Evolving Perspectives

Optimizing Diagnosis and Management of Hypertrophic Cardiomyopathy

Welcome & Introduction

Kim Anderson, MD , FRCP(C), MSc

Accreditation

This event is an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada, and approved by the Canadian Cardiovascular Society. You may claim a maximum of 0.5 hour (credits are automatically calculated).

Faculty

Chair:

- Kim Anderson, MD, FRCPC, MSc

Speakers:

- Amer Johri, MD, MSc, FRCPC, FASE
- Patrick Garceau, MD, FRCPC

Disclosures

	Dr. Kim Anderson
Any direct financial payments including receipt of honoraria	Takeda
Membership on advisory boards or speakers' bureaus	Alnylam, Pfizer and BMS
Funded grants or clinical trials	Astra-Zeneca, Boehringer-Ingelheim, Luitpold, Merck, Bayer, Amgen
Patents on a drug, product or device	No disclosures
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	No disclosures

This program has received an educational grant from Bristol Myers Squibb Canada. This program was developed by the Canadian Heart Failure Society and was planned to achieve scientific integrity, objectivity and balance.

Learning Objectives

1. Explore the signs and symptoms associated with HCM through case-based scenarios
2. Assess the utility of echocardiography in the diagnostic workup of HCM
3. Discuss the evidence on current and new medical therapies for HCM and how to integrate them into clinical practice

Symposium Agenda

2 minutes	Welcome and Introduction Dr. Kim Anderson
9 minutes	Recognizing HCM in Clinical Scenarios and on an Echo Report Dr. Amer Johri
9 minutes	Treatment of HCM Dr. Patrick Garceau
8 minutes	Q&A Period All Panelists
2 minutes	Conclusion Dr. Kim Anderson

Housekeeping

- To collect your MOC Section 1 credits, please remember to complete both the session evaluation and the congress evaluation
- The QR code can be found on your tables and will be displayed on the screen after the presentation
- There are polling questions in this presentation. Please have your phone nearby

Echo Features in Patients with Hypertrophic Cardiomyopathy

A Journey Through the Echo Lab

Amer Johri
MD MSc FRCPC FASE
Professor, Queen's University

Disclosures

	Dr. Amer Johri
Any direct financial payments including receipt of honoraria	Bayer
Membership on advisory boards or speakers' bureaus	Janssen
Funded grants or clinical trials	BMS
Patents on a drug, product or device	No disclosures
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	No disclosures

Hypertrophy

- Important to ensure measurements done accurately – avoid pitfalls:
  - Trabeculations
  - Papillary muscles
  - Non-perpendicular
  - Sigmoid septum

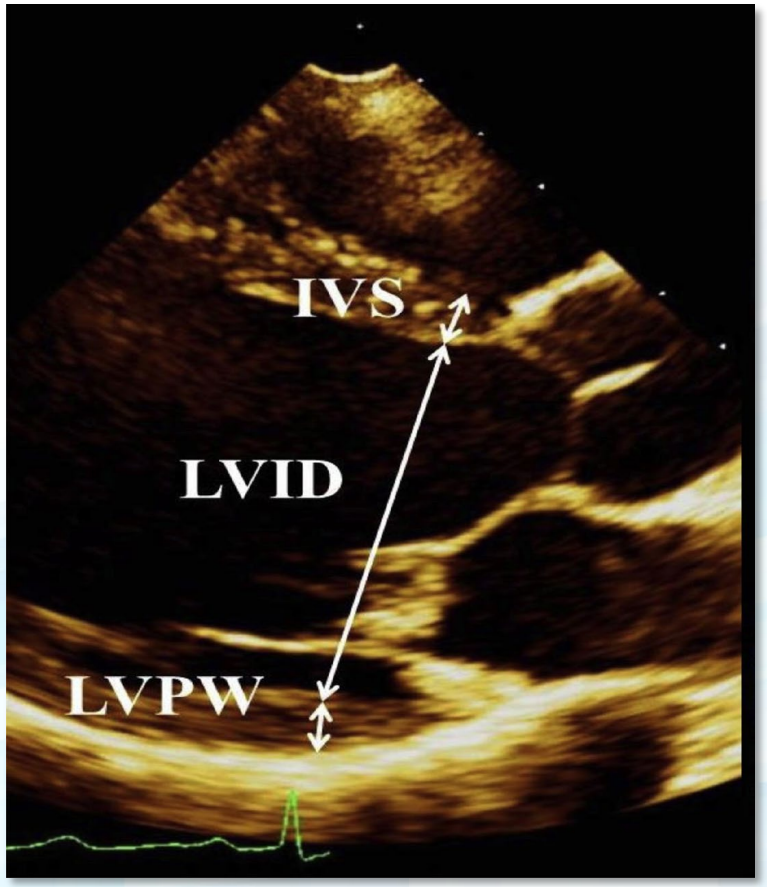
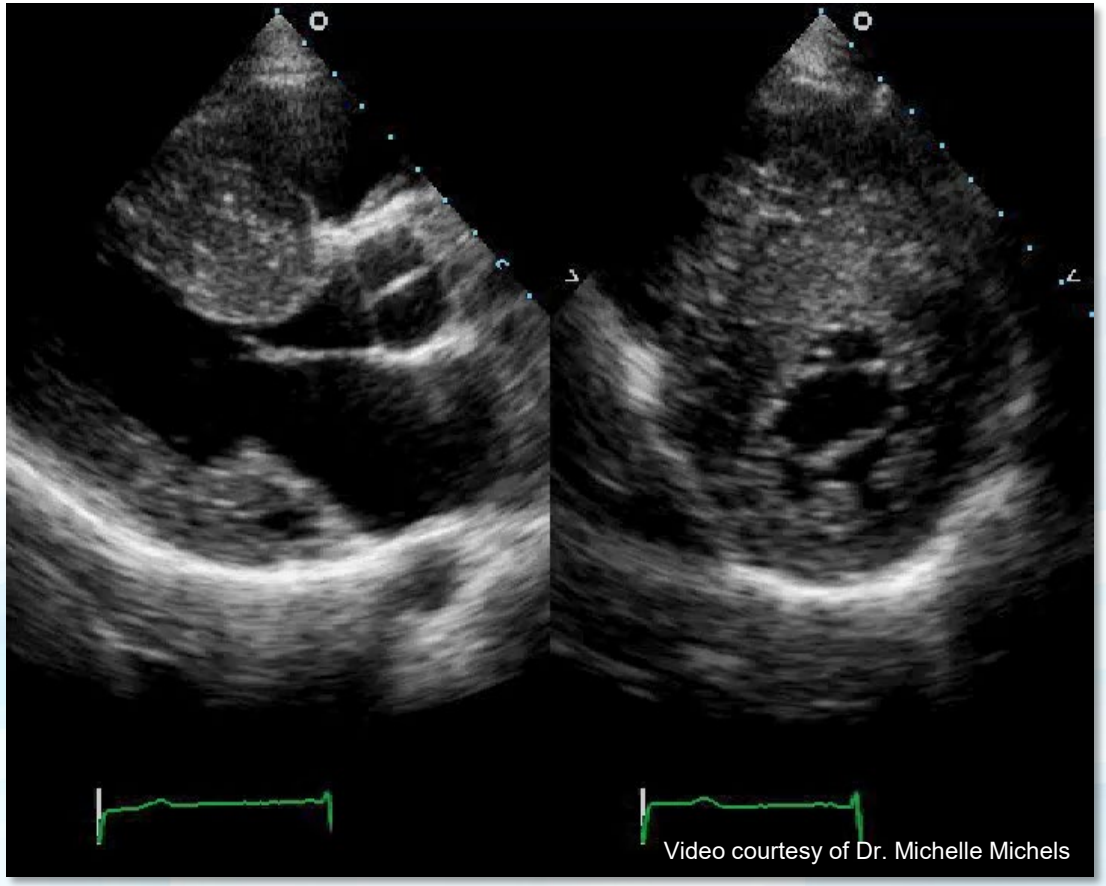


Image from Kristensen CB, et al. Kidney Med. 2020 Aug 6;2(5):578-88.e1.

IVS, interventricular septum; LVID, left ventricular internal diameter; LVPW, left ventricular posterior wall.

Assess Hypertrophy Globally

- Assess wall thickness in all LV segments from base to apex
- LVH is frequently asymmetrical and can be confined to specific LV segments



Asymmetric septal wall hypertrophy with a hyperdynamic LV and SAM

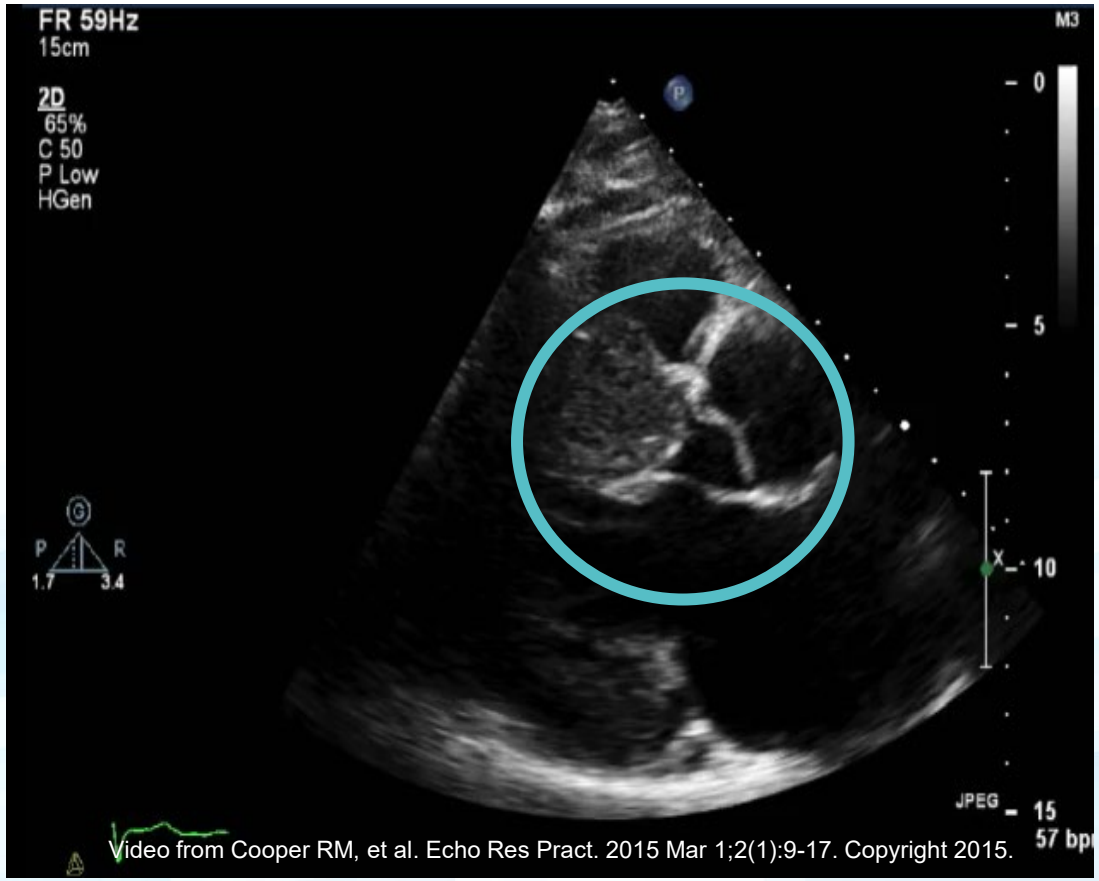
2D, two-dimensional; echo, echocardiogram; LV, left ventricle; LVH, left ventricular hypertrophy; SAM, systolic anterior motion.

Losi MA, et al. *Cardiovasc Ultrasound*. 2010 Mar 17;8:7.
Ommen SR, et al. *Circulation*. 2020 Dec 22;142(25):e558-e631.
Pantazis A, et al. *Echo Res Pract*. 2015 Mar 1;2(1):R45-53.

Use All Available Views to Evaluate the Base

- PLAX view is useful in examining the base and RV where necessary
- Mitral leaflet elongation and abnormal SAM of the anterior mitral leaflet are findings associated with HCM

Basal septum measures 27 mm with the long anterior leaflet contacting the septum

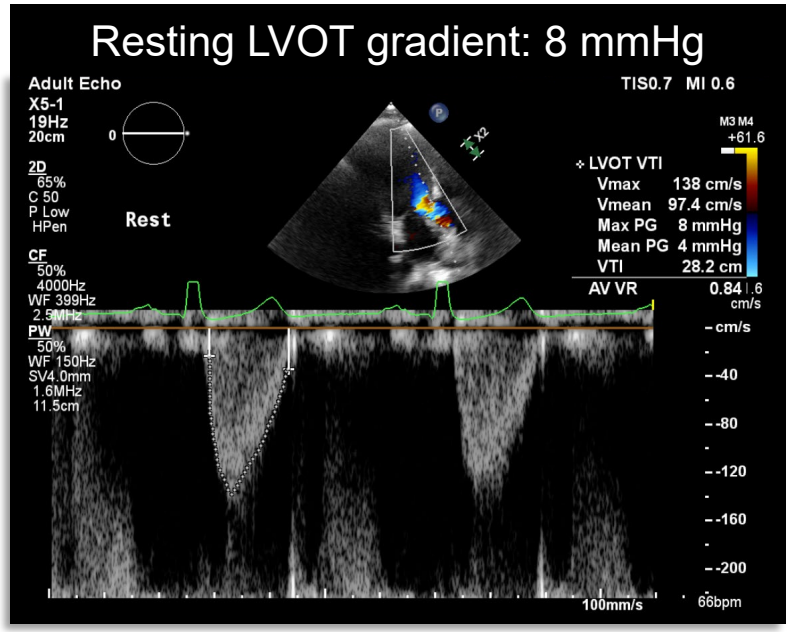


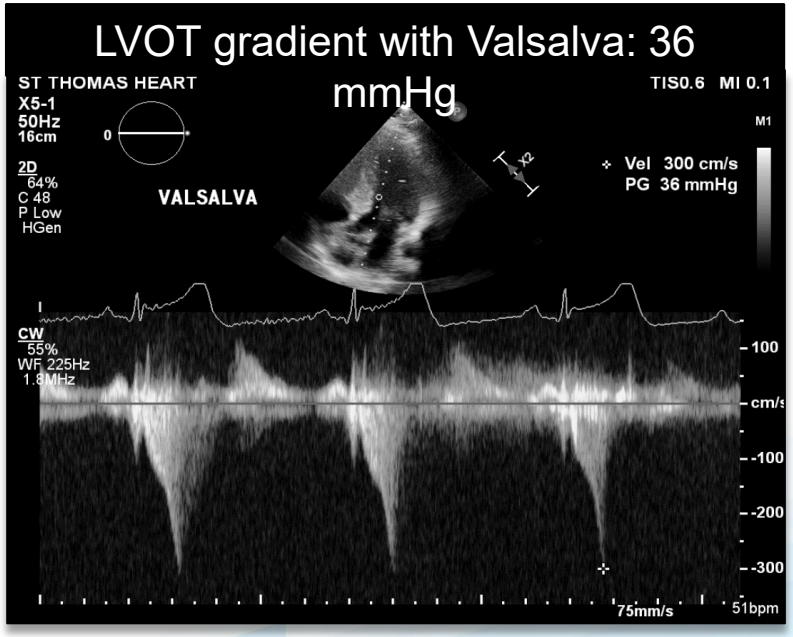
Video from Cooper RM, et al. Echo Res Pract. 2015 Mar 1;2(1):9-17. Copyright 2015.

Elliott PM, et al. *Eur Heart J*. 2014 Oct 14;35(39):2733-79.
Nagueh SF, et al. J *Am Soc Echocardiogr*. 2011 May;24(5):473-98.
Ommen SR, et al. *Circulation*. 2020 Dec 22;142(25):e558-e631.

Echo, echocardiogram; HCM, hypertrophic cardiomyopathy; PLAX, parasternal long-axis; RV, right ventricle; SAM, systolic anterior motion.

Assessment of LVOTO Requires Provocation





Provocative testing
(ACA/AHA Recommendations)

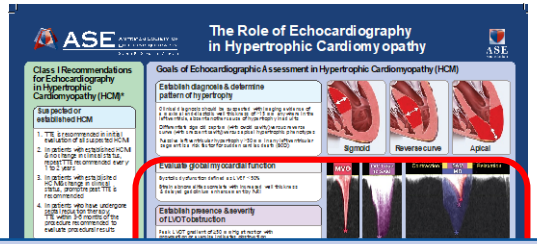
- For patients with HCM and resting LVOT gradient <50 mmHg, a TTE with provocative maneuvers recommended
- For symptomatic patients with HCM who do not have a resting or provocable LVOT gradient ≥50 mmHg on TTE, exercise TTE is recommended

Definition of obstruction by LVOT gradient[1]

Resting obstructive HCM	≥30 mmHg at basal (resting condition)
Provoked obstructive HCM[a]	<30 mmHg at rest but ≥30 mmHg with physiologic provocation (exercise or Valsalva maneuver)
Non-obstructive HCM	<30 mmHg at rest and with provocation

Maron MS, et al. *Circulation*. 2006 Nov 21;114(21):2232-9.
Ommen SR, et al. *J Am Coll Cardiol*. 2020 Dec 22;76(25):e159-e240.

ACA, American College of Cardiology; AHA, American Heart Association; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; TTE, transthoracic echocardiography.



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

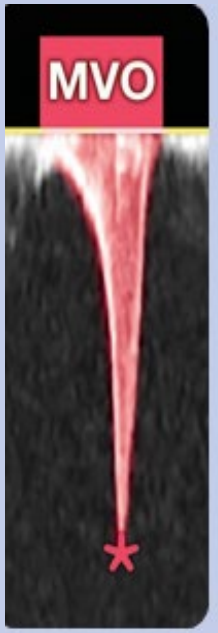
Peak LVOT gradient of ≥50 mmHg at rest or with provocation or exercise indicates obstruction

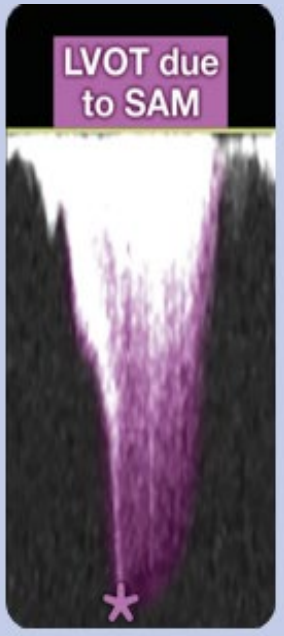
Differentiate SAM-mediated LVOT obstruction from mid-ventricular obstruction (MVO; “dagger”-shaped)

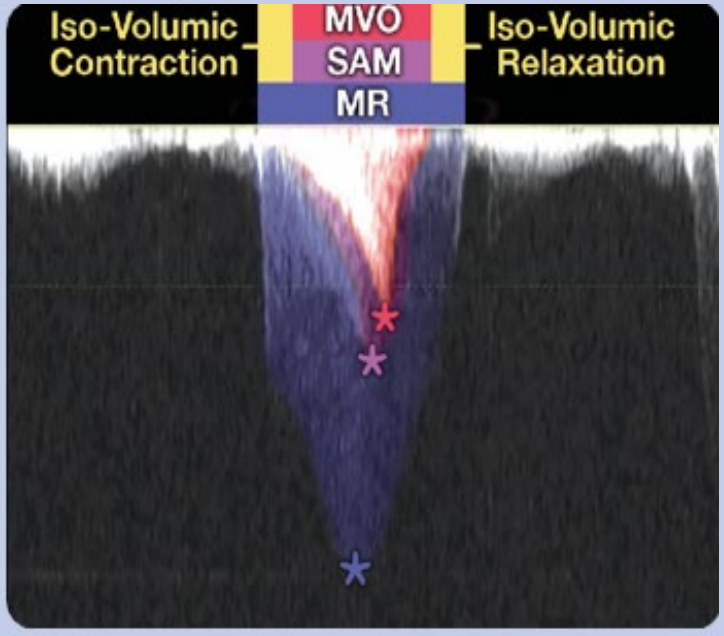
Caution with contamination of LVOT signal with MR.
MR velocity is higher & signal is of longer duration (spanning isovolumic contraction & relaxation) vs. LVOT signal. MR contour may be incomplete if Doppler signal not optimally aligned

Estimated LVOT gradient from MR signal calculated as:
LV pressure – systolic BP, where

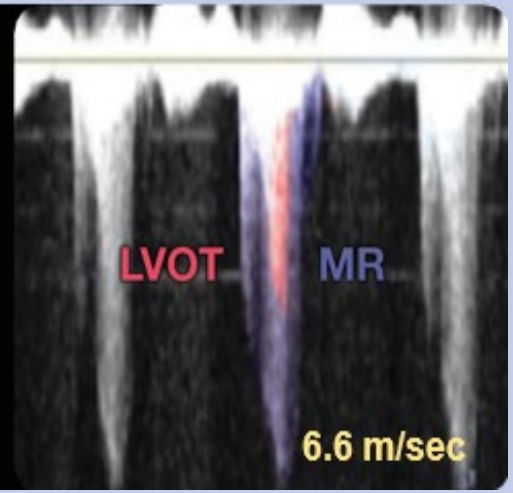
$$\text{LV Pressure} = 4 \times (\text{Peak MR}_{\text{velocity}})^2 + \text{LA Pressure}$$
(assume 10 - 15 mmHg)







Peak MR velocity = 6.6 m/sec
Peak LVSP = 4(6.6²) + LAP(10 mmHg)
SBP = 113 mmHg
LVSP - SBP = LVOT gradient
174 + 10 = 184 - 113 = 71 mmHg



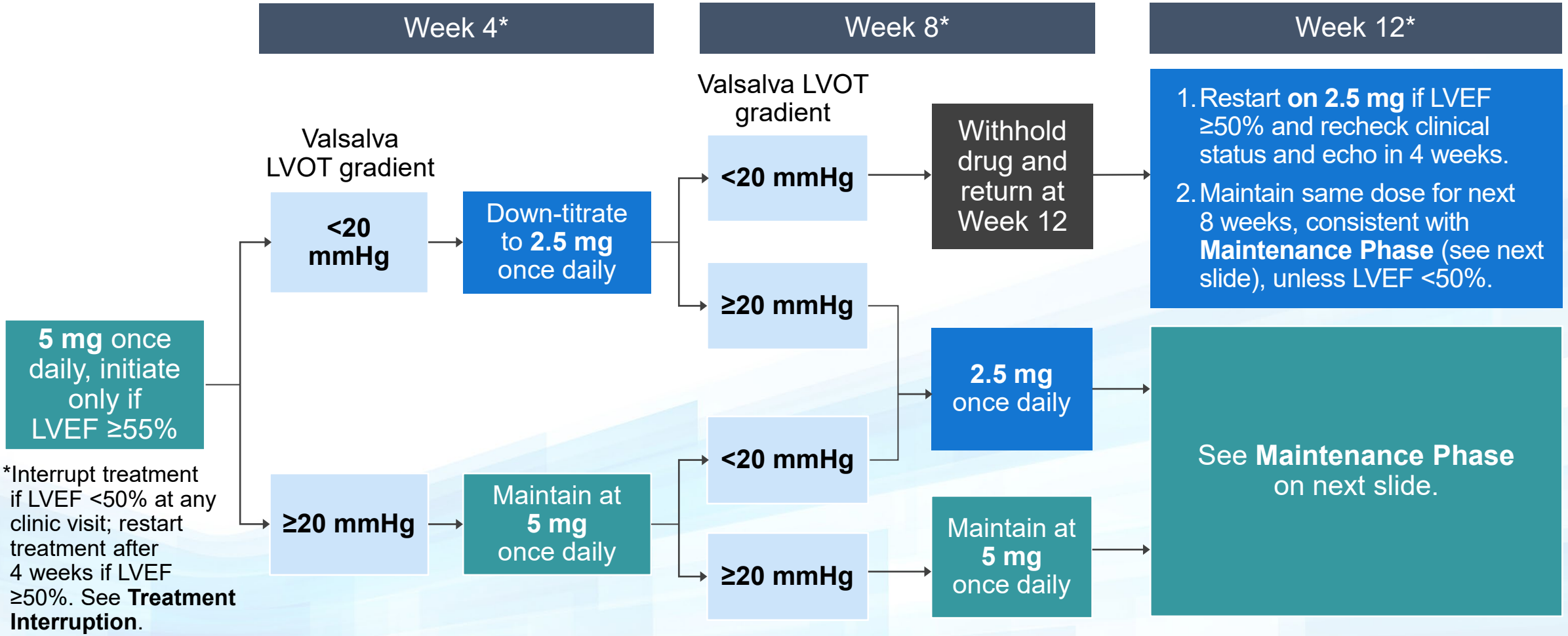
Key Echocardiographic Features:
Parameters and Cut-Off Values Suggestive for HCM

	Echo parameter	Cut-off value suggesting of HCM
Systolic function	Systolic longitudinal dysfunction	Lateral S (TDI) <4 cm/s Worse GLS (> − 10.6%)[a] Paradoxical apical strain (apical HCM)
	Normal/supranormal radial strain	
Diastolic function	Impaired relaxation	Reduced TDI e' velocities (septal e' < lateral e')
	Elevated filling pressures	Increase of A wave velocity during Valsalva maneuver[b] LAVI >34 mL/m^2 [c] Ar-A ≥30 ms E/e' ratio >10[d] PAPs >35 mmHg

[a]Reduction in longitudinal strain is greater for hypertrophied segments; [b]Diastolic dysfunction is the hallmark of the disease; filling pressures are elevated, even in the presence of an impaired relaxation pattern of the transmitral flow; [c]Absence of atrial fibrillation/significant mitral regurgitation; [d]Less specific in HCM as a surrogate for elevated filling pressures.

A, duration of transmitral A wave; Ar, duration of atrial reverse wave of the pulmonary venous flow; E/e', ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e'); GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; LAVI, left atrial volume index; PAPs, systolic pulmonary artery pressure; TDI, tissue Doppler imaging.

ECHO Is Important to Guide Novel Treatments



LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

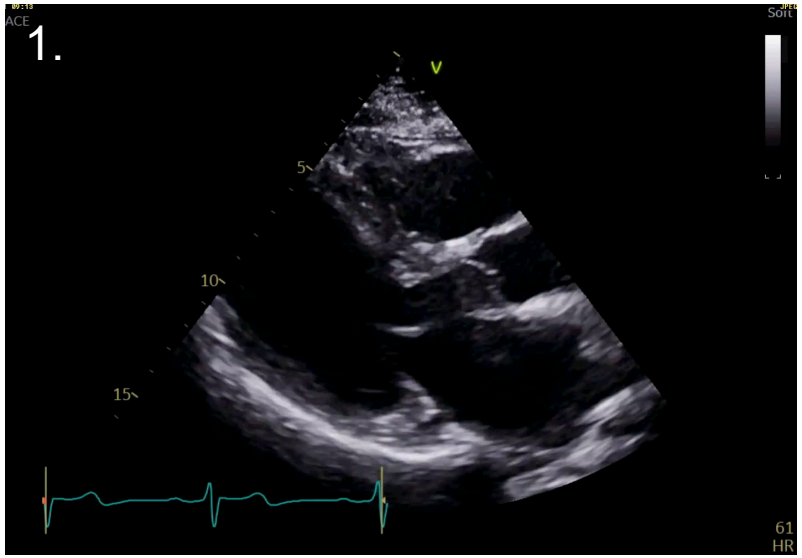
Mavacamten (CAMZYOS™) product monograph. Bristol-Myers Squibb; 2022.

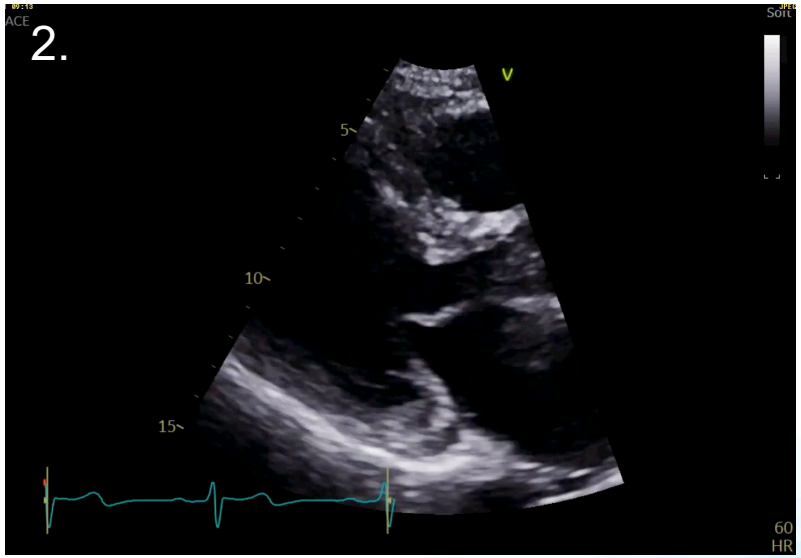
Case 2 – Leanne: Patient Profile and PMHx

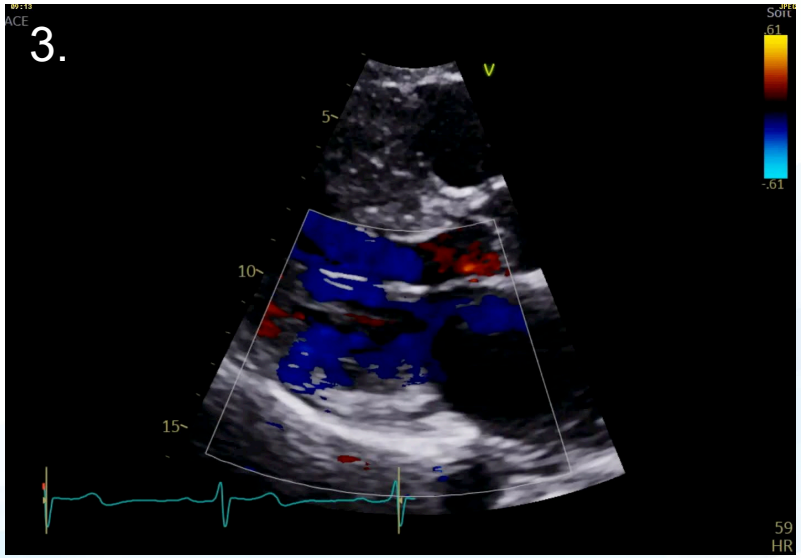
- 53-year-old female, known obstructive HCM diagnosed 15 years ago
- Now presents with worsening NYHA Class II on current medical therapy over the last 6 months
- Previous echo showed a gradient of 20 mmHg that increased to 30 mmHg with Valsalva
- Recent cath is normal
- Medications: Previously tried CCBs and BBs
  - —Feels lightheaded and becomes bradycardic
  - — Tolerates low-dose BB only

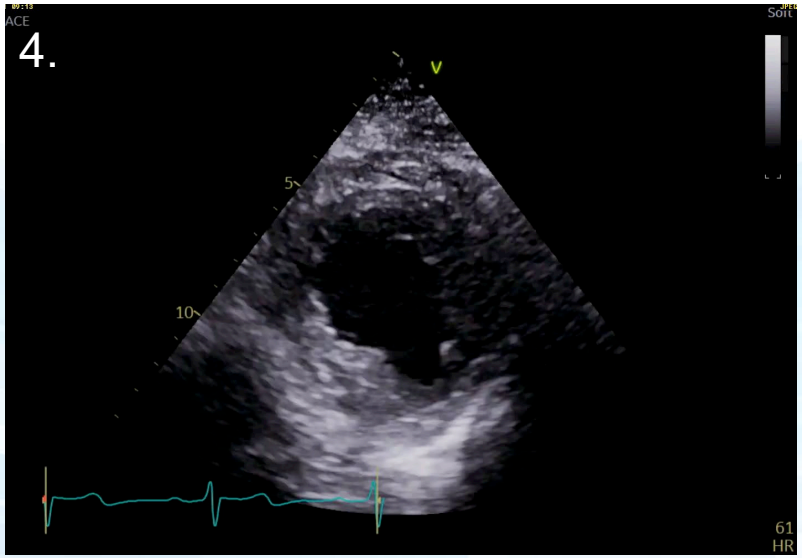
BB, beta-blocker; CCB, calcium channel blockers; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; PMHx, past medical history.

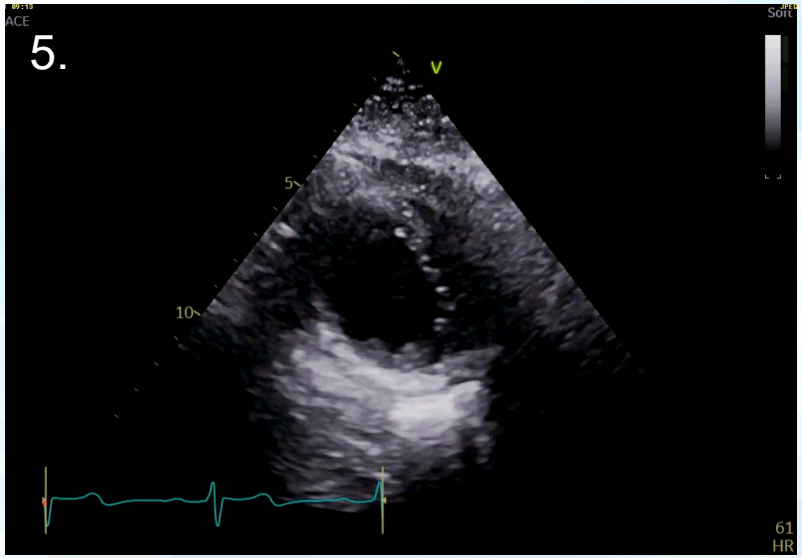
ECHO Findings

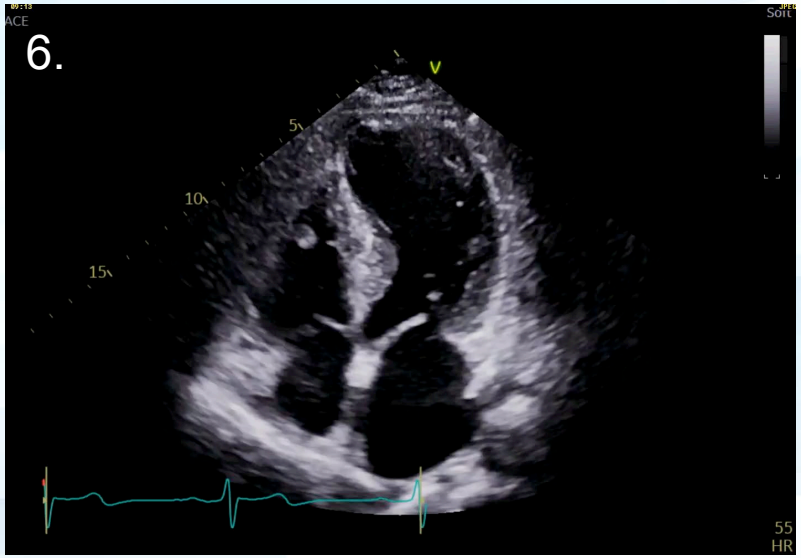




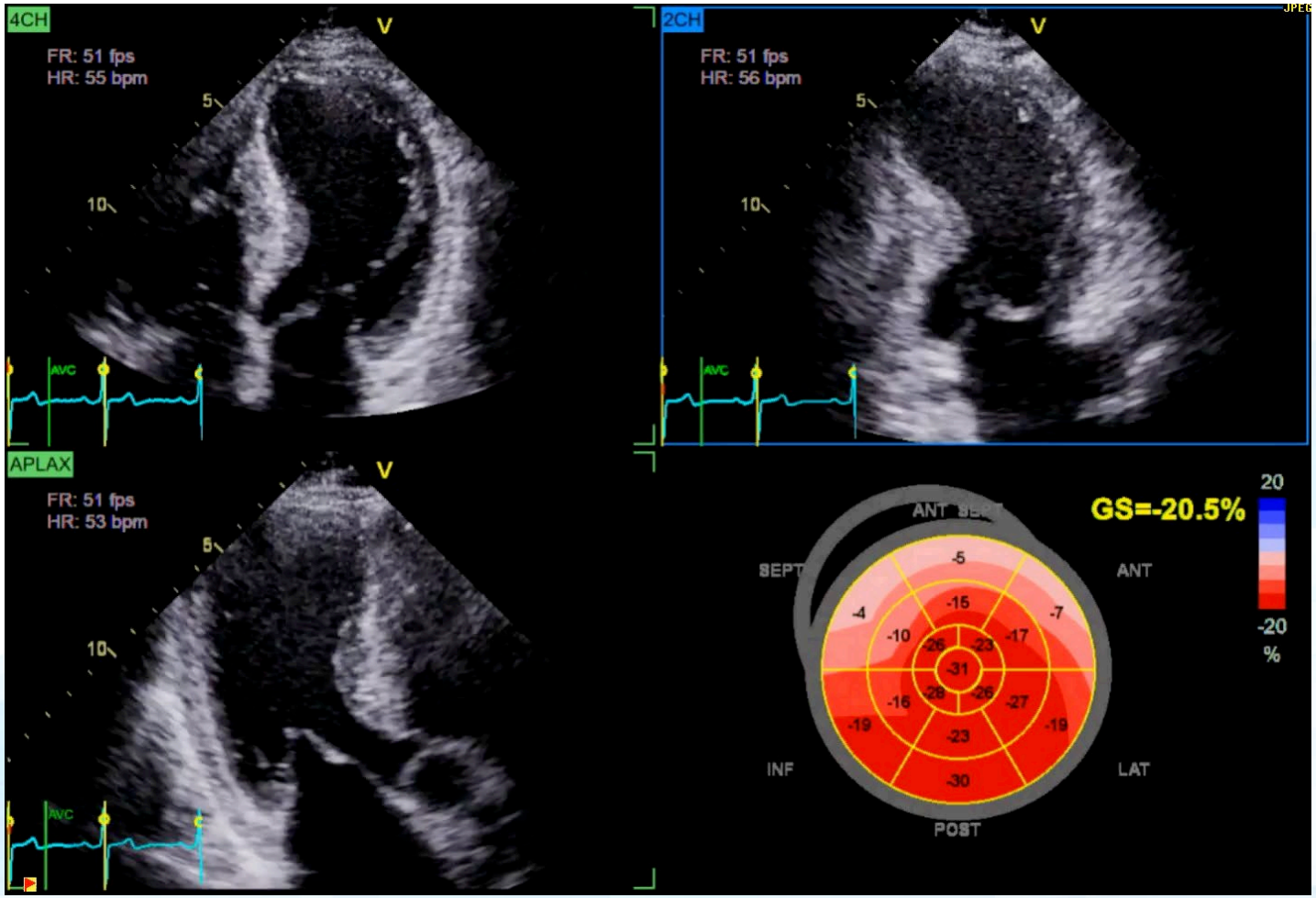








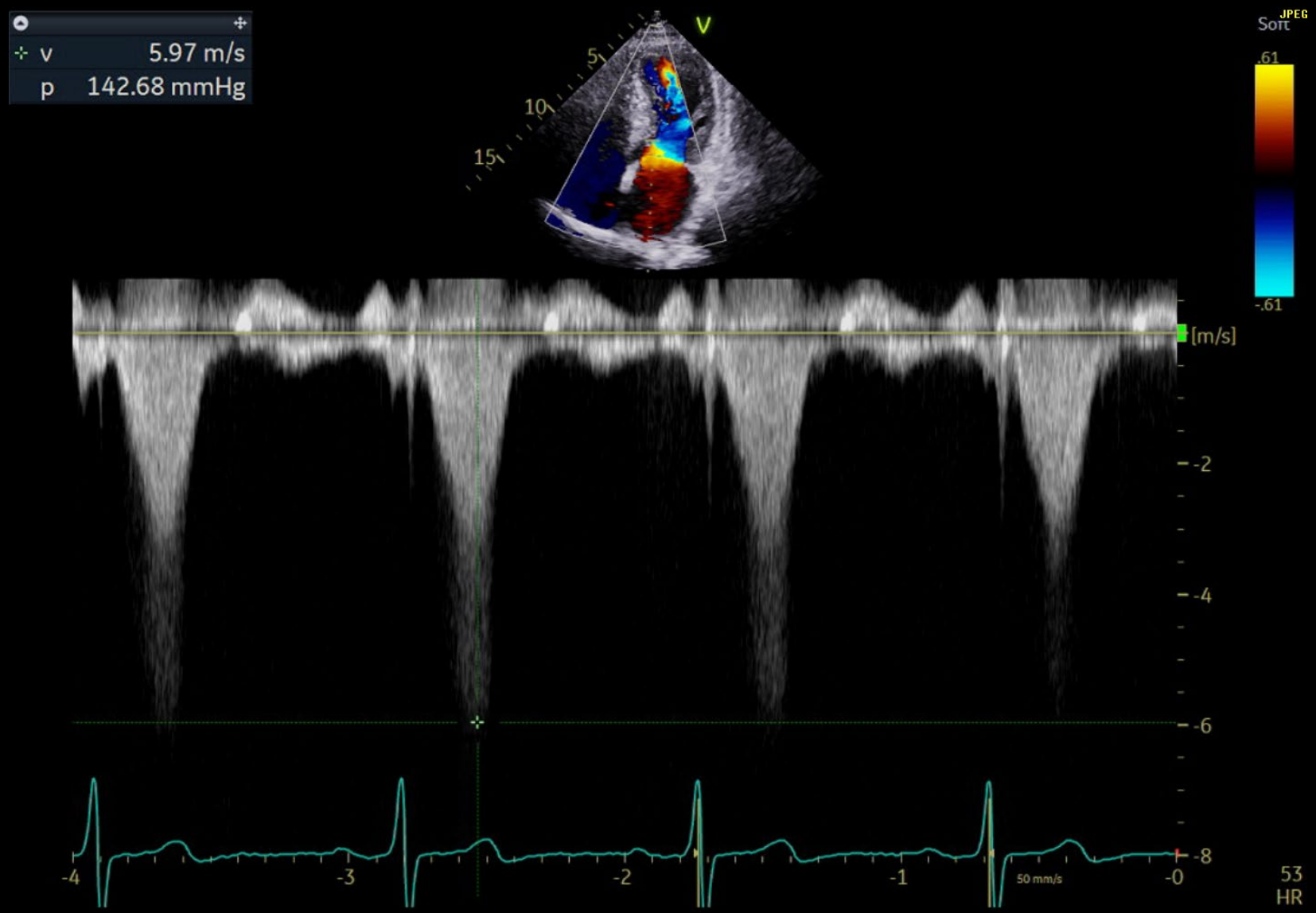
Global Strain

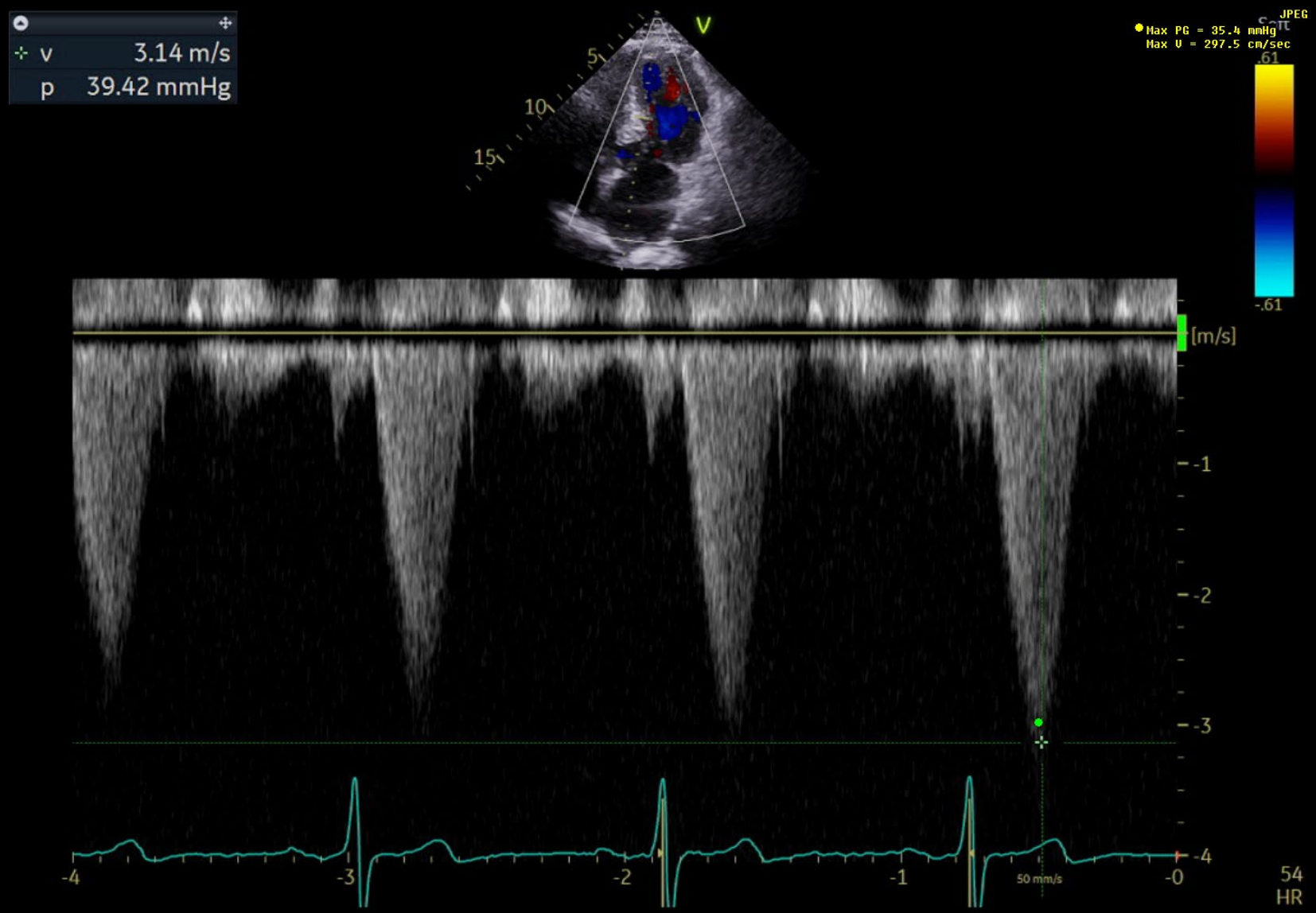


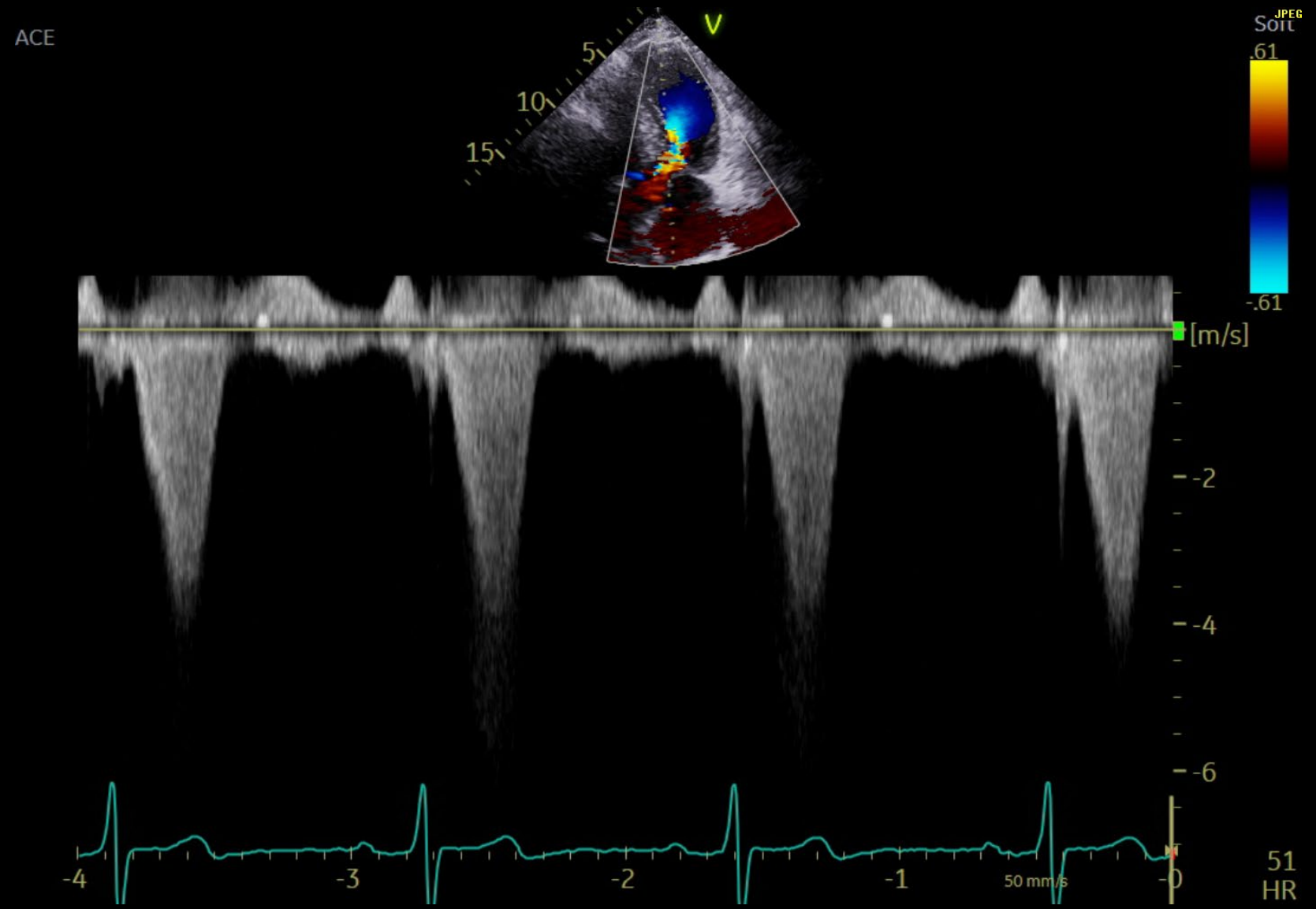
Tips and Tricks

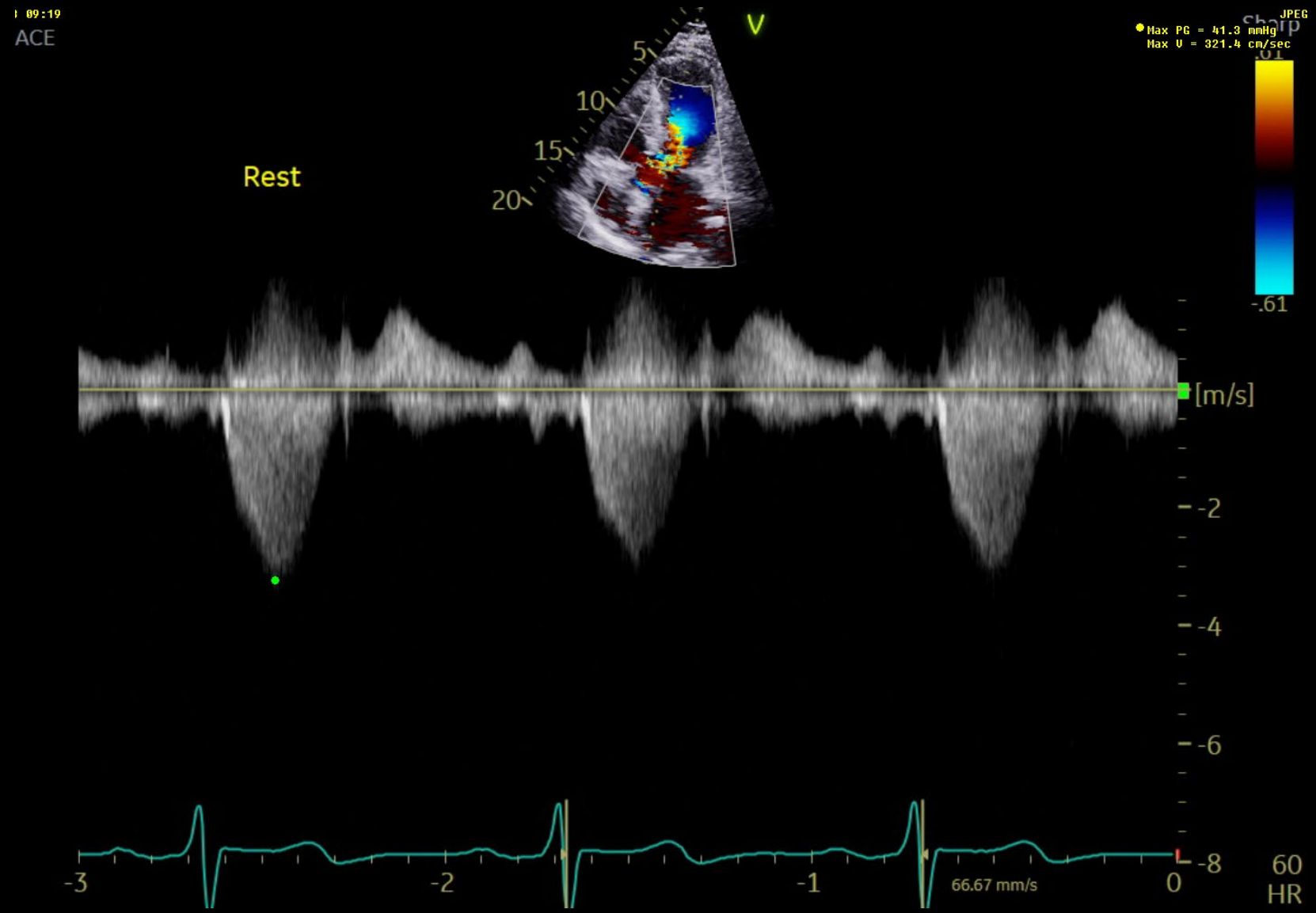
- In this case it was challenging for the sonographer to discern MR from the LVOT gradient
- See how the sonographer interrogates the LVOT in the following image set:

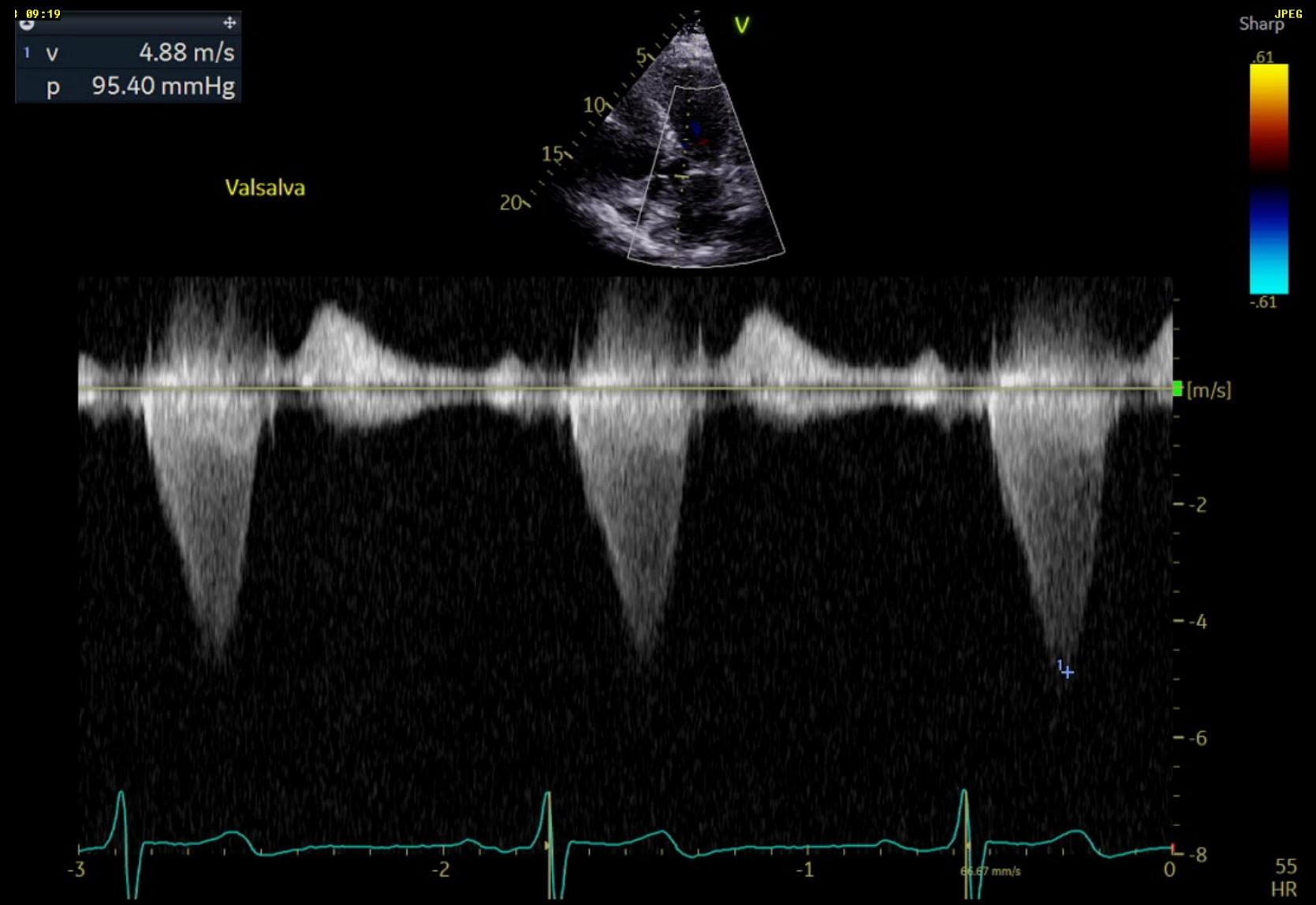
LVOT, left ventricular outflow tract; MR, mitral regurgitation.


v 5.97 m/s
p 142.68 mmHg
V
5
10
15
Soft
JPEG
.61
-.61
[m/s]
-2
-4
-6
-8
-4
-3
-2
-1
50 mm/s
-0
53
HR


v 3.14 m/s
p 39.42 mmHg
V
5
10
15
Max PG = 35.4 mmHg
Max V = 297.5 cm/sec
JPEG
.61
-.61
[m/s]
-1
-2
-3
-4
-4
-3
-2
-1
50 mm/s
-0
54
HR


ACE
V
5
10
15
JPEG
Soft
.61
-.61
[m/s]
-2
-4
-6
-4
-3
-2
-1
50 mm/s
-0
51
HR


09:19
ACE
V
5
10
15
20
Rest
JPEG
Max PG = 41.3 mmHg
Max V = 321.4 cm/sec
-.61
[m/s]
-2
-4
-6
-8
-3
-2
-1
66.67 mm/s
0
60
HR


09:19
v 4.88 m/s
p 95.40 mmHg
Valsalva
V
5
10
15
20
Sharp
JPEG
.61
-.61
[m/s]
-2
-4
-6
-8
-3
-2
-1
0
55
HR

Discussion & Considerations

1. Could the increasing gradients shown by echo be contributing to the patient's increasing symptoms?

2. Is a stress echo needed in this patient?

3. If it is determined her symptoms are due to worsening obstruction, what are the possible next steps?

Treatment of Hypertrophic Cardiomyopathy (HCM)

Patrick Garceau, MD, FRCPC
Cardiologist
Institut de Cardiologie de Montreal

Disclosures

	Dr. Patrick Garceau
Any direct financial payments including receipt of honoraria	BMS, Abbott
Membership on advisory boards or speaker's bureaus	BMS
Funded grants or clinical trials	Abbott, Medtronic
Patent on a drug, product or device	No disclosures
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	No disclosures

Objectives

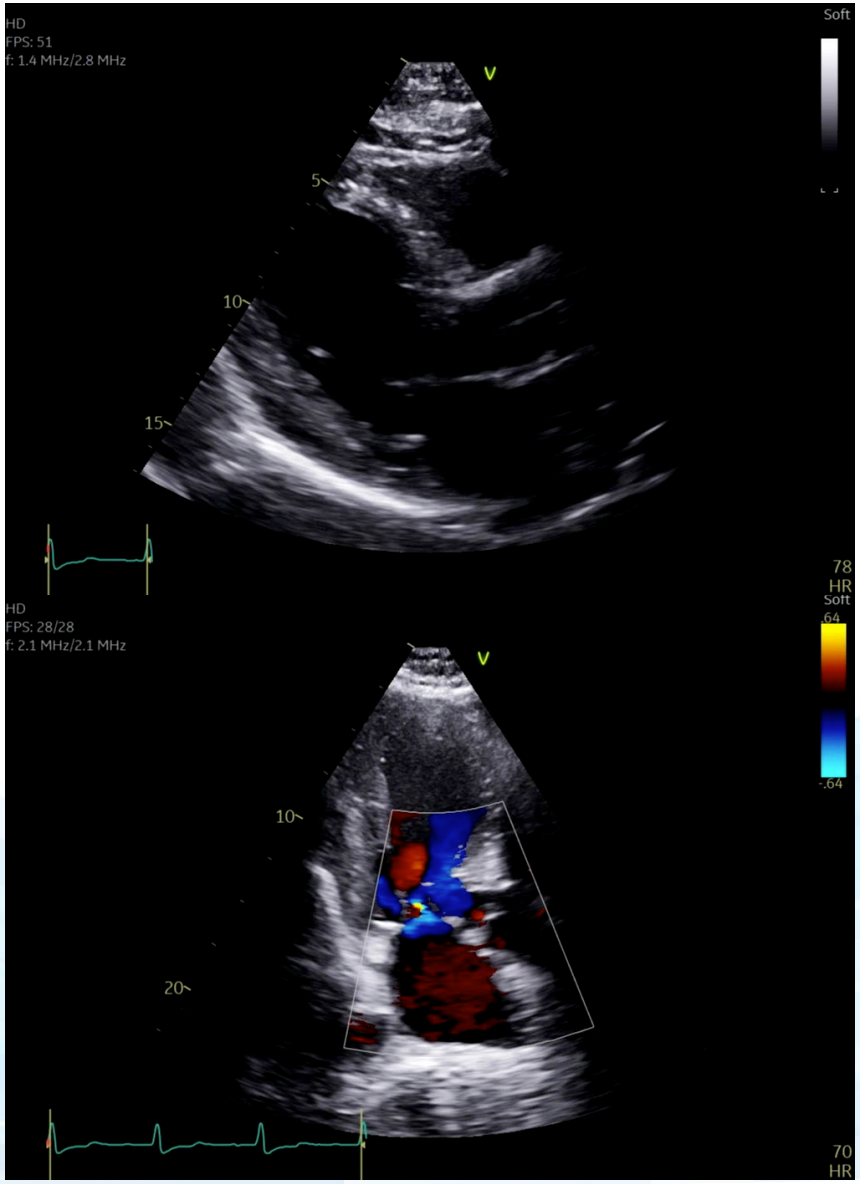
At the end of the presentation, the participants should:

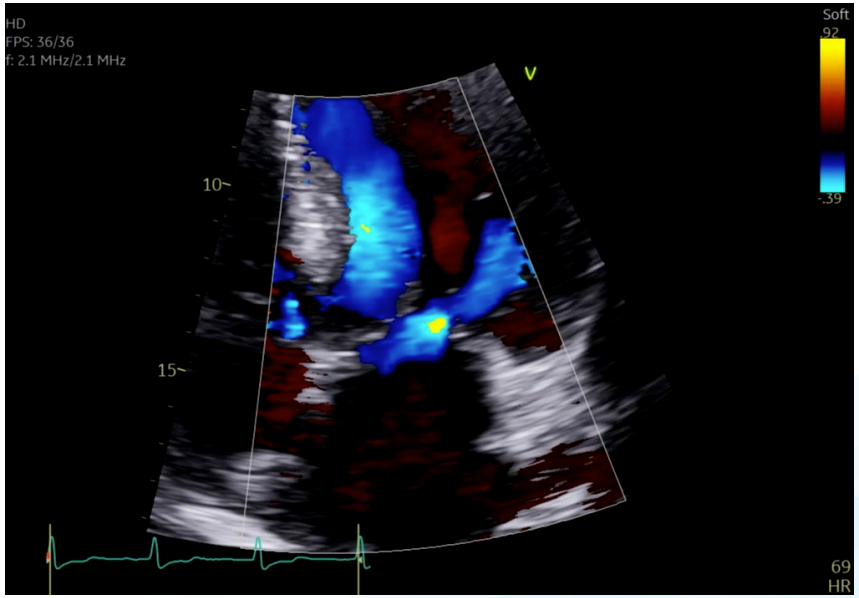
- Know the new therapies in Obstructive HCM (oHCM)
- Recognize when referral for Septal Reduction Therapy should be considered
- Recognize the limitations for treatment of non-obstructive HCM

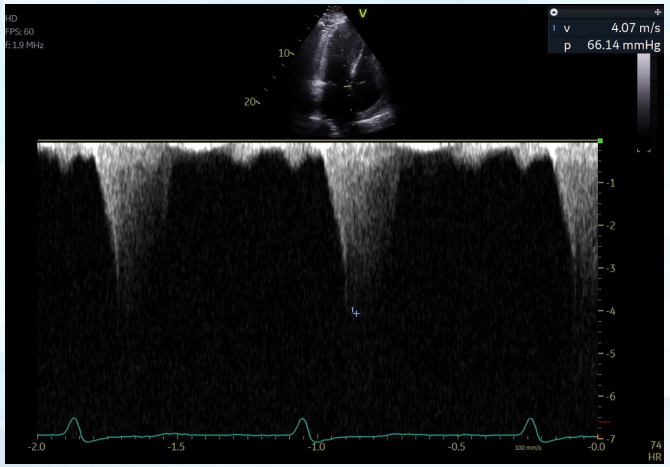
Patient D H

- 67 y old male
- Known for obstructive HCM > 10 years
- Anxiety, Dyslipidemia
- **NYHA 2-3**, Lightheaded when standing, fatigue
- Currently on:
  - Verapamil SR 120 mg BID, Disopyramide 200mg BID, Venlafaxine 150 mg OD, Zopiclone 7.5 mg PRN, Pantoprazole 40 mg OD, Rosuvastatin 10 mg OD
- Intolerance to Bisoprolol and Atenolol

Echocardiogram







Basal septum 22 mm
LVEF 60%
MR grade 4/4
LVOT rest grad 60-70 mmHg

slido

Considering Symptoms, LVOT Obstruction, MR and Comorbidities, Best Approach?

ⓘ Start presenting to display the poll results on this slide.

3 Important Questions in Symptomatic patients With HCM

1) Is there obstruction?

2) What is the mechanism of the obstruction and mitral regurgitation?

3) Associated comorbidities?
   - CAD
   - Concomitant valvular disease
   - Arrythmia
   - Other….

CLINICAL PRACTICE GUIDELINE

2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy

A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Medical Society for Sports Medicine, the Heart Rhythm Society, Pediatric & Congenital Electrophysiology Society, and the Society for Cardiovascular Magnetic Resonance

Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association

Nuno Cardim[1*], (Chair), Maurizio Galderisi[2], (Co-chair), Thor Edvardsen[3], Sven Plein[4], Bogdan A. Popescu[5], Antonello D'Andrea[6], Oliver Bruder[7], Bernard Cosyns[8], Laurent Davin[9], Erwan Donal[10,11], Antonio Freitas[12], Gilbert Habib[13,14], Anastasia Kitsiou[15], Steffen E. Petersen[16], Stephen Schroeder[17], and Patrizio Lancellotti[18,19]

https://doi.org/10.1016/j.jacc.2024.02.014

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

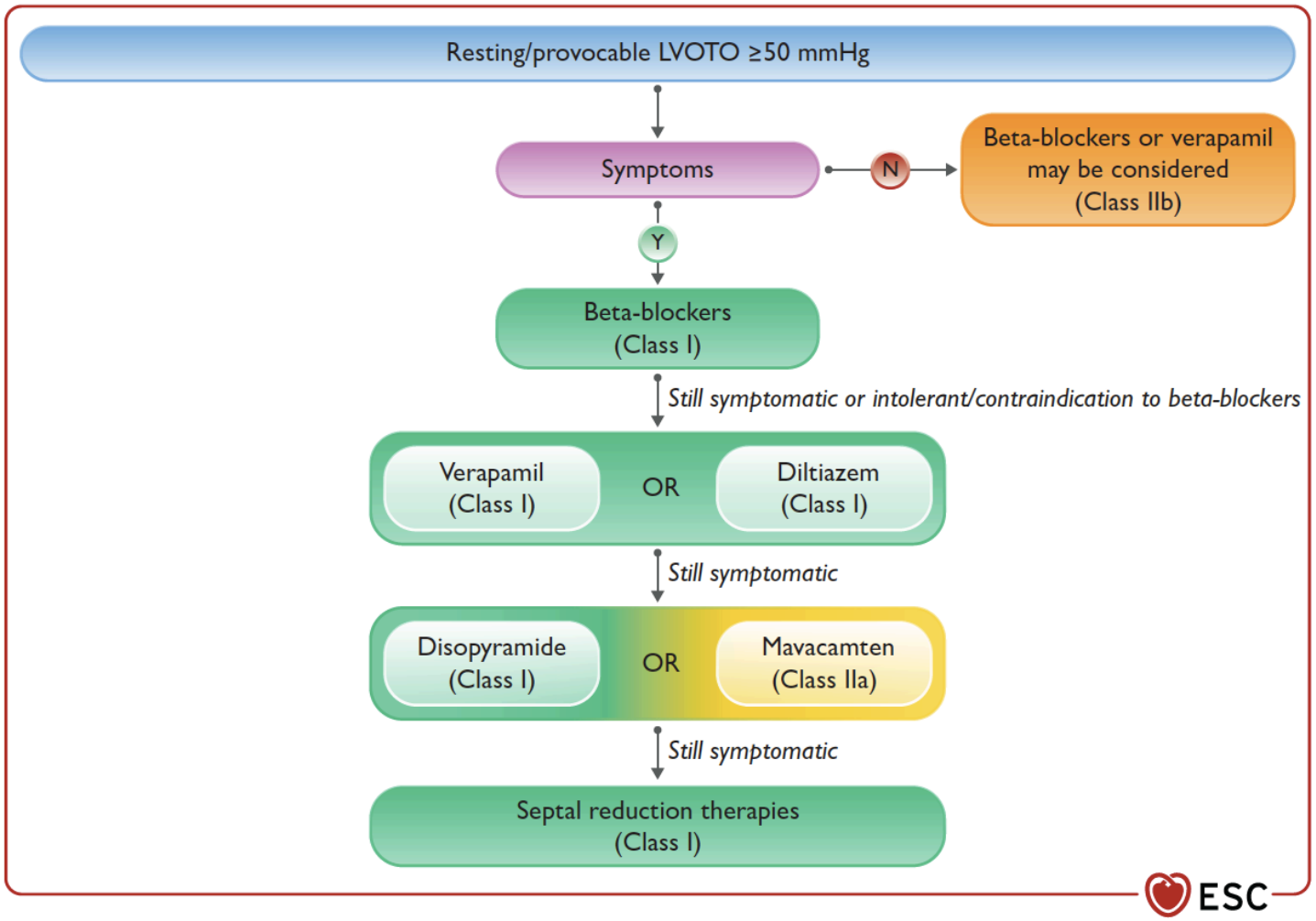
European Heart Journal – Cardiovascular Imaging (2015) **16**, 280

Recommendation Table 18 — Recommendations for treatment of left ventricular outflow tract obstruction (general measures)

Recommendations	Class[a]	Level[b]
Avoidance of digoxin and arterial and venous dilators including nitrates and phosphodiesterase inhibitors, should be considered, if possible, in patients with resting or provocable LVOTO.[626,627]	IIa	C
Restoration of sinus rhythm or appropriate rate control should be considered before invasive management of LVOTO in patients with new-onset or poorly controlled AF.[629,630]	IIa	C

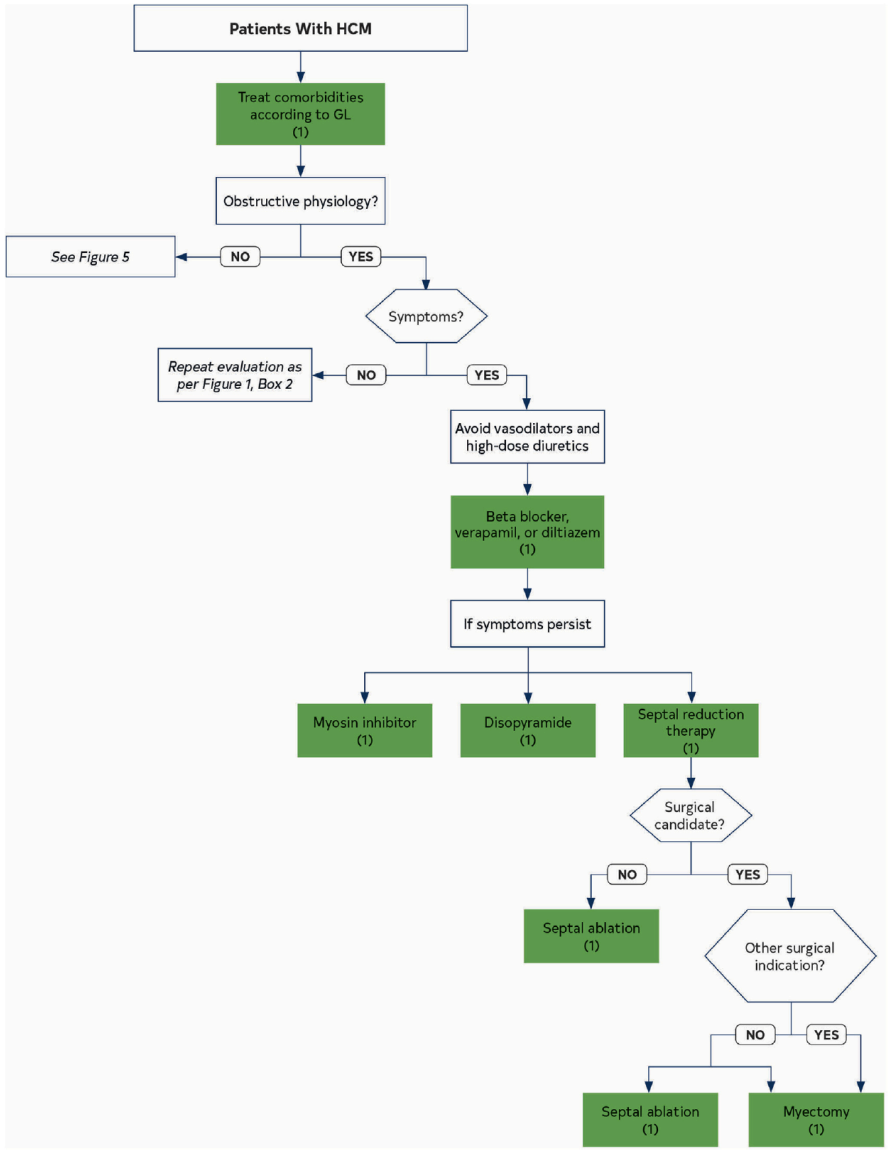
AF, atrial fibrillation; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.

Treatment of Obstructive HCM

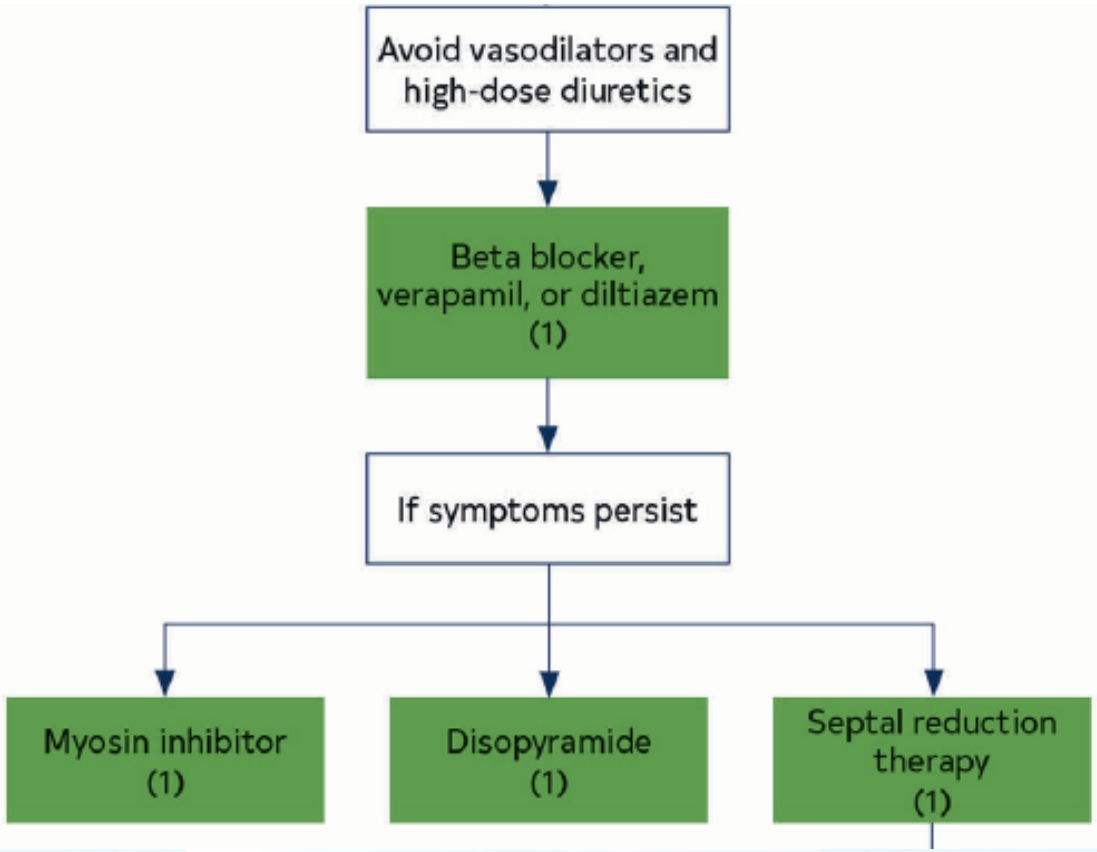


print & web 4C/FPO

FIGURE 4 Management of Symptoms in Patients With HCM

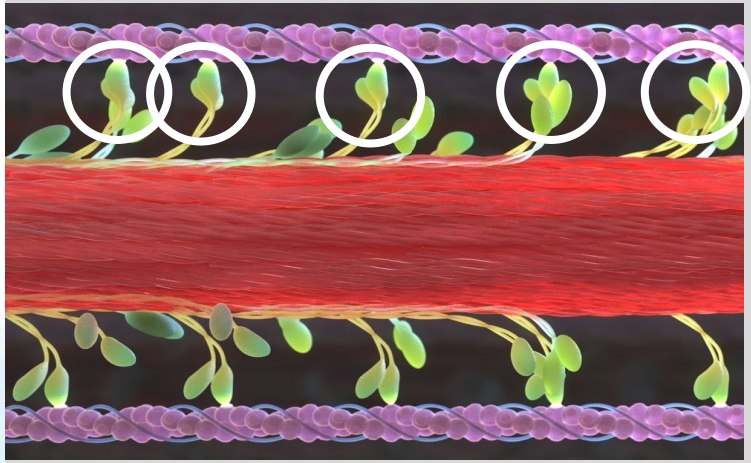


Colors correspond to Table 3. GL indicates guideline; and HCM, hypertrophic cardiomyopathy.



Cardiac-specific Myosin Inhibitor Reduces Excess Actin-myosin Cross-bridging in HCM

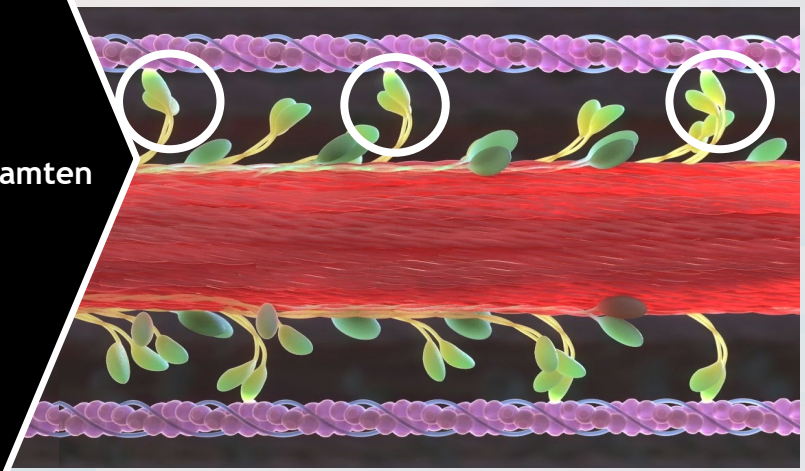
HCM Sarcomere[1,3-5]
Too many myosin-actin cross-bridges



- Hypercontractility
- Impaired relaxation
- Impaired compliance
- Disordered sarcomeres
- Cardiac tissue stiffness
- Fibrosis

After-mavacamten

HCM Sarcomere After Mavacamten Exposure[1,2]
Reduced number of excess myosin-actin cross-bridges



- Attenuated hypercontractility
- Improved relaxation
- Less cardiac tissue stiffens
- Improved myocardial energetics
- Improved compliance

1. Spudich JA et al. *Pflugers Arch* 2019;471:701–717. 2. Trivedi DV et al. *Biophys Rev* 2018;10:27–48. 3. Nag S et al. *Nat Struct Mol Biol* 2017;24:525–533. 4. Alamo L et al. *eLife* 2017;6:e24634.
5. Sequeira V et al. *FEBS Lett* 2019;593:1616–1626.

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**

www.thelancet.com Vol 396 September 12, 2020

Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy

Milind Y. Desai, MD, MBA,[a,b,c] Anjali Owens, MD,[d] Jeffrey B. Geske, MD,[e] Kathy Wolski, MPH,[b,c] Srihari S. Naidu, MD,[f] Nicholas G. Smedira, MD, MBA,[a,g] Paul C. Cremer, MD, MS,[b,c] Hartzell Schaff, MD,[h] Ellen McErlean, RN, MSN,[b,c] Christina Sewell, RN,[b,c] Wanying Li, PhD,[i] Lulu Sterling, PhD,[i] Kathy Lampl, MD,[i] Jay M. Edelberg, MD, PhD,[i] Amy J. Sehnert, MD,[i] Steven E. Nissen, MD[b,c]

JACC VOL. 80, NO. 2, 2022
JULY 12, 2022:95–108

ORIGINAL ARTICLE

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*

DOI: 10.1056/NEJMoa2401424

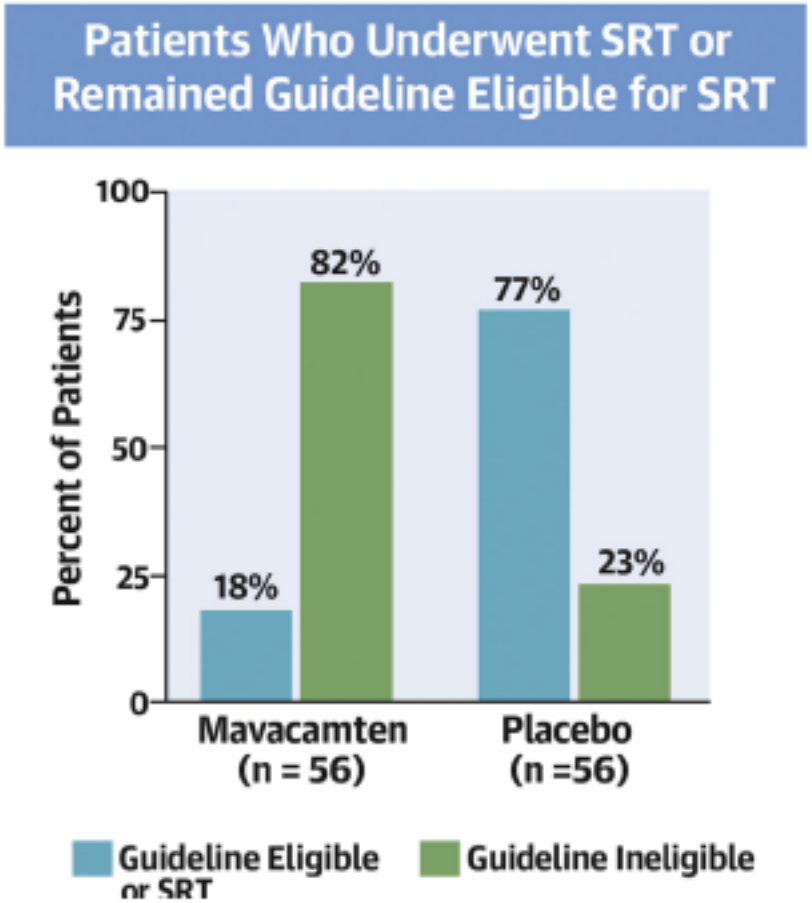
EXPLORER-HCM: Primary and secondary Endpoints

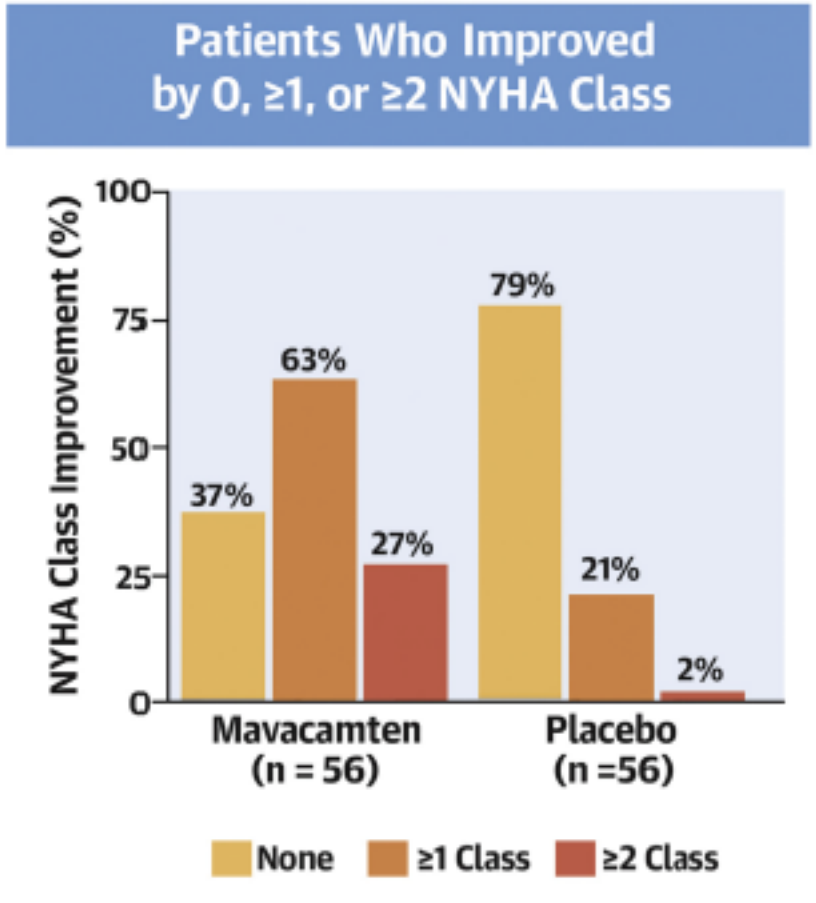
	Mavacamten group (n=123)	Placebo group (n=128)	Difference* (95% CI), p value
Primary endpoint†			
Either ≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	45 (37%)	22 (17%)	19·4 (8·7 to 30·1; p=0·0005)
≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement	41 (33%)	18 (14%)	19·3 (9·0 to 29·6)
≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	29 (24%)	14 (11%)	12·6 (3·4 to 21·9)
Both ≥3·0 mL/kg per min increase in pVO_2 and ≥1 NYHA class improvement	25 (20%)	10 (8%)	12·5 (4·0 to 21·0)
Secondary endpoints‡			
Post-exercise LVOT gradient change from baseline to week 30, mm Hg	−47 (40), n=117	−10 (30), n=122	−35·6 (−43·2 to −28·1; p<0·0001)
pVO_2 change from baseline to week 30, mL/kg per min	1·4 (3·1), n=120	−0·1 (3·0), n=125	1·4 (0·6 to 2·1; p=0·0006)
≥1 NYHA class improvement from baseline to week 30§	80 (65%)	40 (31%)	34% (22 to 45; p<0·0001)
[illegible]	[illegible]	[illegible]	9·1 (5·5 to 12·7; p<0·0001)
Change from baseline to week 30 in HCMSQ-SoB§	−2·8 (2·7), n=85	−0·9 (2·4), n=86	−1·8 (−2·4 to −1·2; p<0·0001)

Data are n (%) or mean (SD). HCMSQ-SoB=Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore. KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score. LVOT=left ventricular outflow tract. pVO_2=peak oxygen consumption. NYHA=New York Heart Association. *Model estimated least-square mean differences were reported for continuous variables. †Patients with a non-evaluable primary endpoint and NYHA secondary endpoint were considered as non-responders. The response rates were calculated with the N value as the denominator. ‡N was the number analysable for secondary endpoints based on availability of both baseline and week 30 values. §Due to the smaller numbers evaluable for patient-reported outcome endpoints, additional post-hoc analyses compared the reasons for missing data.

Table 2: **Primary and secondary endpoints**

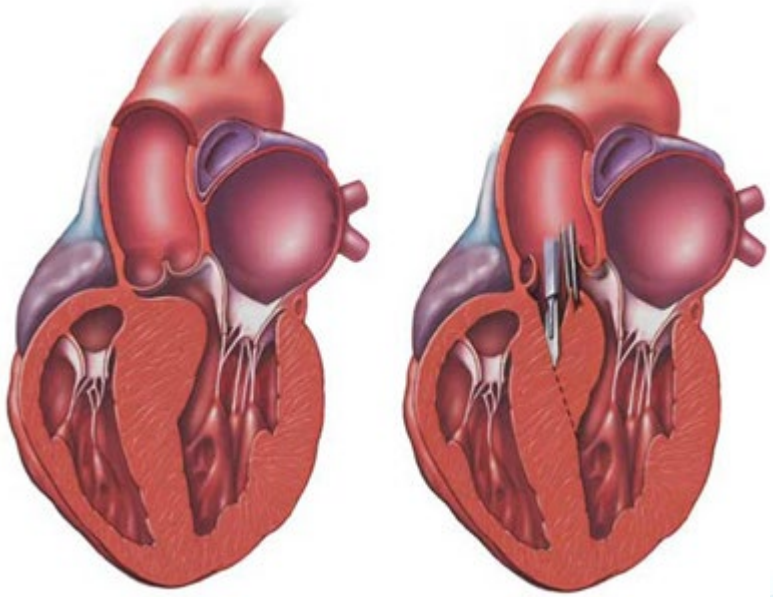
VALOR – HCM
Primary and secondary end-points



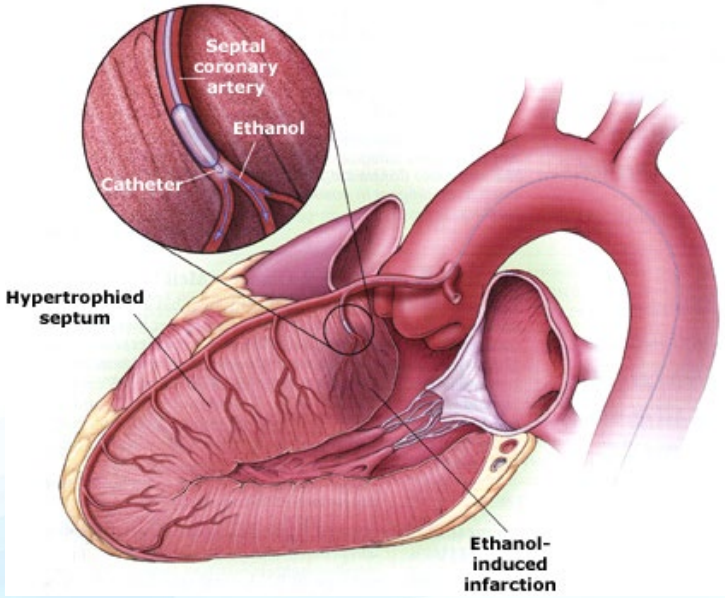


Desai MY, et al. J Am Coll Cardiol. 2022;80(2):95-108.

Septal Reduction Therapy



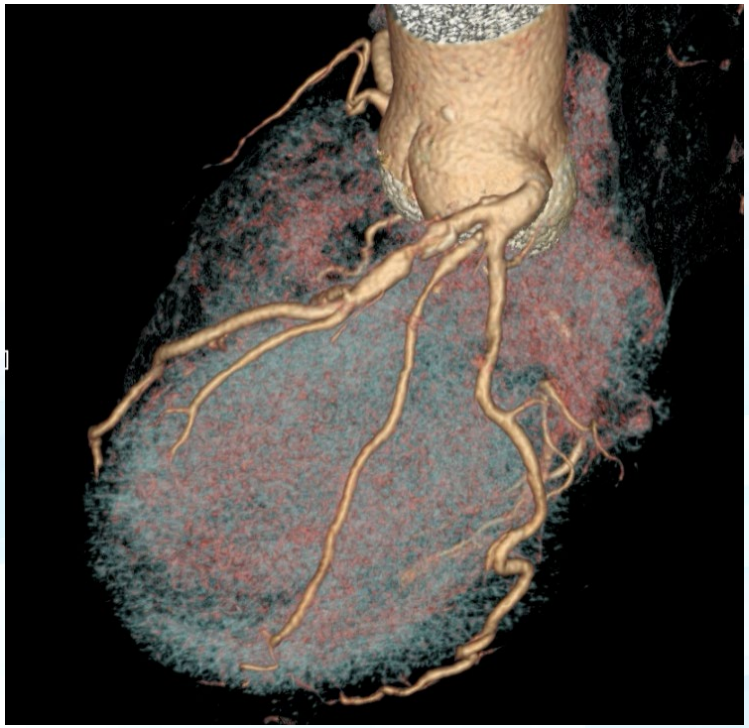
- ↑ Morbidity
- 90-95% success rate
- Concomittant disease (valvular, CAD, …)



- ↑ rate of pacemaker
- 70-75% success rate
- Long-term concerns

Non-Obstructive HCM - Management

- Identification of CAD
  - Coronary CT scan
  - PET –CT (Microvascular disease)
- Baseline level of NT-Pro-BNP
- Right heart catheterization



Non-Obstructive HCM – Management (II)

- Optimizing medical treatment
  - β-Blockers
  - Non-dihydropiridine Calcium Channel Blocker
  - Ranolazine if refractory angina
  - Valsartan
- GDMT for HFrEF
- Diuretics
- Early reference to Heart Transplant clinic

SCD Risk Stratification in Patients With HCM

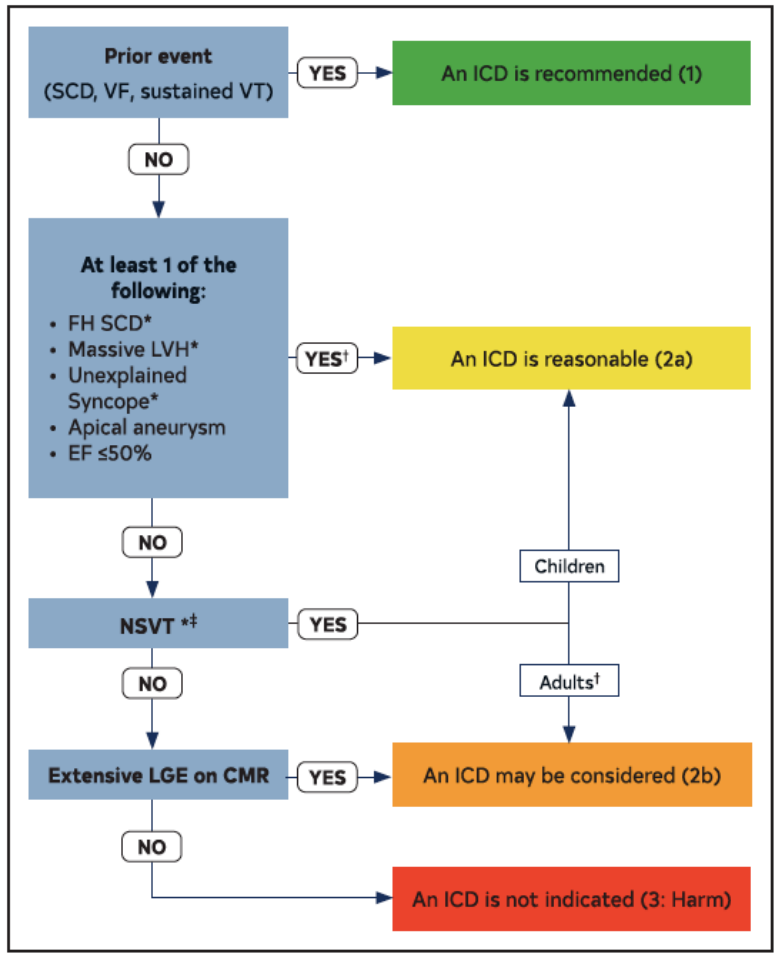
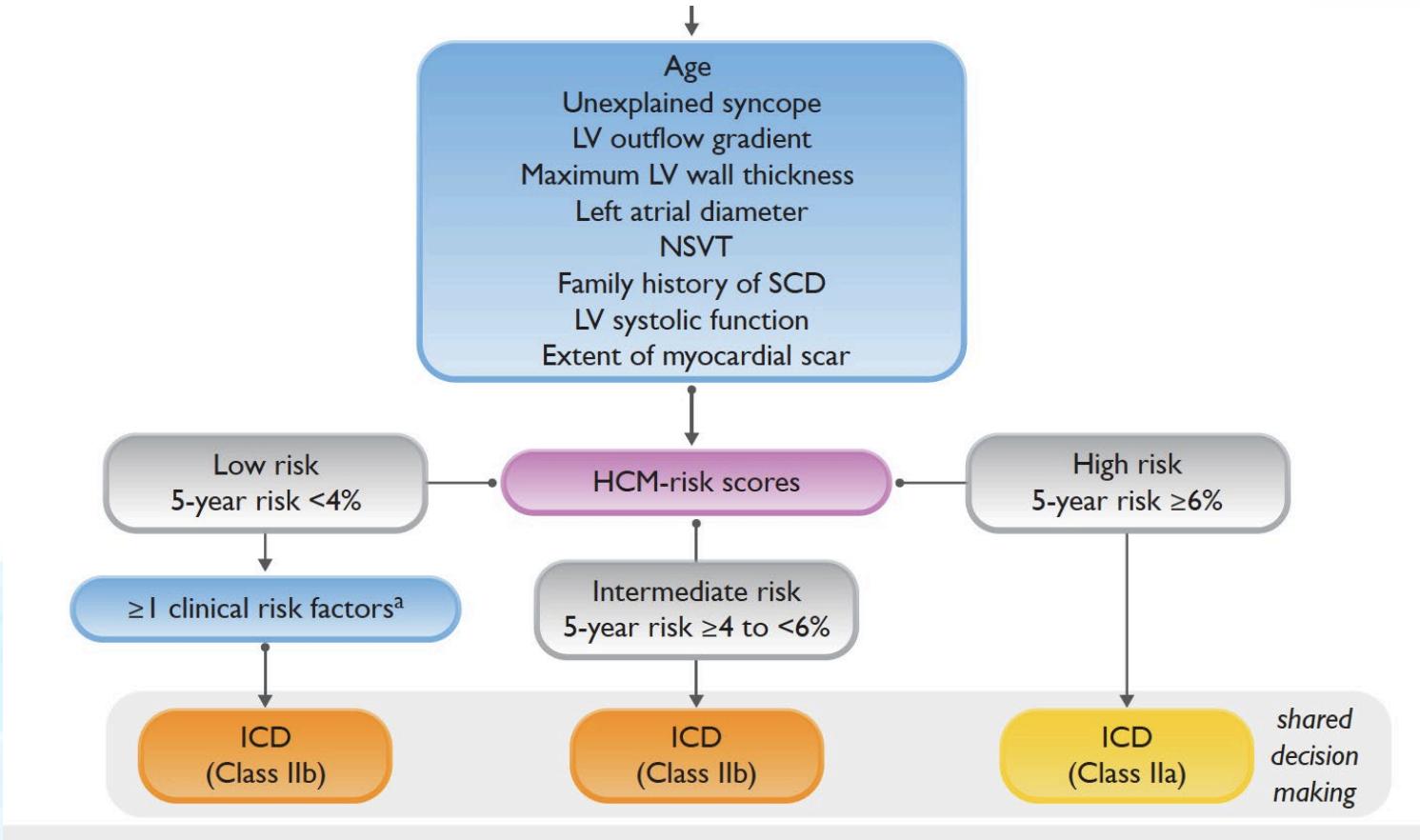


Figure 3. ICD patient selection.



1. Ommen SR et al. *JACC*. 2020;73:1978-1986.
2. Zappenfeld K et al. *Eur Heat J*. 2022;40:3997-4126. 2. Elliott PM et al. *Eur Heart J*. 2014;39:2733-2779.

Conclusions

- Importance of Heart Team for optimal Management
- New emerging therapy for patients with Obstructive HCM
  - Myosin Inhibitors
- Still place for SRT
- Non-obstructive HCM remains a challenge
  - Early referral to specialized center

Q&A Period

All panellists

THANK YOU!

Please remember to complete the session evaluation

Next up: Symposium Shot to the Heart: CV Risk Reduction Through Vaccination with Dr. Shelley Zieroth and Dr. Jacob Udell.