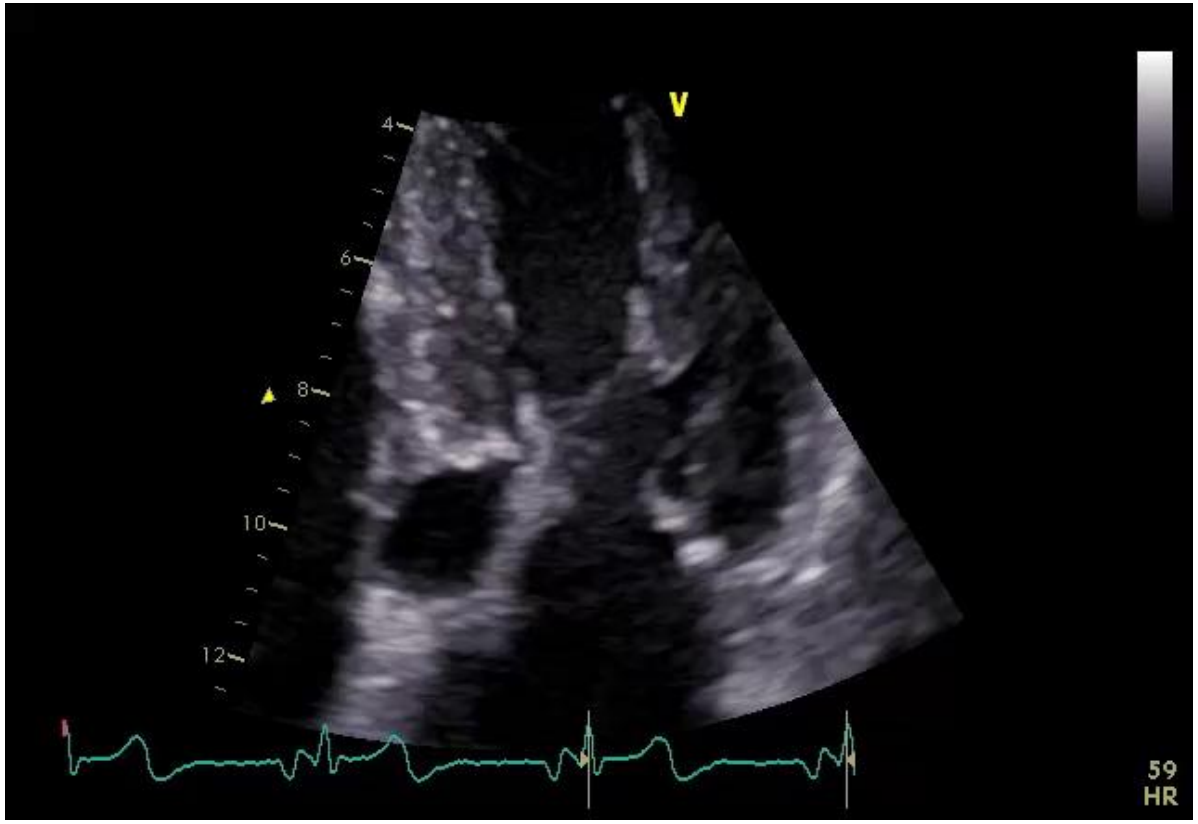
- Male, 45 yo. Pediatric onset diagnosed at age 8
- Development of a moderate phenotype in the fourth decade with maximum wall thickness of 23 mm
- 2021 refused SRT
- February 2024 EAP mavacamten started
- Baseline 2D-Echo:
  - Asymmetric LVH with reverse curve morphology, (MWT 24 mm), (EDV 80 ml, ESV 86 ml, EF 78%) .
  - Anteriorization of medial PM with end-systolic contact with the septum
  - MVO (18 mmHg) and LVOTO 65 mmHg increasing to 81 mm Hg with Valsalva manoeuvre.
  - Triphasic filling pattern (E 60 cm/s, DT 228 ms, A 70 cm/s, E/A 0.73, e' medial 4 cm/s, e' lateral 9 cm/s, E/e' avg 10). Severely dilated left atrium (d 40 mm, volume 95 ml).
  - Mitral valve leaflet thickening, complete SAM with cordal slack. Mild mitral regurgitation with posteriorly directed jet.

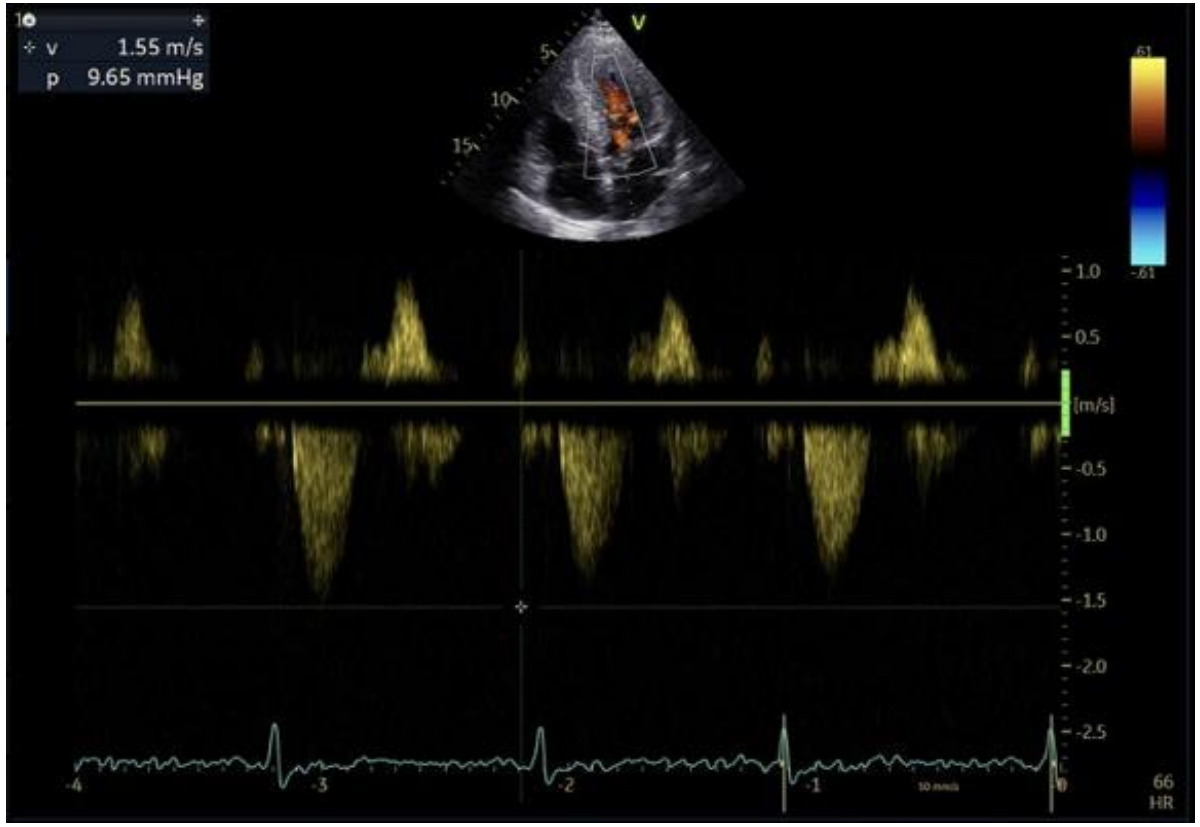
Clinical Case



Nadolol 80 mg

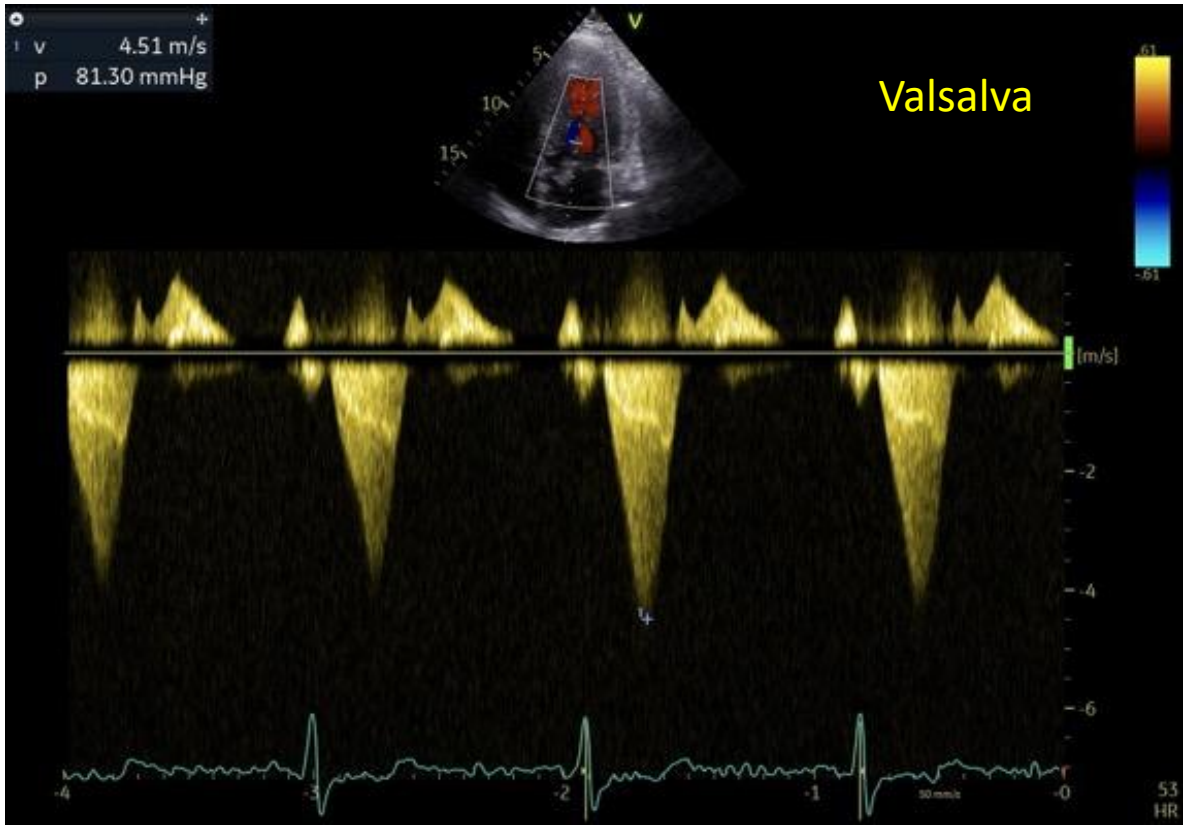
Clinical Case



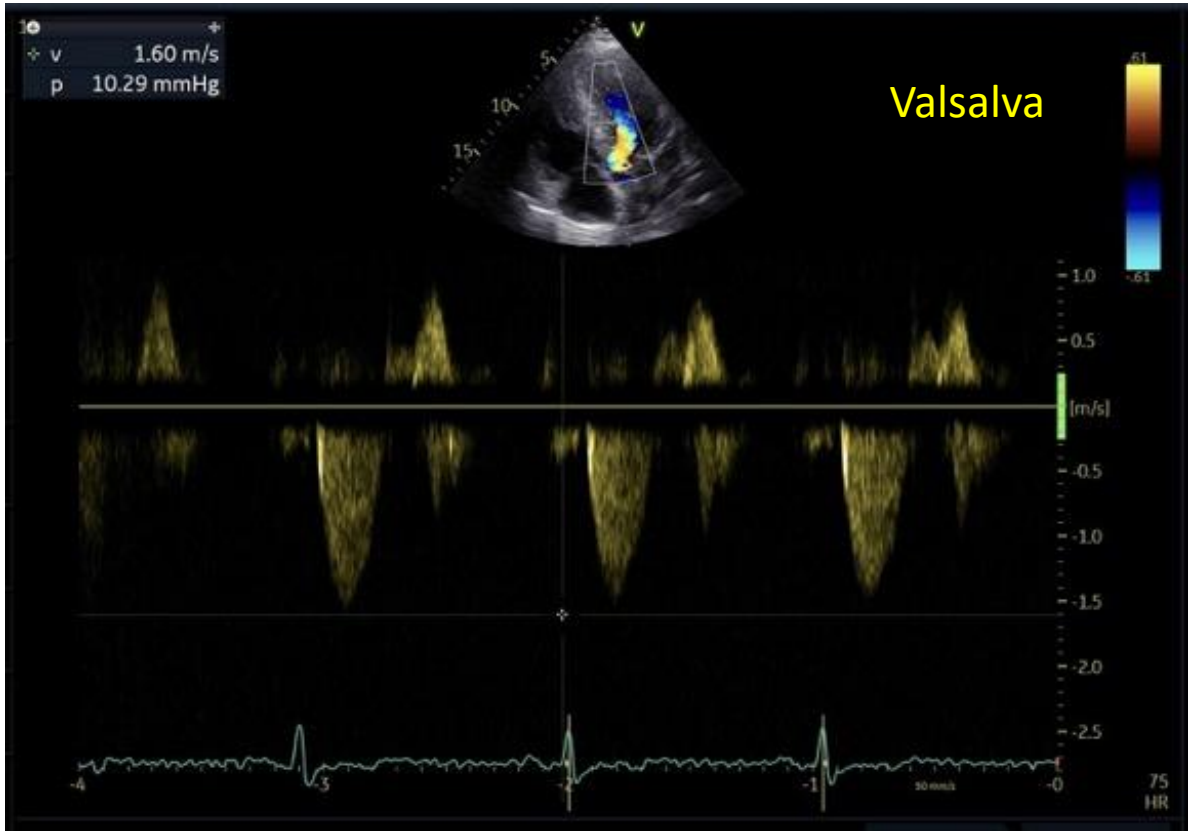


Nadolol 80 mg + Mavacamten 5 mg

Clinical Case

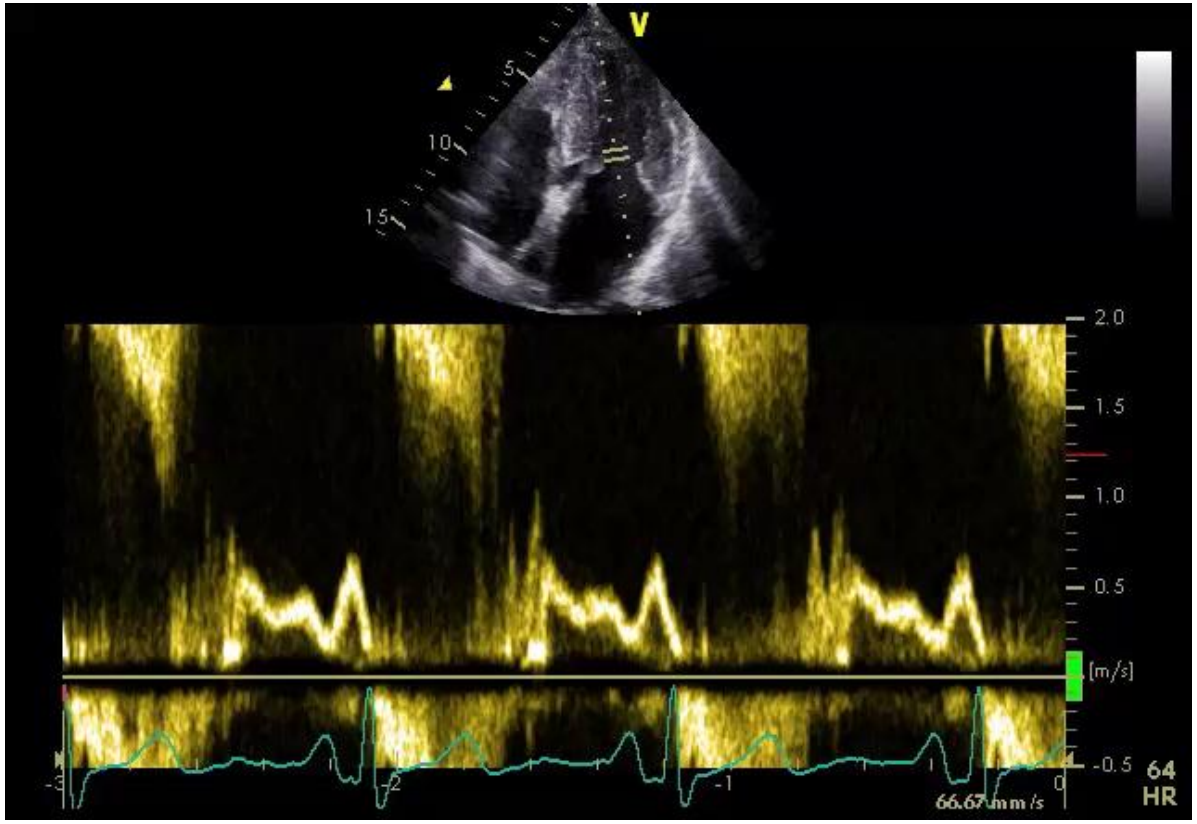


Nadolol 80 mg

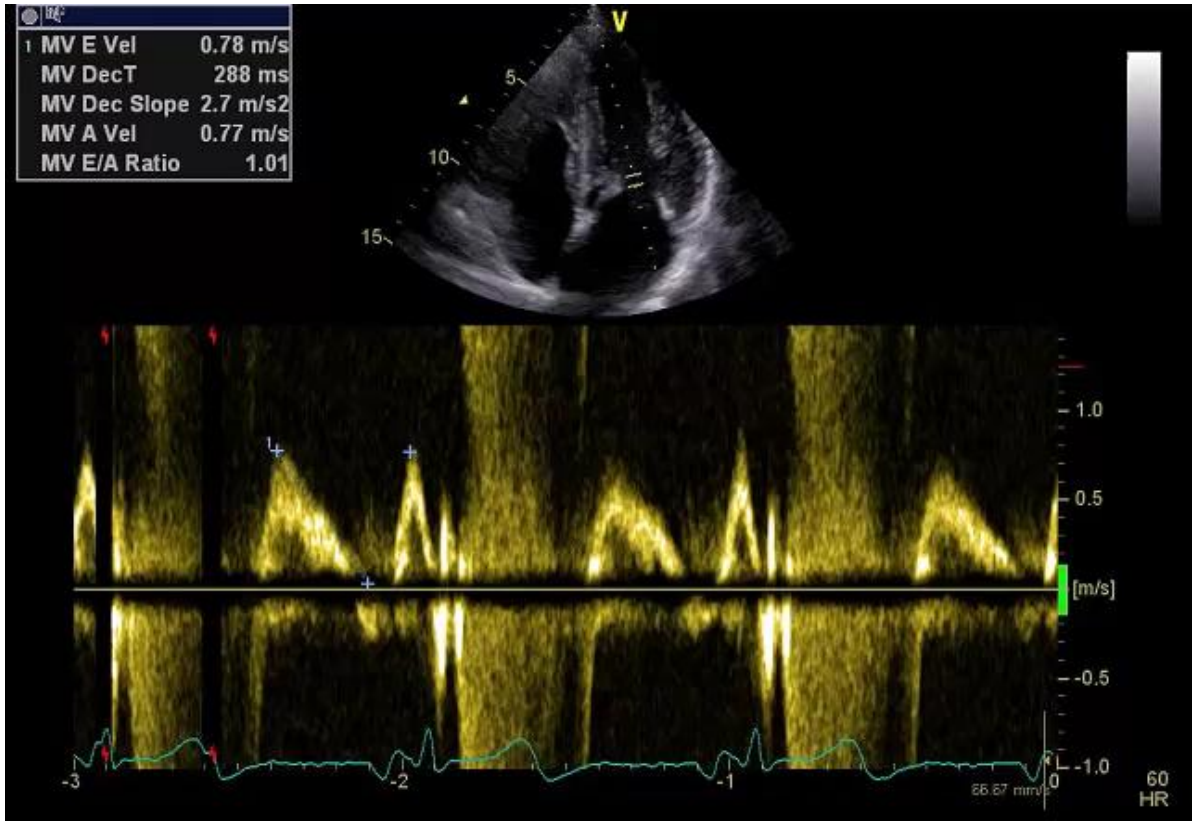


Nadolol 80 mg + Mavacamten 5 mg

Clinical Case



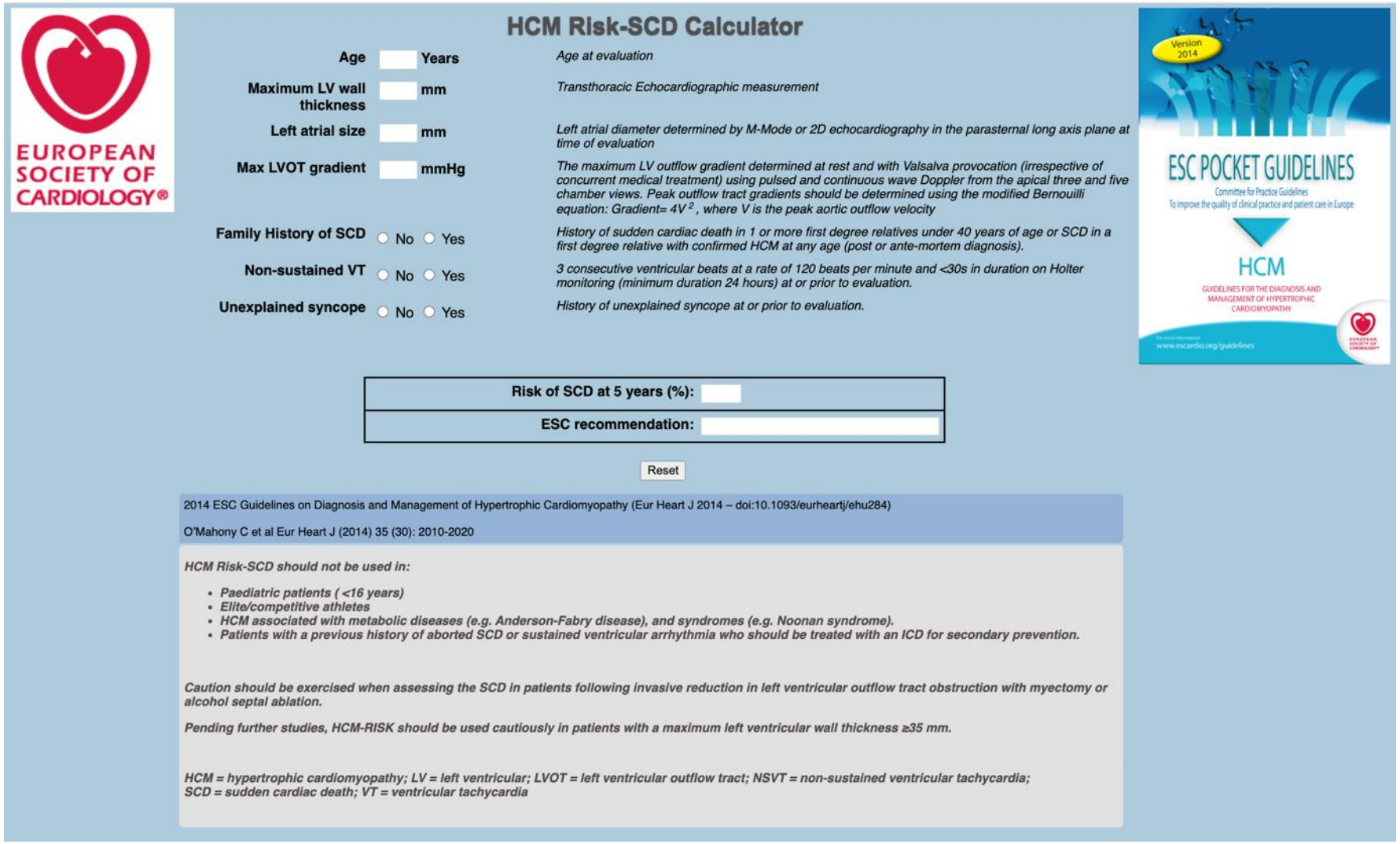
Nadolol 80 mg



Mavacamten 5 mg + nadolol 80 mg

SCD-risk stratification

Risk stratification



ESC Guidelines
for the management
of cardiomyopathies

ACC/AHA Guideline
for the management of
hypertrophic cardiomyopathy

	ESC Guidelines for the management of cardiomyopathies	ACC/AHA Guideline for the management of hypertrophic cardiomyopathy
Definition	***Non-sarcomeric, syndromic causes of hypertrophy are included***	***Only sarcomeric HCM is included***
Diagnostic workup and clinical evaluation	General agreement on core principles, with echo and CMR as imaging modalities of choice Stress (exercise) echo recommended for symptomatic HCM patients (class I)	***Stress echo is reasonable in asymptomatic patients without LVOTO on standard echo (class IIa)***
Genetic testing	No specific recommendation on genes to be tested in HCM patients. An overview of genes associated with monogenic cardiomyopathies is provided, including "minor" HCM genes	The initial tier of genes tested should include genes with strong evidence to be disease-causing in HCM. Genes associated with HCM phenocopies should be included in selected cases (class I)
Management of obstructive symptoms	Mavacamten should be considered in addition to a BB (or CCB) in symptomatic oHCM patients (class IIa) ***or as monotherapy in symptomatic oHCM patients intolerant to BB/CCB (class IIa)***	For oHCM patients with LVOTO symptoms despite BB or CCB, adding a myosin inhibitor or disopyramide, or SRT, is recommended (class I)
Risk stratification for SCD	***SCD risk should be estimated with the HCM Risk-SCD calculator (class I). Decisions about primary prevention ICD should not be based solely on the presence of a LV aneurysm***	***It is reasonable to offer an ICD to adult HCM patients with ≥ 1 major SCD risk factors including apical aneurysm (class IIa). SCD risk prediction tools can be used to inform patients on individual risk***
Exercise recommendations	Selected patients with a low-risk profile may participate in high-intensity exercise and competitive sports after comprehensive expert evaluation and shared decision-making (ESC class IIb, ACC/AHA class IIa)	***For most patients with HCM, universal restriction from vigorous physical activity or competitive sports is not indicated (class III)***

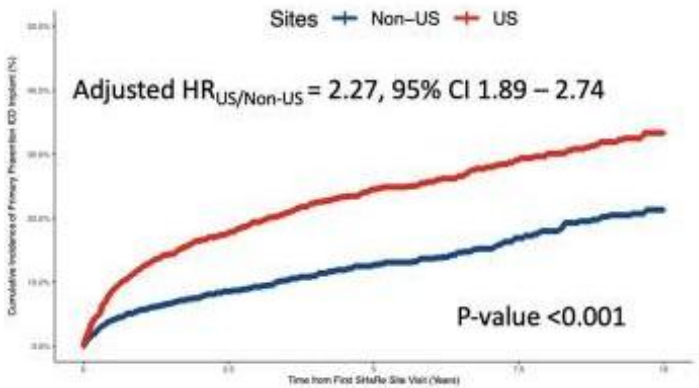
The Evolving Landscape of Hypertrophic Cardiomyopathy Management:
A Comparison of ACC/AHA and ESC Guidelines
Bertero E, Canepa M, Olivotto I *(EHJ Accepted)*

Worldwide Differences in Primary Prevention ICD Utilization and Outcomes in Hypertrophic Cardiomypathy

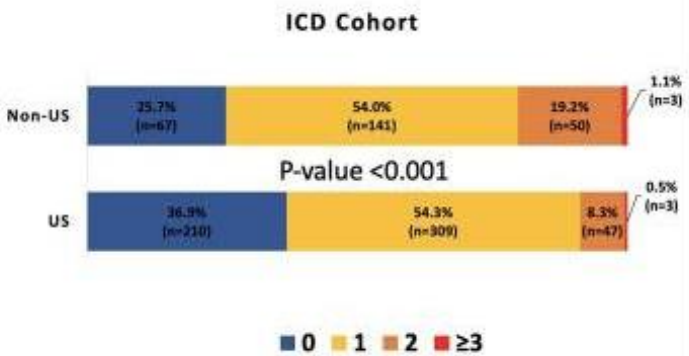
SHARE

US HCM Centres (N=2,650)	Non-US HCM Centres (N=2,660)
• Boston Children's Hospital • Brigham and Women's Hospital • Children's Hospital of Pennsylvania • Cincinnati Children's Hospital • University of Michigan • University of Pennsylvania • Yale • Stanford	• Erasmus Medical Center, Netherlands • Royal Brompton Hospital, United Kingdom • Royal Prince Alfred Hospital, Australia • University of Florence, Italy • University of São Paolo, Brazil

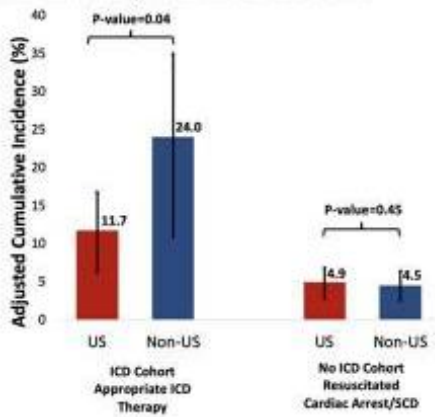
1 2-fold Higher ICD Utilization in US sites



2 Lower Burden of Traditional SCD Risk Factors at Time of ICD Implant in US vs. Non-US sites

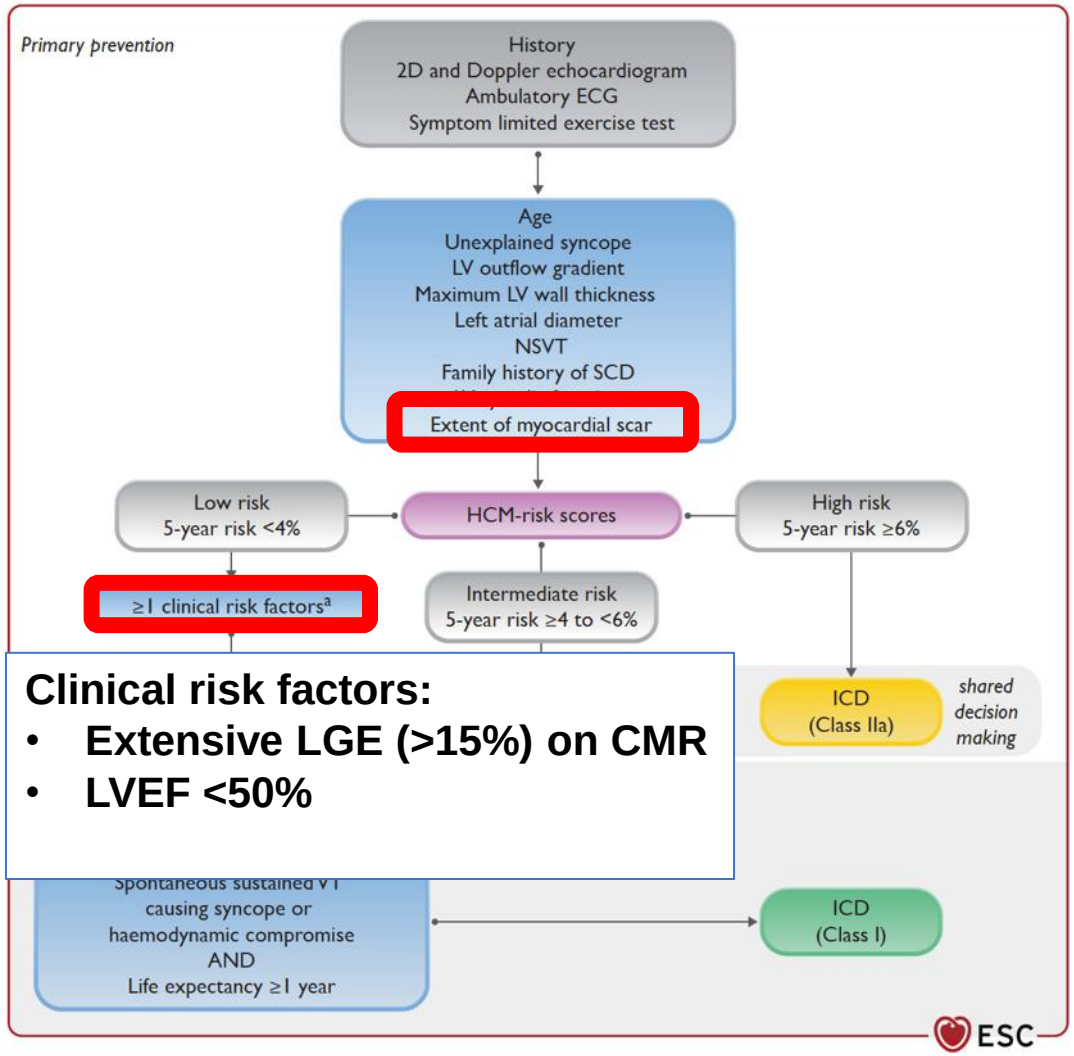


3 ICD Cohort: ↓ Appropriate Therapy in US sites No ICD Cohort: No excess Resuscitated Cardiac Arrest/SCD in Non-US sites



Nauffal et al. Eur Heart J. 2021

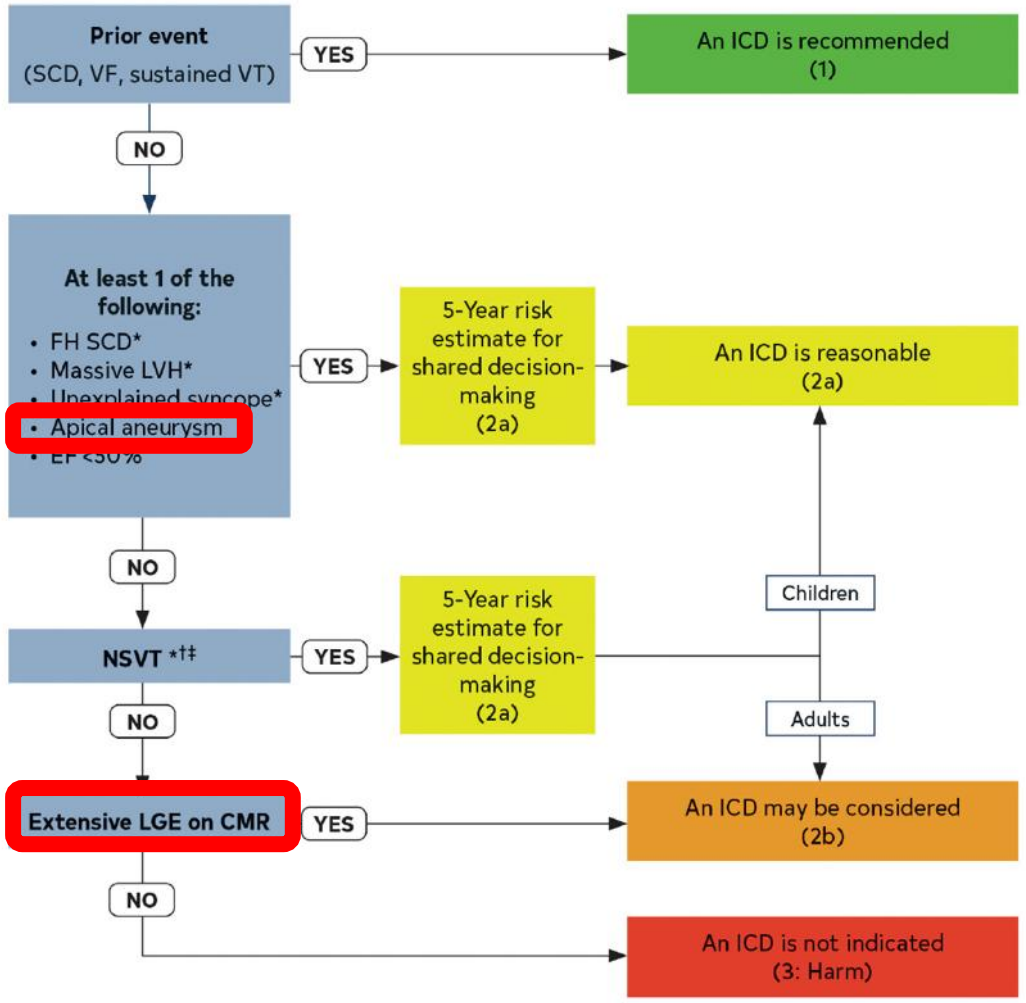
Risk stratification



Clinical risk factors:

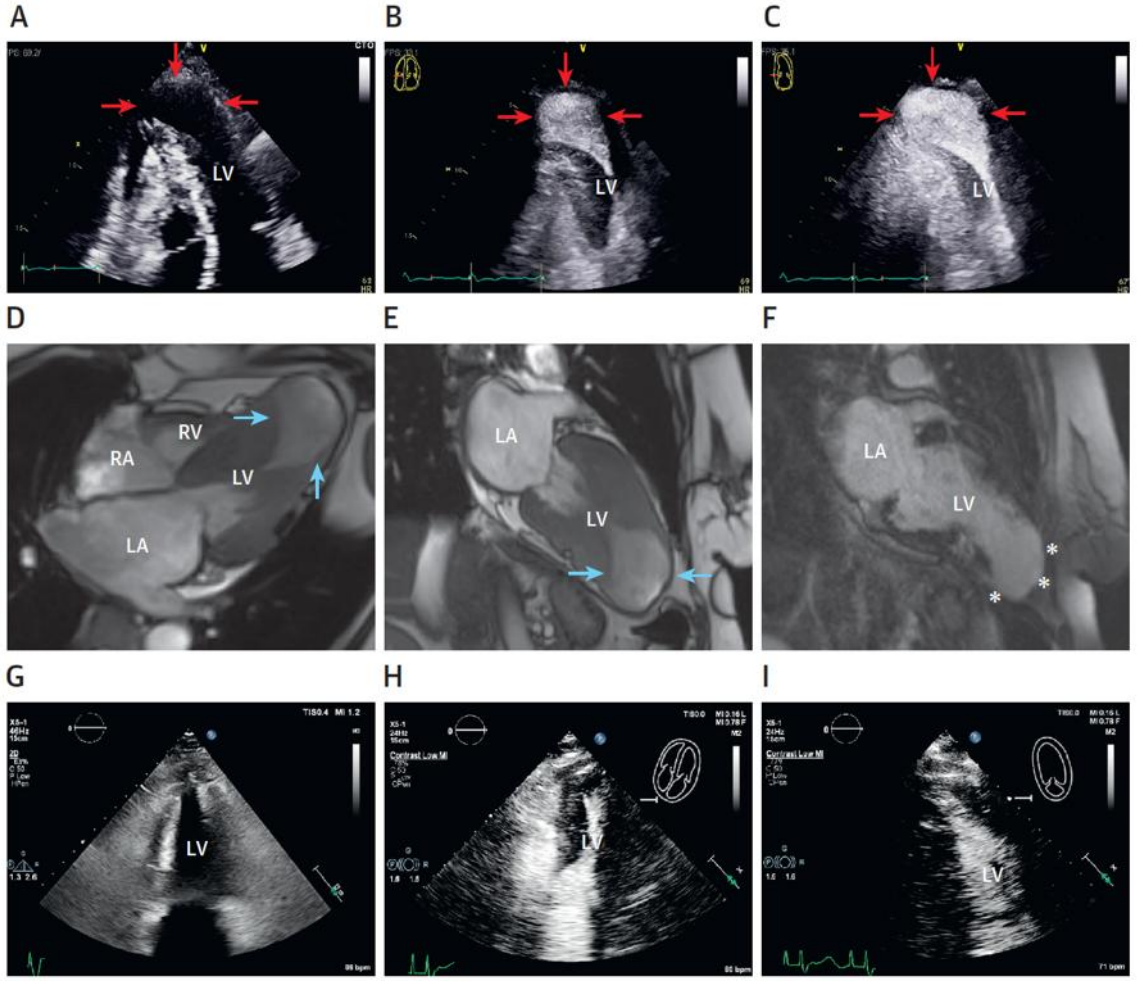
- **Extensive LGE (>15%) on CMR**
- **LVEF <50%**

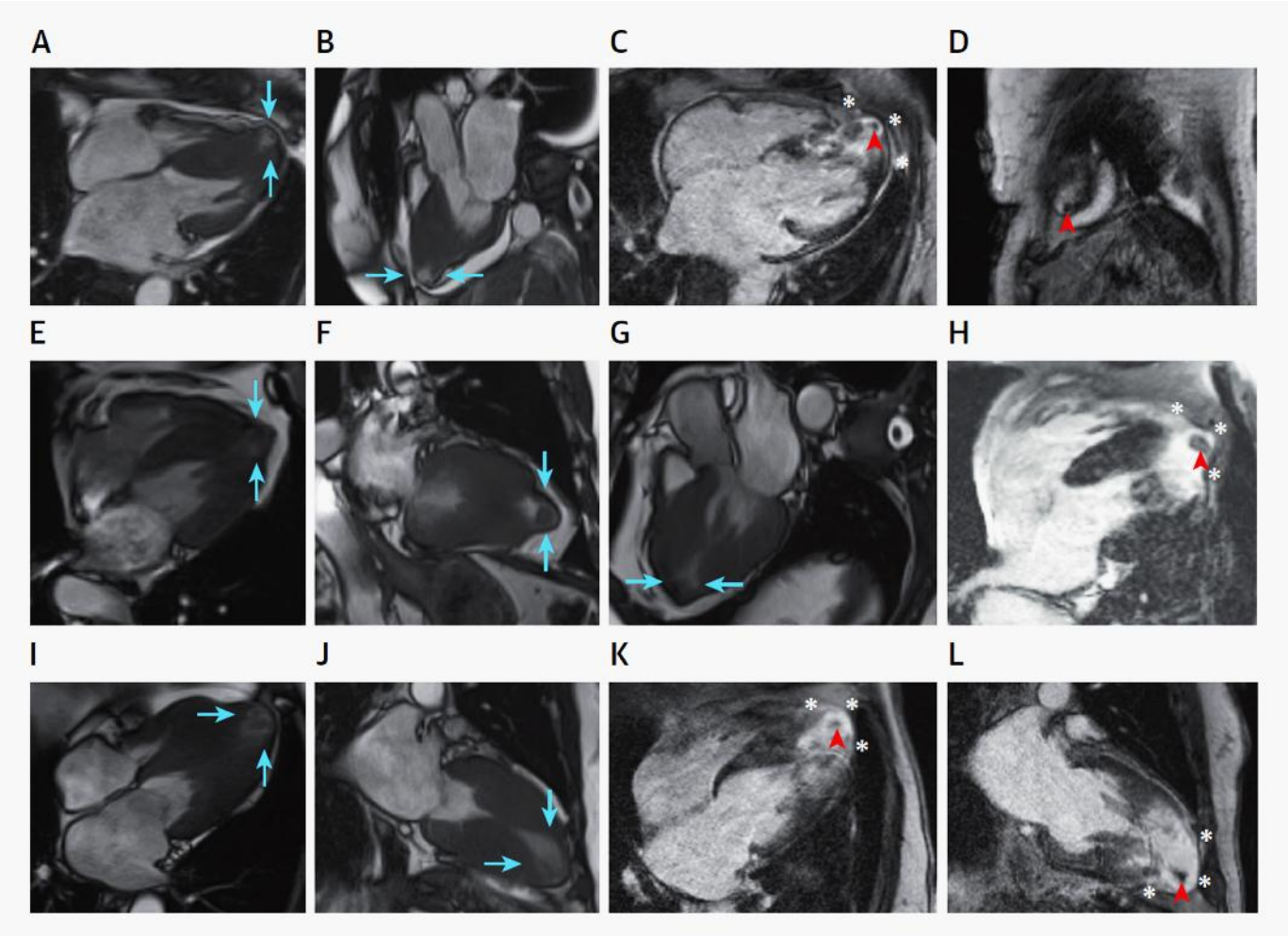
Arbelo E et al. Eur Heart J 2023



Ommen et al. Circulation 2024

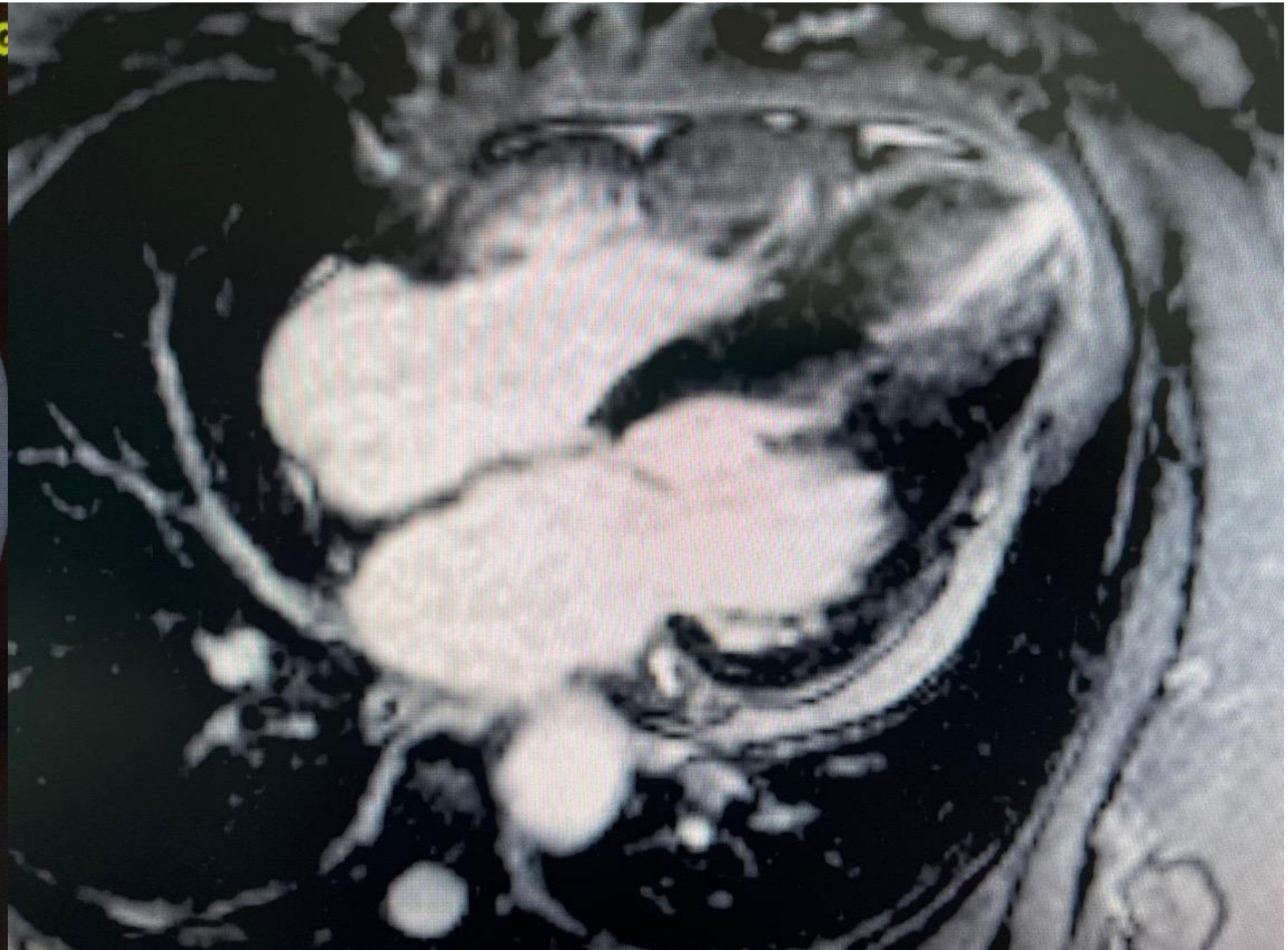
Apical aneurysms





Lee DZJ et al. Jacc Img 2022

Apical aneurysms



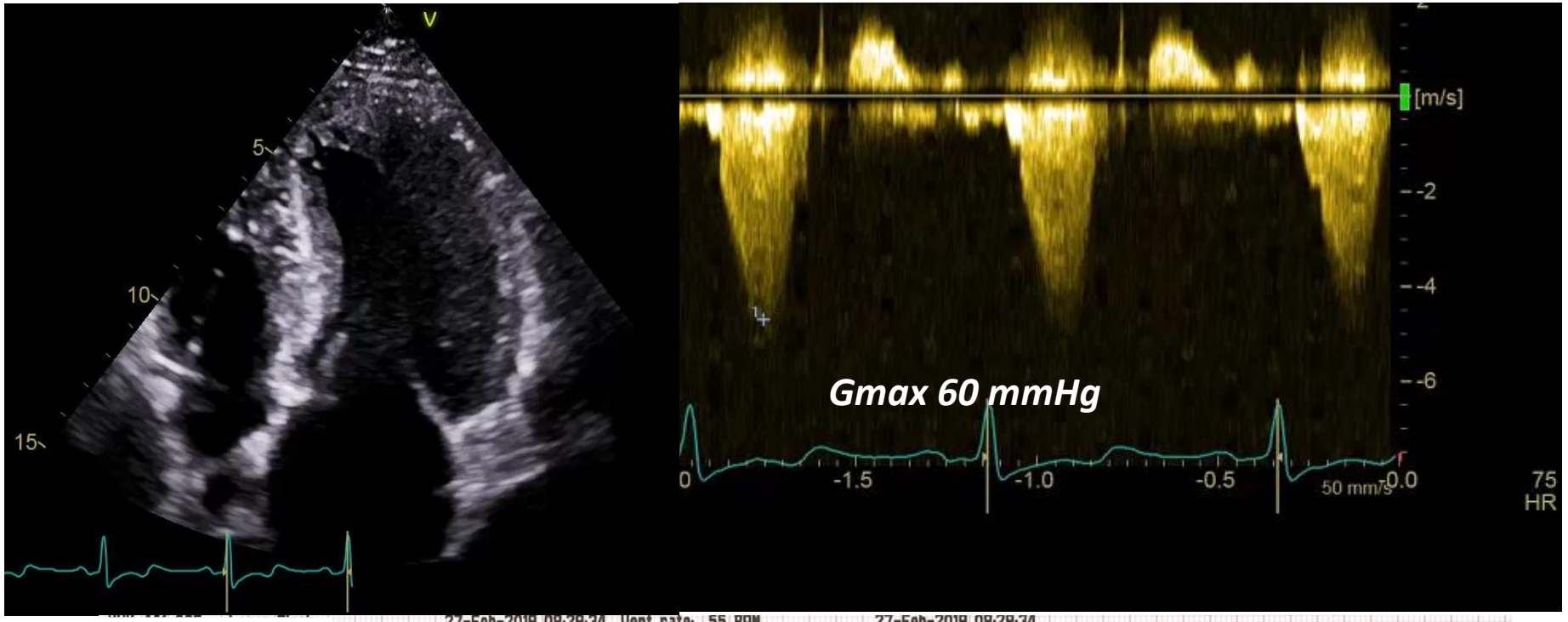
Imaging the arrhythmic risk

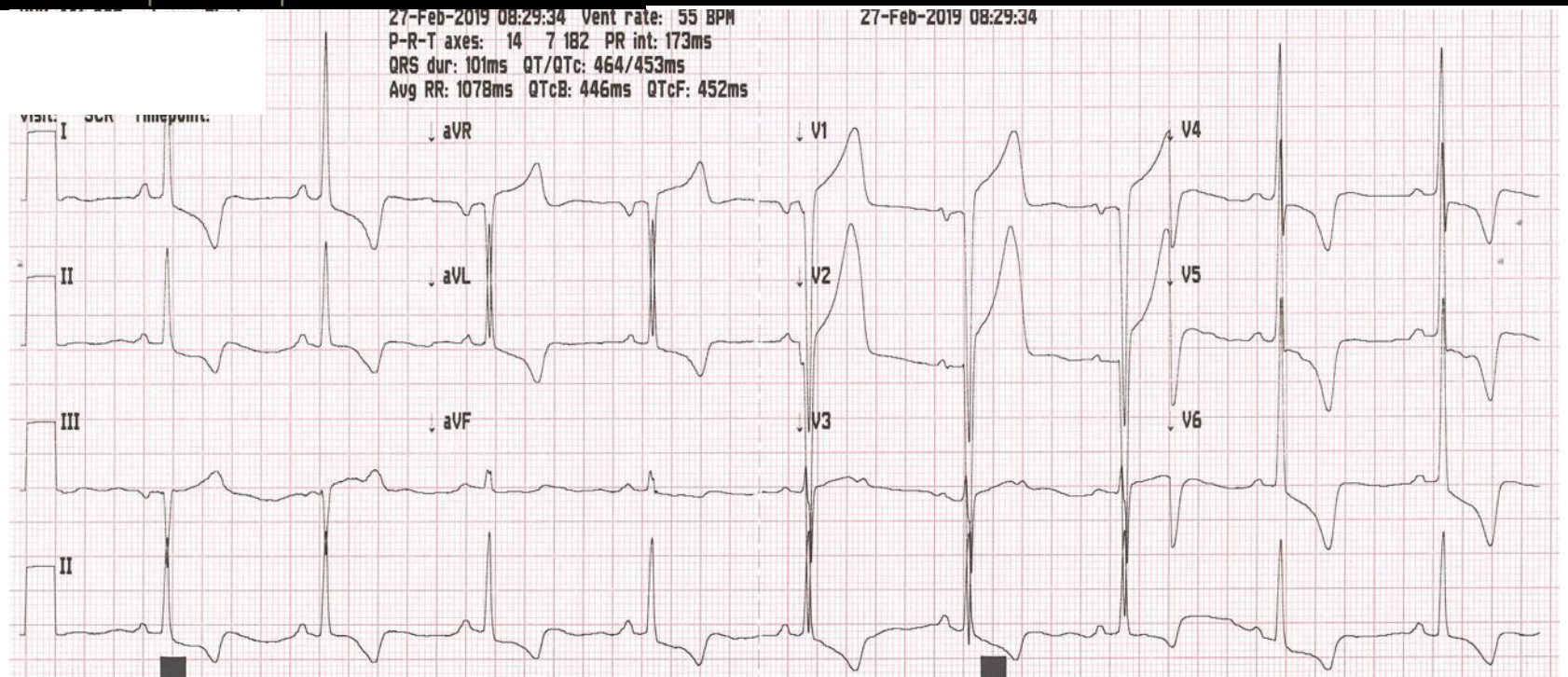
Table 3 Summary of Key Imaging Markers and Approach in SCD Risk Stratification

Imaging Parameter	SCD risk threshold	Imaging Approach	Practical Points and/or Caveats
Established markers			
LV maximal wall thickness*	Highest risk in those with LVH ≥ 30 mm, although relationship between wall thickness and SCD is continuous	Echo or CMR	Limited negative predictive value of 30 mm threshold, most SCD occurs below this threshold
Late gadolinium enhancement**	Highest risk in those with LGE > 15%, although relationship between LGE and SCD is continuous	CMR	Abnormal threshold of >6SD above normal myocardium
LVOT obstruction	>30 mm Hg	Echo	Varies according to loading conditions and activities
LV apical aneurysm*	Presence associated with increased risk even in those > 60 years old	Echo or CMR	CMR more sensitive, suspect in those with mid cavity obliteration
Left atrial size	LA volume (> 34 ml/m^2) using biplane LA volumes or anteroposterior diameter (>48 mm)	Echo	Single 2-D measurement may erroneously estimate size
LV ejection fraction*	LV ejection fraction <50%	Echo or CMR	Consider use of contrast echo or CMR to optimally assess LVEF
Emerging marker			
LV global longitudinal strain	No clear threshold value, abnormal results portend a worse prognosis	Echo (CMR approaches emerging)	Further standardization needed between platforms

*Major risk factor for SCD and if present, is considered class IIA indication for ICD implantation.
**In HCM patients without major risk factors for SCD and uncertain on whether to implant ICD, decision on ICD implantation may be reached based on late gadolinium enhancement findings.

Nagueh et al. J. Am. Soc. Echocardiogr. 2022





Courtesy of Iacopo Olivotto

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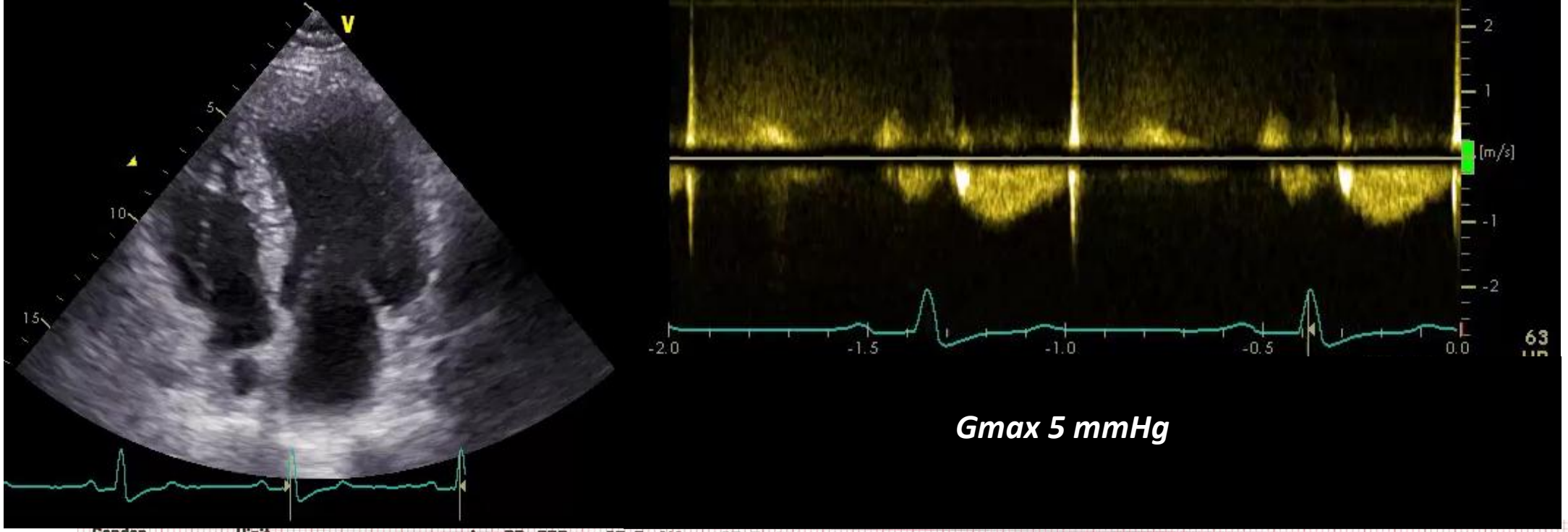
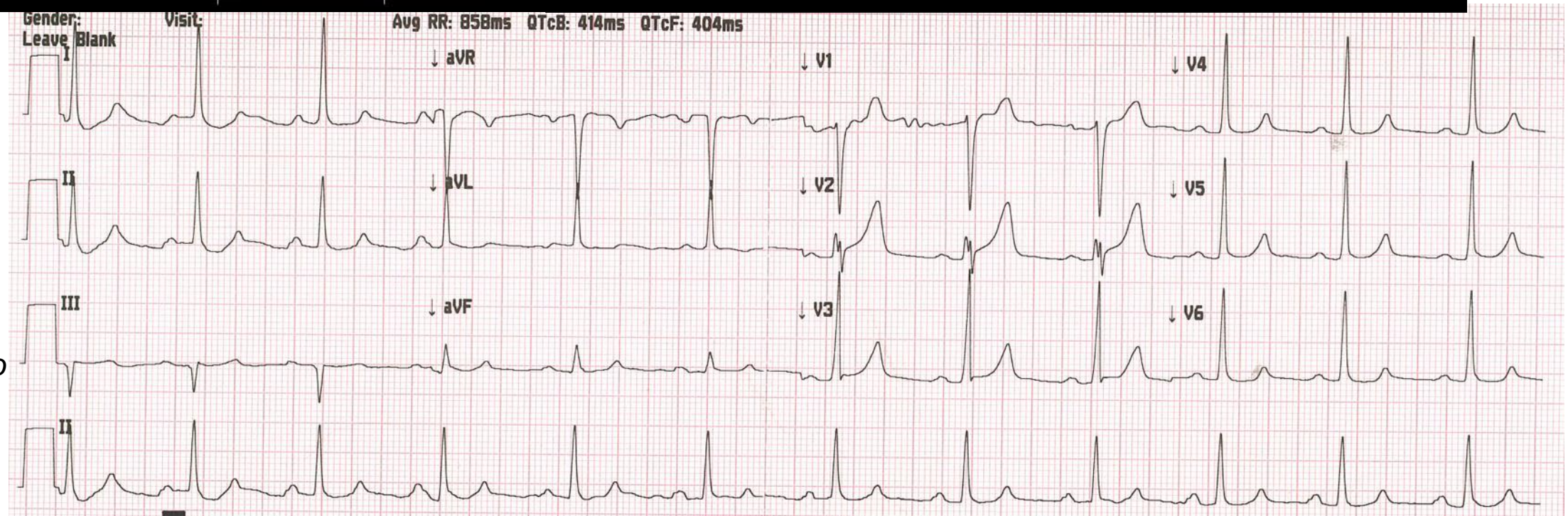


Gmax 5 mmHg



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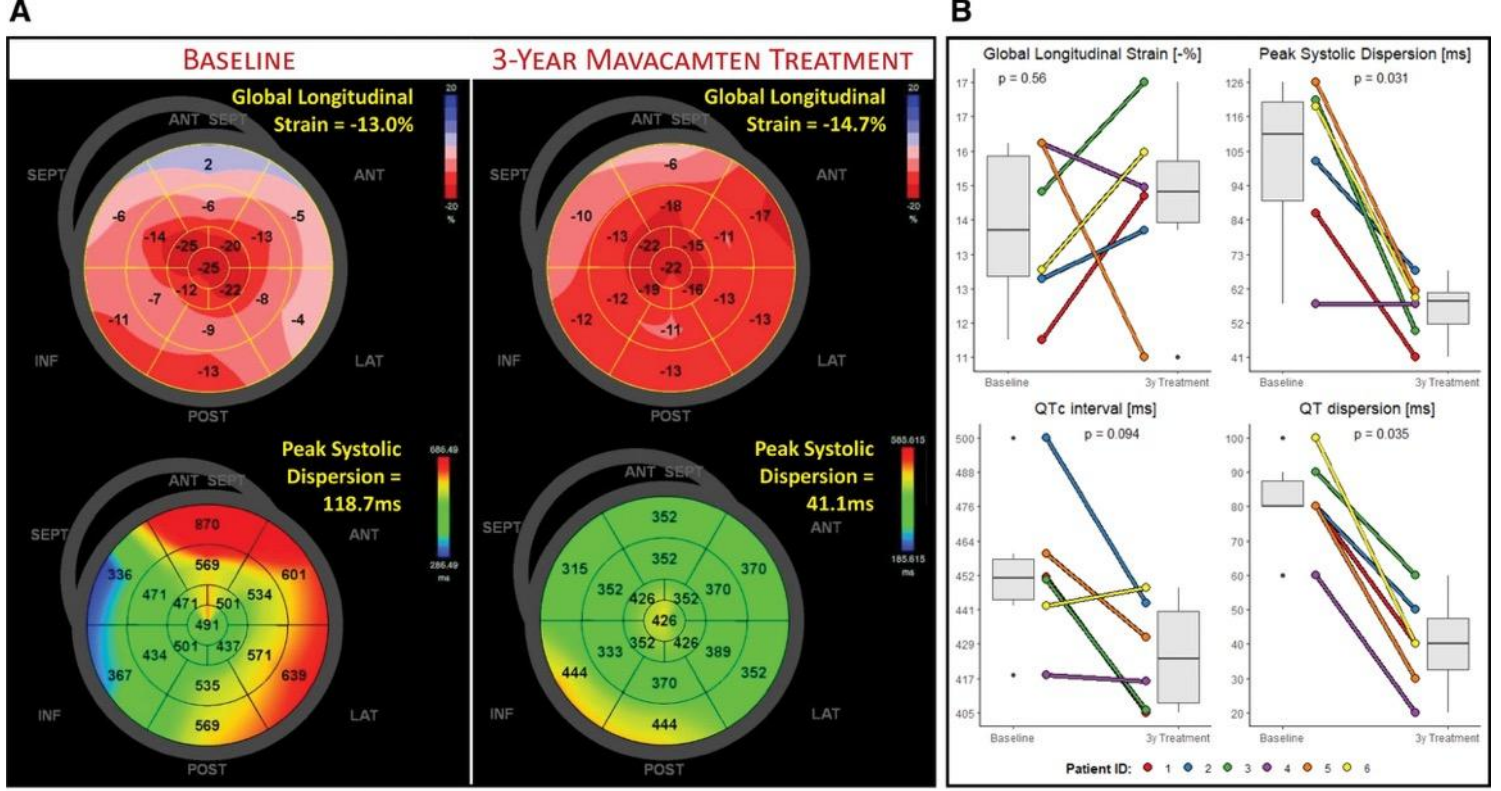
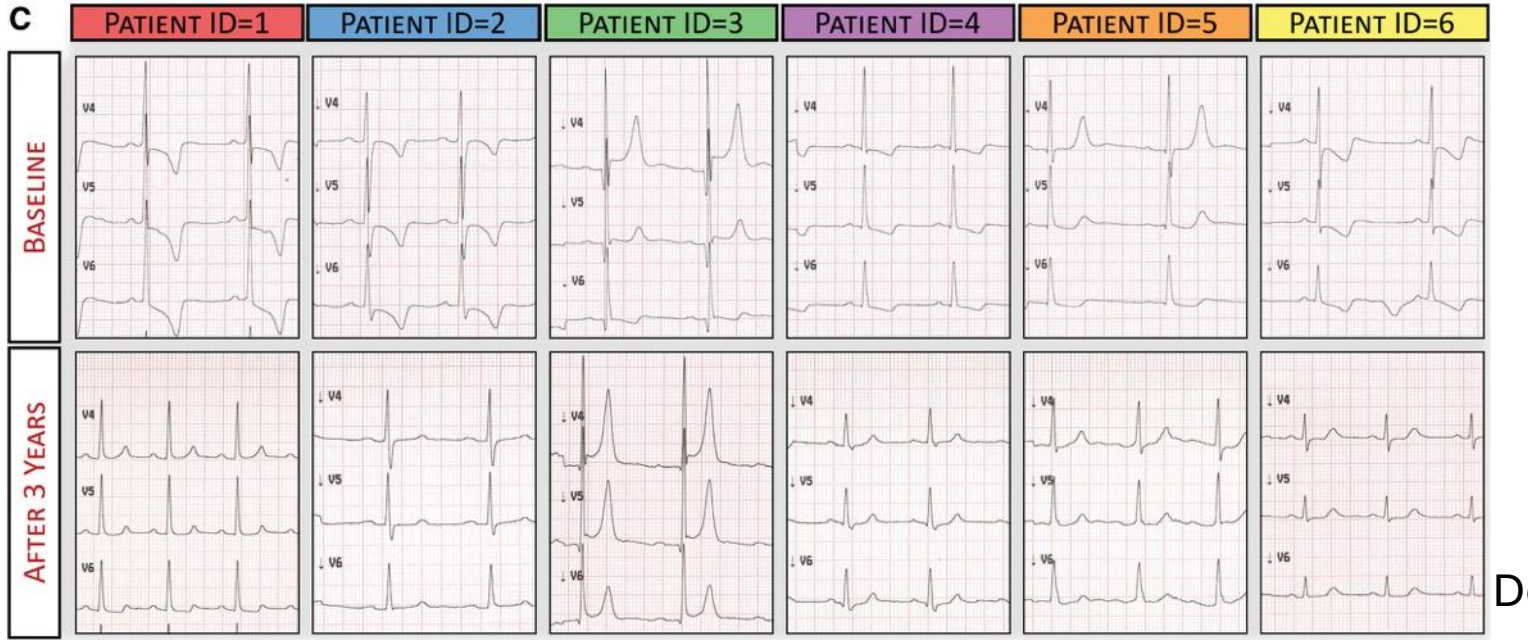
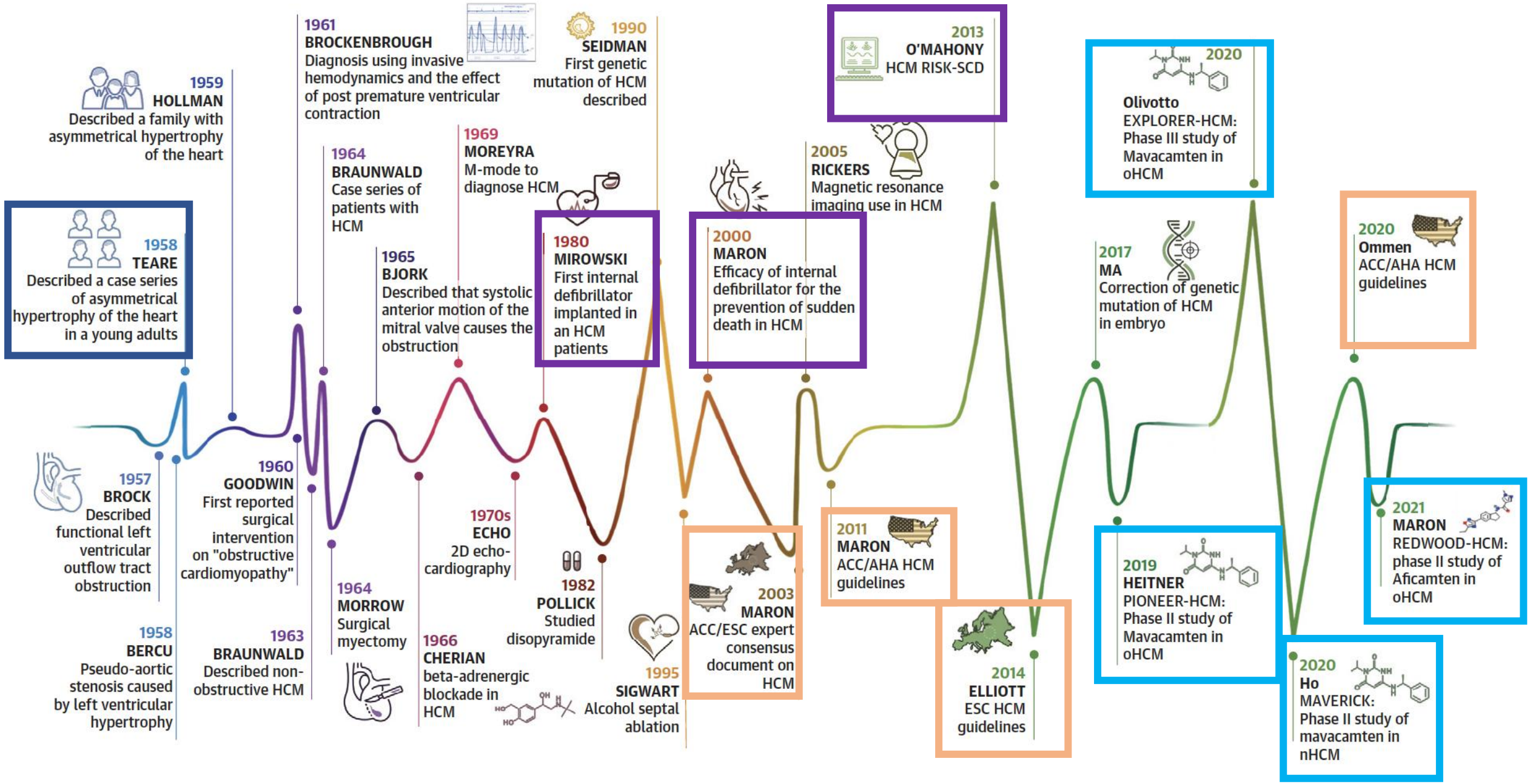




Del Franco A et al. Circ HF 2024

HCM timeline of the Major Advances and RCTs in HCM



Masri A. et al., Structural Heart 2021