FORUM EUROPÉEN, CŒUR, EXERCICE & PRÉVENTION

Actualités dans la prise en charge de la cardiomyopathie hypertrophique obstructive

Gilbert Habib
La Timone Hospital
Marseille - France

Paris, 20 Mars 2025

Avec le soutien organisationnel de Bristol-Myers Squibb

www.forumeuropeen.com

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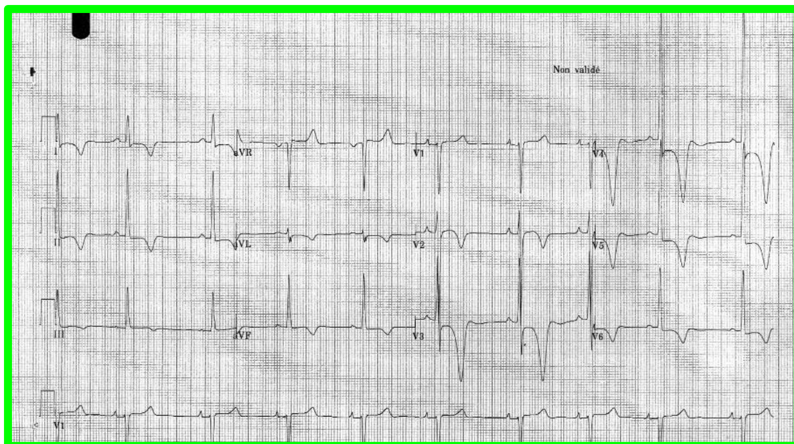
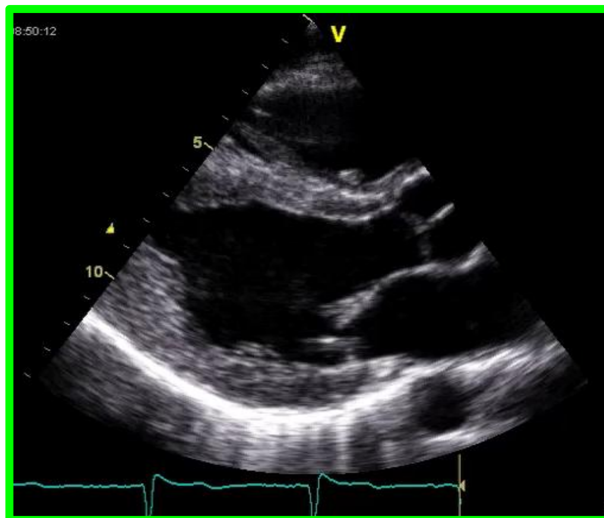
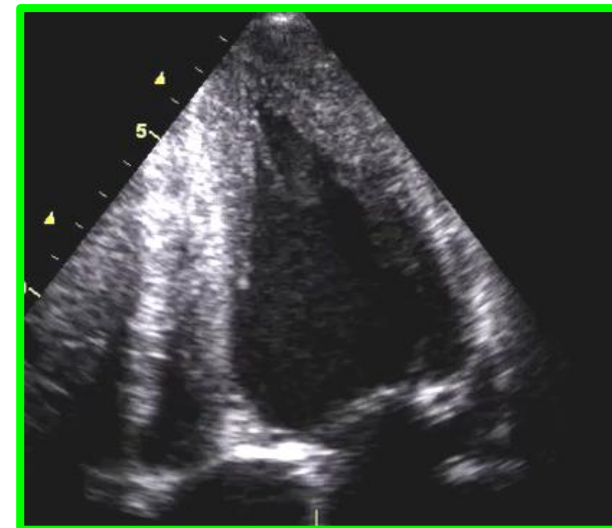
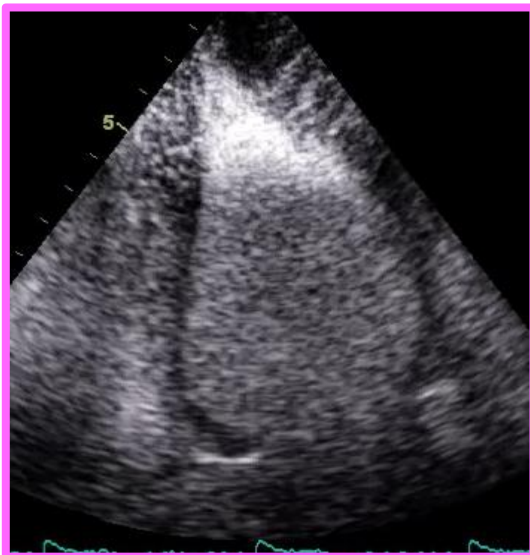
Le contenu et/ou les opinions exprimées lors de cette présentation ont été réalisés en toute indépendance

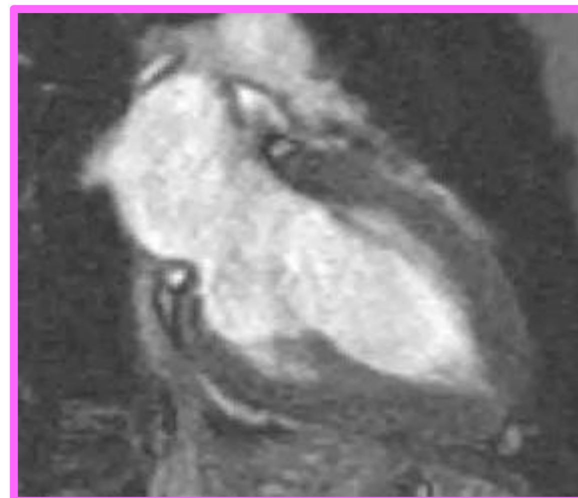
Un joueur de l'OM











L'obstruction dans les CMH

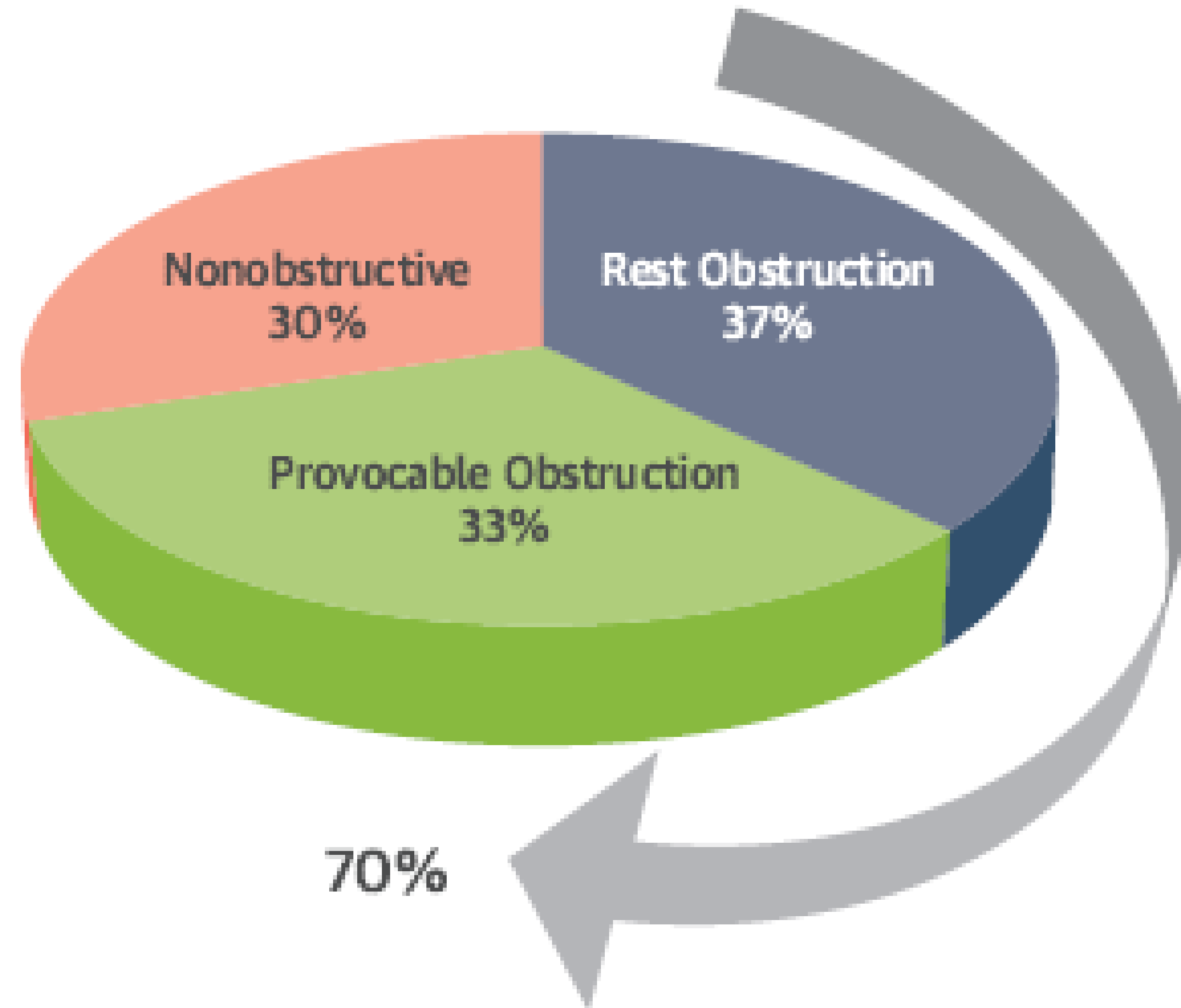
2022

JACC STATE-OF-THE-ART REVIEW

Management of Hypertrophic Cardiomyopathy

JACC State-of-the-Art Review

Barry J. Maron, MD,[a] Milind Y. Desai, MD,[b] Rick A. Nishimura, MD,[c] Paolo Spirito, MD,[d] Harry Rakowski, MD,[e] Jeffrey A. Towbin, MD,[f] Joseph A. Dearani, MD,[g] Ethan J. Rowin, MD,[a] Martin S. Maron, MD,[a] Mark V. Sherrid, MD[h]

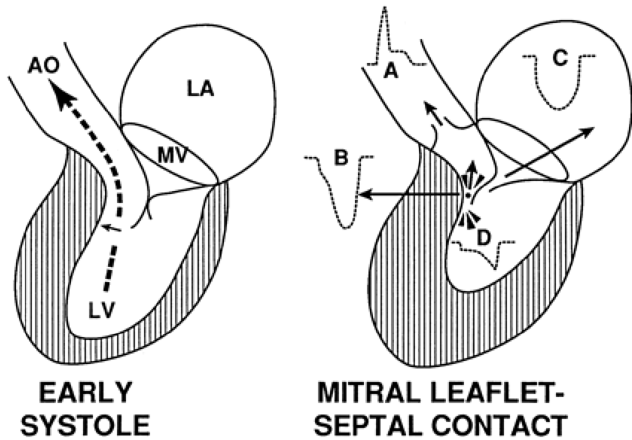


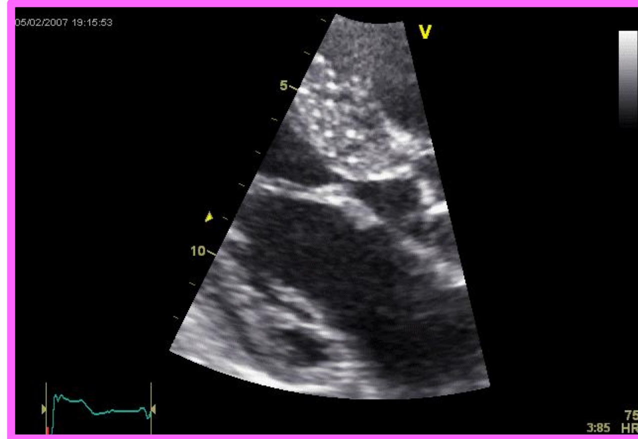
Prise en charge des CMH obstructives

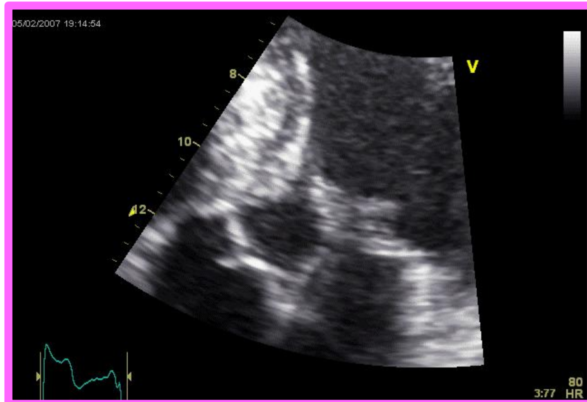
1. ***Comprendre le mécanisme et quantifier l'obstruction***

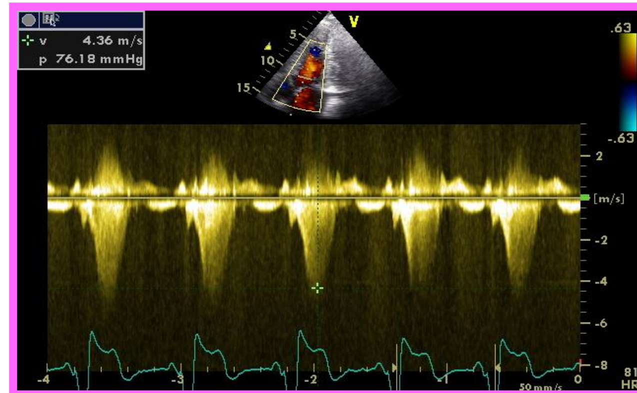
2. **Prescrire un traitement adapté**

Mécanisme de l'obstruction sous-aortique



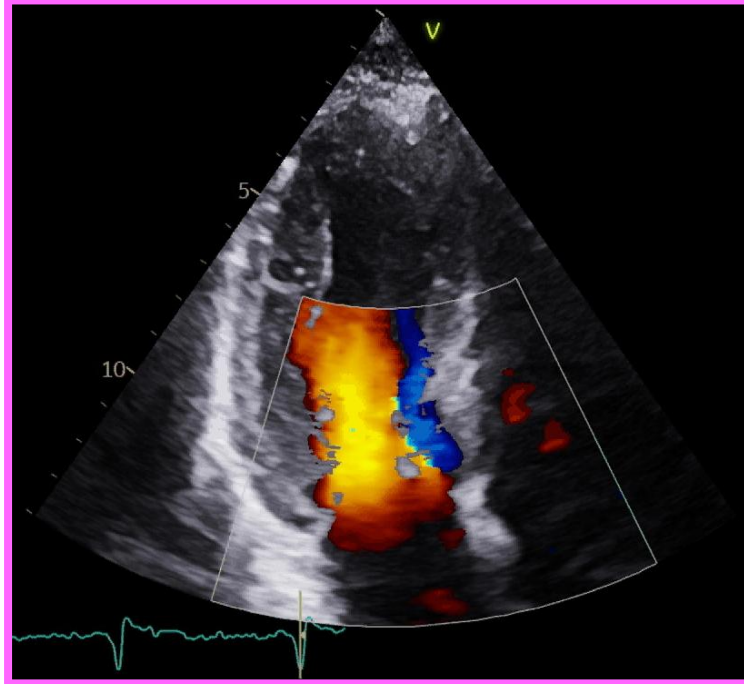


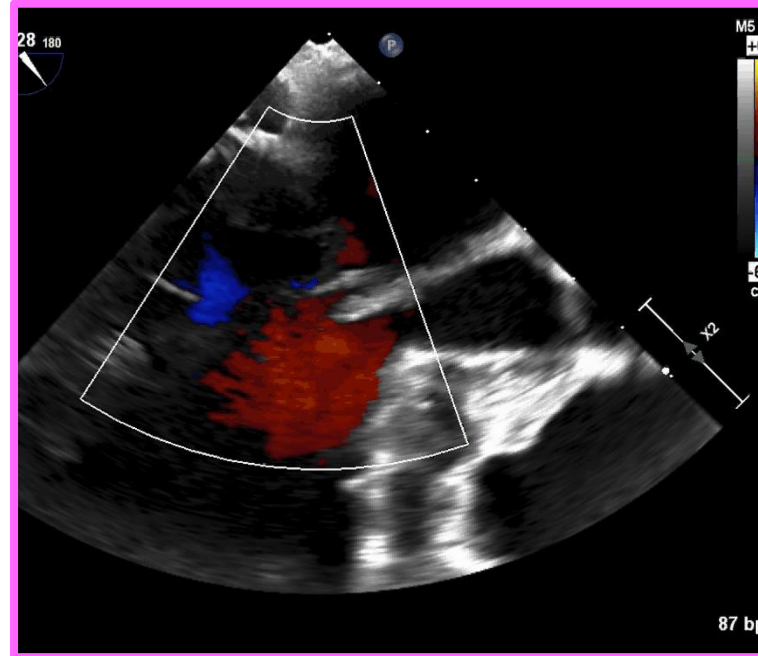


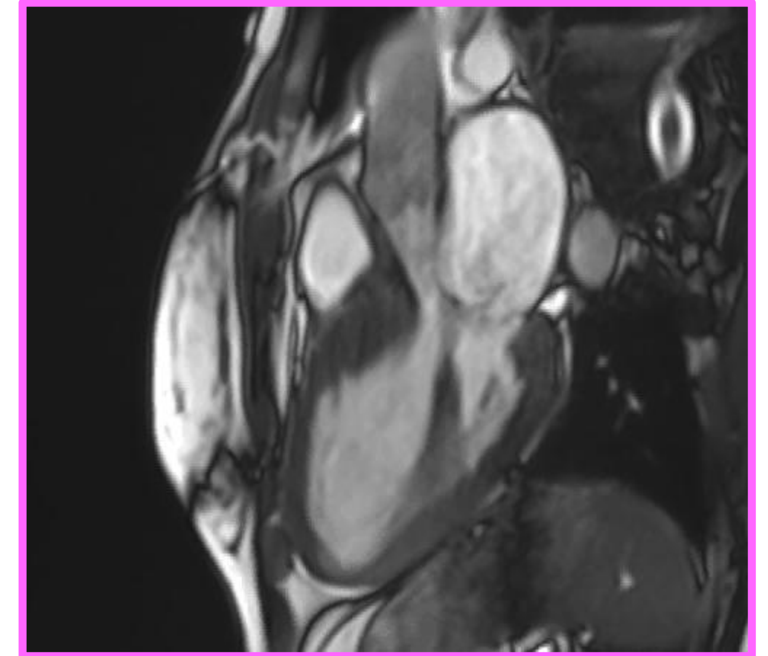


- hypertrophie septale sous aortique
- chambre de chasse de taille réduite
- déplacement antérieur des piliers
- élongation du feuillet antérieur
- hypercontractilité VG
- effet Venturi
- mouvement antérieur de la mitrale (SAM)

Mécanisme de l'obstruction sous-aortique







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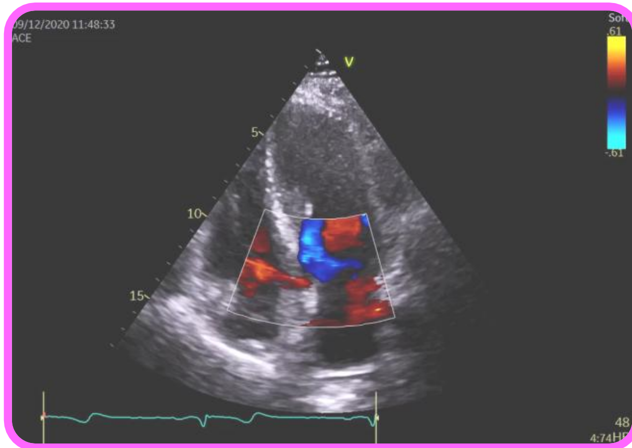
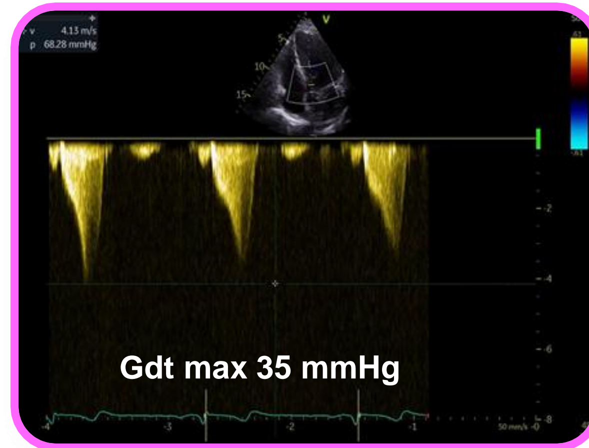
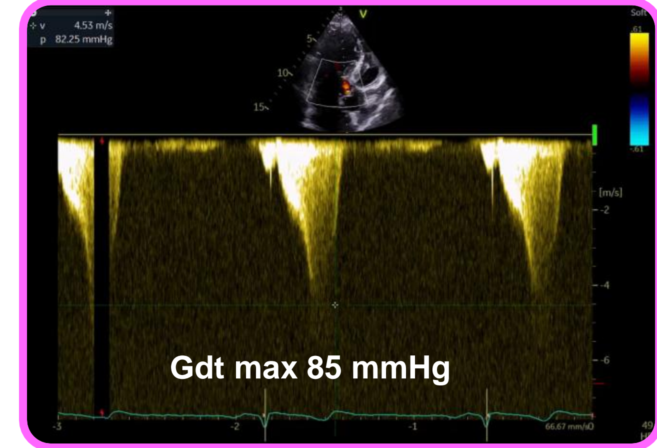
Quantification de l'obstruction intra-VG

- Manœuvres de Valsalva assis et penché en avant
- Puis debout
- Echocardiographie d'effort chez patients symptomatiques
- Echocardiographie dobutamine contre-indiquée



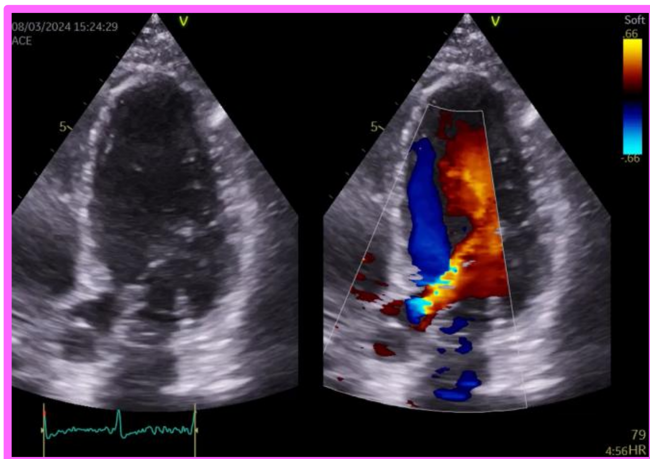


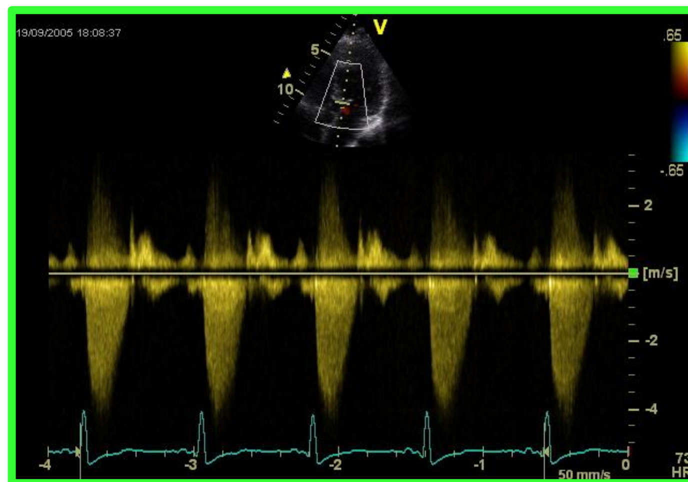


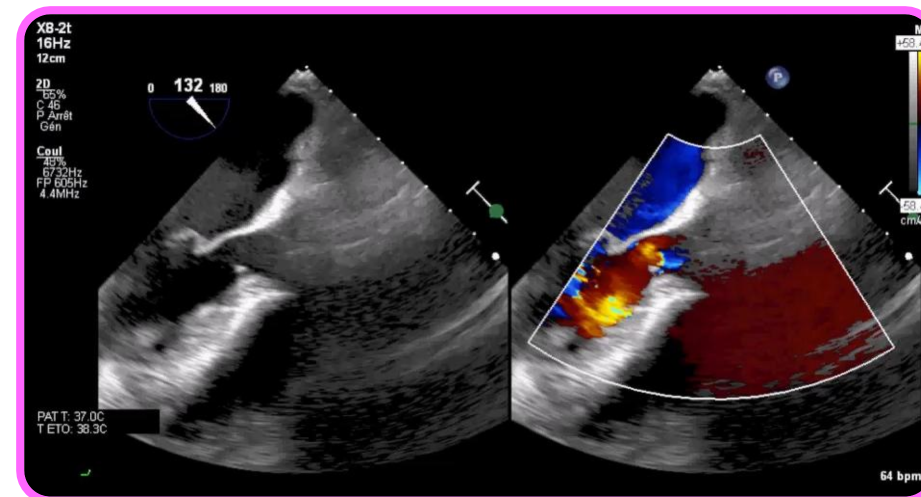
basal **Valsalva**

- **Obstruction = gradient maximal ≥ 30mmHg**
- **Indication thérapeutique = gradient maximal ≥ 50 mmHg**

Diagnostic différentiel







Recommendation Table 16 — Recommendation for evaluation of left ventricular outflow tract obstruction

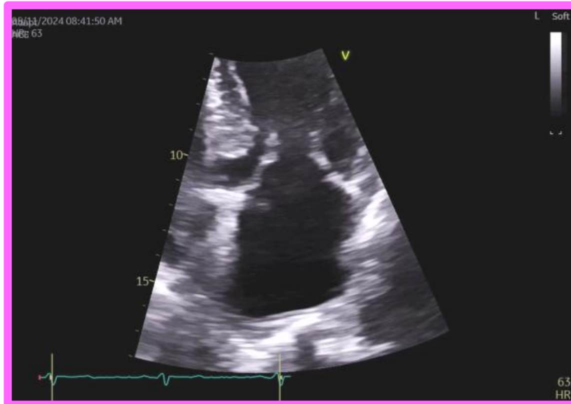
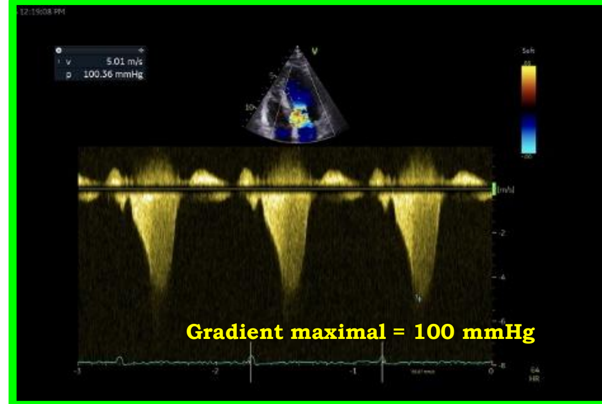
Recommendations	Class[a]	Level[b]
Transoesophageal echocardiography should be considered in patients with HCM and LVOTO if the mechanism of obstruction is unclear or when assessing the mitral valve apparatus before a septal reduction procedure, or when severe mitral regurgitation caused by intrinsic valve abnormalities is suspected.[599–602]	IIa	C

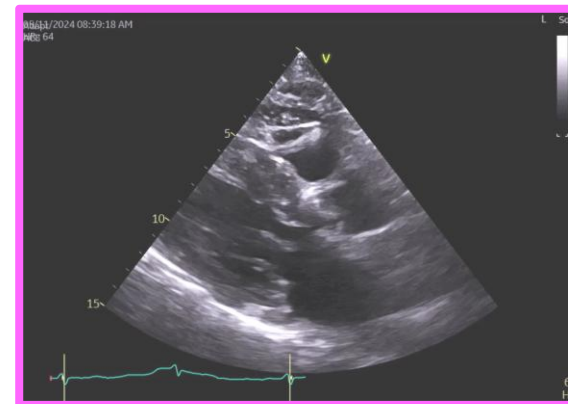
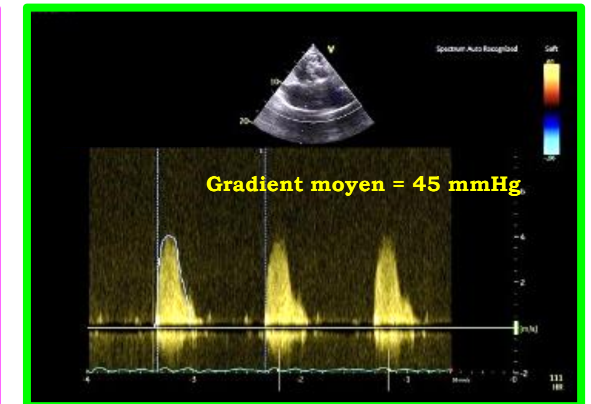
membrane / diaphragme sous-aortique

Cas particulier 1: CMO + sténose aortique

- Patiente de 86 ans
- CMO connue + RA minime
- Echec d'alcoolisation en 2020
- NYHA 3 malgré Propranolol 160 mg/j
- NT-proBNP = 1450 ng/l

- Obstruction = gradient maximal = 70 mmHg
- gradient maximal Valsalva = 100 mmHg
- Gradient aortique moyen = 45 mmHg

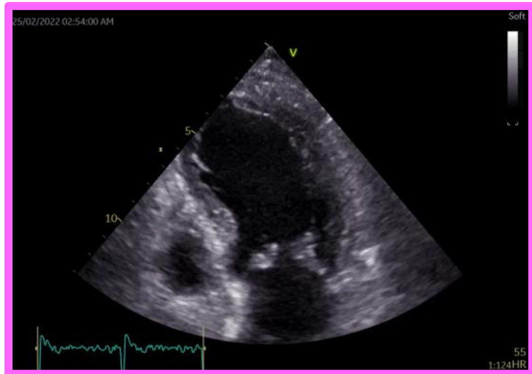



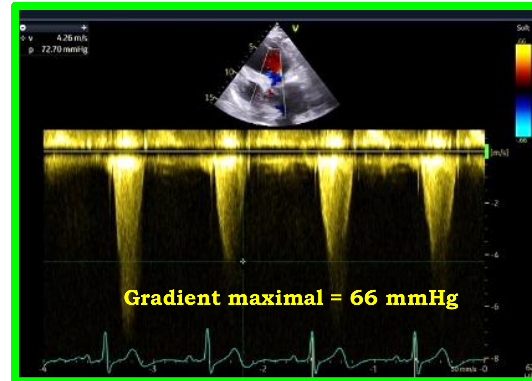
- TAVI janvier 2025
- Début mavacamten février 2025

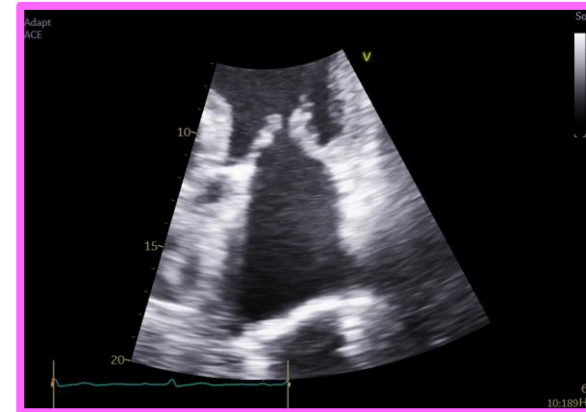
Cas particulier 2: CMO + Insuffisance mitrale

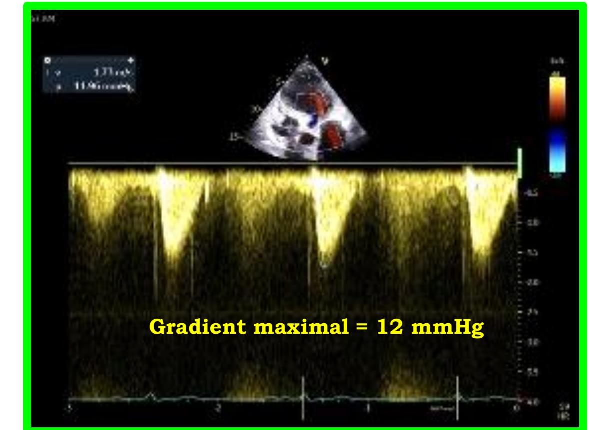
- Patiente de 75 ans
- Jusqu'alors asymptomatique
- CMO connue stable sous betabloquants
- Mutation MYBPC3

- Aggravation récente
- NYHA 3
- NT-proBNP = 2500 ng/l





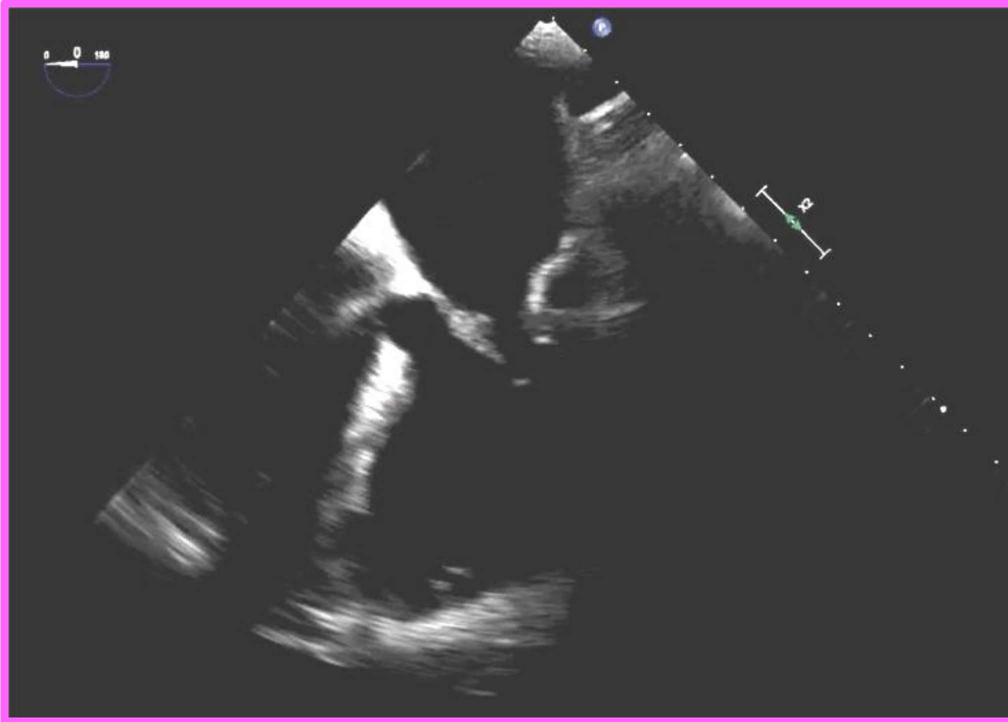


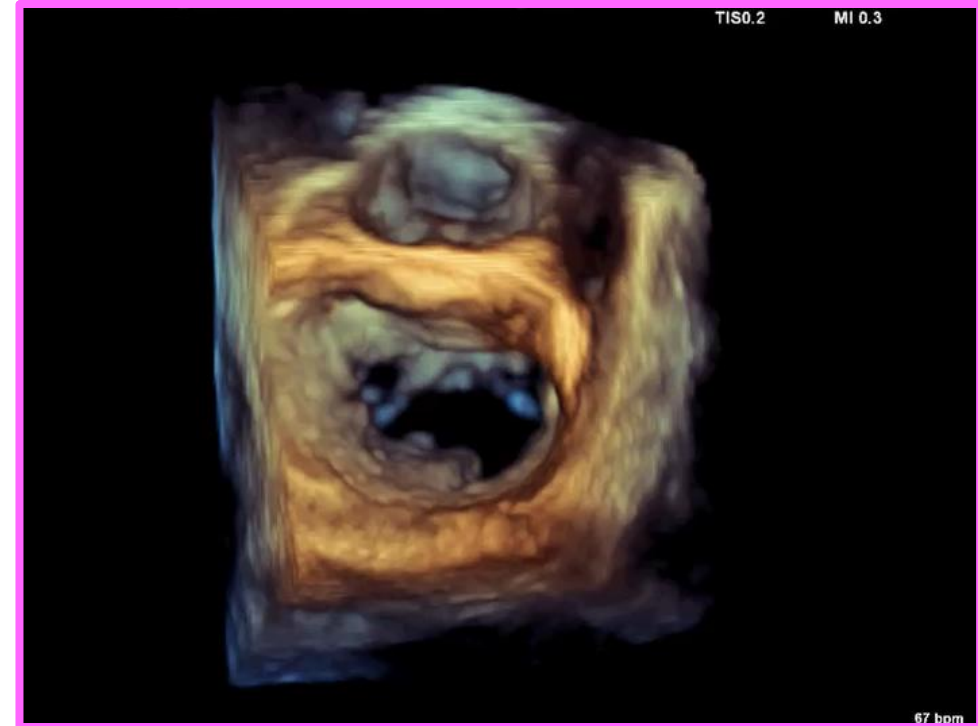


- Obstruction = gradient maximal = 66 mmHg
- PVM avec IM minime

- Obstruction = gradient maximal = 15 mmHg
- IM sévère par PVM avec rupture de cordages

Cas particulier 2: CMO + Insuffisance mitrale





Traitement des CMH obstructives

1. **Comprendre le mécanisme et quantifier l'obstruction**

2. ***Prescrire un traitement adapté***

Traitement des CMH obstructives

- ✓ Traitement « classique » béta bloquants, inhibiteurs calciques, disopyramide
- ✓ Alcoolisation septale
- ✓ Chirurgie myomectomie
- ✓ Inhibiteurs de la myosine

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)

CLINICAL PRACTICE GUIDELINES

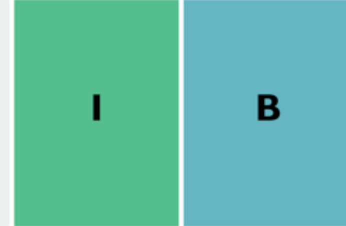
2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

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

Les bétabloquants

- ✓ Peu de preuves
- ✓ BB non vasodilatateurs
- ✓ AMM en France
  - ➢ *Propranolol*
  - ➢ *Nadolol*
  - ➢ *Pindolol*

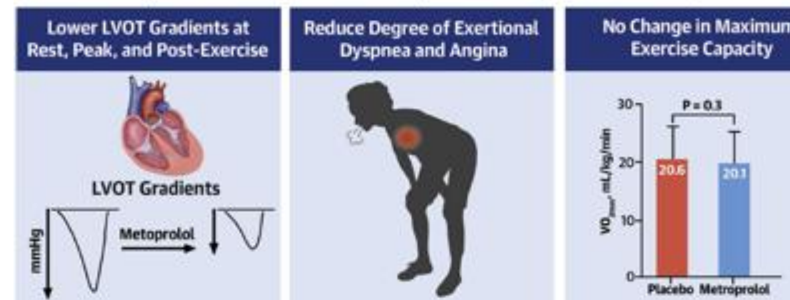
Recommendation	Class	Level
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked[c] LVOTO.[631–633,648–650]	I	B

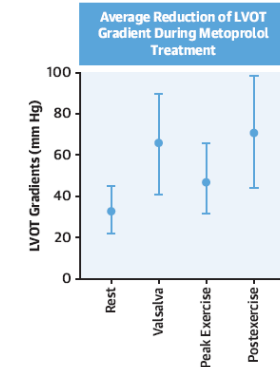


COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM and symptoms* attributable to LVOTO, nonvasodilating beta blockers, titrated to effectiveness or maximally tolerated doses, are recommended.[1–3]

Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy

Anne M. Dybro, MD,[a,b] Torsten B. Rasmussen, MD, PhD,[a,b] Roni R. Nielsen, MD, PhD,[a,b] Mads J. Andersen, MD, PhD,[a] Morten K. Jensen, MD, PhD,[a] Steen H. Poulsen, MD, DMSc[a,b]





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Les inhibiteurs calciques bradycardisants

VERAPAMIL

Débuter 40 mg 2 ou 3/jour, jusqu'à 480 mg/jour

DILTIAZEM

Débuter 60 mg 2 ou 3/jour, jusqu'à 360 mg/jour

Attention si obstruction trop importante (Gmax > 100 mmHg) ou HTP

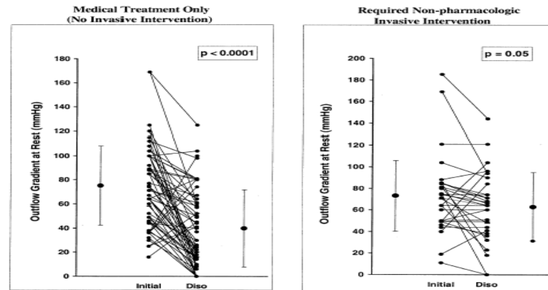
Recommendation	Class	Level
Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provoked[c] LVOTO who are intolerant or have contraindications to beta-blockers.[633,637–641]	I	B

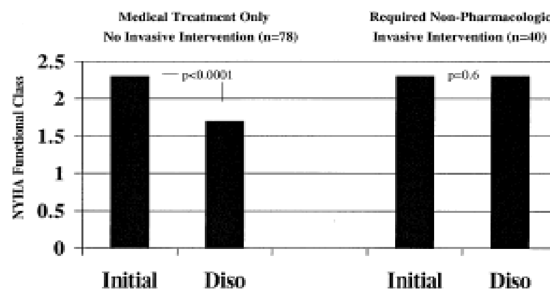
COR	LOE	Recommendation
1	B-NR† C-LD‡	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta blockers are ineffective or not tolerated, substitution with nondihydropyridine calcium channel blockers (eg, verapamil,† diltiazem‡) is recommended.[4–6]

COR	LOE	Recommendation
3: Harm	C-LD	7. For patients with obstructive HCM and severe dyspnea at rest, hypotension, very high resting gradients (eg, >100 mm Hg), as well as all children <6 weeks of age, verapamil is potentially harmful.[4,16]

Le disopyramide

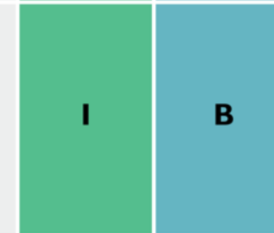
- ✓ 400-600 mg/j
- ✓ Attention surveillance du QT
- ✓ Association avec un bloqueur du NAV



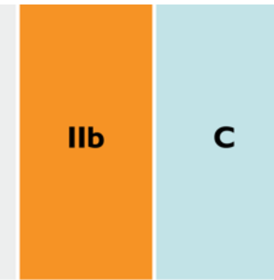


Sherrid 2005 *JACC 2005;45:1251*

Disopyramide,[d] titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provoked[c] LVOTO.[632–634]



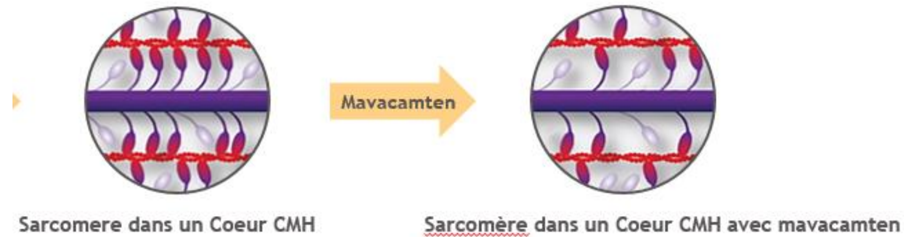
Disopyramide, titrated to maximum tolerated dose, may be considered as monotherapy in patients who are intolerant to or have contraindications to beta-blockers and verapamil/diltiazem to improve symptoms in patients with resting or provoked[c] LVOTO.[632]



3. For patients with obstructive HCM who have persistent symptoms* attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers,§ is recommended.[7–14]

Les Inhibiteurs de la myosine

MAVACAMTEN®



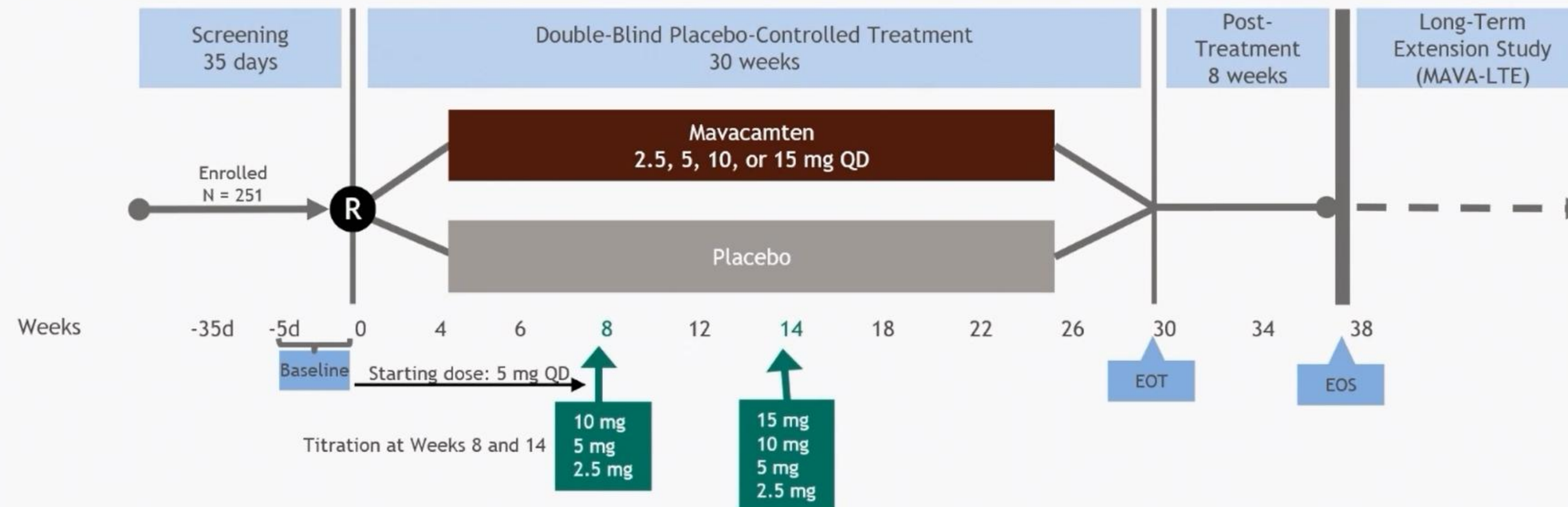
Recommendation	Class	Level
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provoked[c] LVOTO.[622,642–646]	IIa	A

Recommendation	Class	Level
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in symptomatic adult patients with resting or provoked[c] LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/ diltiazem, or disopyramide.[622,644–646]	IIa	B

COR	LOE	Recommendation
1	B-R	3. For patients with obstructive HCM who have persistent symptoms* attributable to LVOTO despite beta blockers or nondihydropyridine calcium channel blockers, adding a myosin inhibitor (adult patients only), or disopyramide (in combination with an atrioventricular nodal blocking agent), or SRT performed at experienced centers,§ is recommended.[7–14]

COR	LOE	Recommendation
3: Harm	C-EO	11. In pregnant women, use of mavacamten is contraindicated due to potential teratogenic effects.

Inhibiteurs de la myosine – Mavacamten



Inhibiteurs de la myosine – Mavacamten

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

Mavacamten

- First-in-class, selective inhibitor of cardiac myosin
- Reduces excessive actin-myosin cross-bridges, thus creating more favorable sarcomere function

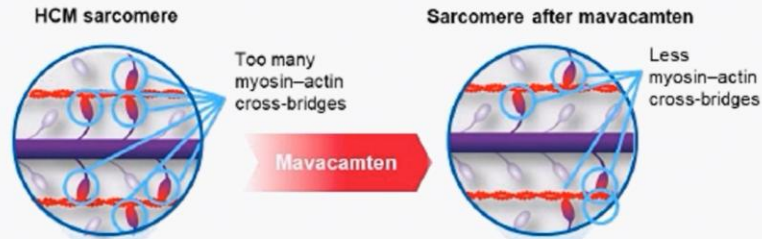
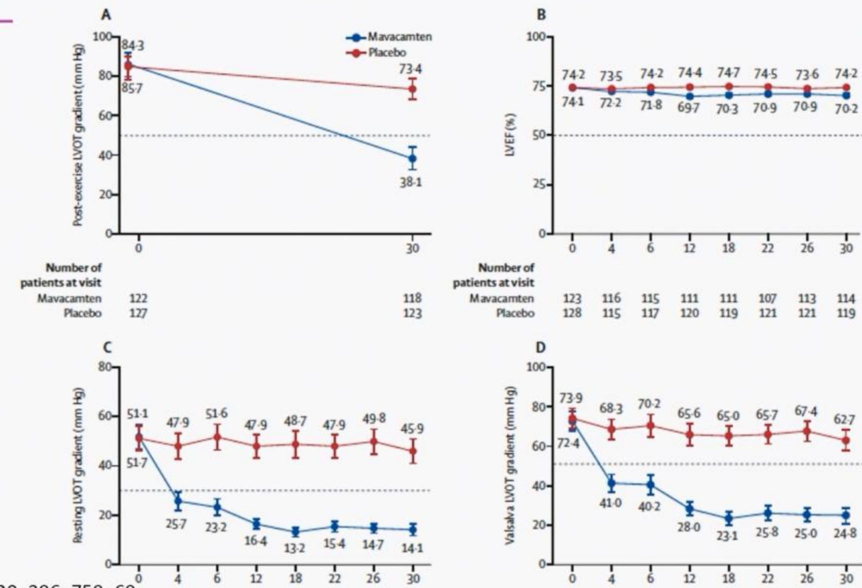


Figure 2: HCM sarcomere. Mavacamten reduces myosin-actin cross bridges.

Olivotto I. Lancet 2020; 396: 759–69

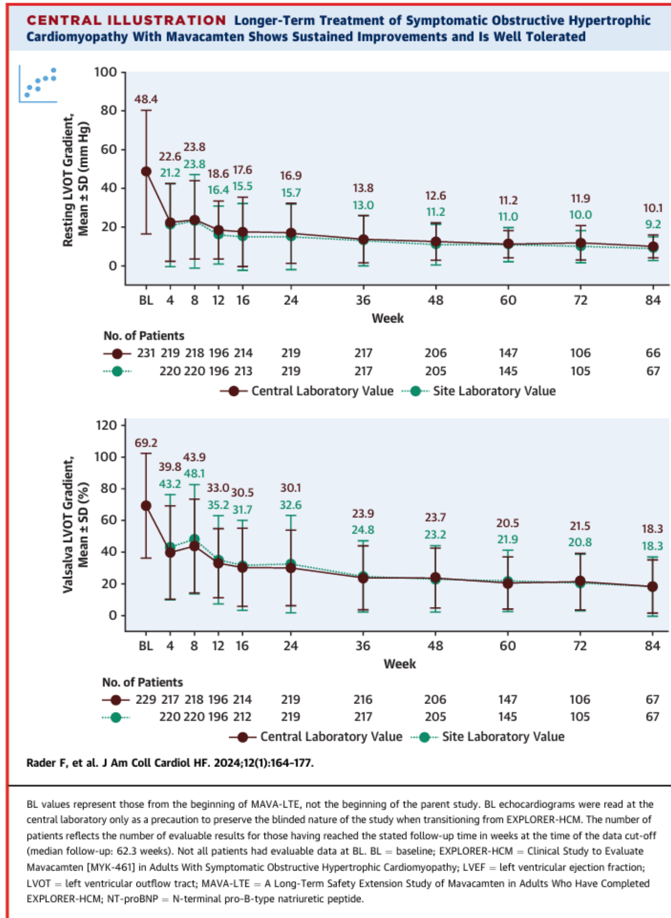
Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial

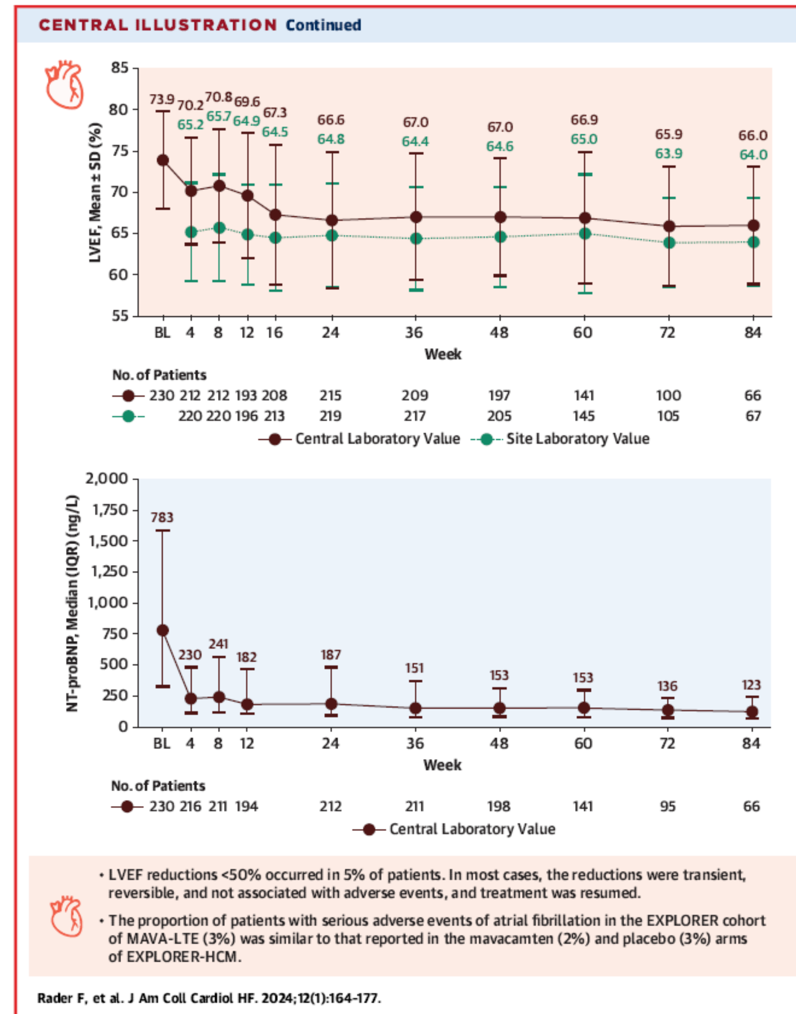


Olivotto I. Lancet 2020; 396: 759–69

Mavacamten: résultats à long terme: MAVA-LTE

Rader F. JACC HF 2024





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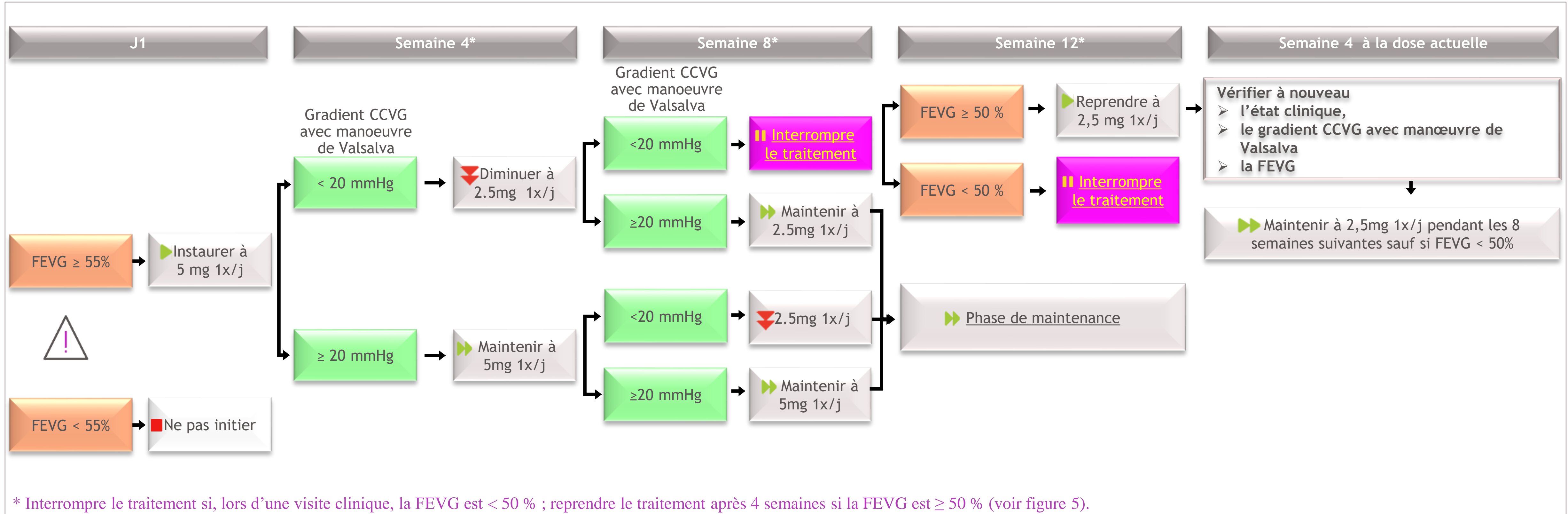
Mavacamten en pratique

- ✓ **Indication**
  - ➢ CMH obstructive (>50mmHg de gradient max au repos, au Valsalva ou à l'effort)
  - ➢ Symptomatique (NYHA II-III)
  - ➢ Malgré traitement optimal (bétabloquants, inhibiteurs calciques) ou intolérance
- ✓ **Génotypage CYP2C19 > posologie de départ (2,5 ou 5mg)**
- ✓ **Contre-indications :**
  - ➢ FEVG<55%
  - ➢ Grossesse (test de grossesse négatif + contraception efficace)
- ✓ **Interactions médicamenteuses : avec tous les inducteurs/inhibiteurs du CYP2C19 et CYP3A4 (peu de contre-indications absolues si métaboliseur normal)**

Ajustement du traitement sous Mavacamten

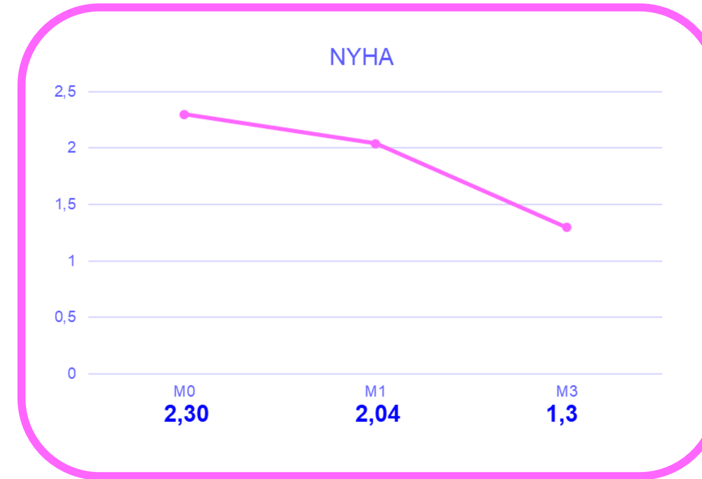


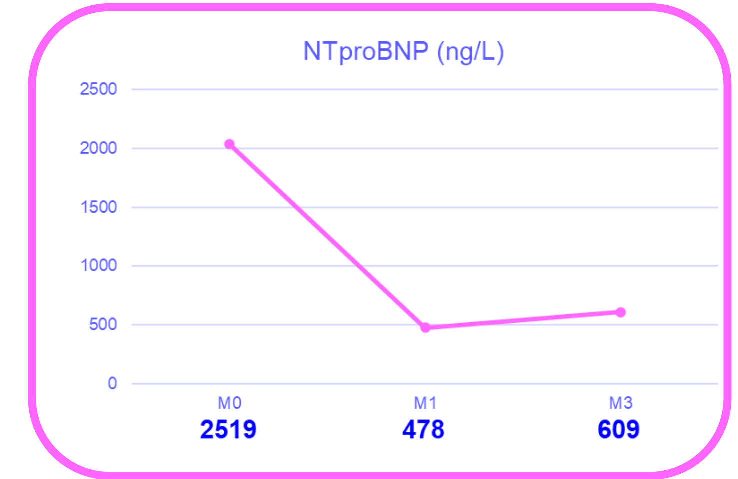
CCVG, chambre de chasse ventriculaire gauche; FEVG, fraction d'éjection ventriculaire gauche

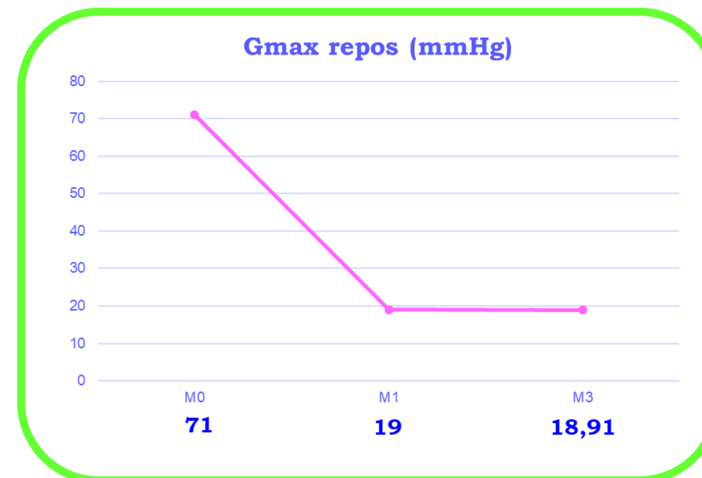
European Summary of Product Characteristics, CAMZYOS® (mavacamten), site EMA consulté le 07 juillet 2023: https://www.ema.europa.eu/en/documents/product-information/camzyos-epar-product-information_fr.pdf

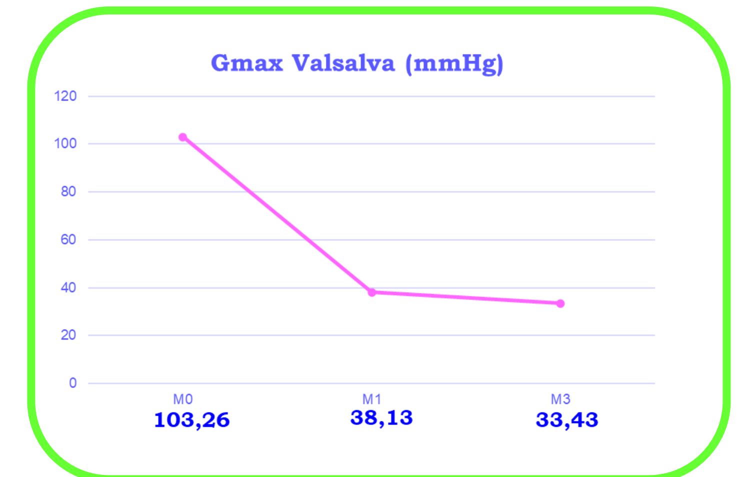
Mavacamten en pratique: expérience marseillaise

- ✓ 60 patients
- ✓ 62,09 ans
- ✓ 72% femmes
- ✓ 90,48% bétabloquants
- ✓ 9,52% anticalciques
- ✓ 13,64% DAI









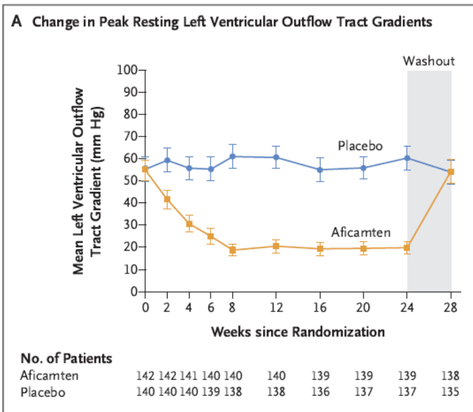
ORIGINAL ARTICLE

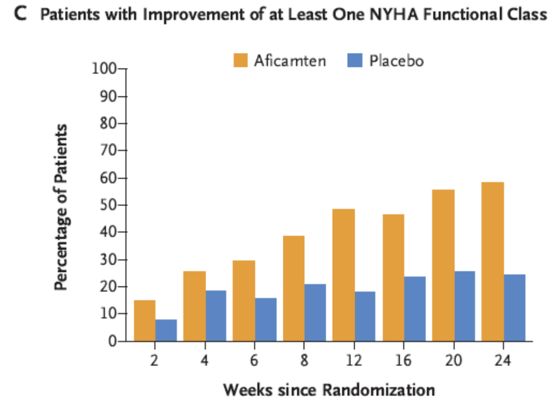
Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

SEQUOIA HCM

Maron MS, NEJM 2024

- ✓ 282 CMHo, 142 Aficamten vs 140 placebo
- ✓ FU 24 weeks
- ✓ Critère principal: change VO2 max à 24 semaines
- ✓ 10 critères secondaires





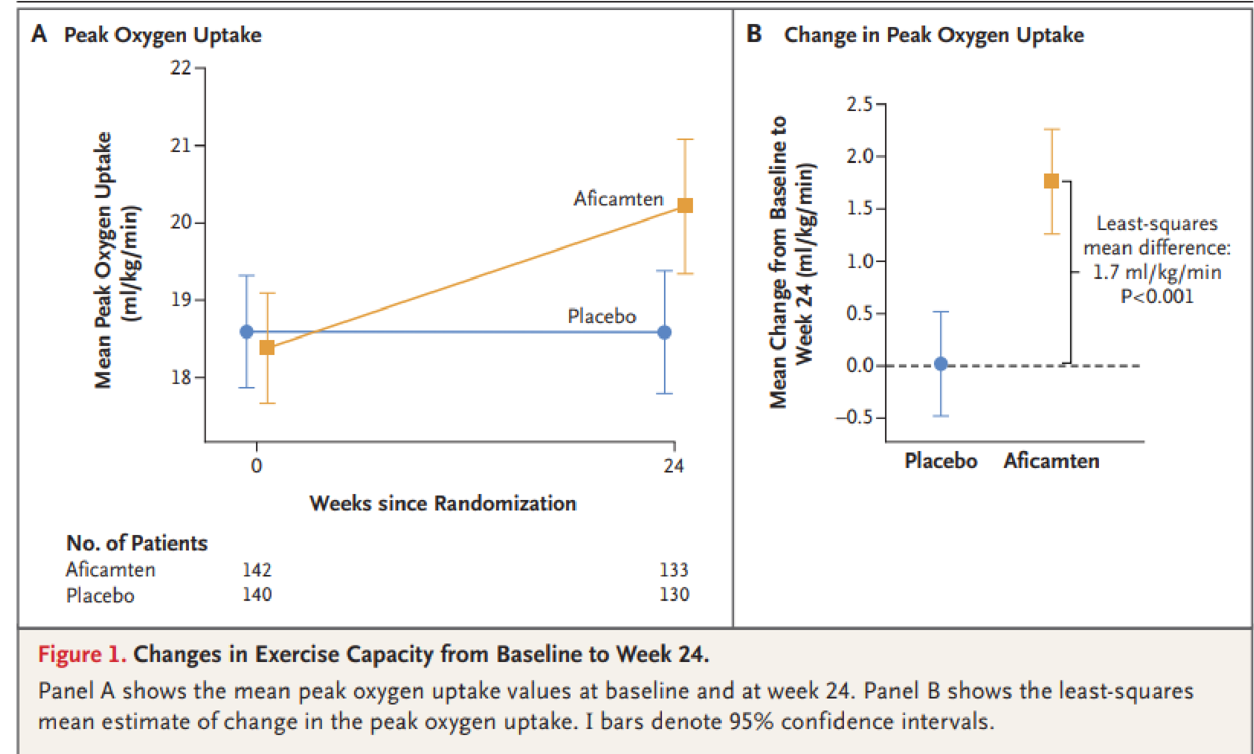


Figure 1. Changes in Exercise Capacity from Baseline to Week 24.
Panel A shows the mean peak oxygen uptake values at baseline and at week 24. Panel B shows the least-squares mean estimate of change in the peak oxygen uptake. I bars denote 95% confidence intervals.

Mavacamten

- First-in-class, selective inhibitor of cardiac myosin
- Reduces excessive actin-myosin cross-bridges, thus creating more favorable sarcomere function

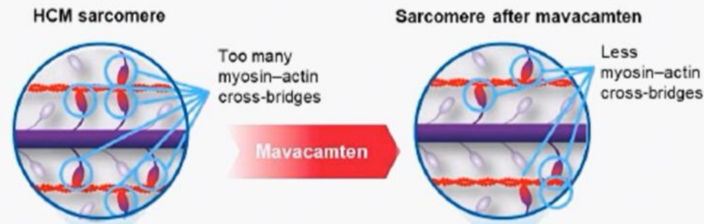


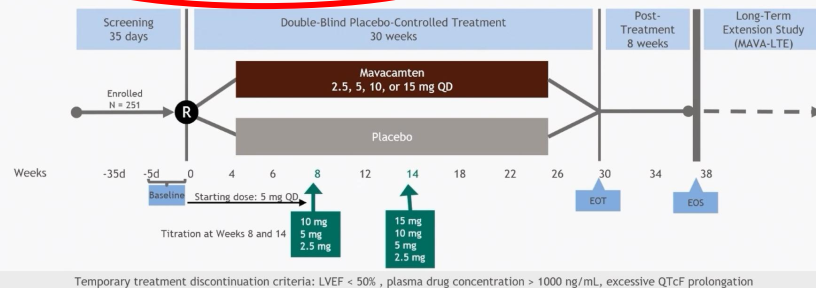
Figure 2: HCM sarcomere. Mavacamten reduces myosin-actin cross bridges.

A PHASE 3, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF CK-3773274 IN ADULTS WITH SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY AND LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Protocol Amendment 02 dated 10 December 2021

EXPLORER-HCM: study design[1,2]

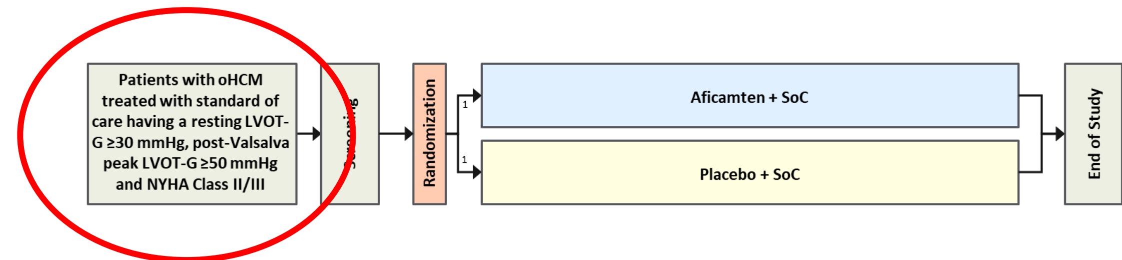
Patients with LVOT gradient ≥ 50 mm Hg and NYHA class II to III symptoms, LVEF ≥ 55%, were randomized 1:1 to receive once-daily oral mavacamten (starting dose of 5 mg with a 2-step dose titration) or placebo for 30 weeks



Temporary treatment discontinuation criteria: LVEF < 50% , plasma drug concentration > 1000 ng/mL, excessive QTcF prolongation

EOS, end of study; EOT, end of treatment; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; QD, once daily.

1. Ho CY et al. *Circ Heart Fail* 2020;13. doi: 10.1161/CIRCHEARTFAILURE.120.006853. 2. Olivotto I et al. *Lancet* 2020;396:759–769. 3. Olivotto I, et al. Oral presentation at ESC Congress 2020 – The Digital Experience; August 29–September 1, 2020.

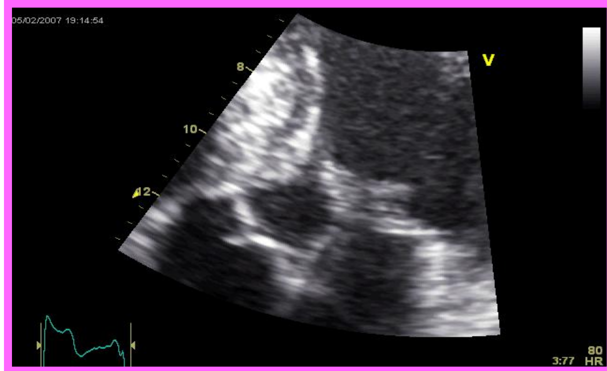


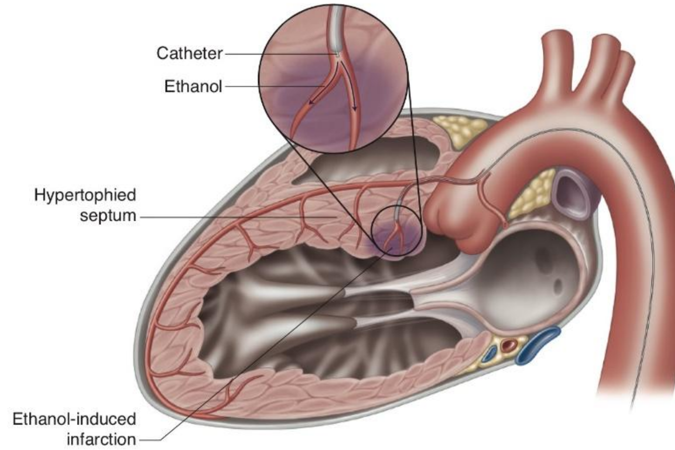
Study Visits	Screen	D1	W2	W4	W6	W8	W12	W16	W20	W24	W28
Echocardiogram	↑	↑	↑*	↑*	↑*	↑*	↑	↑	↑	↑	↑
CPET	↑									↑	
KCCQ		↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
NYHA	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Dose Titration			↑	↑	↑						

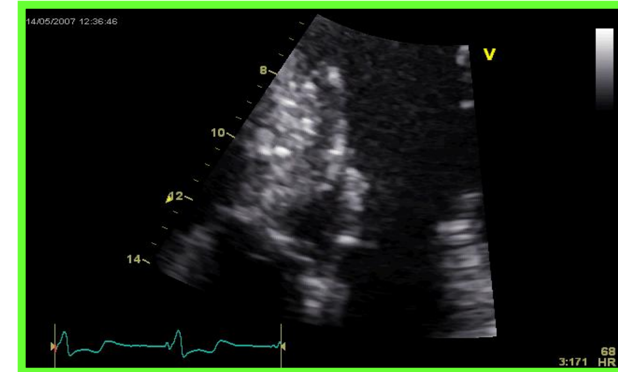
* Focused echocardiogram

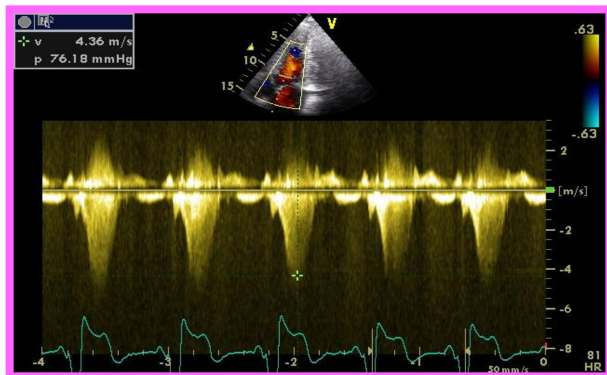
données non enregistrées

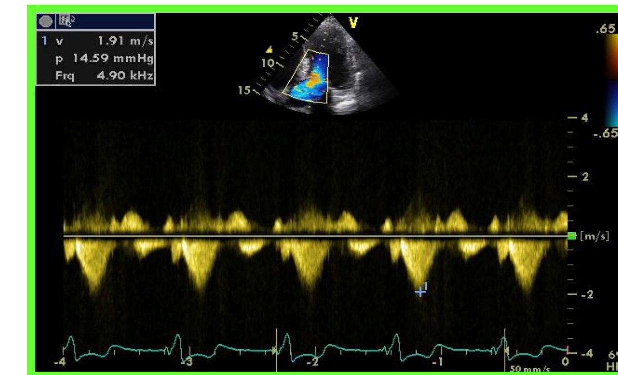
Alcoolisation septale







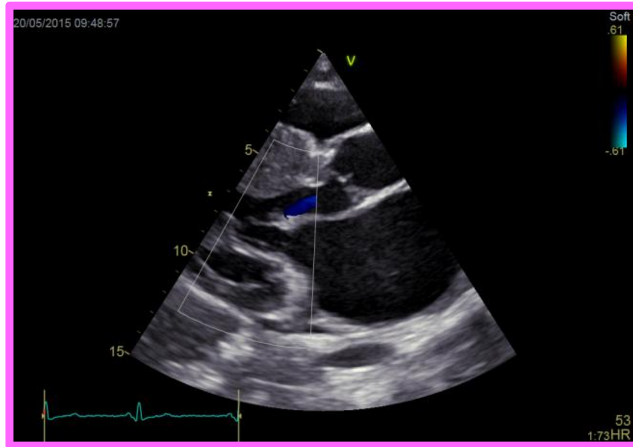


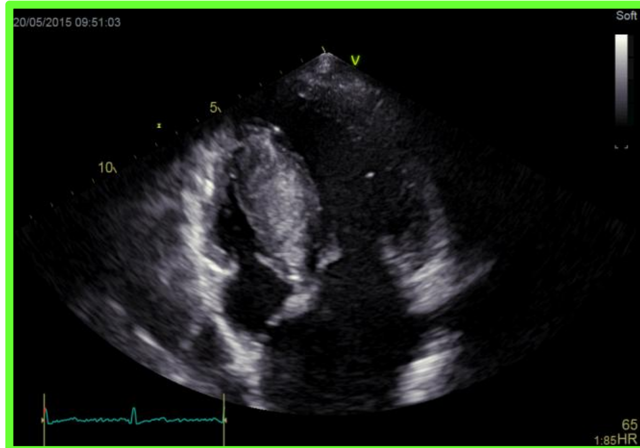


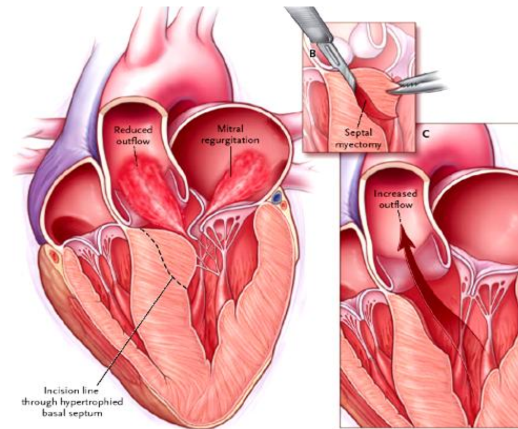
Avant alcoolisation septale

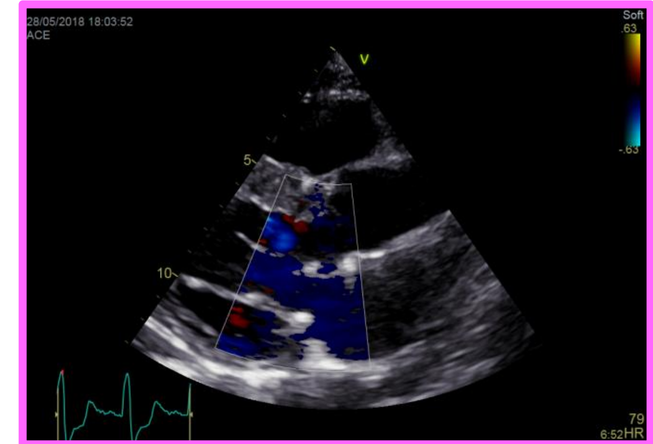
Après alcoolisation septale

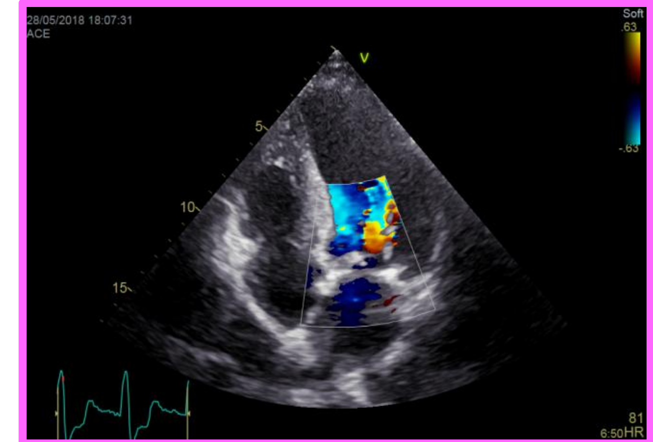
Myomectomie







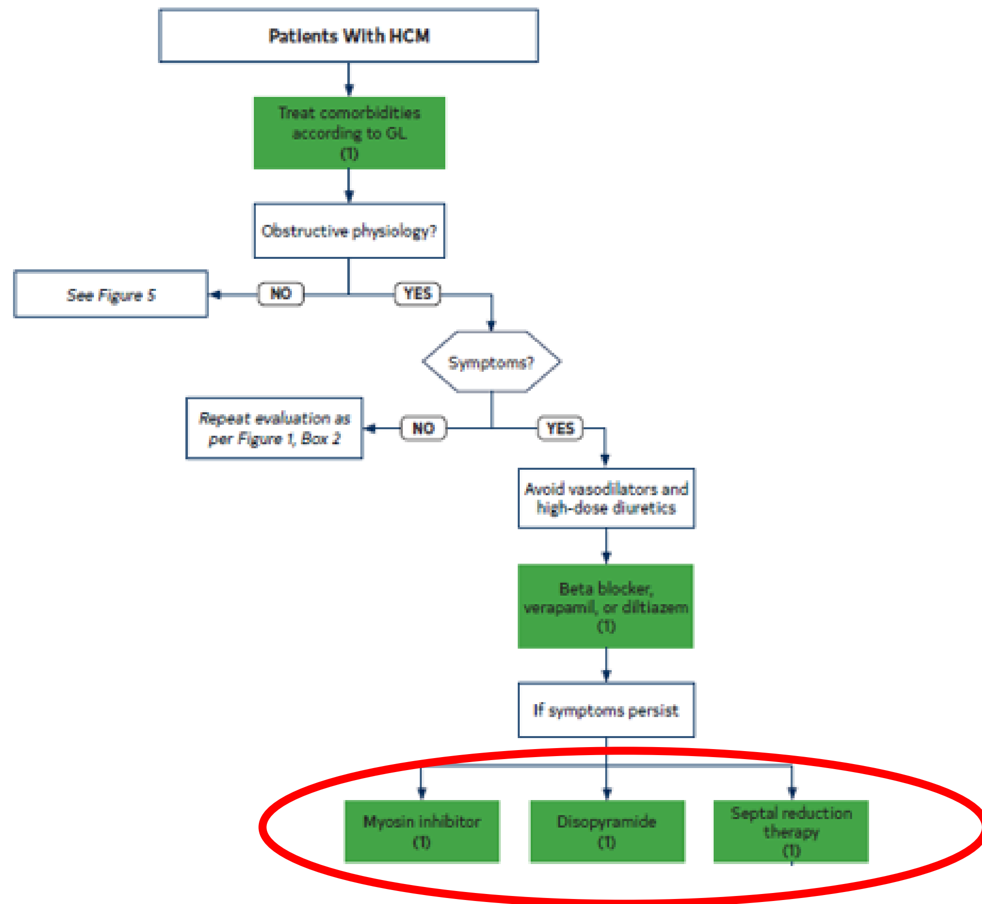


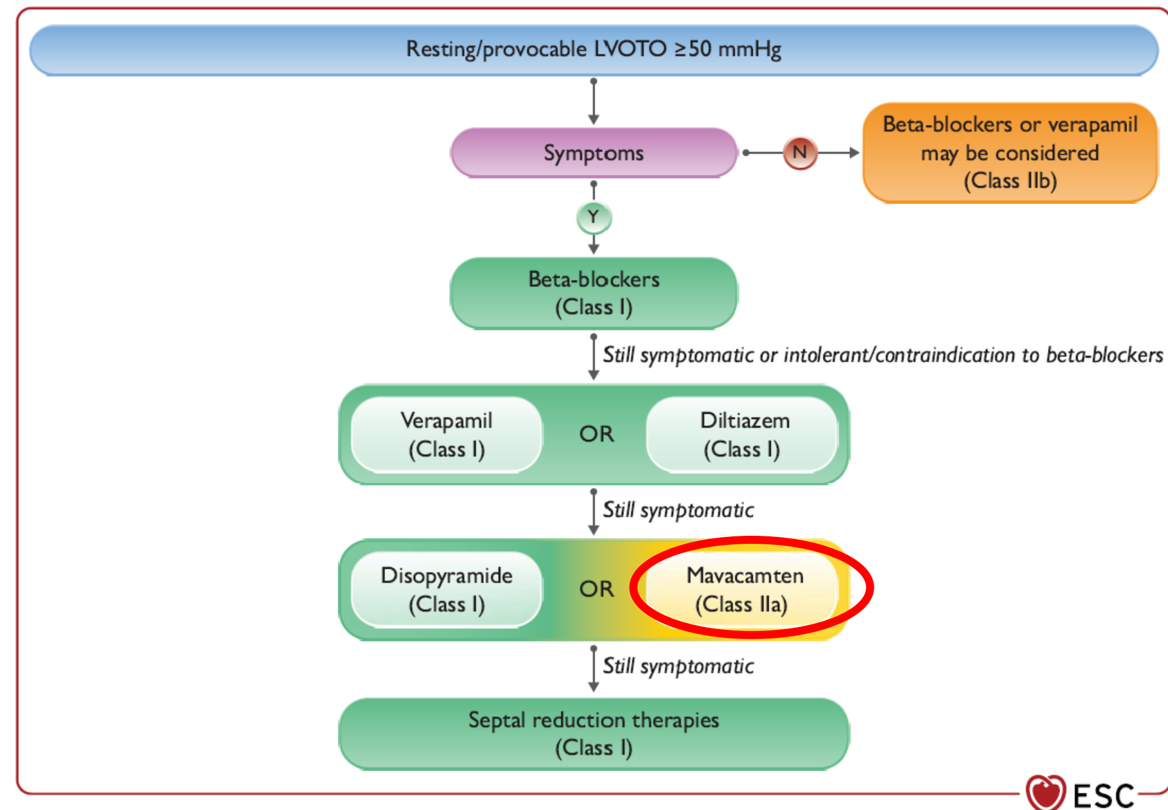


Pré-opératoire

Post-opératoire

Quel traitement pour quel patient ?

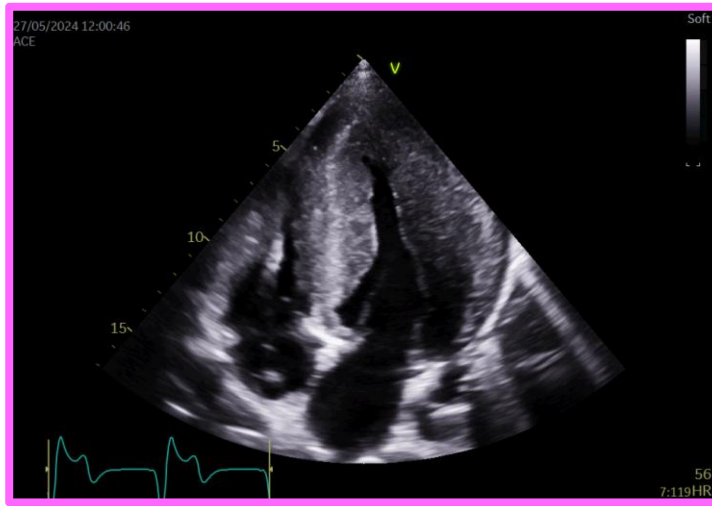


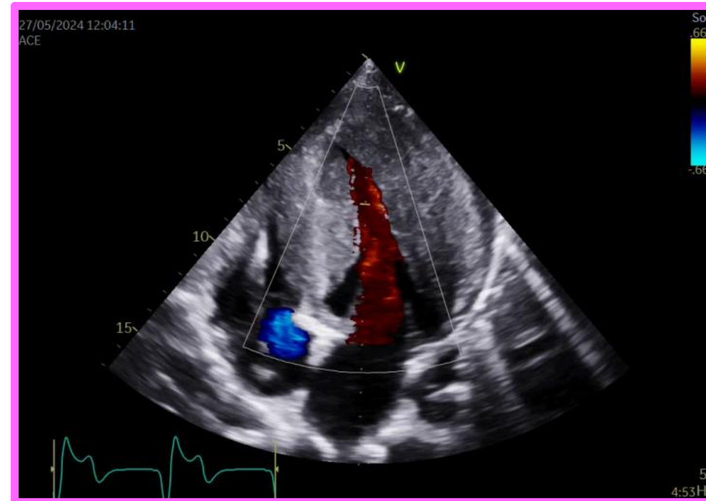


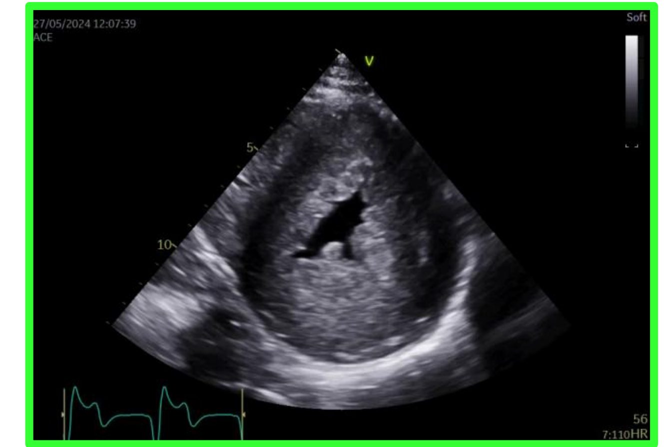
ACC/AHA 2024

CM – ESC Guidelines 2023

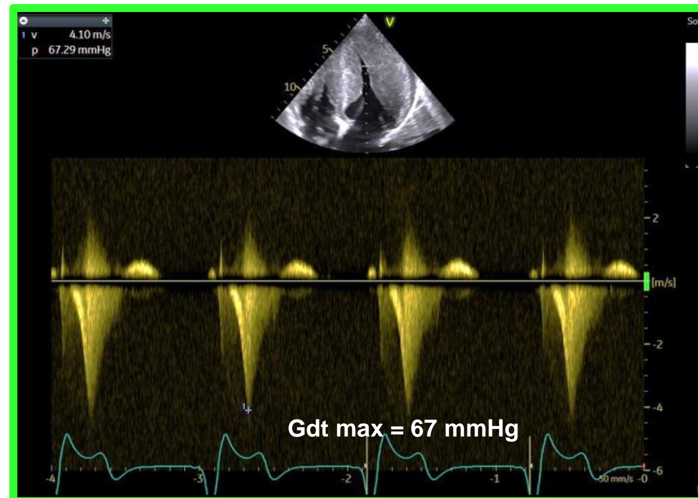
CMH extrême – greffe cardiaque

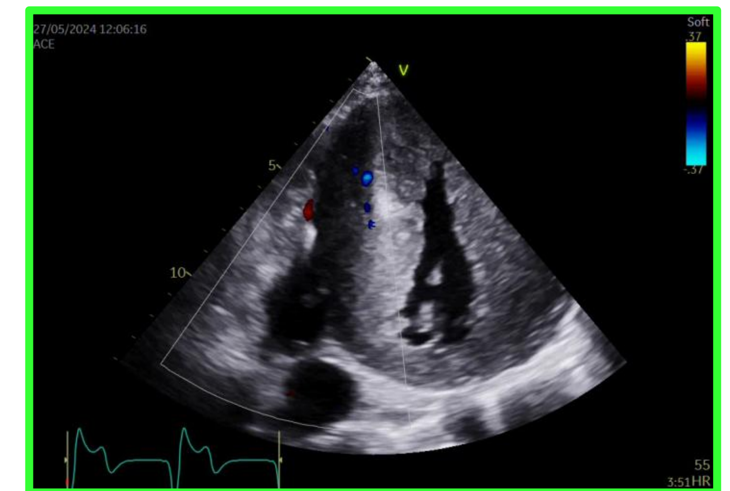






- Patiente de 20 ans
- CMO de l'enfance mutation PRKAG2
- Insuffisance cardiaque sévère
- Greffe cardiaque 2024

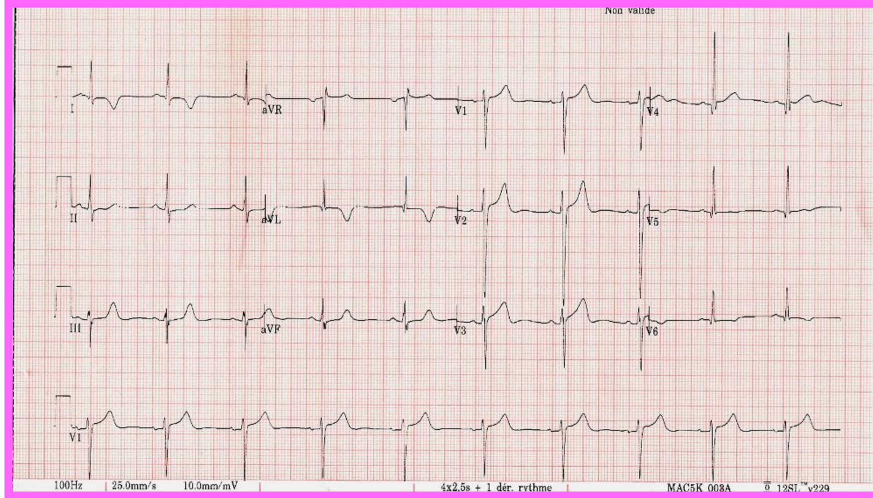


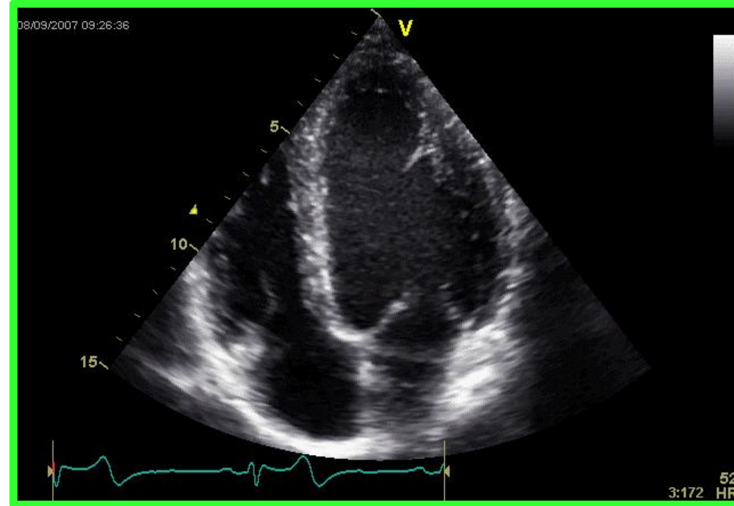


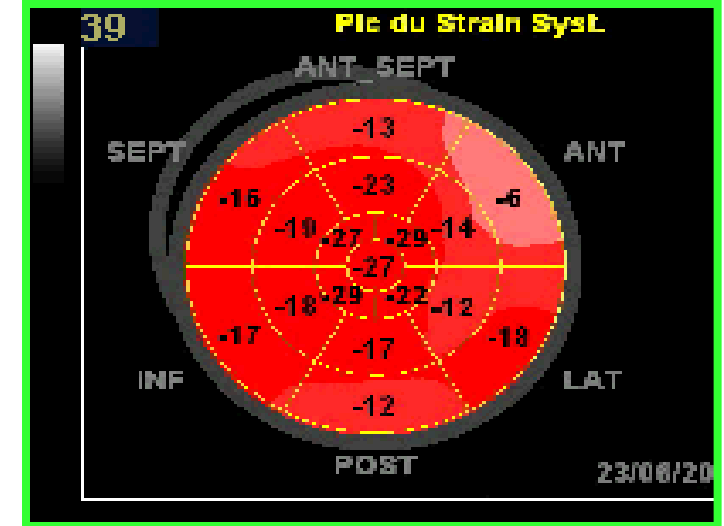
Conclusions: Prise en charge de la CMO en 2025

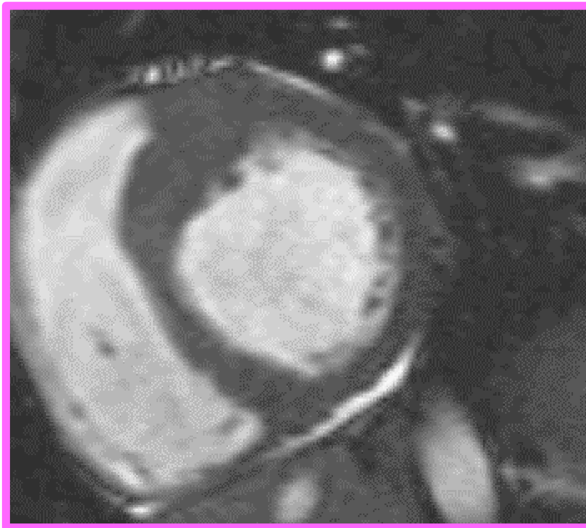
1. Importance de documenter la cause des symptômes
2. Rechercher l'obstruction par l'échocardiographie avec manœuvre de Valsalva et effort
3. Le traitement conventionnel utilise les bétabloquants/ les anticalciques / le disopyramide
4. Les inhibiteurs de la myosine sont indiqués chez les patients qui restent symptomatiques et obstructifs
5. Le Mavacamten démontre une amélioration spectaculaire des symptomes et de l'obstruction
6. Leur role dans les CMH non obstructives est en cours d'étude
7. Leur role dans la prevention de la mort subite reste à démontrer
8. D'autres voies de recherche sont ouvertes !! (Gliflozines, mitotropes, thérapie génique)

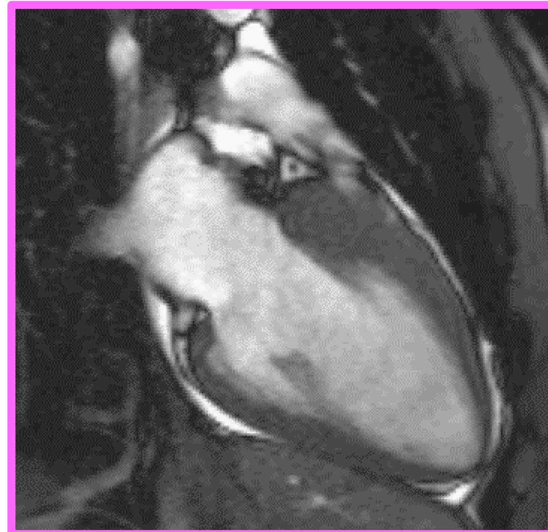
Un joueur du centre de formation de l'OM

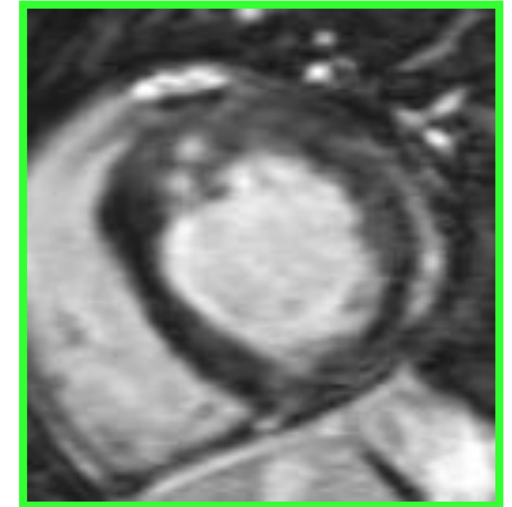












Centre de Référence
Constitutif des
Cardiomyopathies

Aix*Marseille université

FACULTÉ DE MÉDECINE DE MARSEILLE

La Timone Hospital; Marseille, France

Etudes futures ou en cours

1. Études sur les CMH obstructives

- ✓ MAPLE-HCM - Phase 3, Randomized, Double-Blind Trial and Safety of Aficamten vs Metoprolol in oHCM
- ✓ SONATA-HCM: LEXICON: Phase 3, Randomized, Double-blind, Multicenter Study of Sotagliflozin in oHCM or n-oHCM

2. Etudes sur les CMH non obstructives

- ✓ REDWOOD-HCM: Phase 2,Randomized, Double-Blind Trial and Safety of Aficamten vs placebo in n-oHCM
- ✓ ACACIA -HCM - Phase 3,Randomized, Double-Blind Trial and Safety of Aficamten vs placebo in n-oHCM
- ✓ MAVERICK-HCM: Phase 2,Randomized, Double-Blind Trial and Safety of Mavacamten vs placebo in n-oHCM
- ✓ ODYSSEY-HCM: Phase 3,Randomized, Double-Blind Trial and Safety of Mavacamten vs placebo in n-oHCM
- ✓ Ninerafaxstat: phase 2 randomized, cardiac mitotrope
- ✓ Thérapie génique 1st case of gene therapy in sarcomeric HCM (phase 1b, Cleveland 2023)

Amélioration de la fonction diastolique sous Mavacamten

Graphical Abstract

Main objective :

Evaluate the effect of Mavacamten on diastolic function after titration in patients with obstructive HCM.

Methodology:

Single-center prospective observational study including :

55 patients
Mean age 67.5 [11.99] years
22 men [40%]

Mean titration duration :
5.11 months

Median dose :
5 mg daily

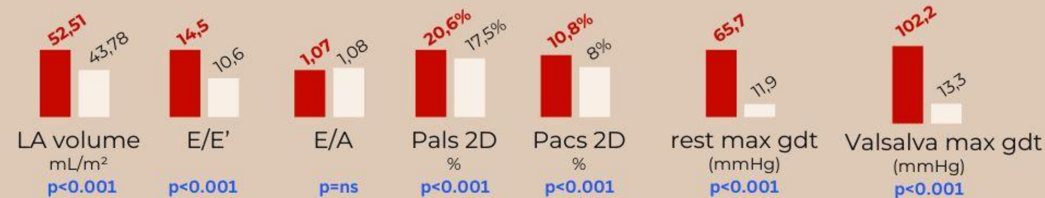
Patient titration endpoint criteria:

- Left ventricular **outflow tract obstruction <30 mmHg**
- Left ventricular ejection fraction **(LVEF) ≥55%**

Parameters evaluated :

Diastolic function markers :
Left atrial volume, E/E', E/A, Pals 2D, Pacs 2D,
Other parameters:
Max gradient (rest and Valsalva), LVEF, LV global Strain, NYHA, Nt-proBNP.

Main results :



Other parameters

LVEF :	LV global Strain :	NYHA :	NT-proBNP :
69% → 66% (p<0.001)	-14.56% → -14.89% (p=ns)	2.53 → 1.44 (p<0.001)	2276.8 pg/mL → 395.3 pg/mL (p<0.001)

Conclusion :

Mavacamten significantly improves **diastolic function** in patients with **obstructive HCM**, as evidenced by the **decrease in left atrial volume and improvement in the E/E' ratio**. However, the observed reduction in **PALS and PACS** post-treatment suggests **persistent left atrial stiffness despite reduced volume overload.**

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DE MARSEILLE

VALOR-HCM (Mavacamten)

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

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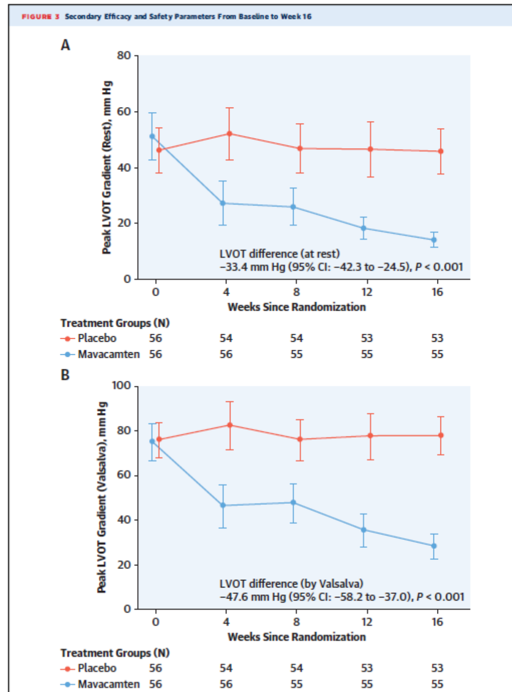
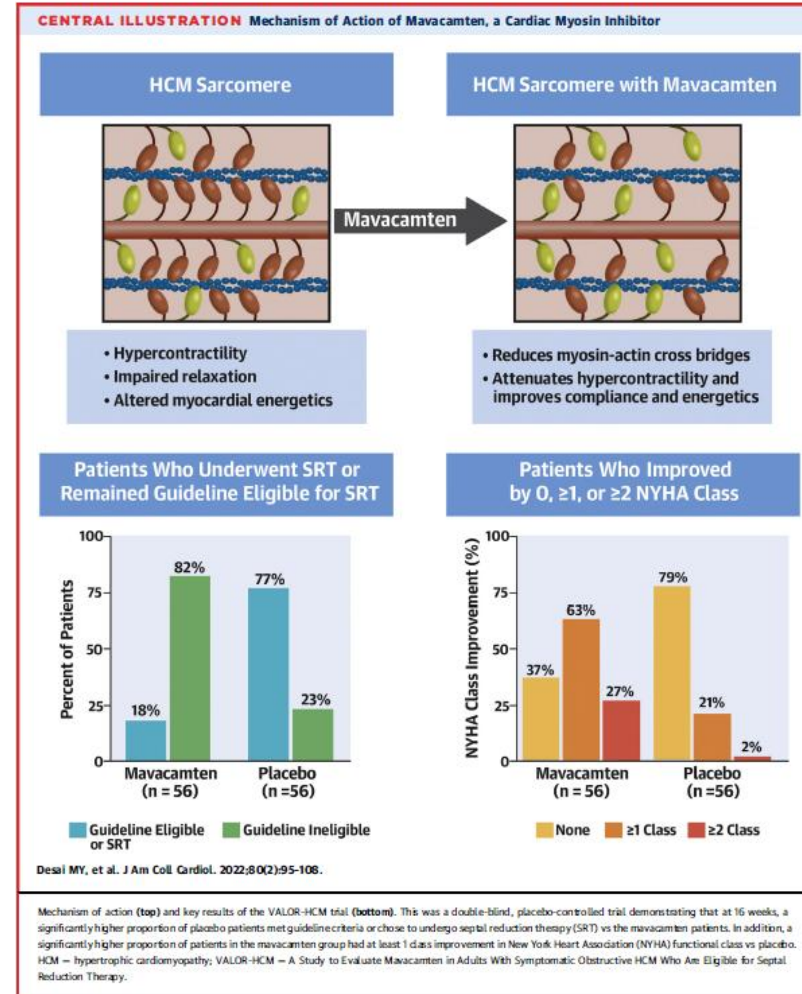


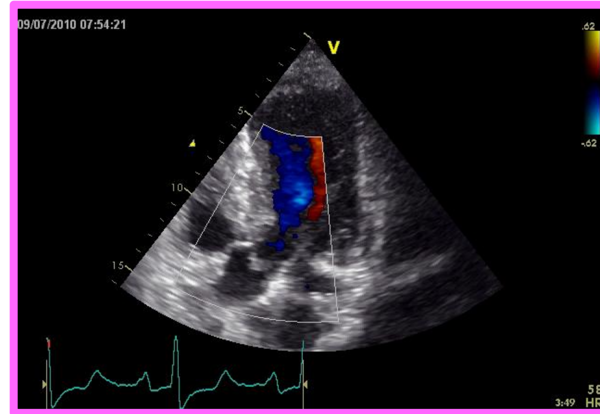


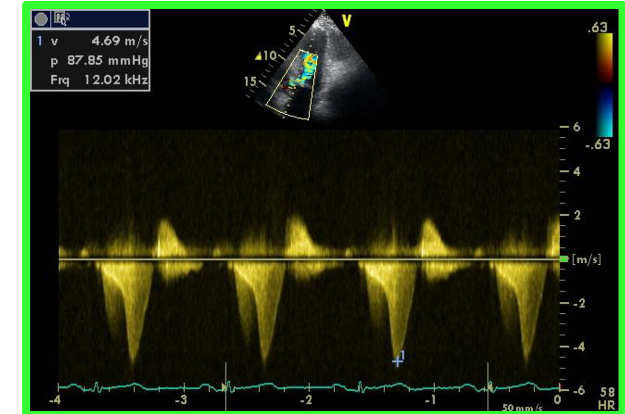
Mechanism of action **(top)** and key results of the VALOR-HCM trial **(bottom)**. This was a double-blind, placebo-controlled trial demonstrating that at 16 weeks, a significantly higher proportion of placebo patients met guideline criteria or chose to undergo septal reduction therapy (SRT) vs the mavacamten patients. In addition, a significantly higher proportion of patients in the mavacamten group had at least 1 class improvement in New York Heart Association (NYHA) functional class vs placebo. HCM = hypertrophic cardiomyopathy; VALOR-HCM = A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy.

L'insuffisance cardiaque dans les CMH

- **Obstruction symptomatique – FEVG normale**

  - ✓ *obstruction sous-aortique*
  - ✓ *dysfonction diastolique*
  - ✓ *insuffisance mitrale*





- **CMH évoluée « restrictive »**

  - ✓ *Fibrose myocardique*
  - ✓ *Régression de l'hypertrophie*
  - ✓ *Régression de l'obstruction*
  - ✓ *Diminution de la FEVG*
  - ✓ *Dilatation OG*
  - ✓ *Profil restrictif et HTAP*
  - ✓ *Elévation du BNP / NT-proBNP*