Cardiac Myosin Inhibitors:
Current Role and Future Perspectives

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& Careggi University Hospital

University of Florence, Italy

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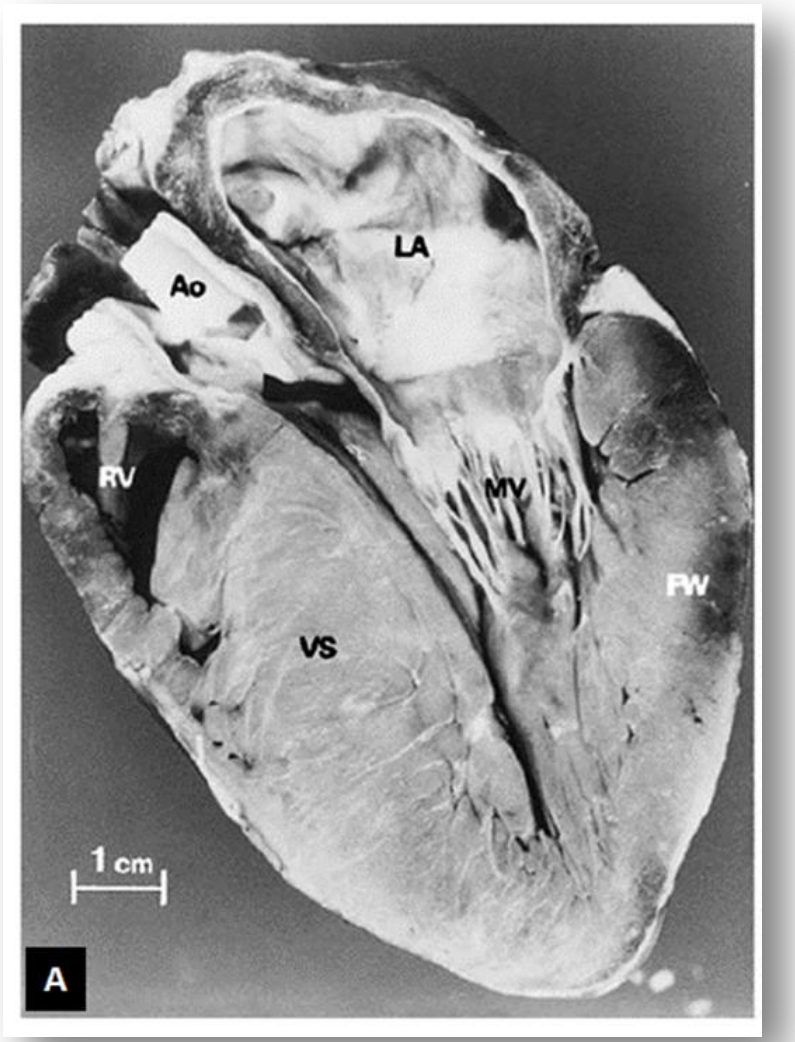
Teare D. Asymmetrical hypertrophy of the heart in young adults. *Brit. Heart J.* 20:1-8, 1958.

[Department of Pathology, St. George's Hospital Medical School, London, England]



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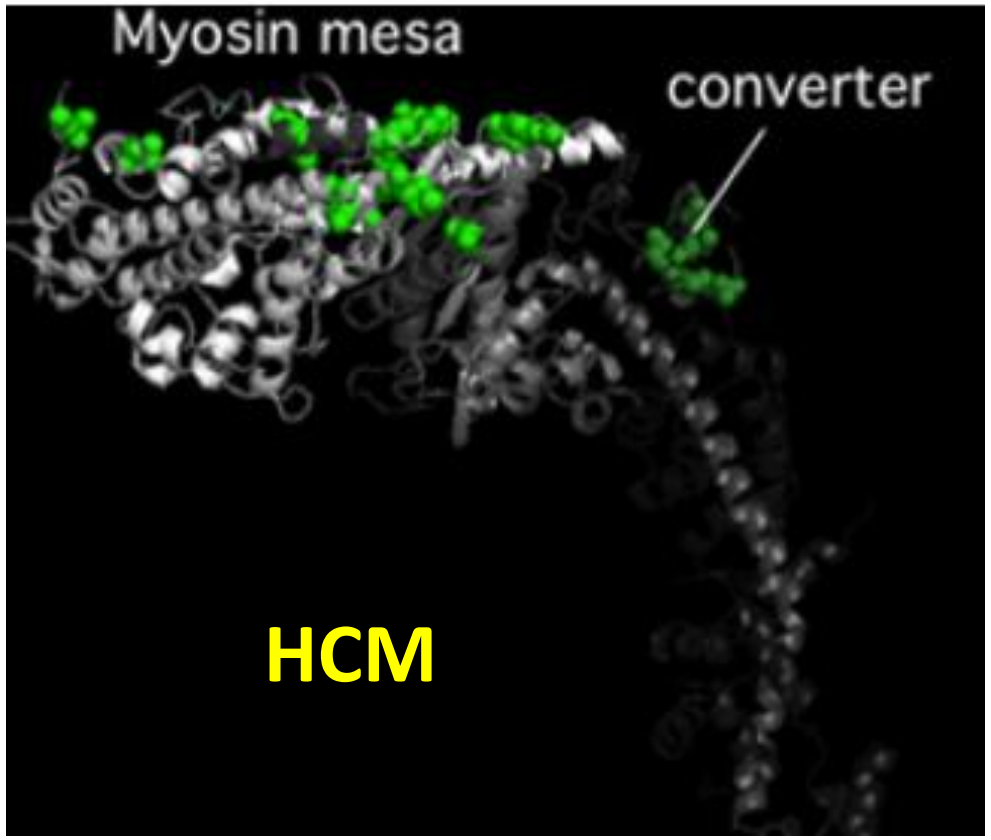
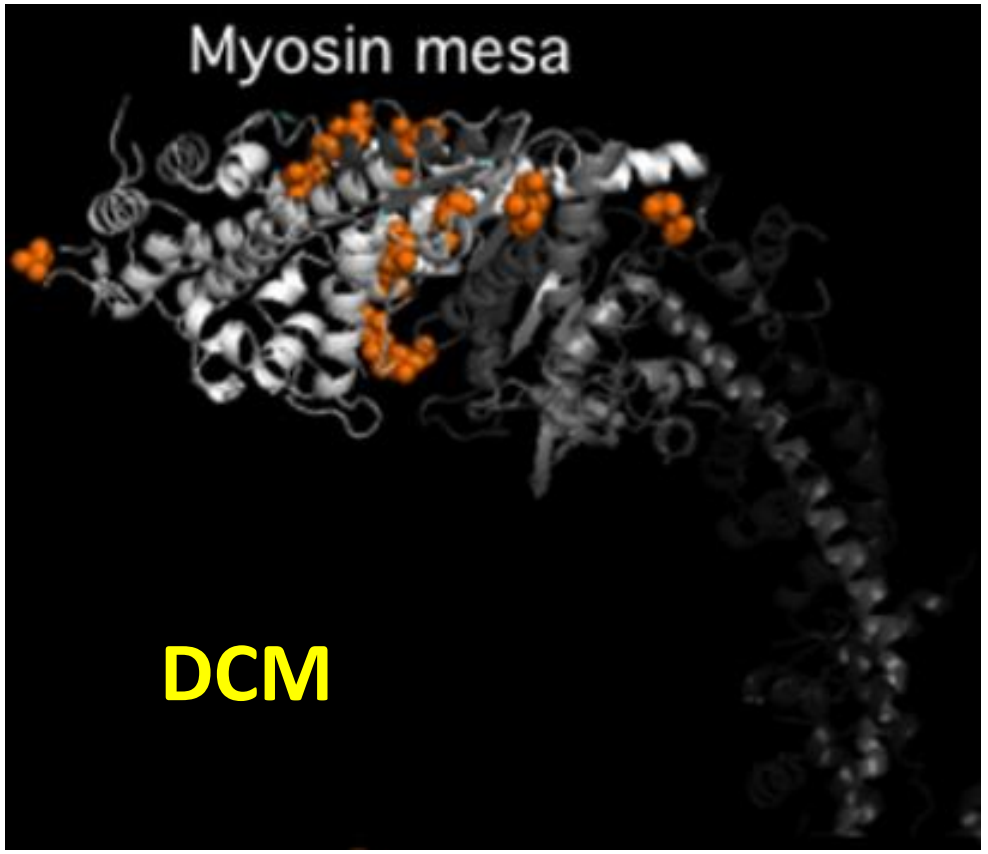
Biochemical Society Transactions (2015) Volume 43, part 1

The myosin mesa and a possible unifying hypothesis for the molecular basis of human hypertrophic cardiomyopathy

James A. Spudich[*1]
*Department of Biochemistry, Stanford University School of Medicine, Stanford, CA 94305, U.S.A.

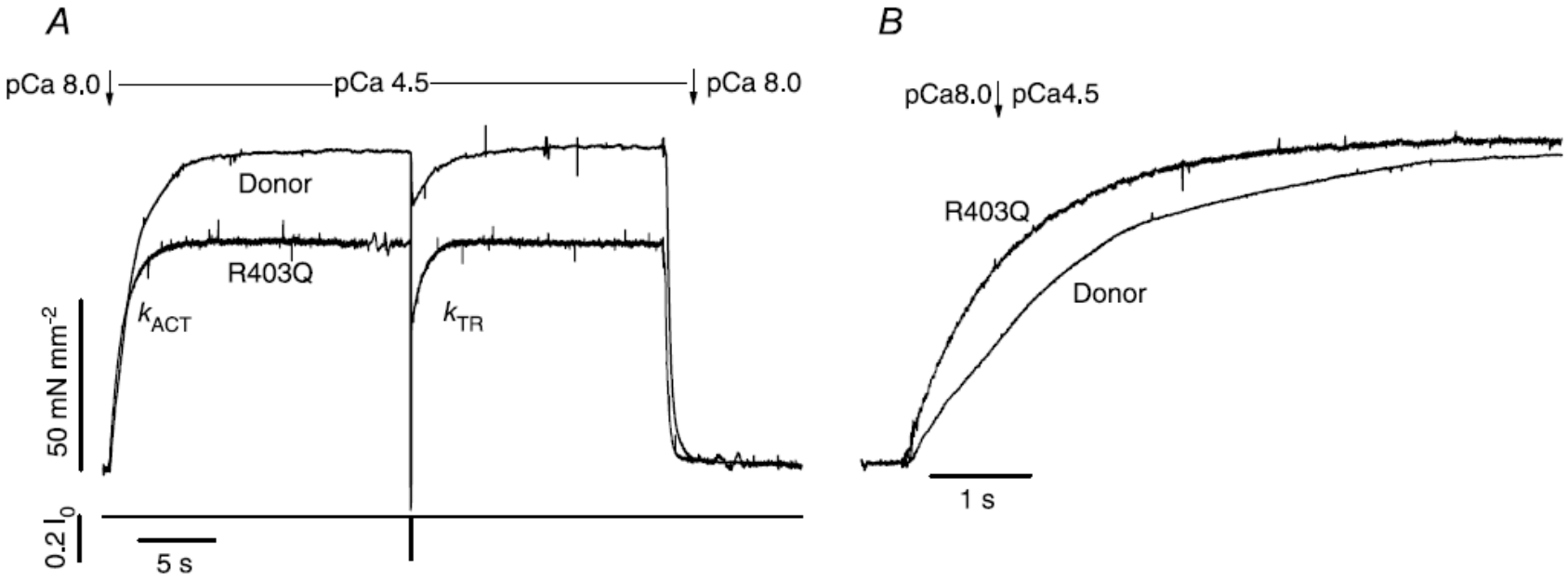




The familial hypertrophic cardiomyopathy-associated myosin mutation R403Q accelerates tension generation and relaxation of human cardiac myofibrils

Alexandra Belus[1,2], Nicoletta Piroddi[1,2], Beatrice Scellini[1,2], Chiara Tesi[1,2], Giulia D, Amati[3], Francesca Girolami[4], Magdi Yacoub[5,6], Franco Cecchi[5,6], Iacopo Olivotto[6] and Corrado Poggesi[1,2]

J Physiol 586.15 (2008) pp 3639–3644



. The results show that the R403Q mutation leads to an apparent gain of protein function but a greater energetic cost of tension generation. Increased energy cost of tension generation may be central to the FHC disease process, help explain some unresolved clinical observations, and carry significant therapeutic implications.

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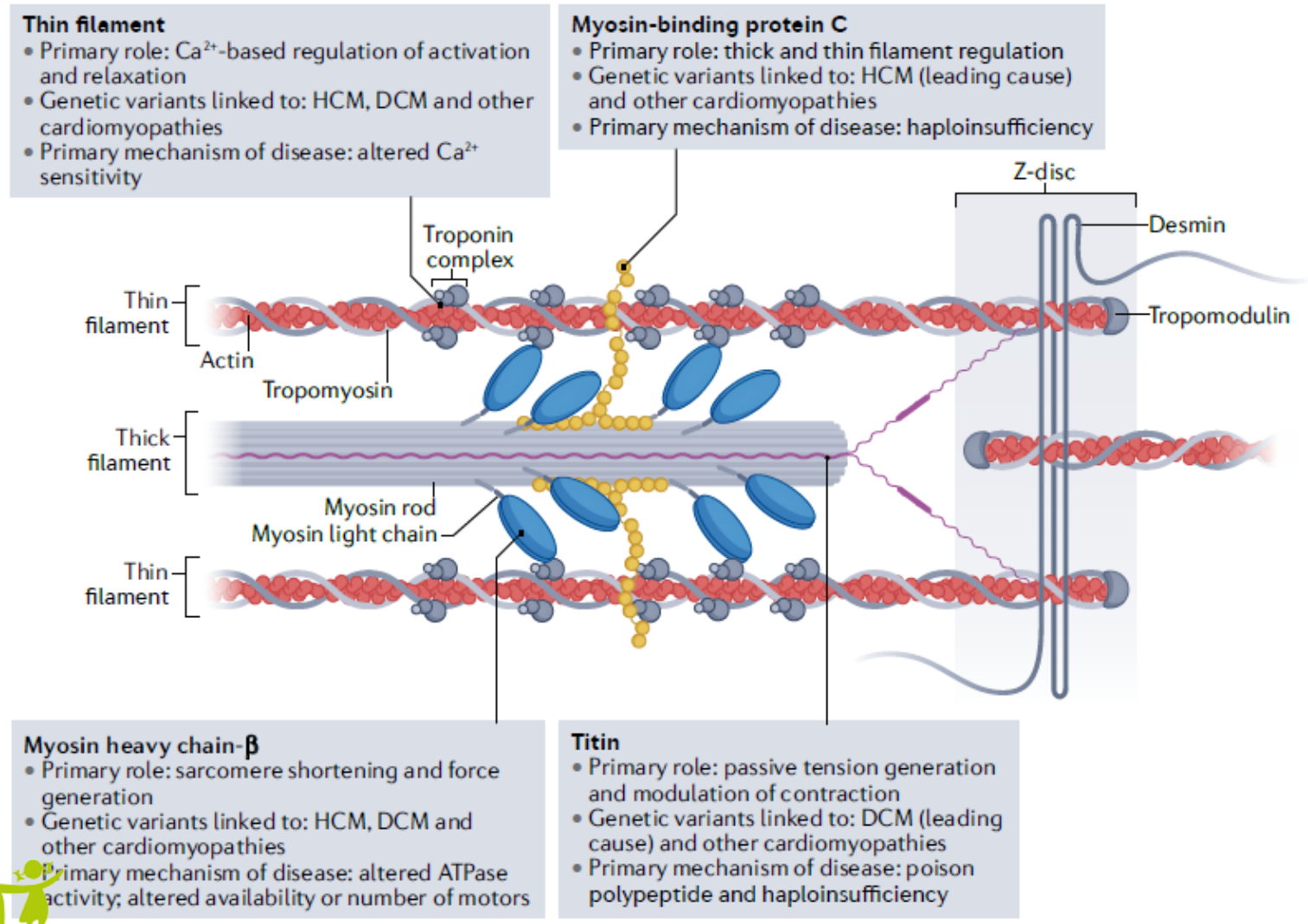
The Cardiac Sarcomere and its Components



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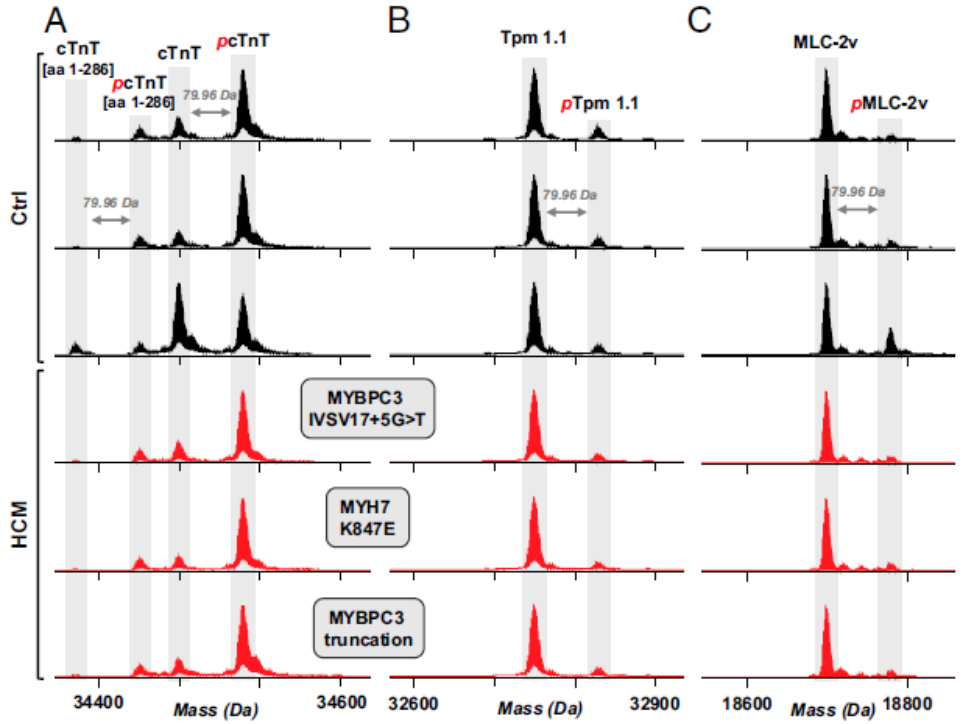
Lehman, Crocini and Leinwand, Nat Cardiol Rev 2022

Distinct hypertrophic cardiomyopathy genotypes result in convergent sarcomeric proteoform profiles revealed by top-down proteomics

PNAS | October 6, 2020 | vol. 117 | no. 40 | 24691–24700

This study suggests that the manifestations of severe HCM coalesces at the proteoform level despite distinct genotype, which underscores the importance of molecular characterization of HCM phenotype and presents an opportunity to identify broad-spectrum treatments to mitigate the most severe manifestations of this genetically heterogenous disease



Altered phosphorylation of cTnT, Tpm1.1, and MLC-2v. Representative deconvoluted mass spectra from donor hearts (black) and HCM tissues (red) for (A) cTnT, (B) Tpm1.1, and (C) MLC-2v.

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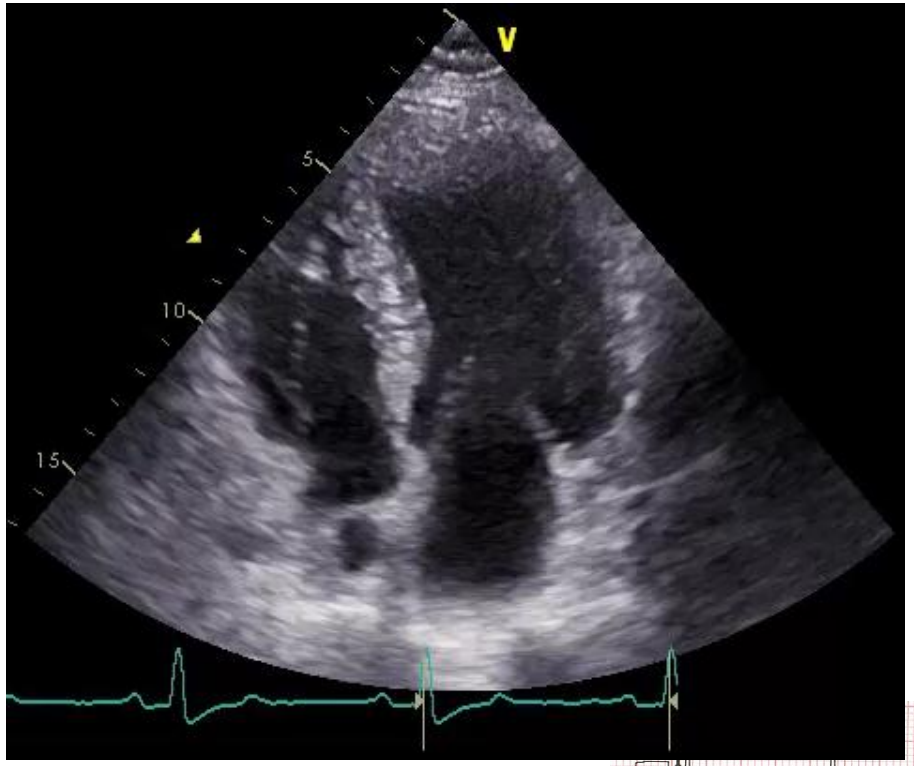

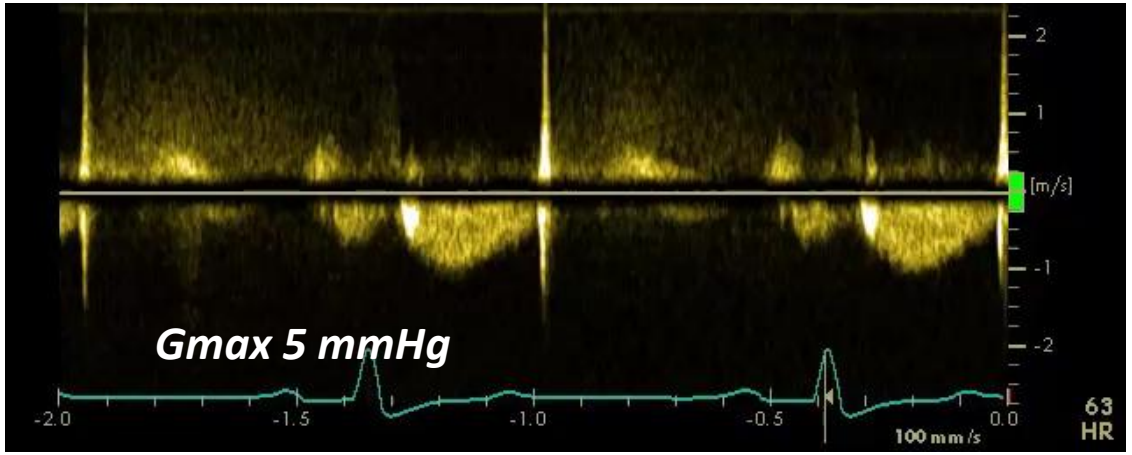

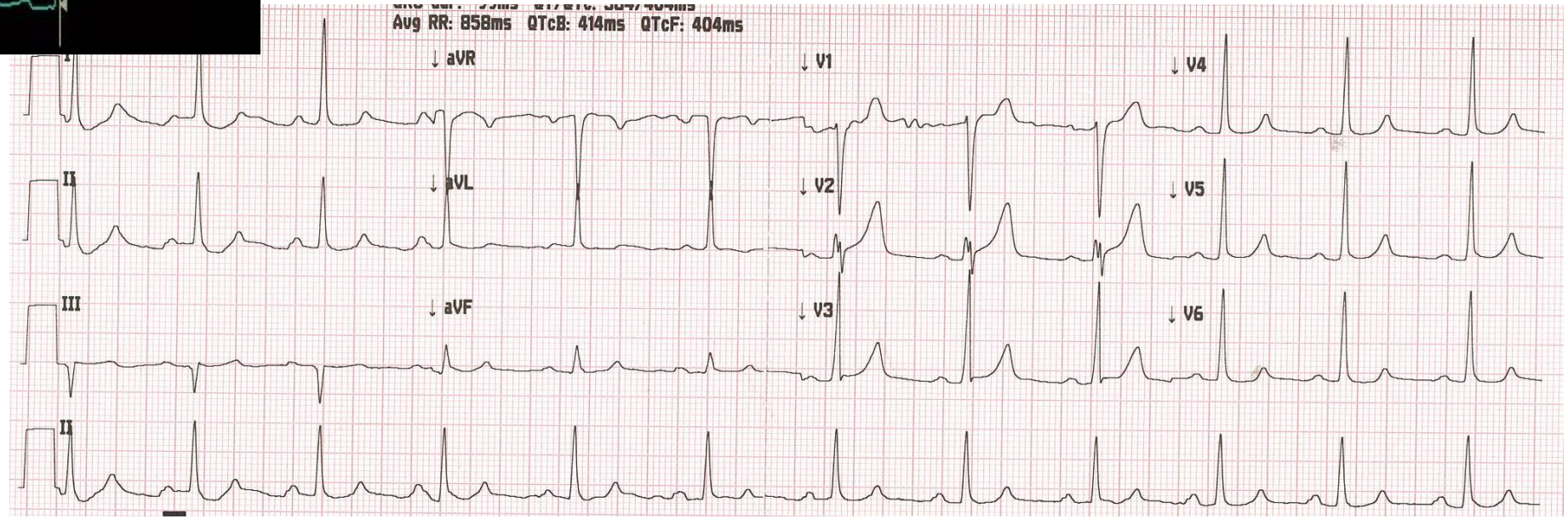

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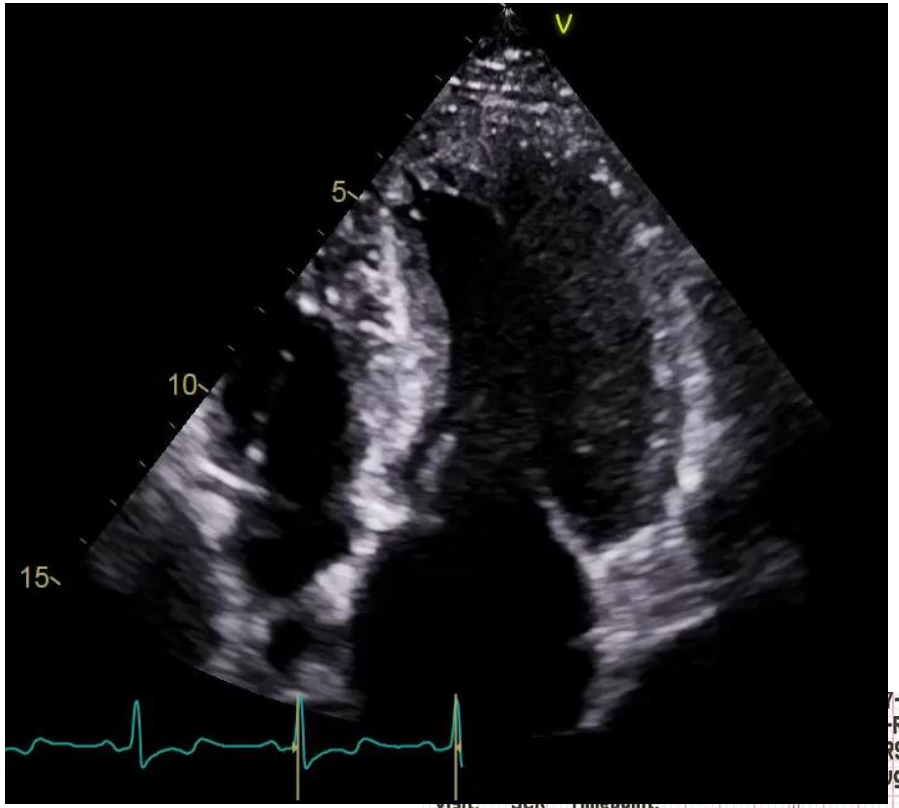

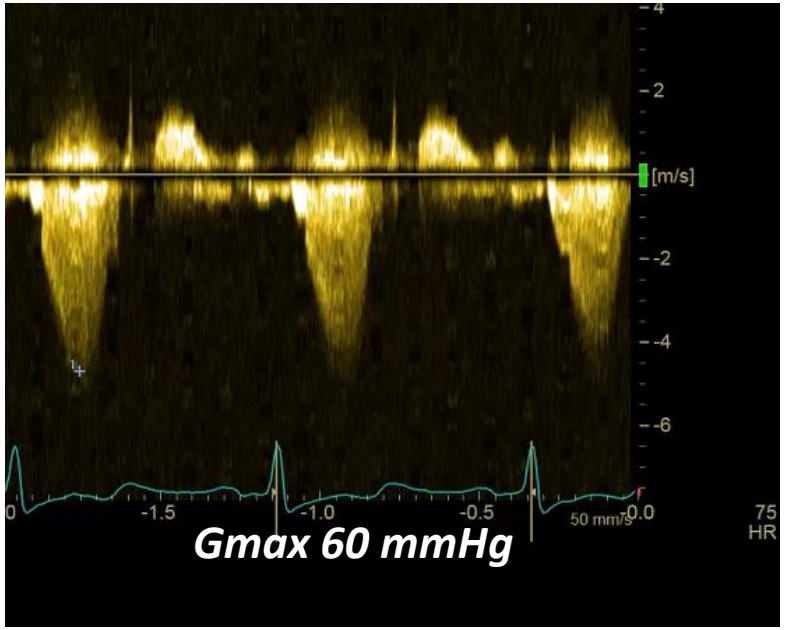

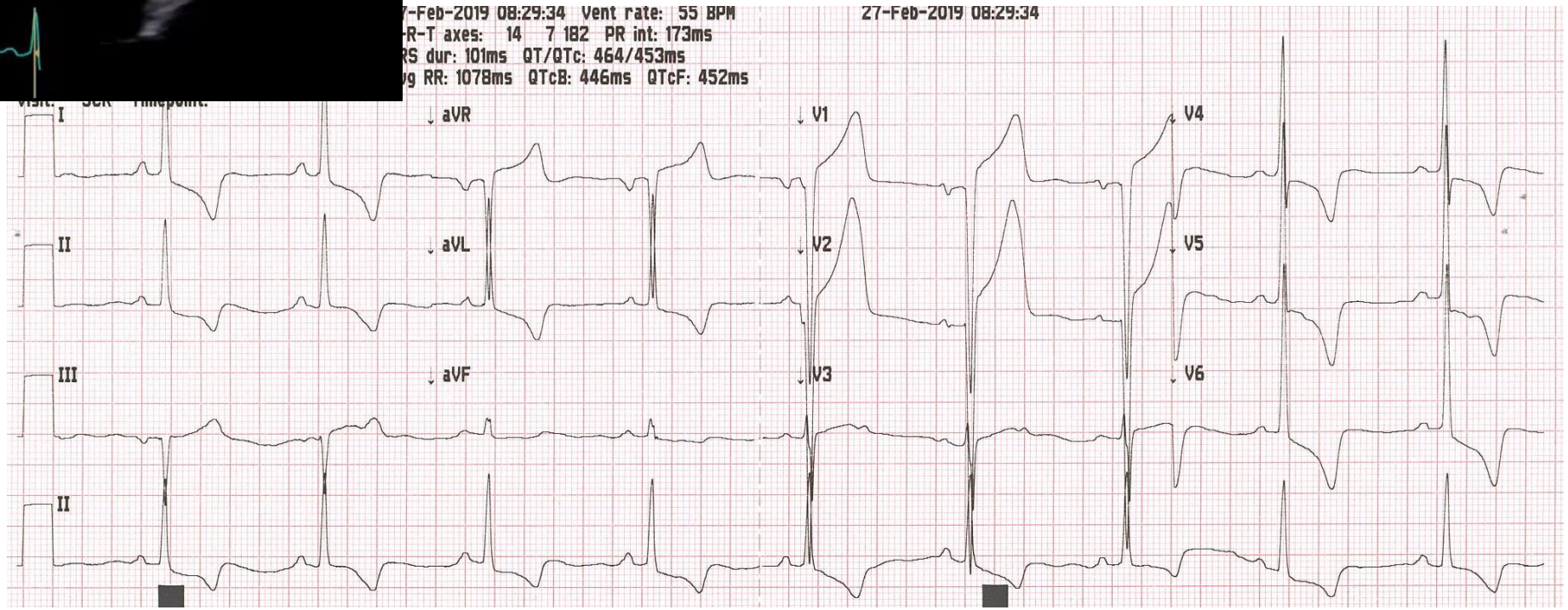

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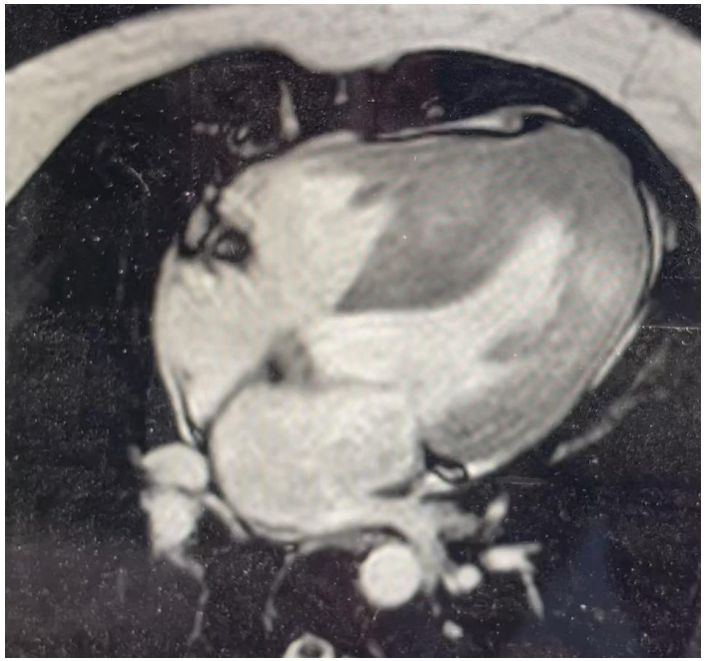
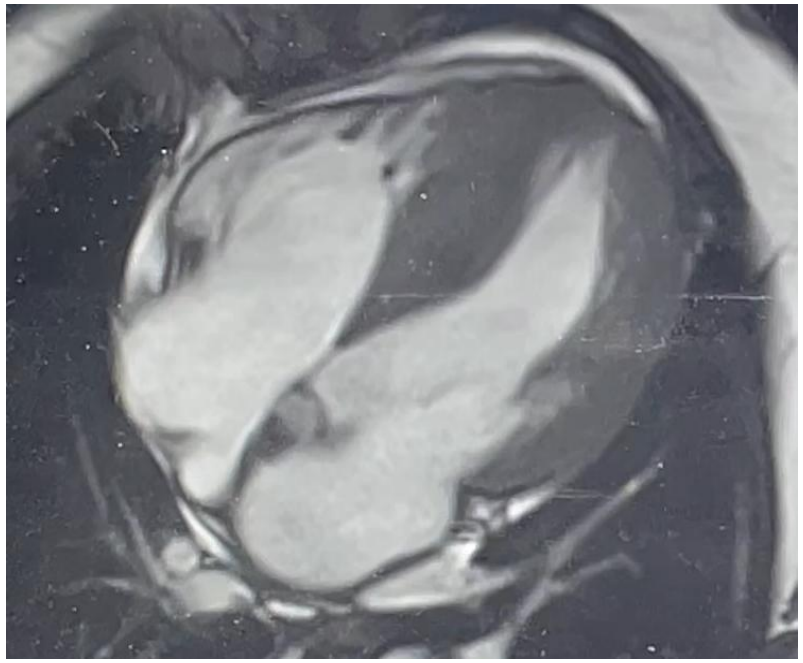
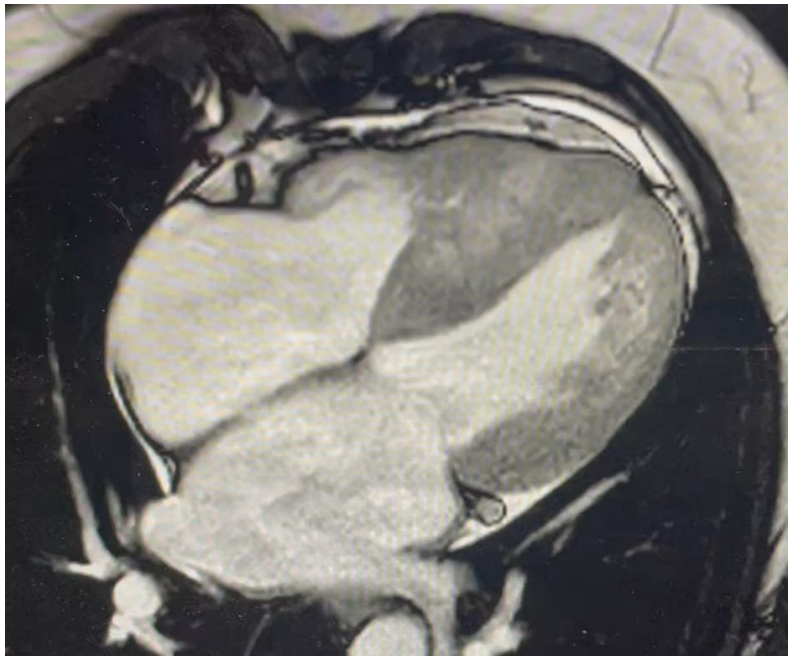
2014



2017



2022



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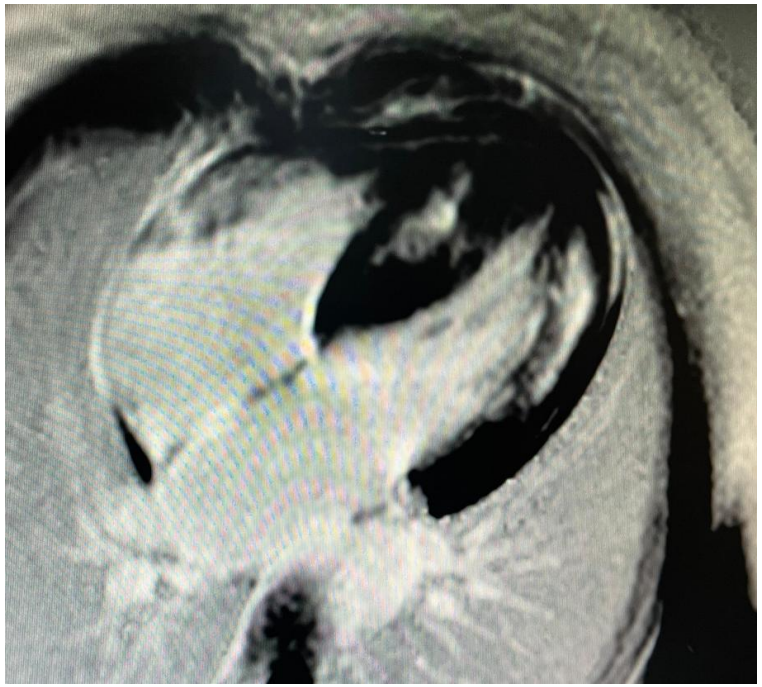
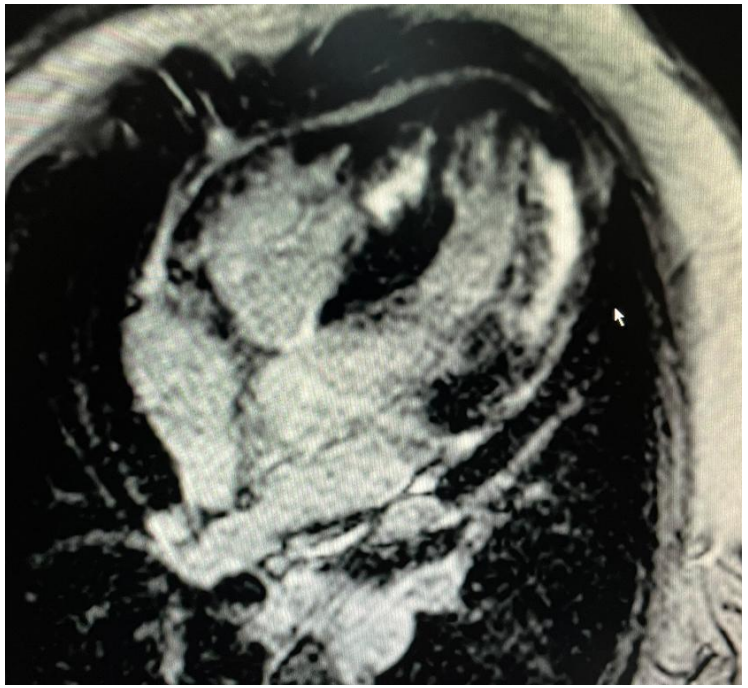
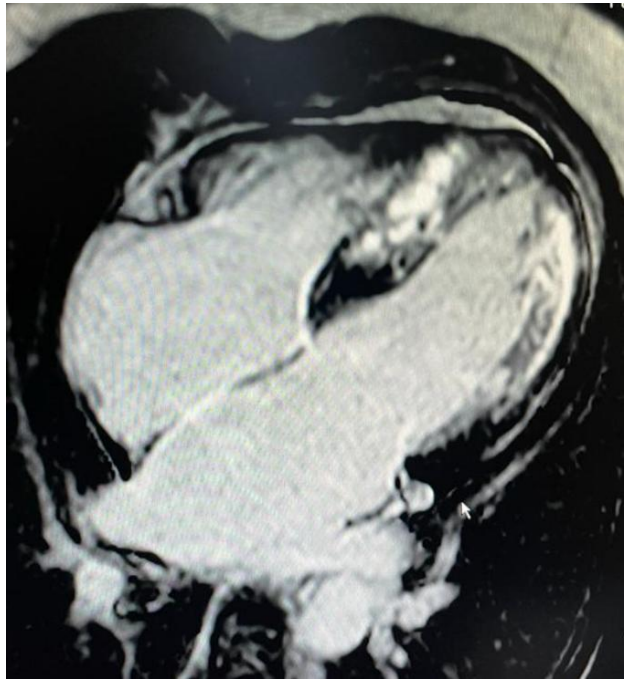
2014

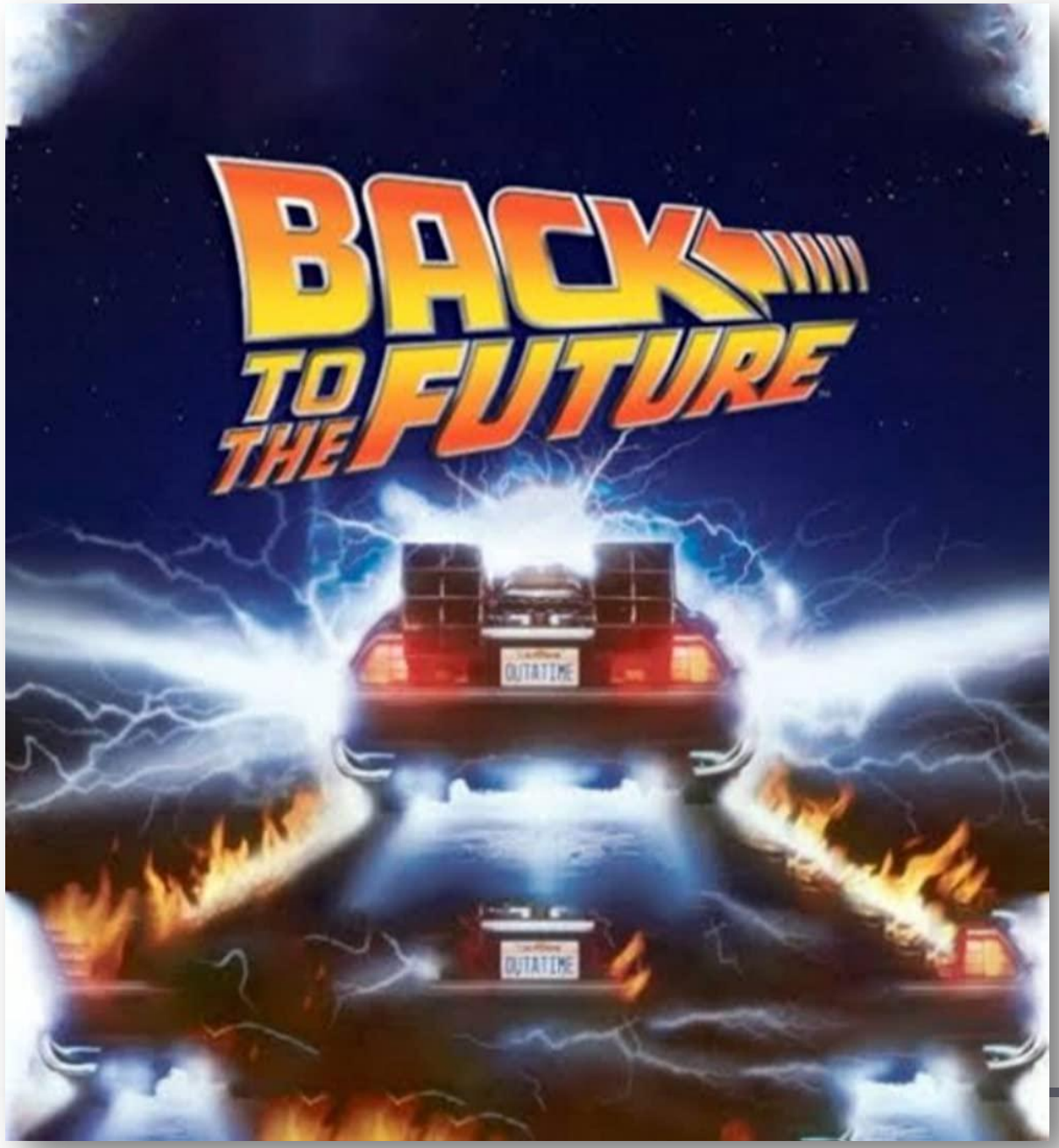


2017



2022





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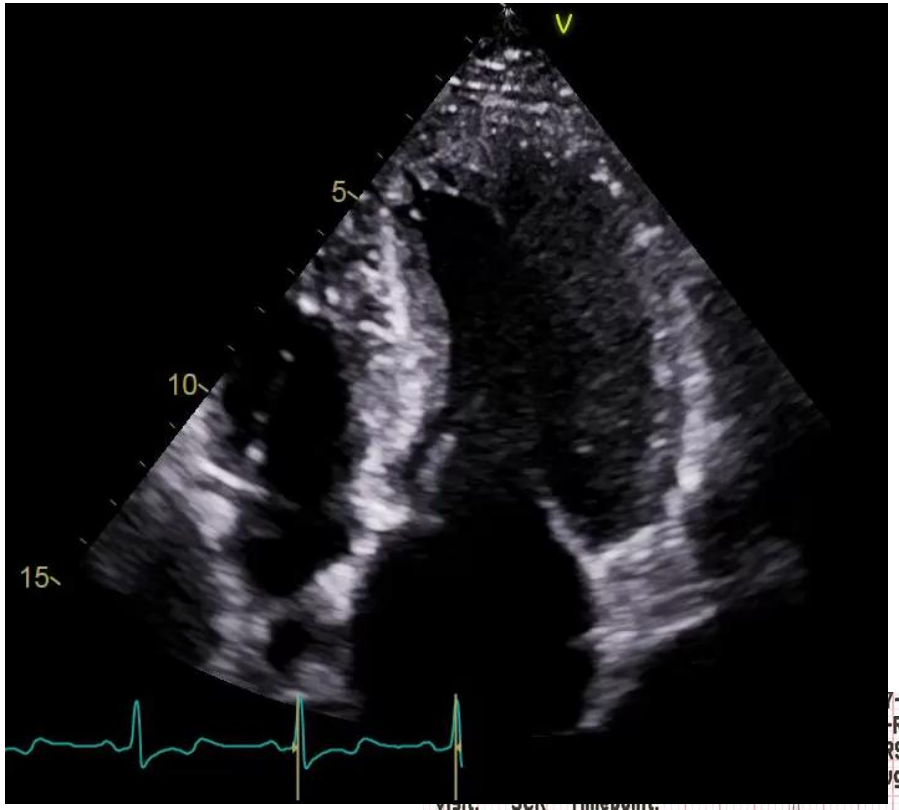
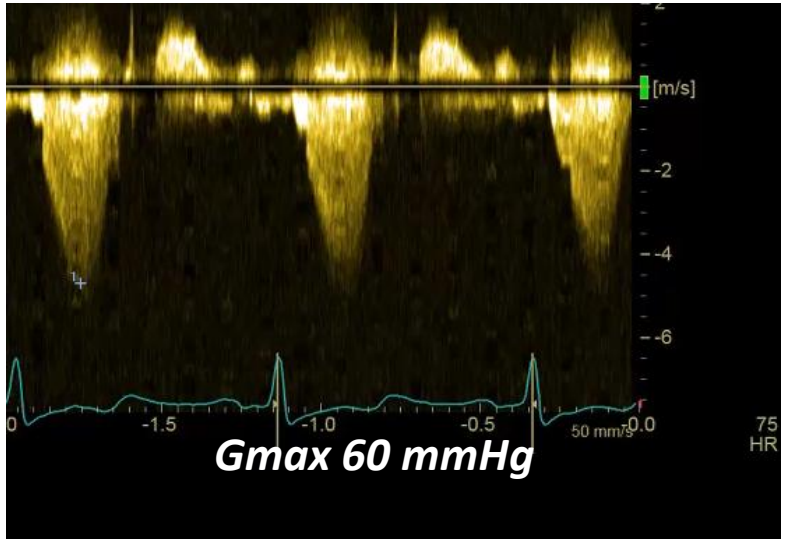
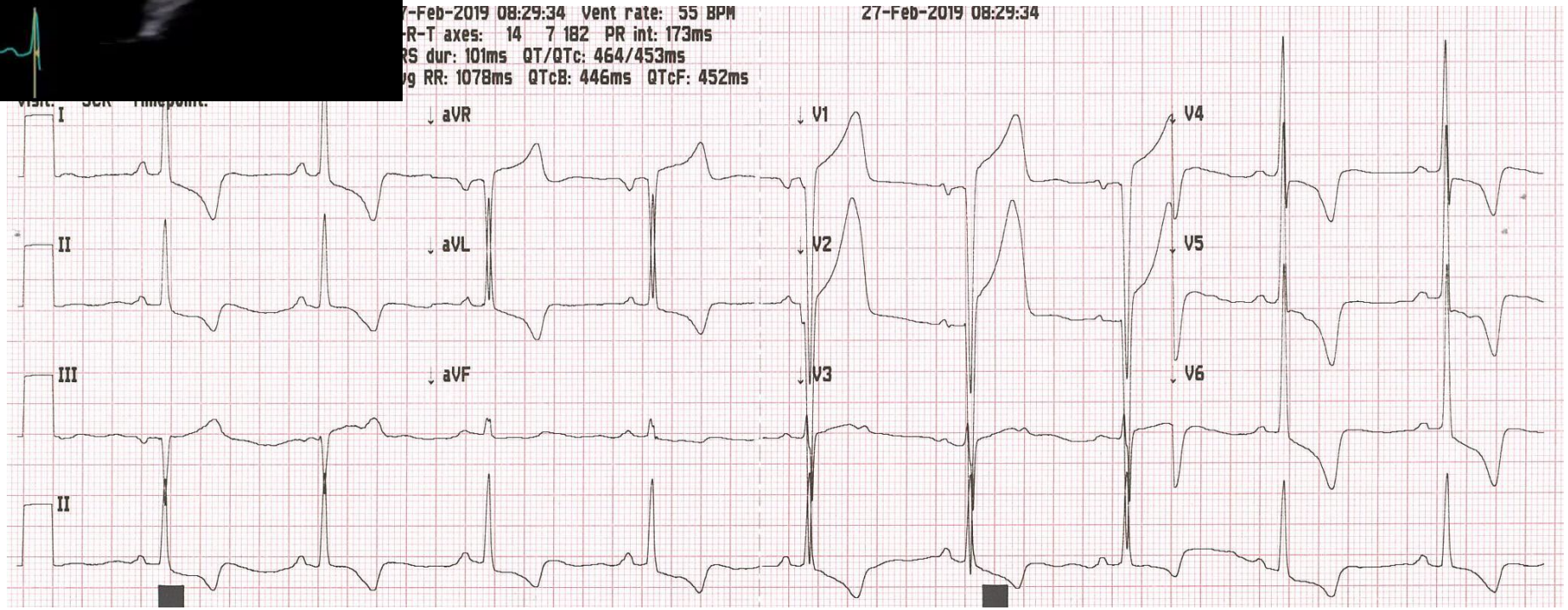
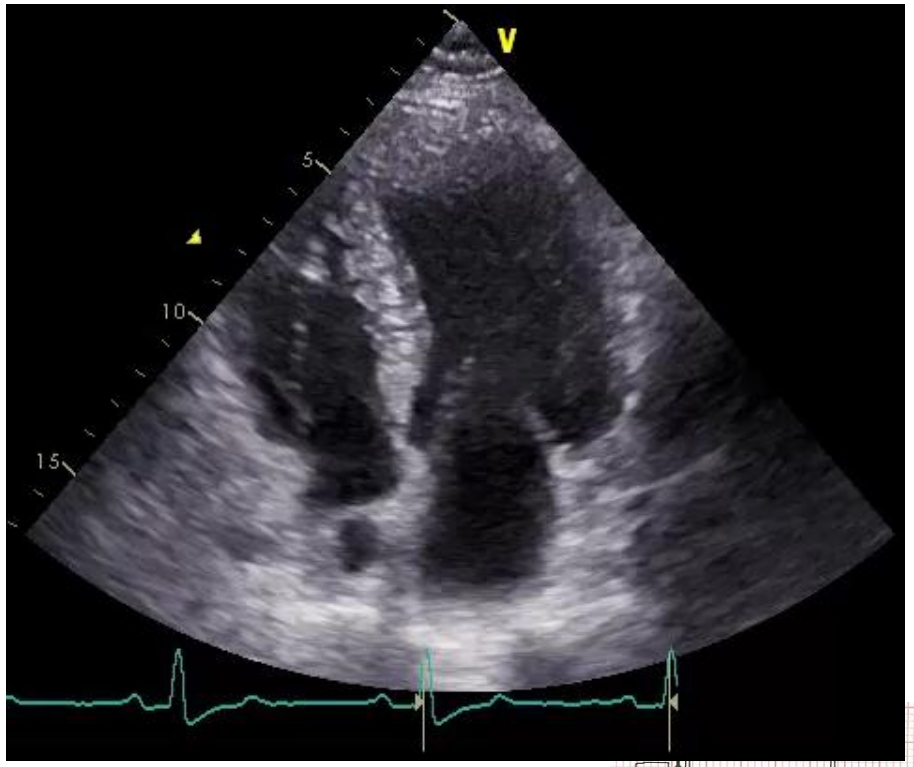
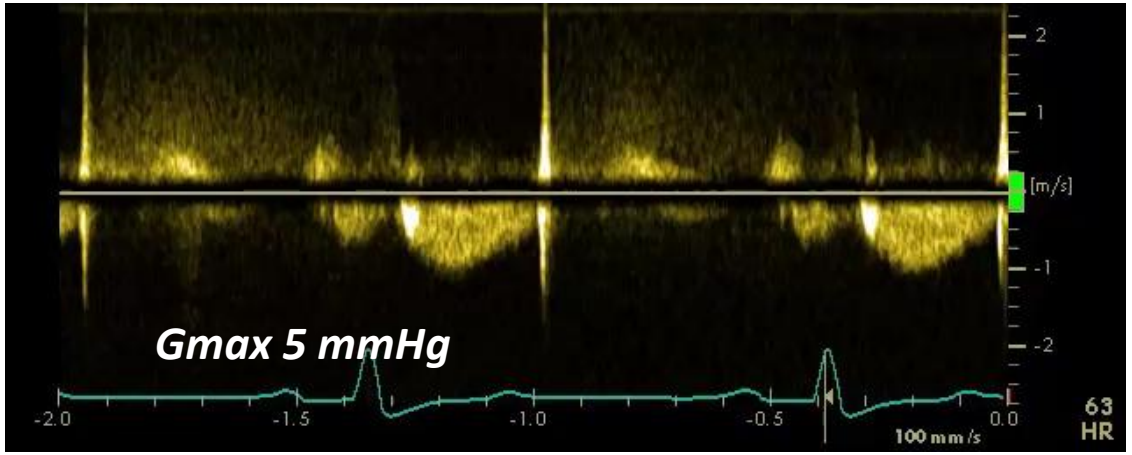

V
5
10
15

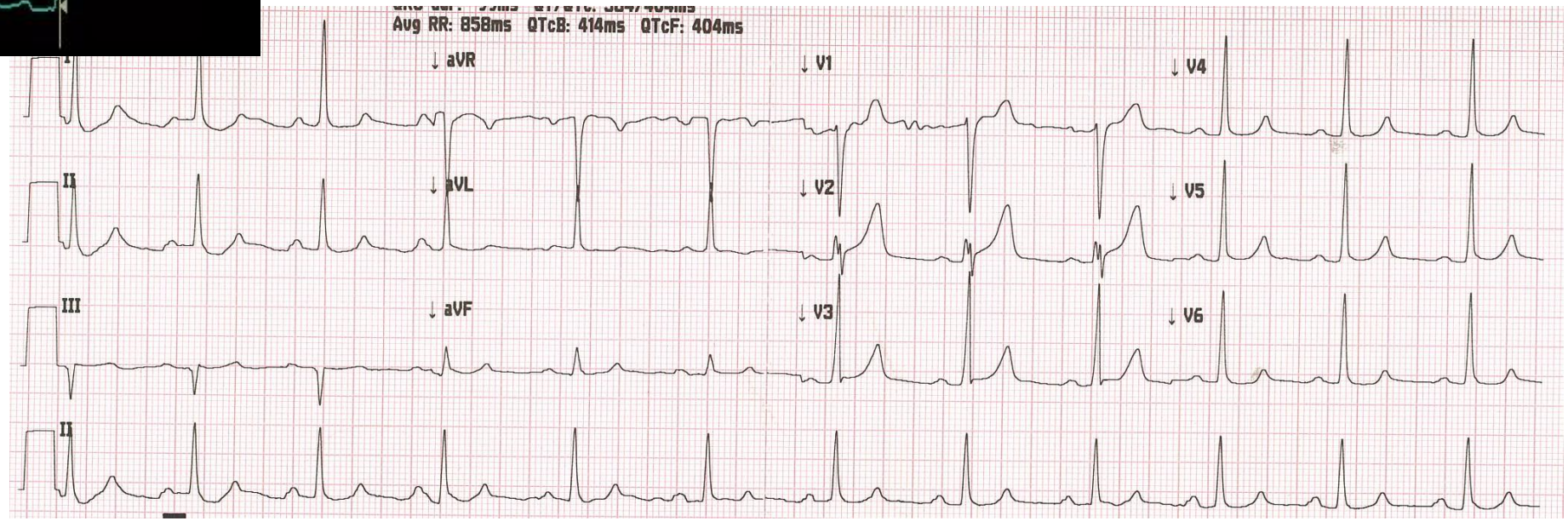

[m/s]
-2
-4
-6
-1.5
-1.0
-0.5
0.0
50 mm/s
75
HR

Gmax 60 mmHg

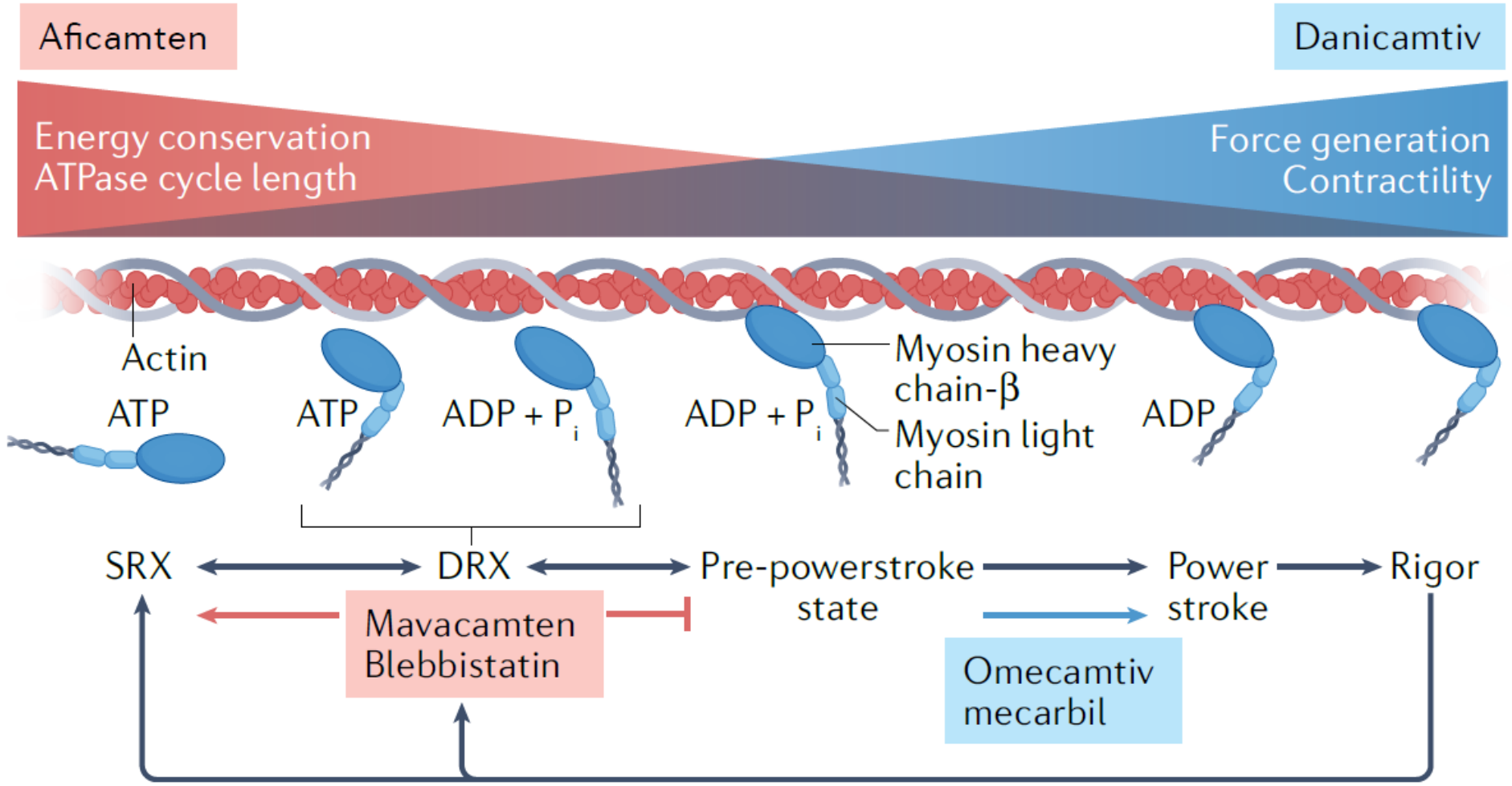

7-Feb-2019 08:29:34 Vent rate: 55 BPM
-R-T axes: 14 7 182 PR int: 173ms
RS dur: 101ms QT/QTc: 464/453ms
g RR: 1078ms QTcB: 446ms QTcF: 452ms
27-Feb-2019 08:29:34
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II


V
5
10
15


Gmax 5 mmHg
2
1
[m/s]
-1
-2
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s
63
HR


Avg RR: 858ms QTcB: 414ms QTcF: 404ms
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

The Molecular Mechanisms of Myosin Modulation by Targeted Small Molecules



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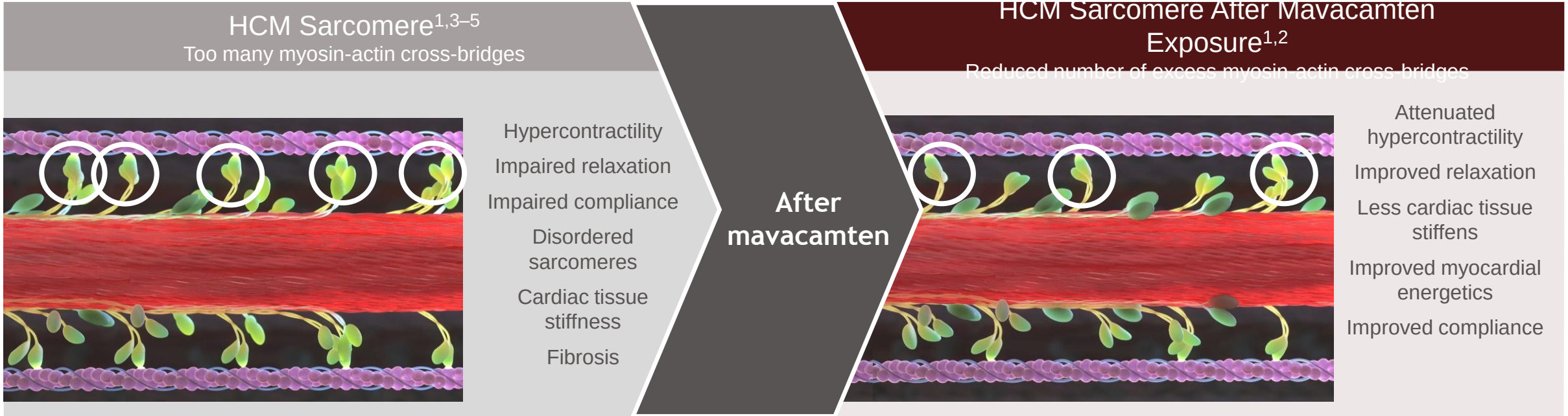
Lehman, Crocini and Leinwand, Nat Cardiol Rev 2022

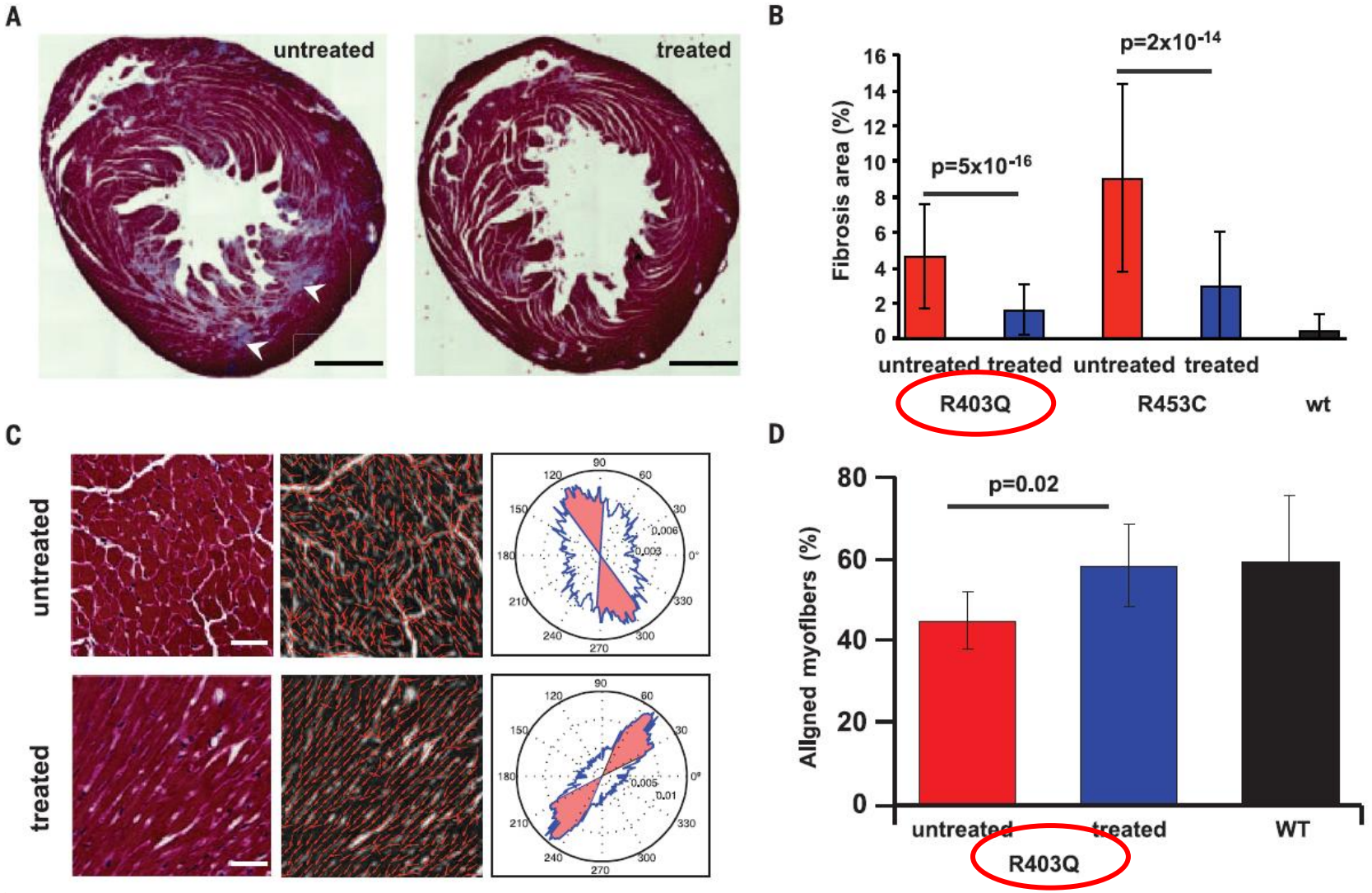
Mavacamten is a cardiac-specific myosin inhibitor designed to target the underlying pathophysiology of HCM[1,2]



ATP, adenosine triphosphate; HCM, hypertrophic cardiomyopathy; LV, left ventricular.

1. Anderson RL et al. *Proc Natl Acad Sci U S A* 2018;115:E8143–E8152. 2. Green EM et al. *Science* 2016;351:617–621. 3. Ho CY et al. *Circ Heart Fail* 2020;13. doi:10.1161/CIRCHEARTFAILURE.120.006853. 4. Sequeira V et al. *FEBS Lett* 2019;593:1616–1626. 5. Alamo L et al. *eLife* 2017;6. doi:10.7554/eLife.24634.

POTENTIAL FOR DISEASE MODIFICATION ?



Green et al, Science, 2016

IDEAL ENDPOINT

- Objective
- Reproducible
- Easy to measure
- Captures overall disease burden
- Has prognostic implications
- Relevant to the FDA
- RELEVANT TO PATIENTS

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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**

Lancet **2020; 396: 759–69**

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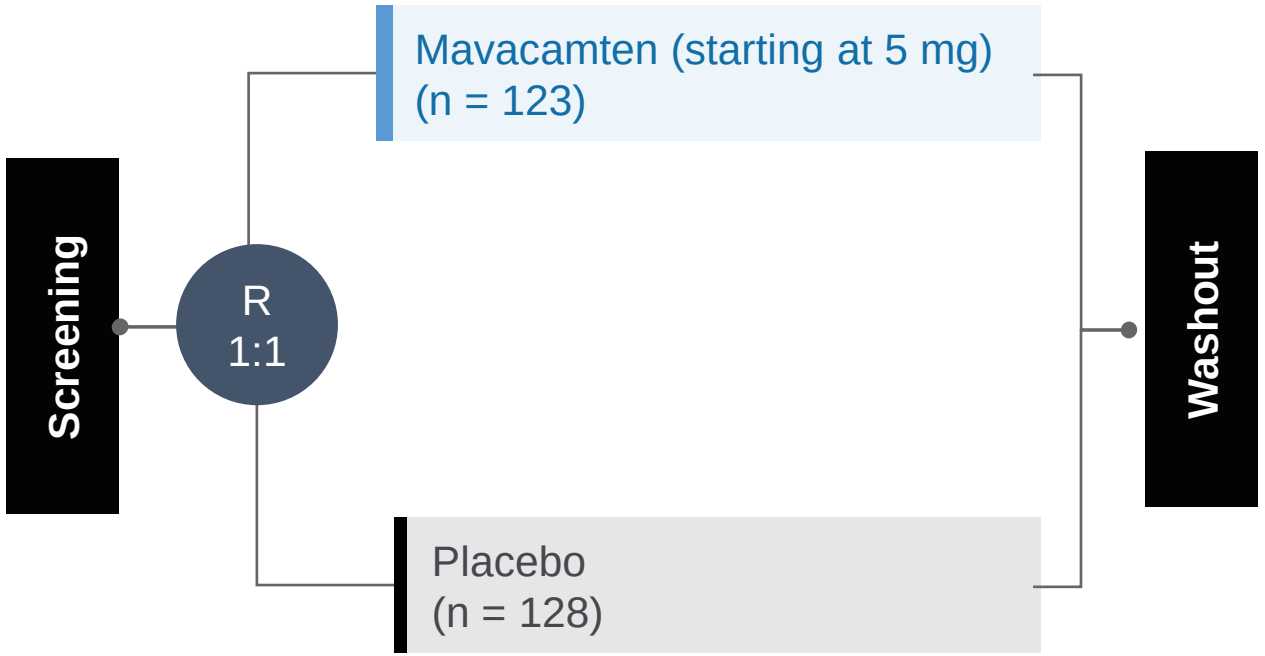
EXPLORER-HCM: Mavacamten in Symptomatic Patients With oHCM

- **Mavacamten**
- Myosin ATPase inhibitor

- Phase 3
- Randomized
- Double blind
- Placebo controlled

- 251 patients
- 68 clinical centers
- 13 countries

- Patients with:
- HCM with an LVOT gradient ≥ 50 mm Hg
- NYHA Class II to III



30 wk

Visits for assessment of patient status occurred every 2 to 4 wk

Primary endpoint

≥ 1.5 mL/kg/min increase in pVO2 and ≥ 1 NYHA class reduction

or

≥ 3.0 mL/kg/min pVO2 increase without NYHA class worsening

- ATPase, adenosine triphosphatase; NYHA, New York Heart Association; pVO2, peak oxygen consumption.
- Olivotto I, et al. Lancet. 2020;396:759-769.

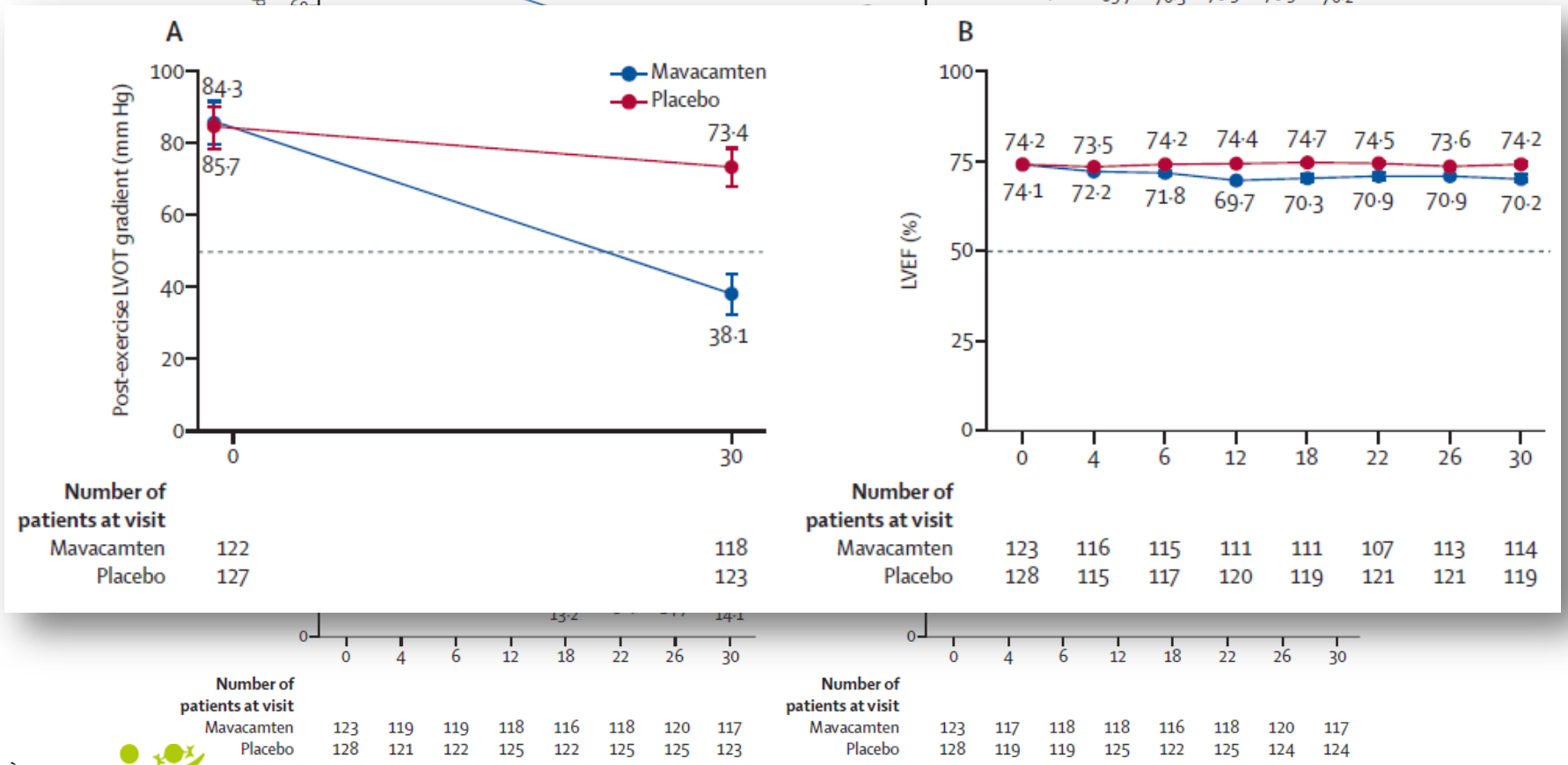
EXPLORER-HCM: Primary and Secondary Endpoints

	Mavacamten (n = 123)	Placebo (n = 128)	Difference (95% CI) *P* Value
Primary endpoint			
Either ≥ 1.5 mL/kg/min increase in pVO2 with ≥ 1 NYHA class improvement or ≥ 3.0 mL/kg/min increase in pVO2 with no worsening of NYHA class	37%	17%	19.4 (8.7, 30.1) .0005
Secondary endpoints			
Postexercise LVOT gradient change from baseline to wk 30, mm Hg	–47 (40) n = 117	–10 (30) n = 122	–35.6 (–43.2, –28.1) < .0001
pVO2 change from baseline to wk 30, mL/kg/min	1.4 (3.1) n = 120	–0.1 (3.0) n = 125	1.4 (0.6, 2.1) .0006
≥ 1 NYHA class improvement from baseline to wk 30	80 (65%)	40 (31%)	34% (22%, 45%) < .0001
Change from baseline to wk 30 in KCCQ-CSS	13.6 (14.4) n = 92	4.2 (13.7) n = 88	9.1 (5.5, 12.7) < .0001
Change from baseline to wk 30 in HCMSQ-SoB score	–2.8 (2.7) n = 85	–0.9 (2.4) n = 86	–1.8 (–2.4, –1.2) < .0001

- HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score.
- Olivotto I, et al. Lancet. 2020;396:759-769.

LVOT Gradients and LVEF Over Time

EXPLORER-HCM



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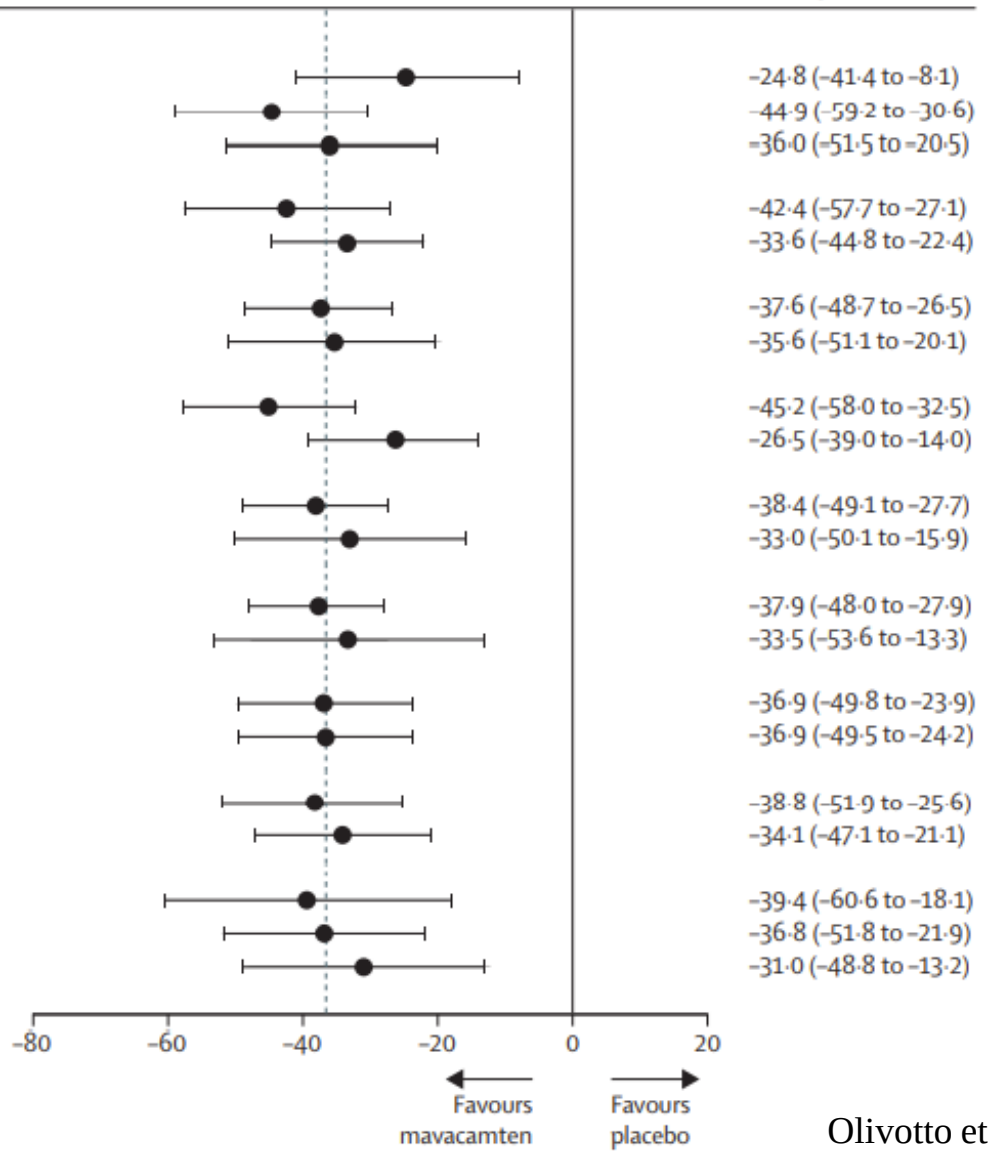
Olivotto et al, Lancet 2020

Exercise Gradient

EXPLORER-HCM

B

	Mavacamten (n [mean])	Placebo (n [mean])	Mean difference, mm Hg (95% CI)
Age, years			
≤49	26 (−37·0)	23 (−12·2)	−24·8 (−41·4 to −8·1)
50–64	48 (−57·1)	61 (−12·2)	−44·9 (−59·2 to −30·6)
≥65	43 (−42·5)	38 (−6·5)	−36·0 (−51·5 to −20·5)
Sex			
Women	54 (−47·9)	43 (−5·5)	−42·4 (−57·7 to −27·1)
Men	63 (−46·7)	79 (−13·1)	−33·6 (−44·8 to −22·4)
Body-mass index, kg/m²			
<30	72 (−47·5)	74 (−9·9)	−37·6 (−48·7 to −26·5)
≥30	45 (−46·9)	48 (−11·3)	−35·6 (−51·1 to −20·1)
LVEF at baseline			
<75%	66 (−52·8)	64 (−7·6)	−45·2 (−58·0 to −32·5)
≥75%	51 (−40·1)	58 (−13·6)	−26·5 (−39·0 to −14·0)
NYHA class at baseline			
II	82 (−48·7)	90 (−10·3)	−38·4 (−49·1 to −27·7)
III	35 (−43·9)	32 (−10·9)	−33·0 (−50·1 to −15·9)
β blocker usage at baseline			
Yes	89 (−47·1)	92 (−9·1)	−37·9 (−48·0 to −27·9)
No	28 (−47·9)	30 (−14·4)	−33·5 (−53·6 to −13·3)
Type of exercise testing			
Bicycle	51 (−48·2)	57 (−11·4)	−36·9 (−49·8 to −23·9)
Treadmill	66 (−46·5)	65 (−9·6)	−36·9 (−49·5 to −24·2)
NT-proBNP at baseline, ng/L			
≤median of 710 ng/L	53 (−48·8)	64 (−10·0)	−38·8 (−51·9 to −25·6)
>median of 710 ng/L	61 (−45·7)	56 (−11·6)	−34·1 (−47·1 to −21·1)
HCM genetic testing result			
Pathogenic or likely pathogenic	25 (−49·8)	21 (−10·5)	−39·4 (−60·6 to −18·1)
Variant of uncertain significance	32 (−49·5)	40 (−12·7)	−36·8 (−51·8 to −21·9)
Negative	28 (−38·9)	34 (−7·9)	−31·0 (−48·8 to −13·2)



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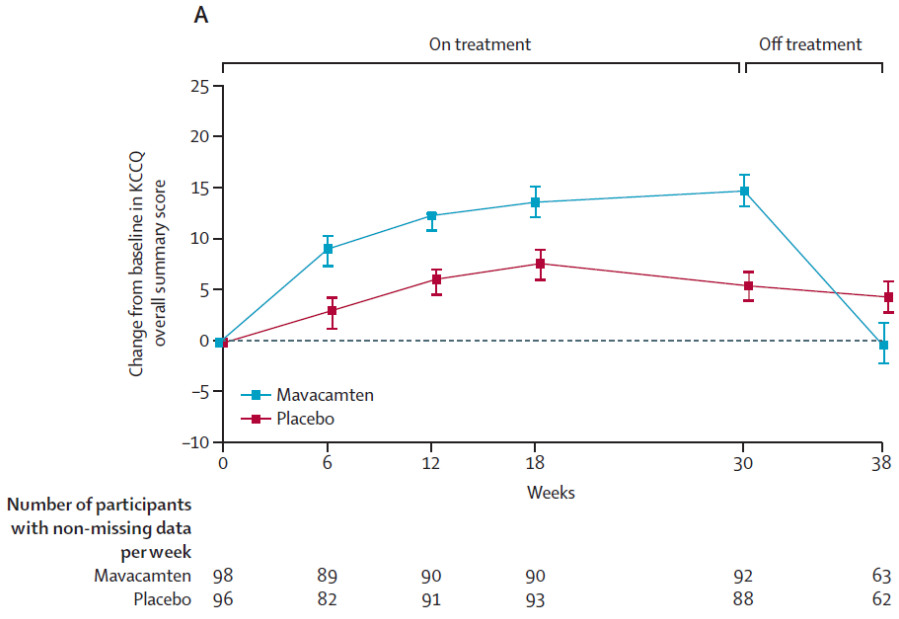
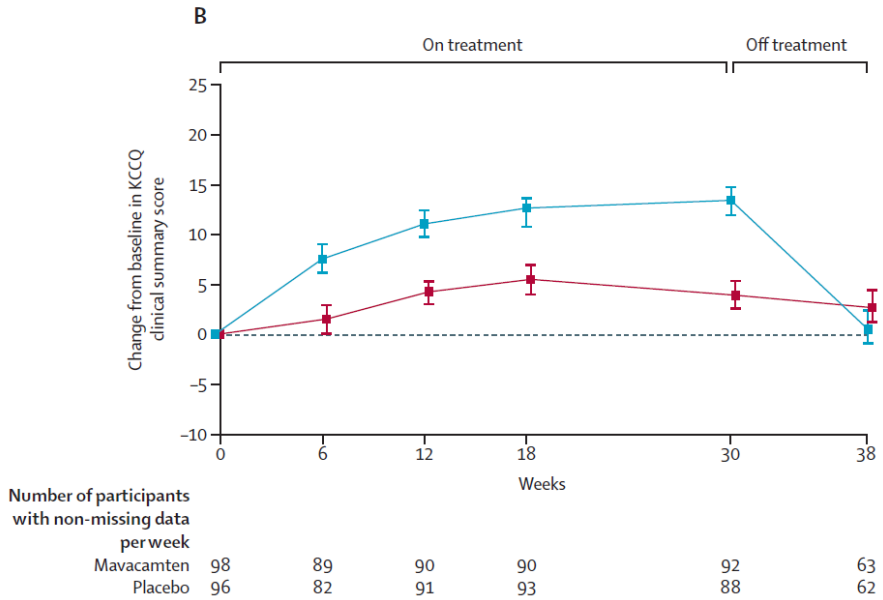
Olivotto et al, Lancet 2020

EXPLORER-HCM

Quality of Life



mean change from baseline in KCCQ-OS
+9·1 (95% CI 5·5–12·8; p<0·0001)



mean change from baseline in KCCQ-CS
+9·1 (95% 5.5-12.7) ; p<0·0001)

Spertus et al. Lancet, May 15 2021

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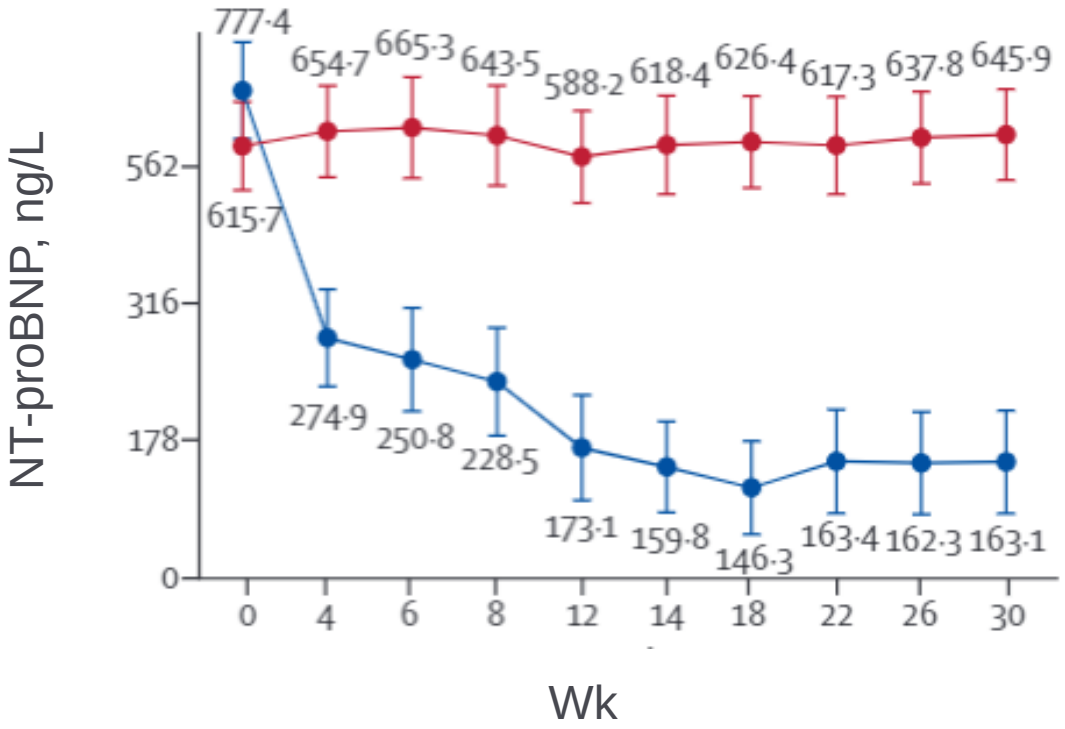
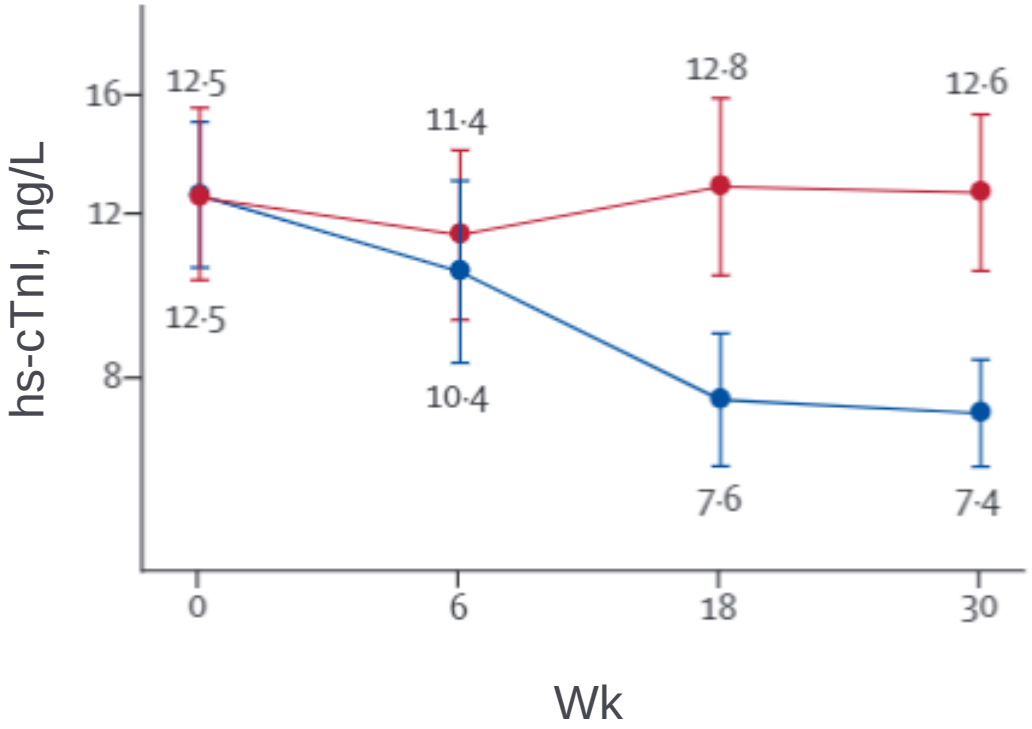
Meyer

EXPLORER-HCM: Cardiac Biomarkers

NT-proBNP

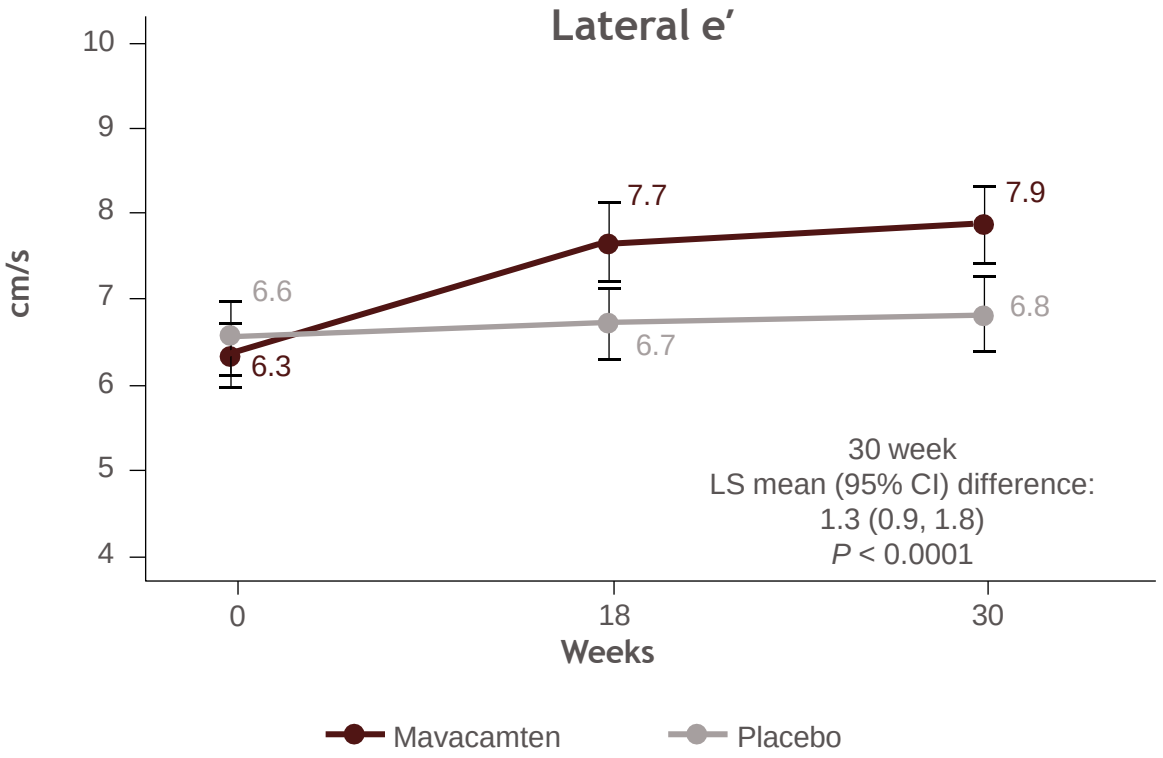


hs-cTnI



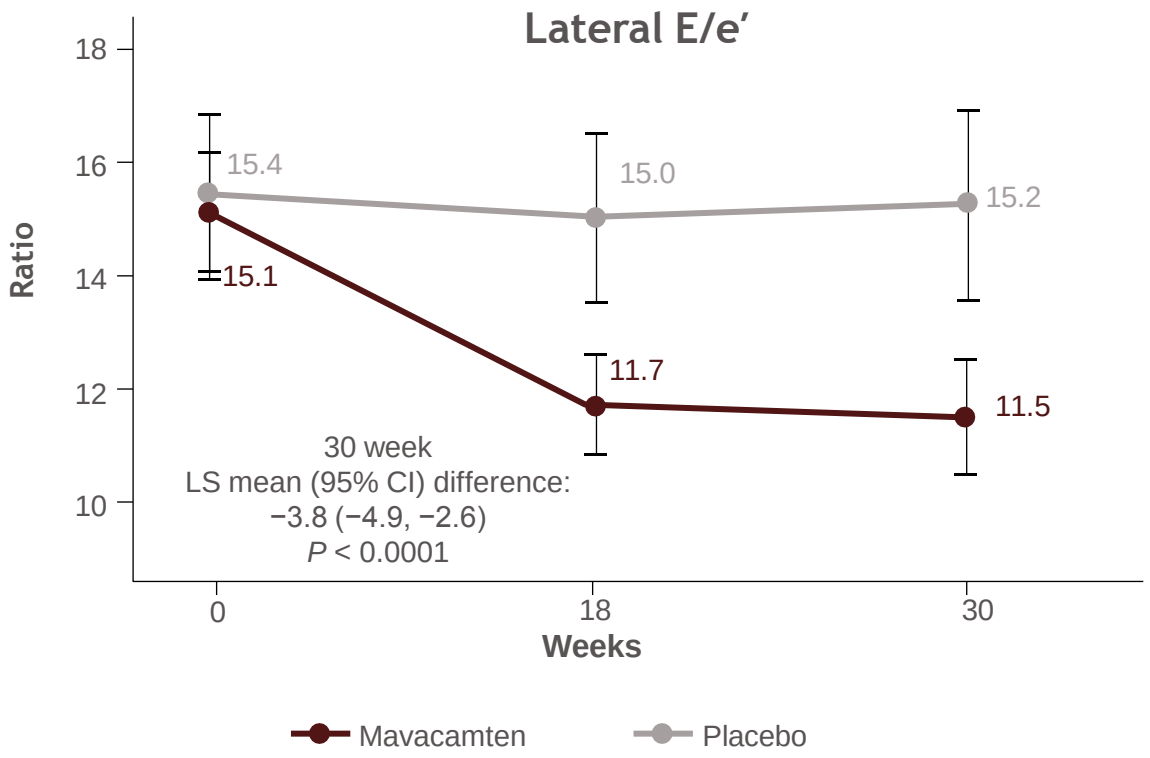
- hsTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro B-type natriuretic peptide.
- Olivotto I, et al. Lancet. 2020;396:759-769.

EXPLORER-HCM echocardiographic secondary analysis: change in lateral e′ and lateral E/e′



Number of patients at visit

Mavacamten	118	110	111
Placebo	126	113	118



Number of patients at visit

Mavacamten	118	110	108
Placebo	122	112	117

Hegde S et al. J Am Coll Cardiol 2021

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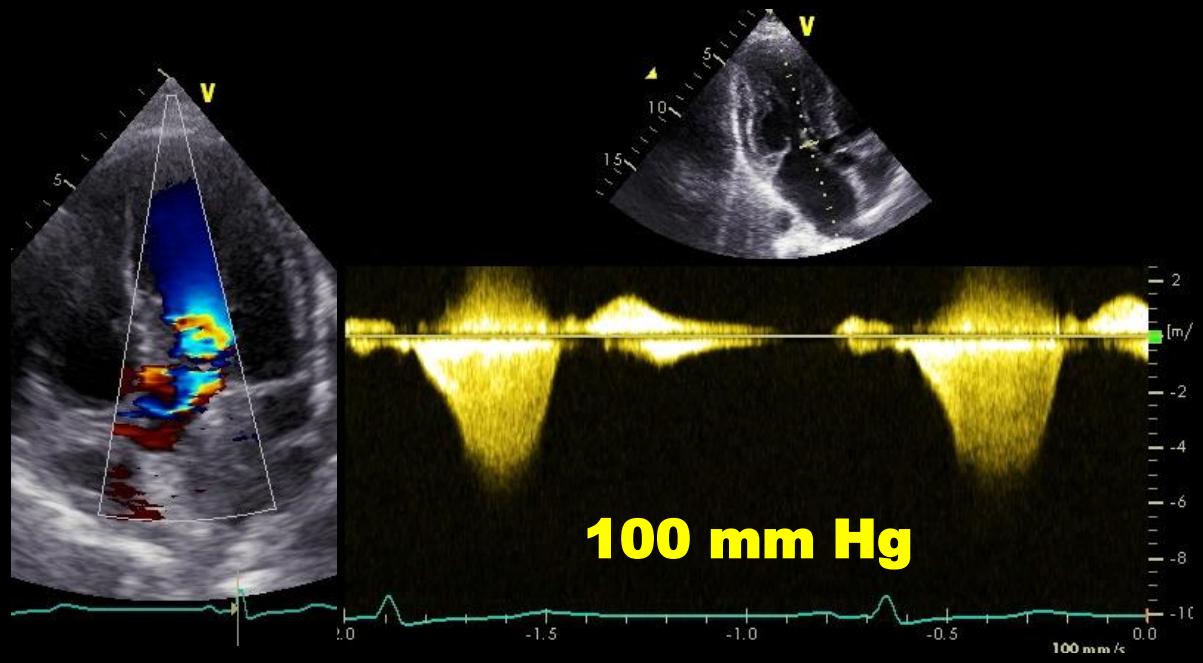
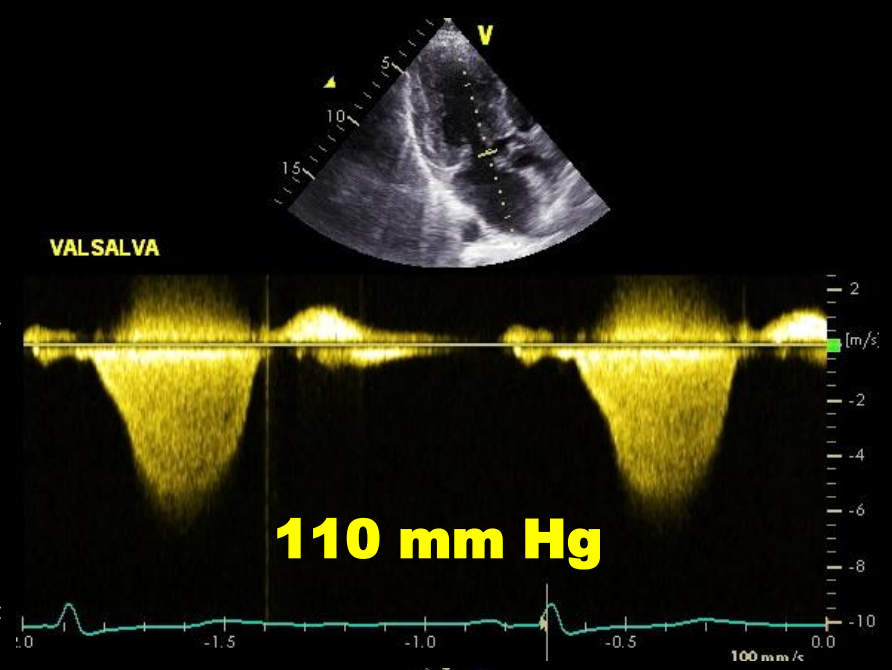
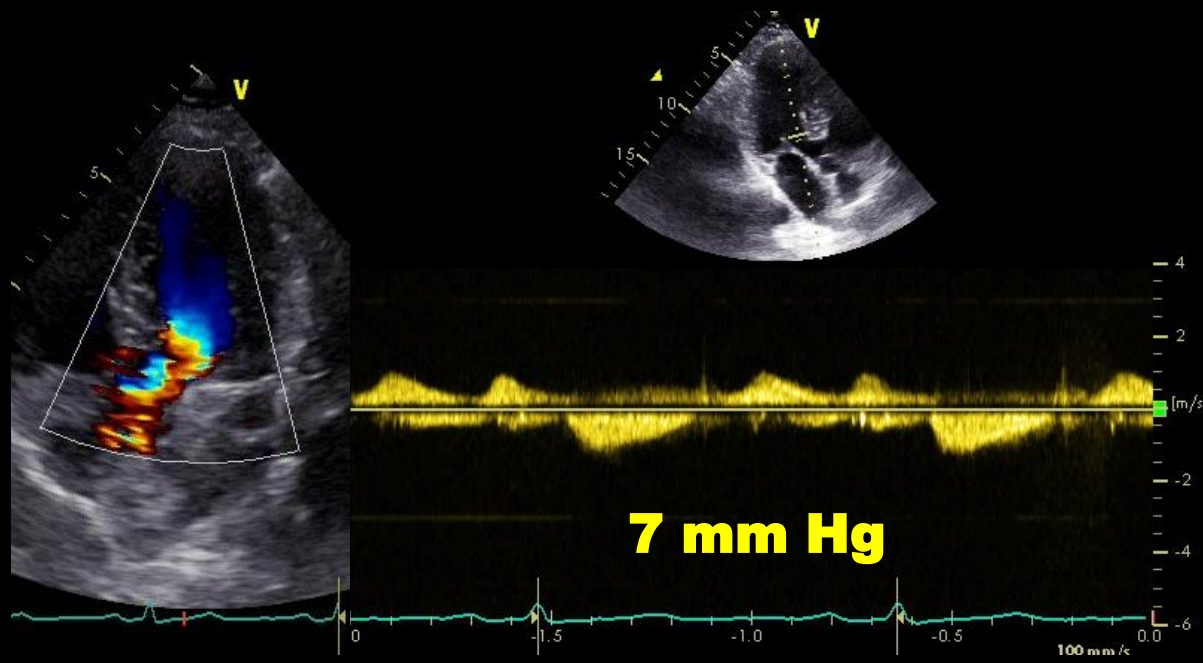
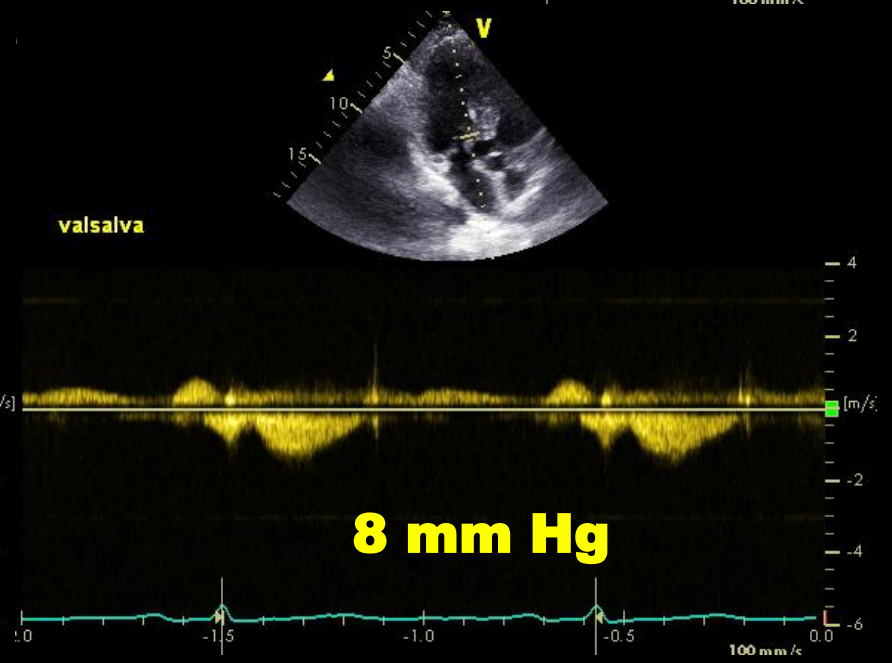
Before mavacamten

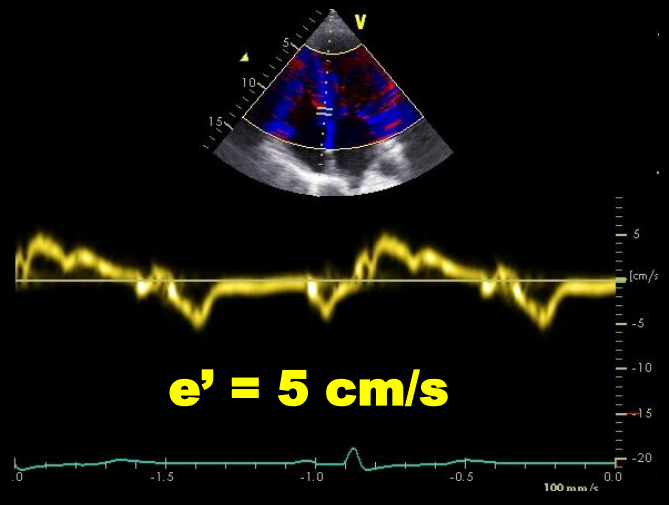
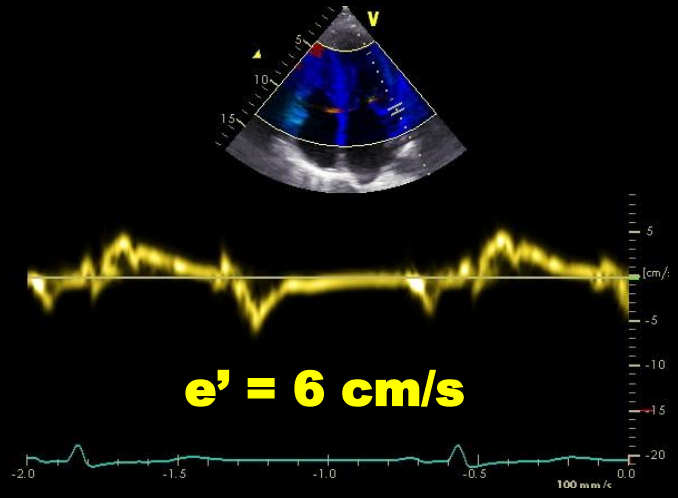
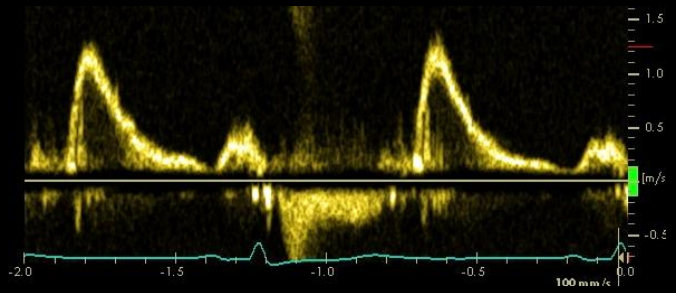
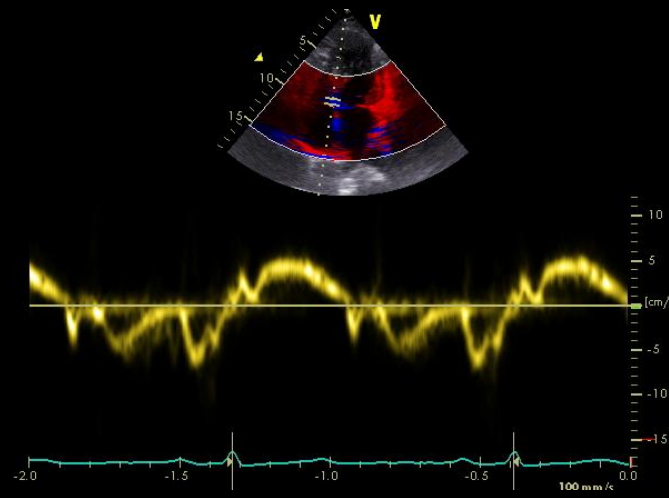
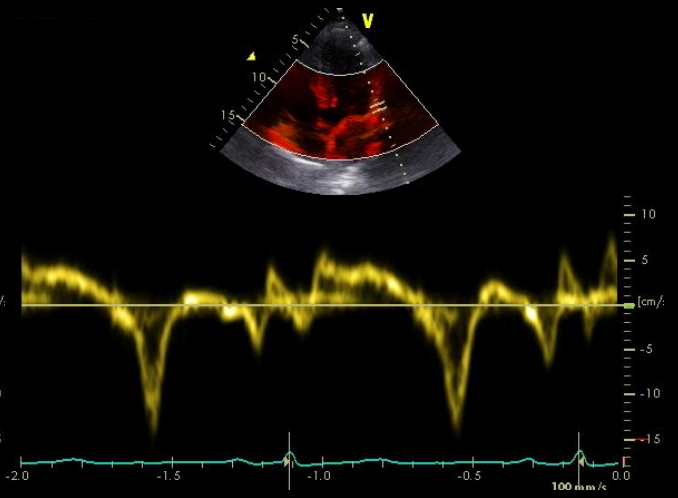
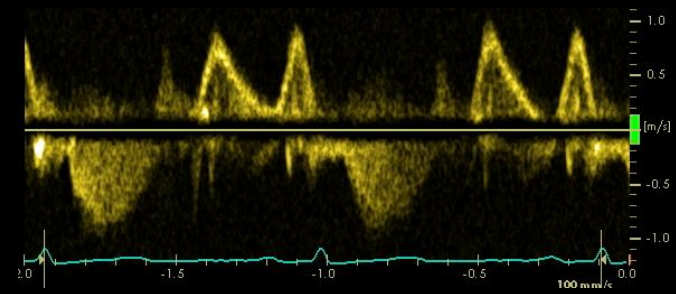




On mavacamten

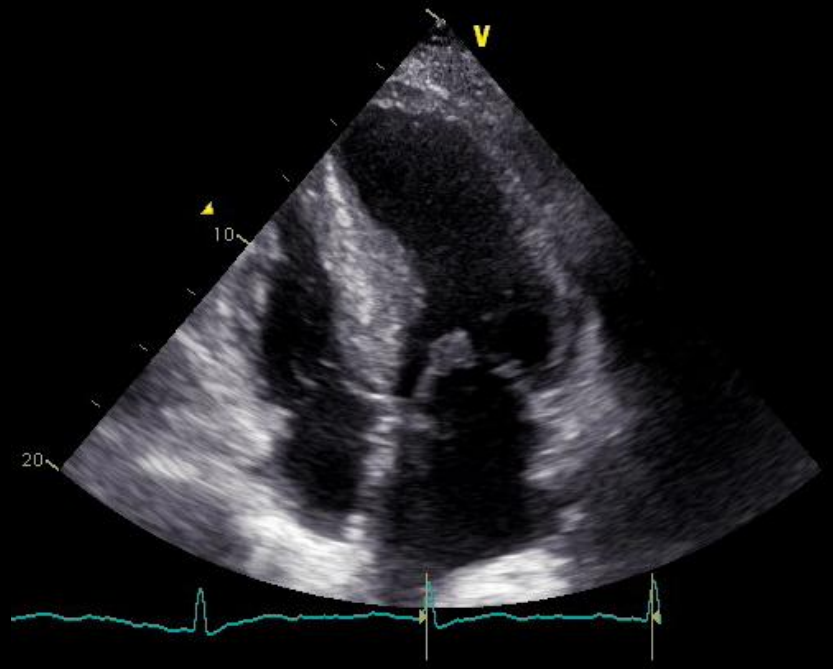
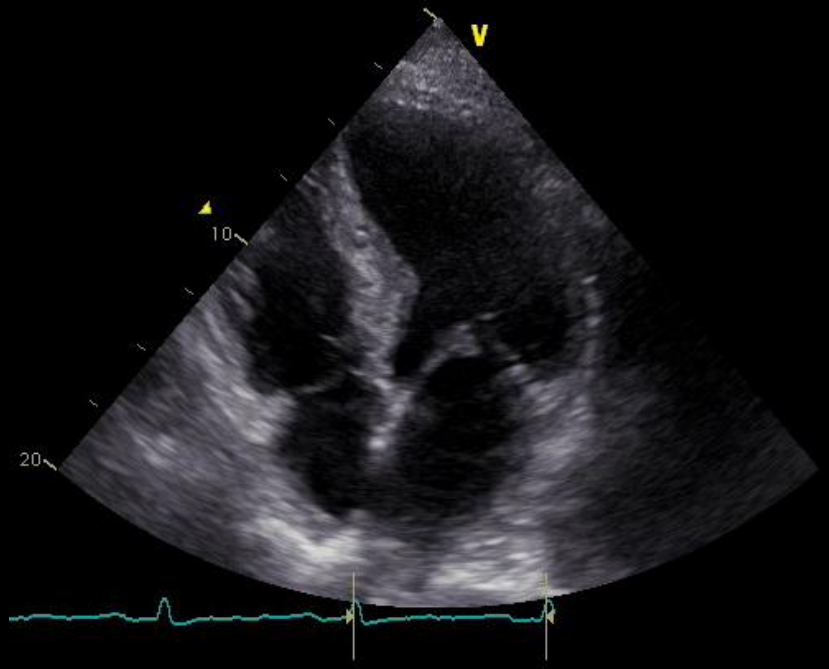
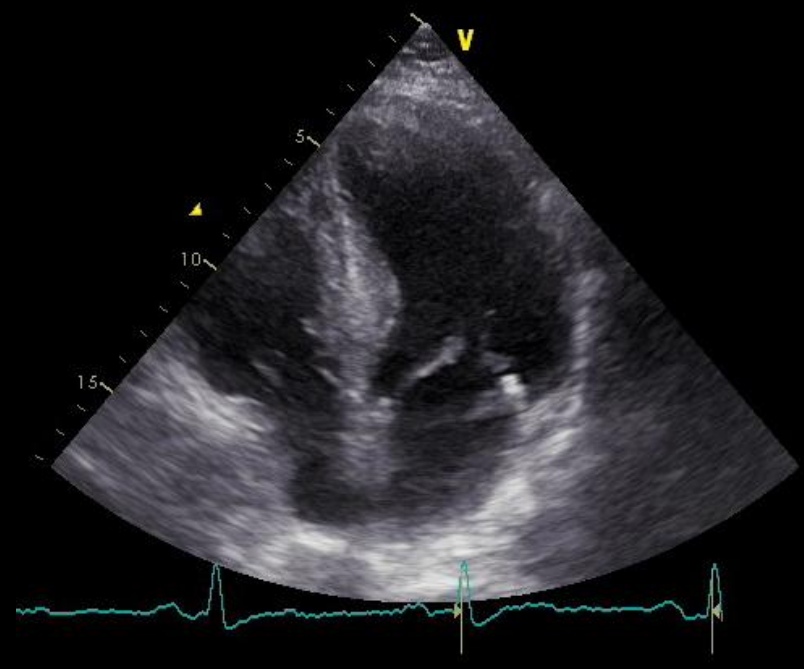




	Septal TDI	Lateral TDI	Mitral inflow
Before mavacamten E/e' mean = 23	 e' = 5 cm/s	 e' = 6 cm/s	E = 129 cm/s 
On mavacamten E/e' mean = 9	 e' = 5 cm/s	 e' = 14 cm/s	E = 89 cm/s 

LV EF

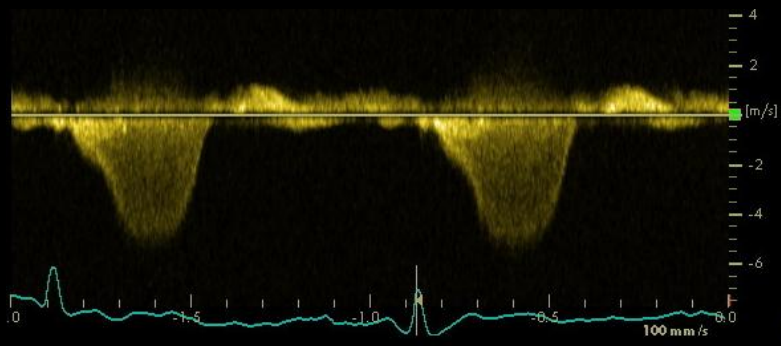
6-week washout

Baseline	W16	W22
		
73%	40%	60%

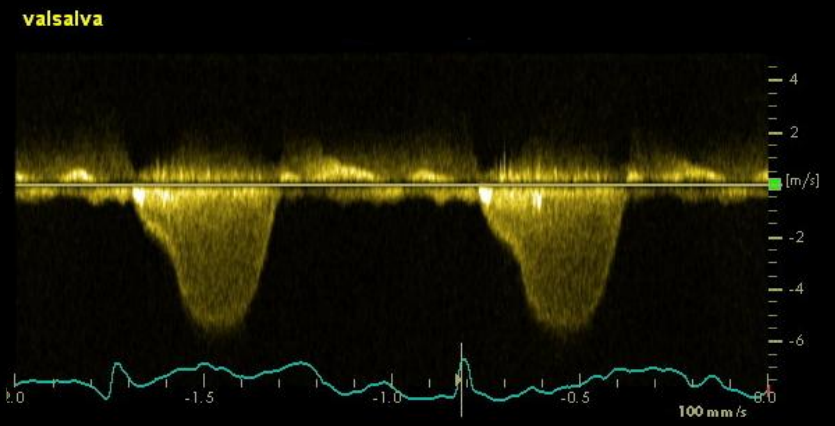
LVOTG

Baseline

NT-proBNP = 2024 pg/ml



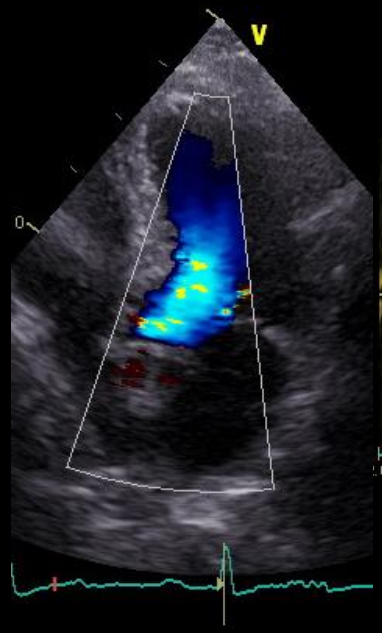
127 mm Hg

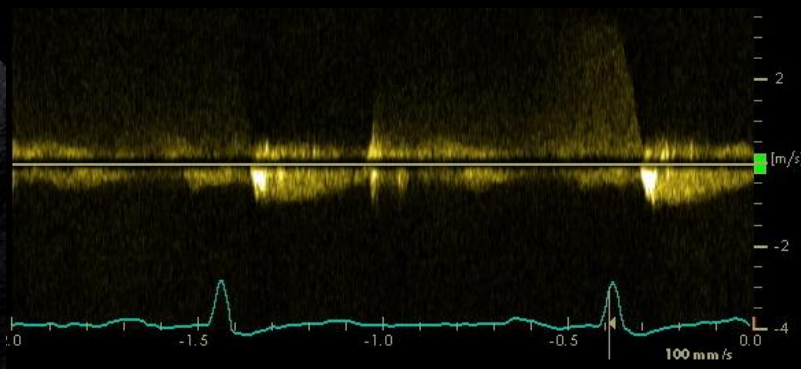


144 mm Hg

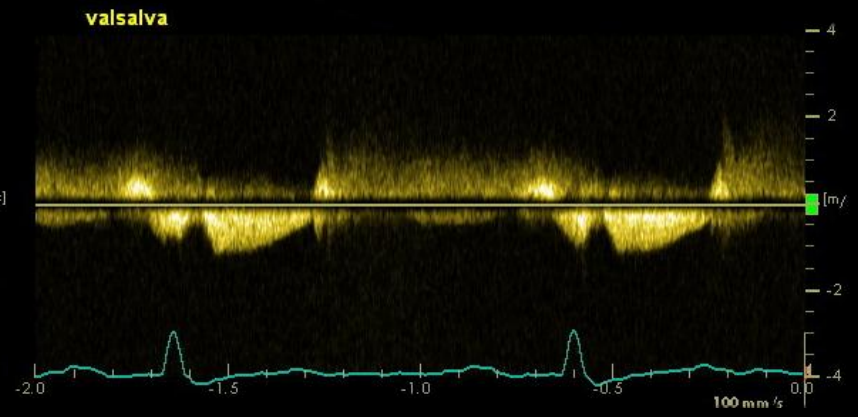
3rd year on mavacamten

NT-proBNP = 85 pg/ml



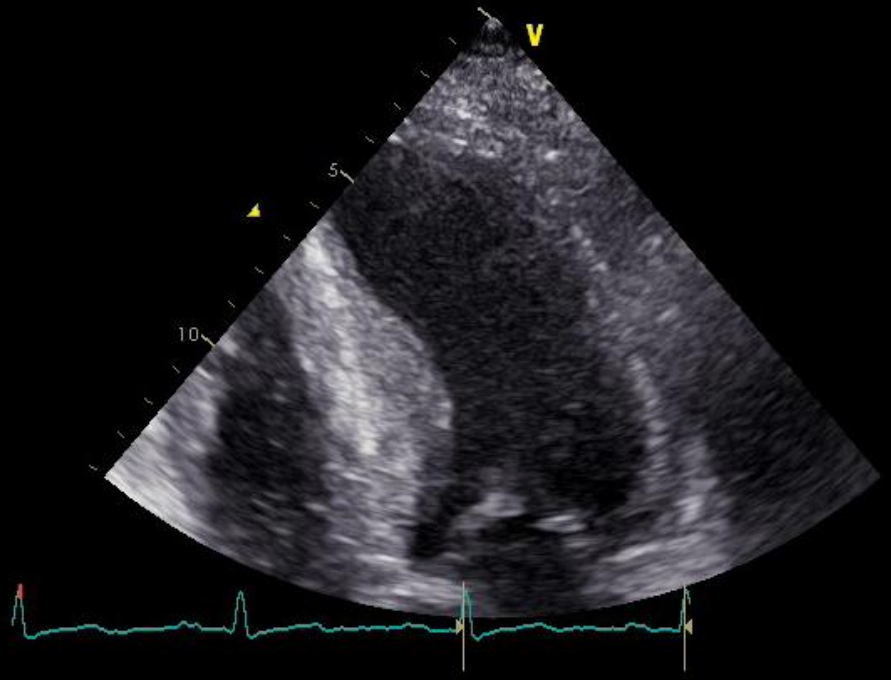


4 mm Hg



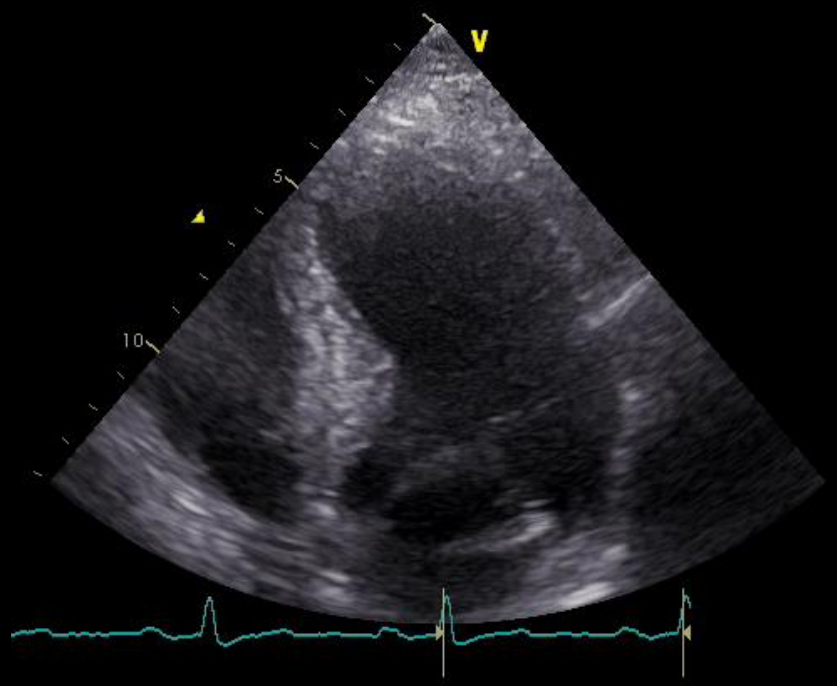
5 mm Hg

Baseline



LV EF = 73 %

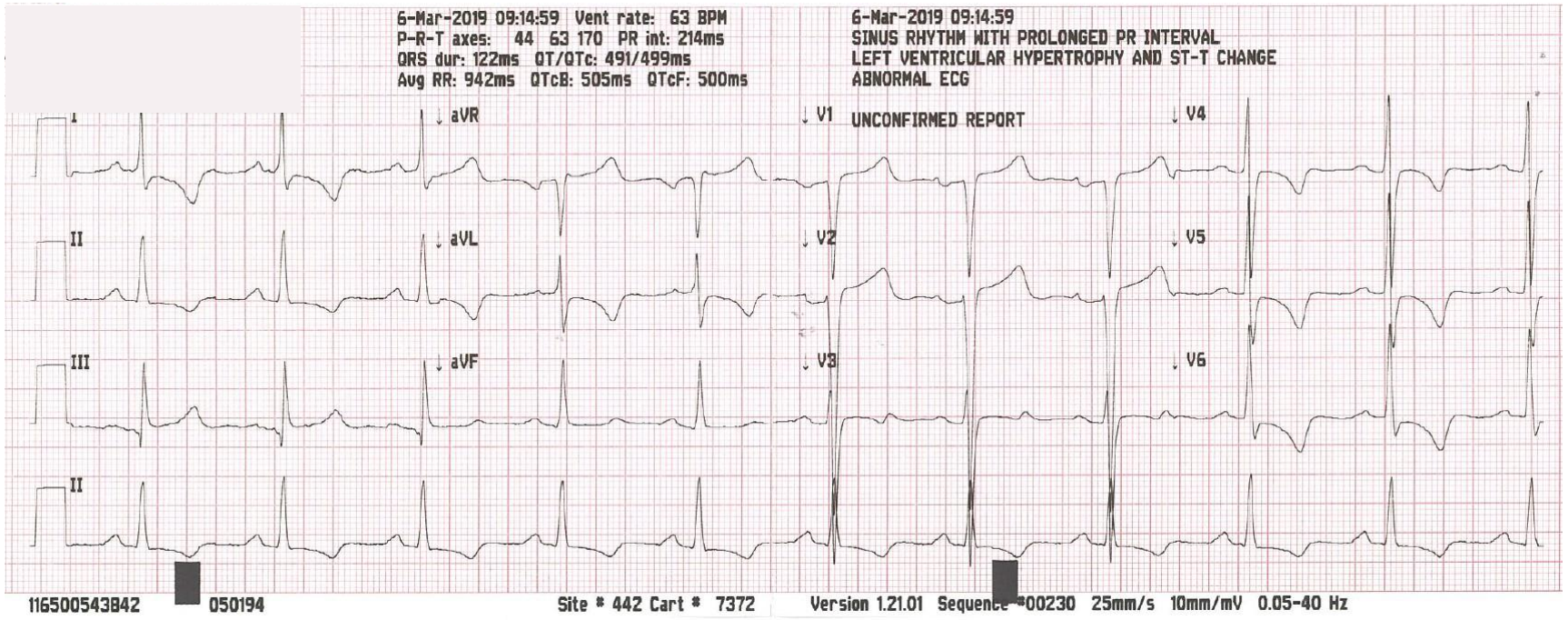
3rd year on mavacamten



LV EF = 58%

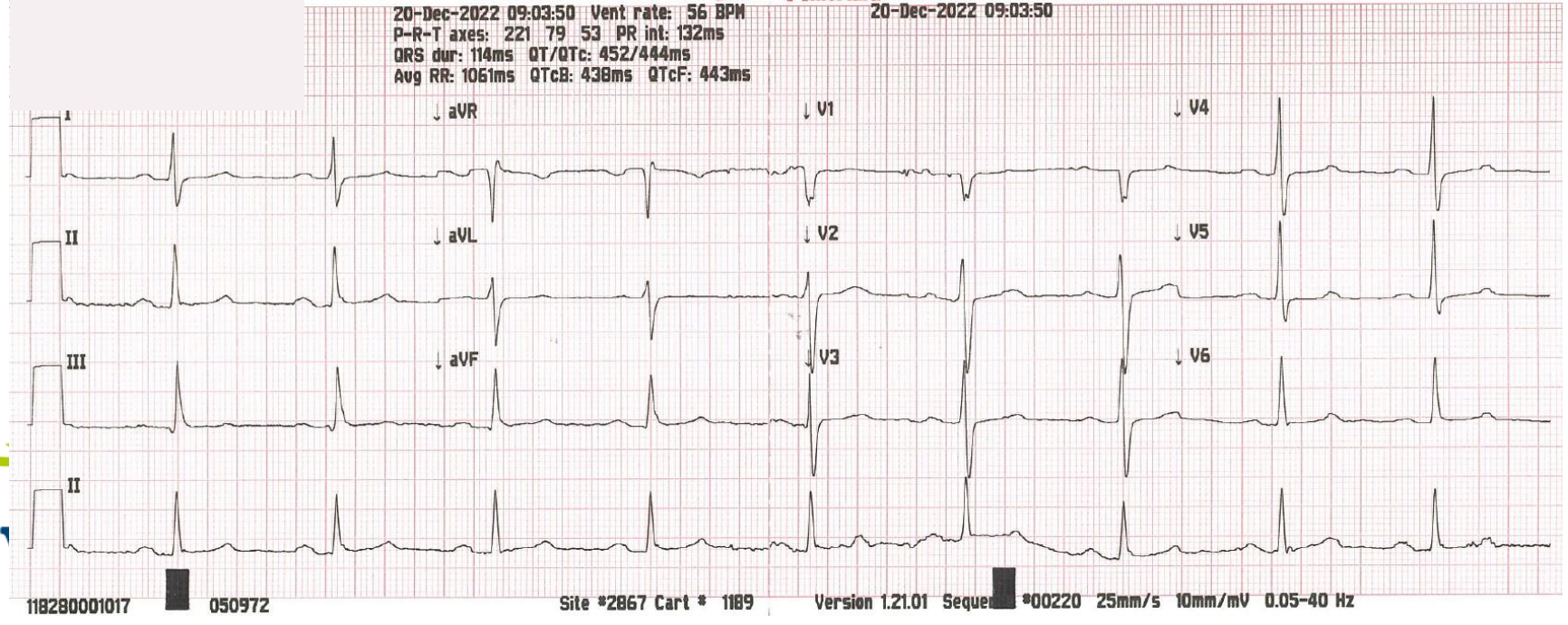
Baseline

NT-proBNP = 2024 pg/ml



3rd year on mavacamten

NT-proBNP = 85 pg/ml



HCM Detection Algorithms from Mayo & UCSF Showed a Marked Reduction in HCM Risk Score Following Mavacamten Treatment in the PIONEER-OLE Cohort

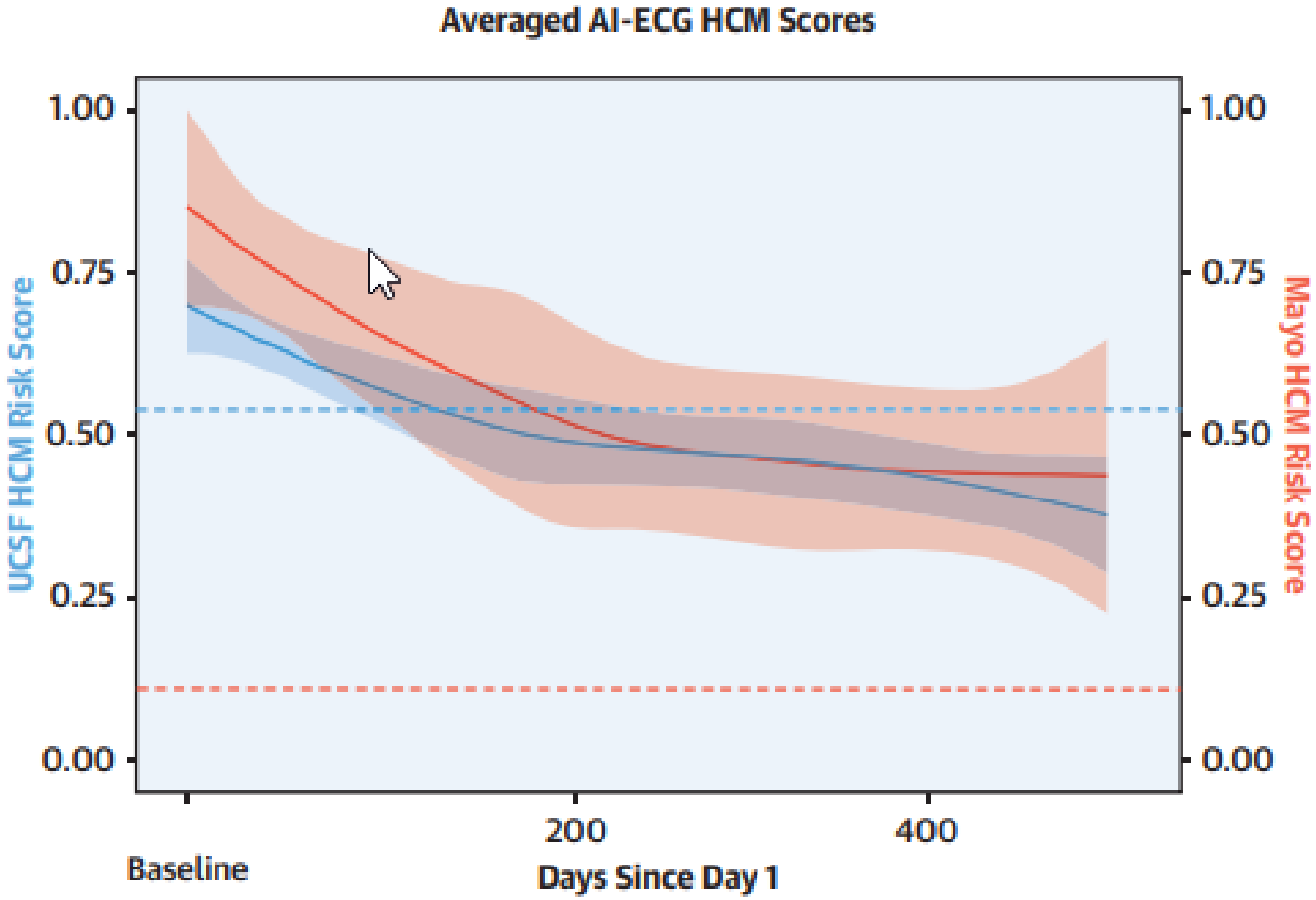
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 79, NO. 10, 2022
ISSN 0735-1097/$36.00

Letters

Assessment of Disease Status and Treatment Response With Artificial Intelligence–Enhanced Electrocardiography in Obstructive Hypertrophic Cardiomyopathy

Although hypertrophic cardiomyopathy (HCM) causes significant morbidity and is a leading cause of sudden death in adolescents, initial detection remains difficult. Although echocardiography is an important to approximate HCM prevalence. Both algorithms were then applied to all ECGs (n = 216) from each patient in PIONEER-OLE who had pretreatment and on-treatment through January 29, 2020. We examined longitudinal associations of AI-ECG–predicted HCM scores with echocardiographic and laboratory metrics important to HCM clinical decision-making.

Mean age of the PIONEER-OLE cohort at baseline was 57.8 years; 69.2% of patients were men, and 92.3% had New York Heart Association functional class II symptoms. Median follow-up was 79 weeks (range: 25.0-90.1 weeks). To discriminate PIONEER-OLE pretreatment HCM ECGs from ECGs of age and/or sex-matched non-HCM control subjects, area under the receiver-operating characteristic curves were 0.938 (95% CI: 0.924-0.950) for the UCSF algorithm and 0.979 (95% CI: 0.942-1.000) for the Mayo algorithm. Sensitivity and specificity were 84.6% and



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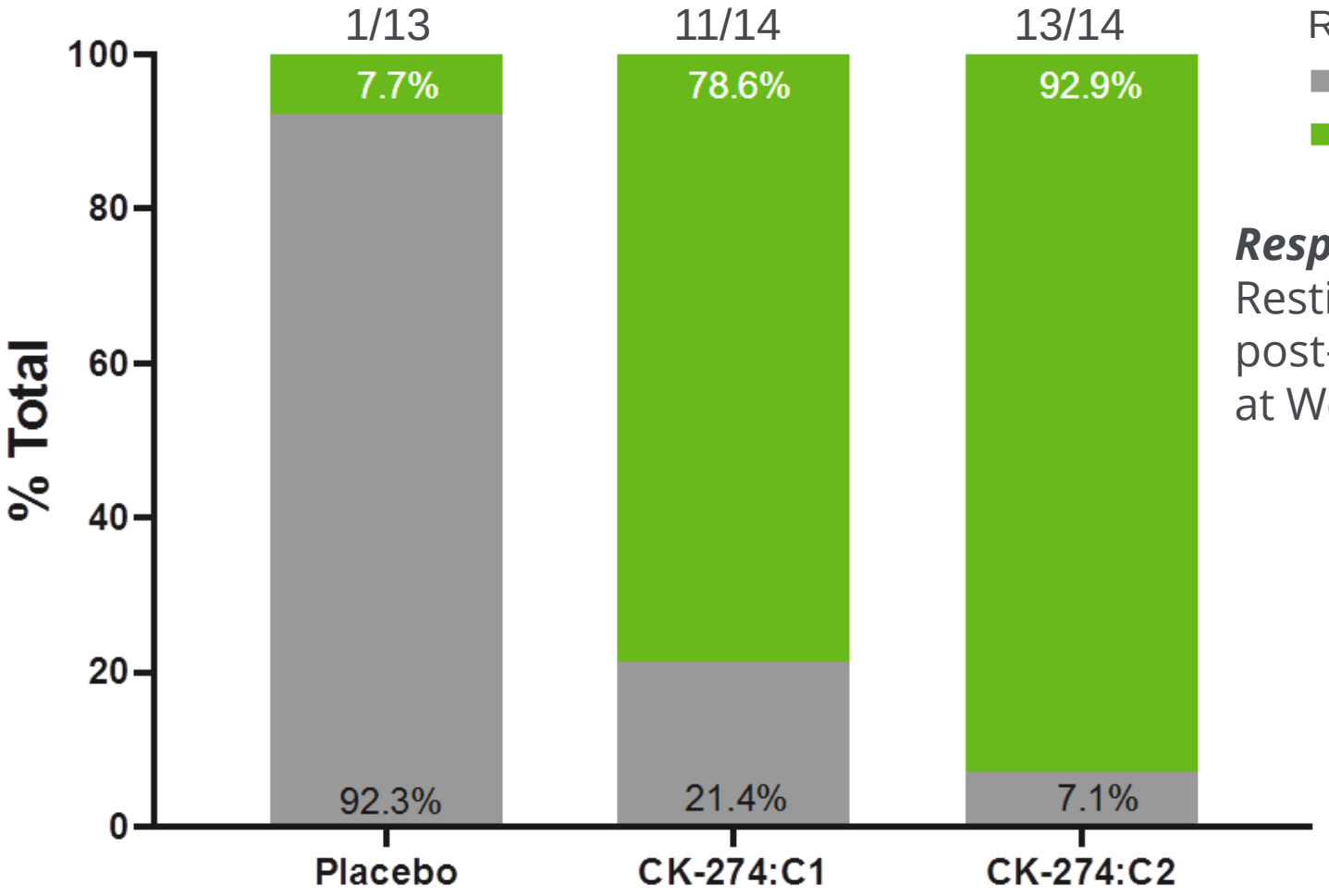
Meyer

CK-274 (Aficamten): Next-In-Class Cardiac Myosin Inhibitor

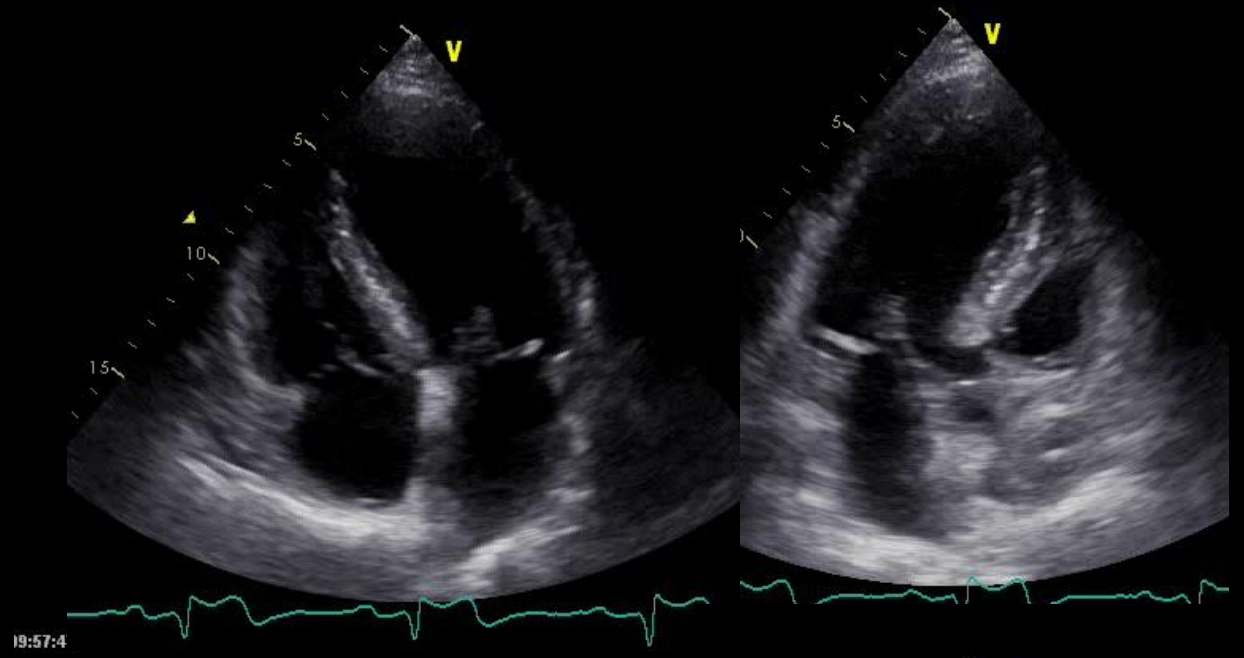
- Potential *in vivo* pharmacodynamic advantages related to distinctive binding site
- Optimized for
  - Onset of action (reach steady state within two weeks)
  - Rapid reversibility of effect
  - Minimal drug-drug interactions
  - Favorable tolerability
  - Ease of titration for personalized dosing
- Clear pharmacokinetic/pharmacodynamic (PK/PD) relationship observed
- Shallow exposure-response relationship

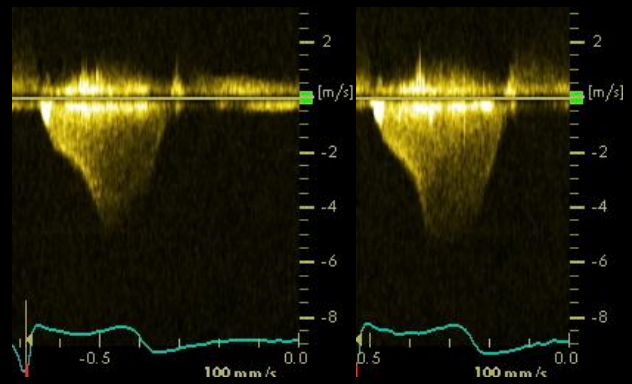
High Response Rates on Treatment with CK-274



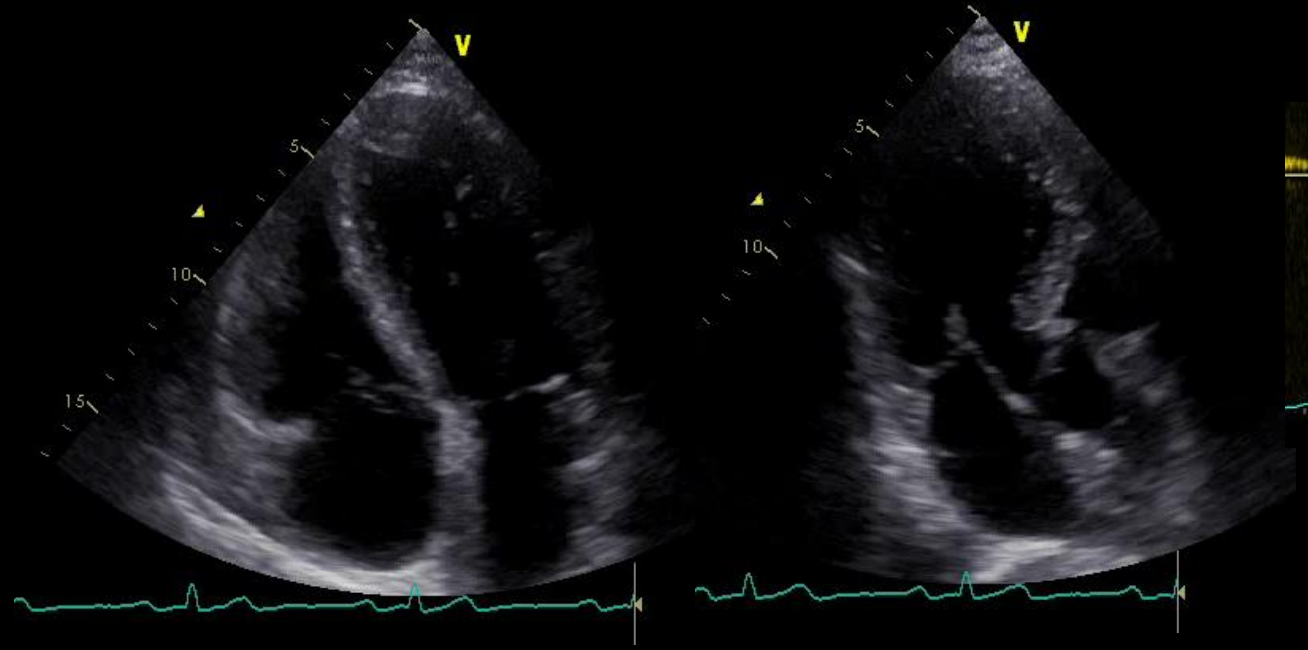
Responder Definition:
Resting LVOT-G <30 mmHg and post-Valsalva LVOT-G <50 mmHg at Week 10

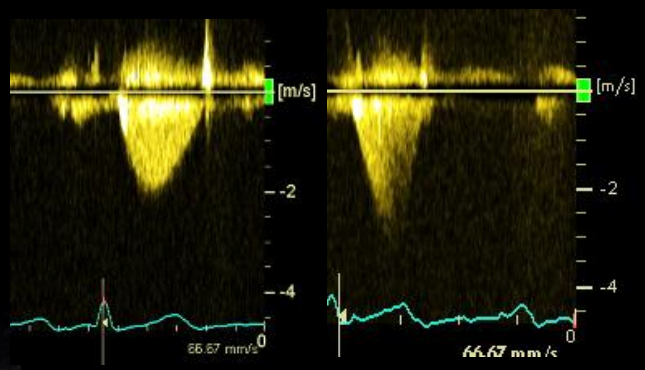
Before





6 weeks aficamten



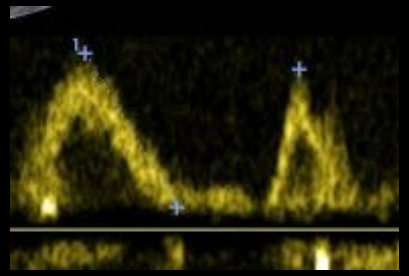


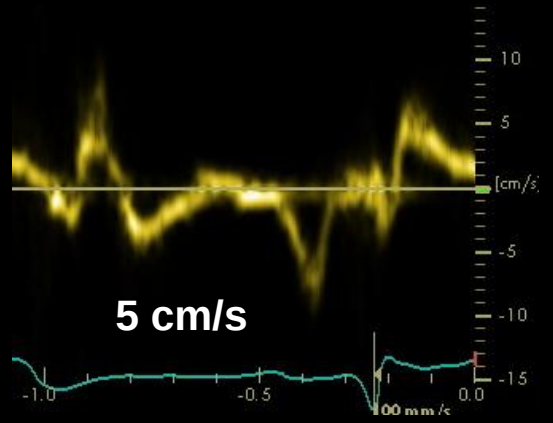
e’ septal

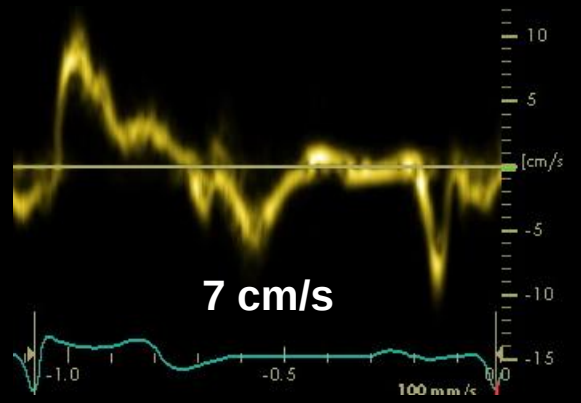
e’ lateral

E/e’ = 15

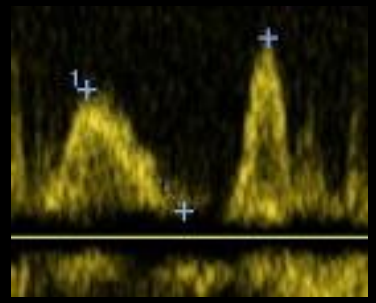
Before

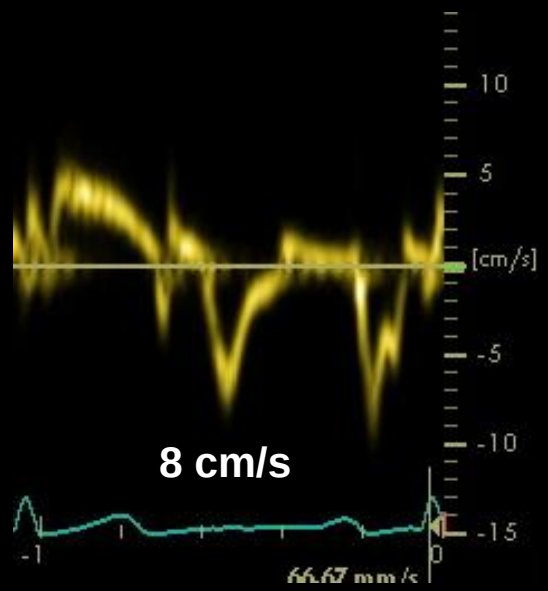


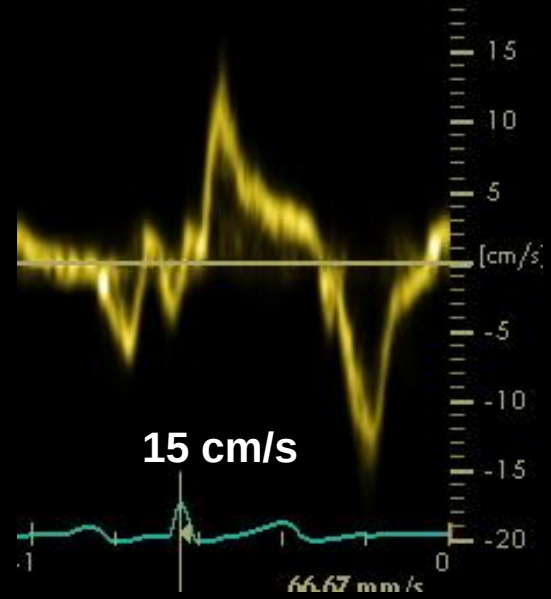




6 weeks aficamten

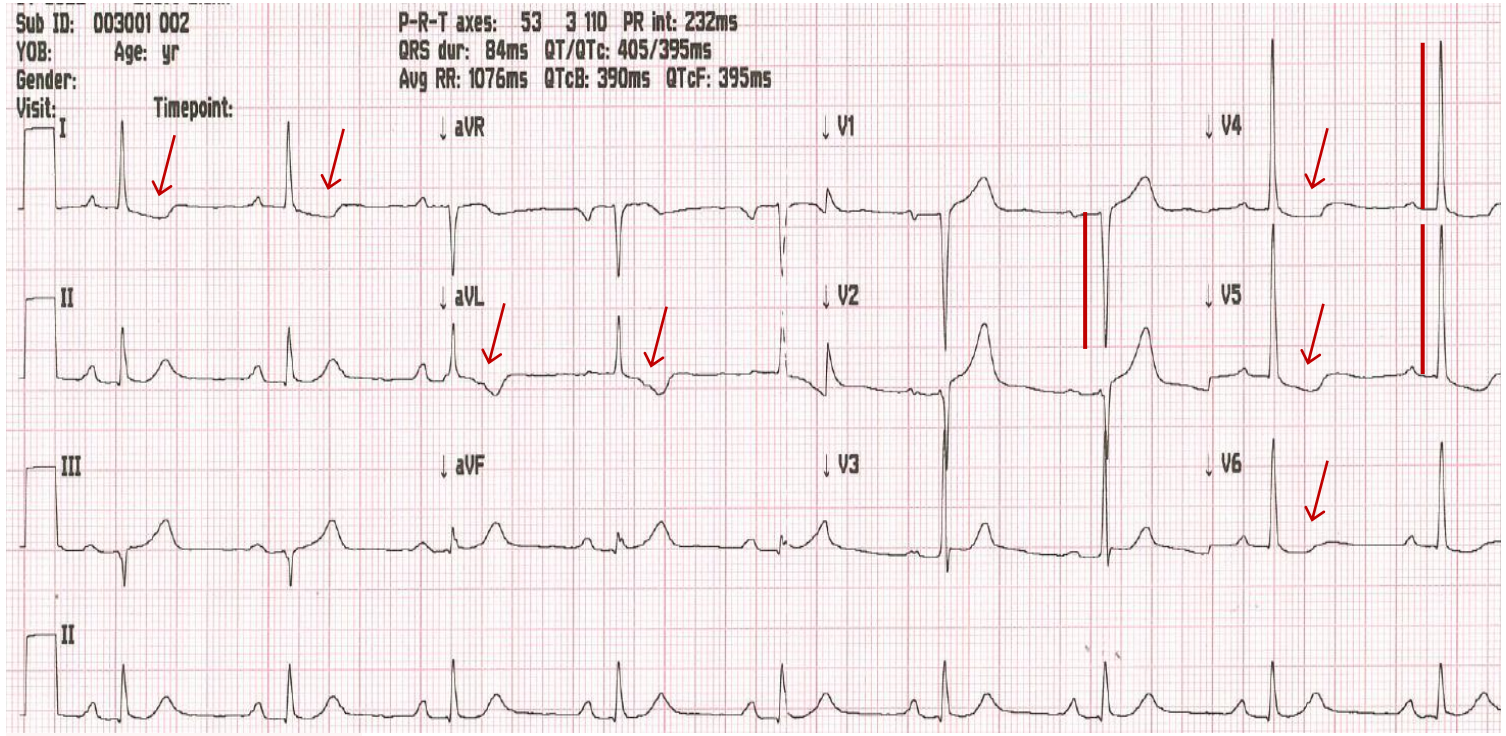




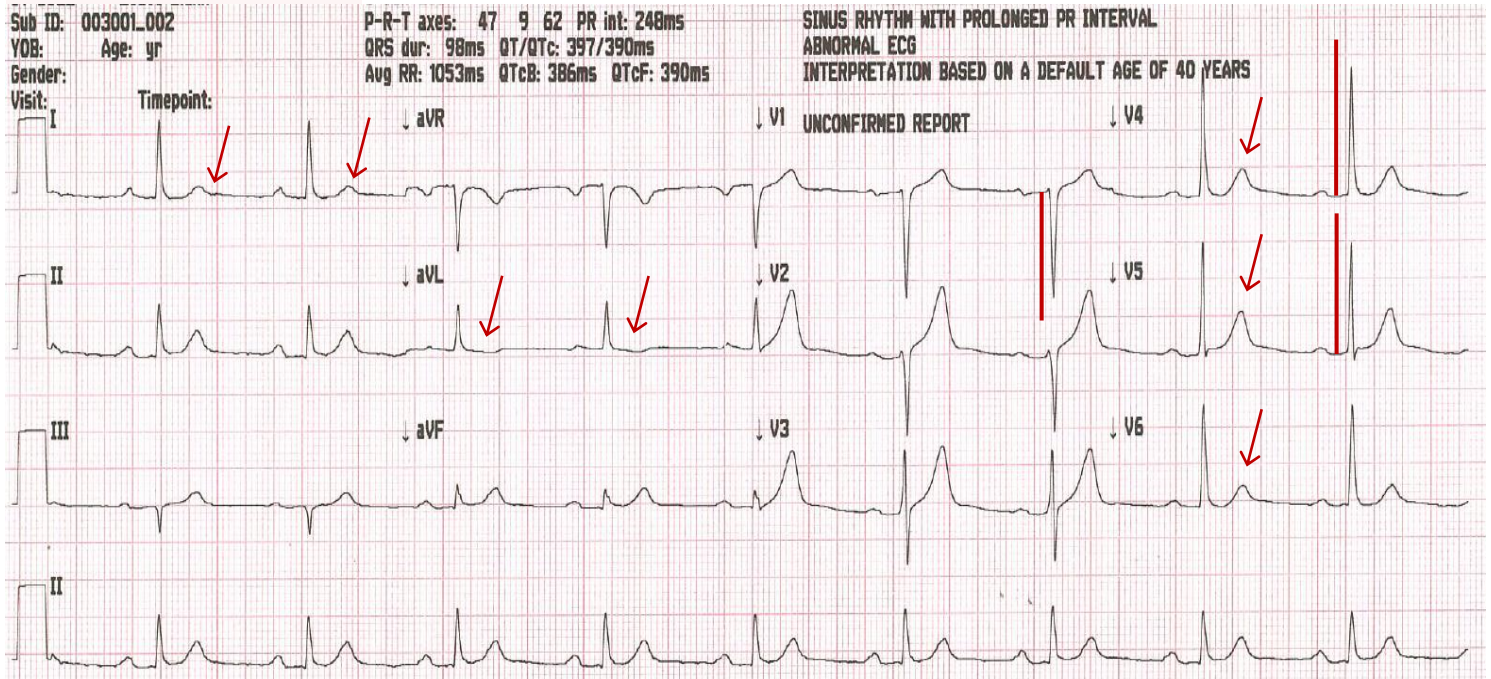


E/e’ = 5

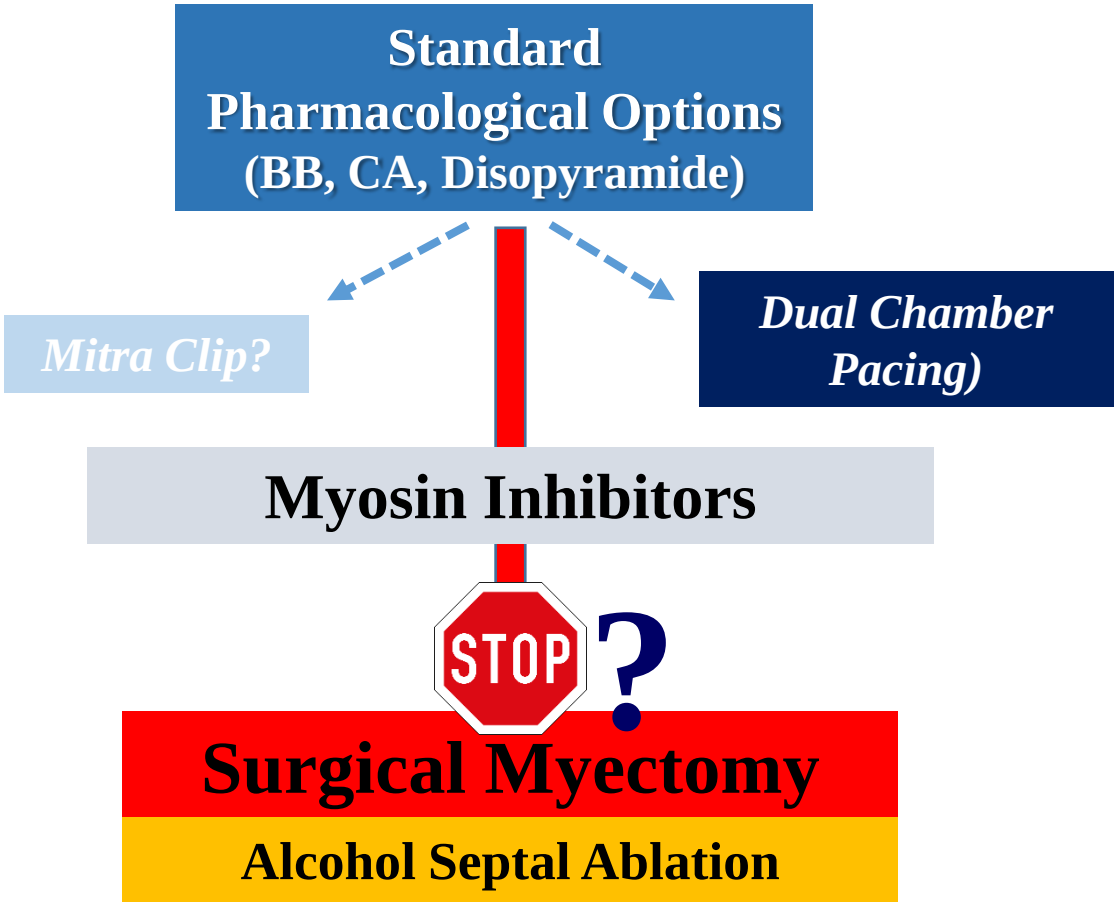
Before



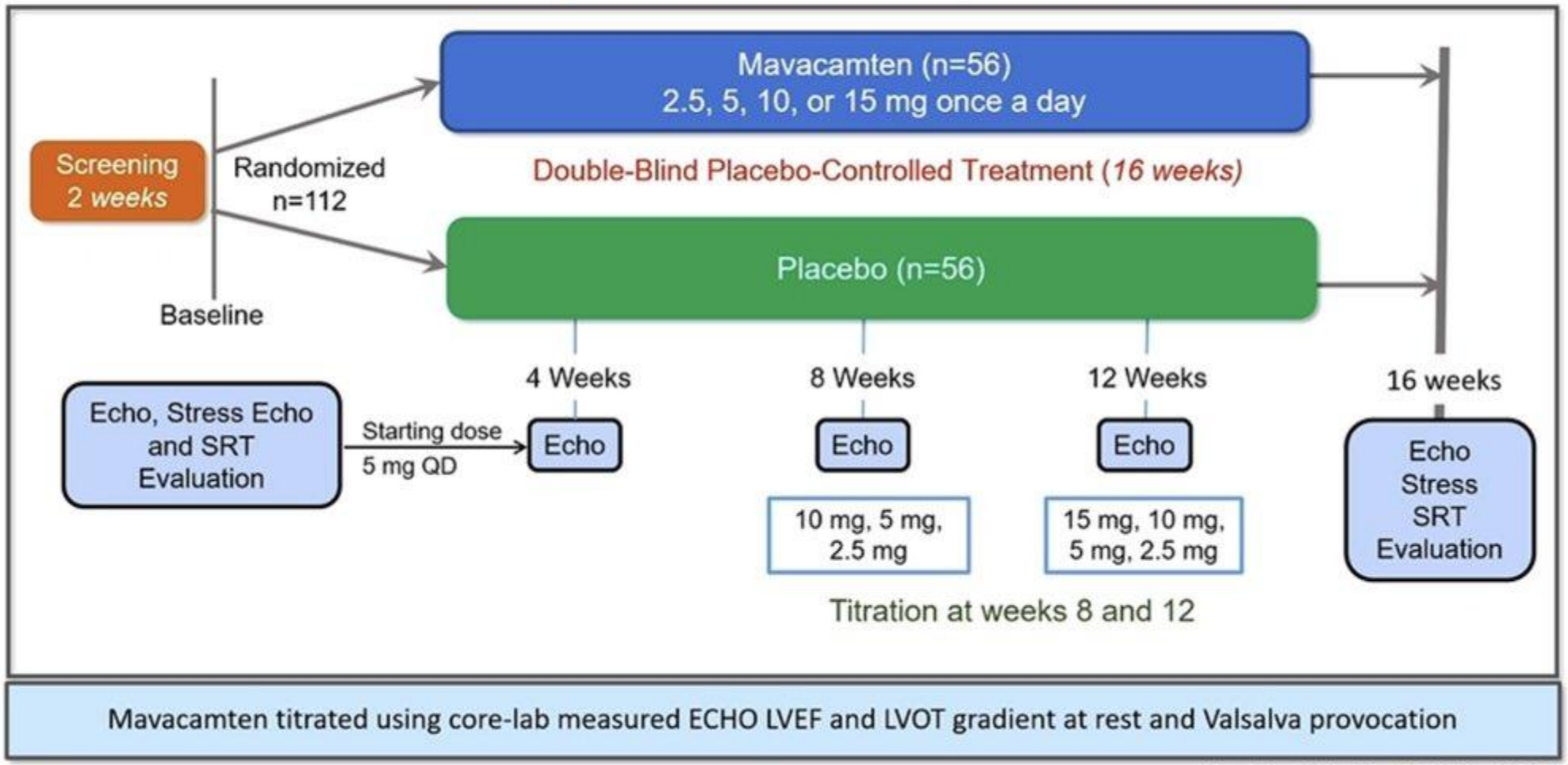
6 weeks aficamten



Treatment Options for Symptomatic LVOT Obstruction: WHAT WILL CHANGE?



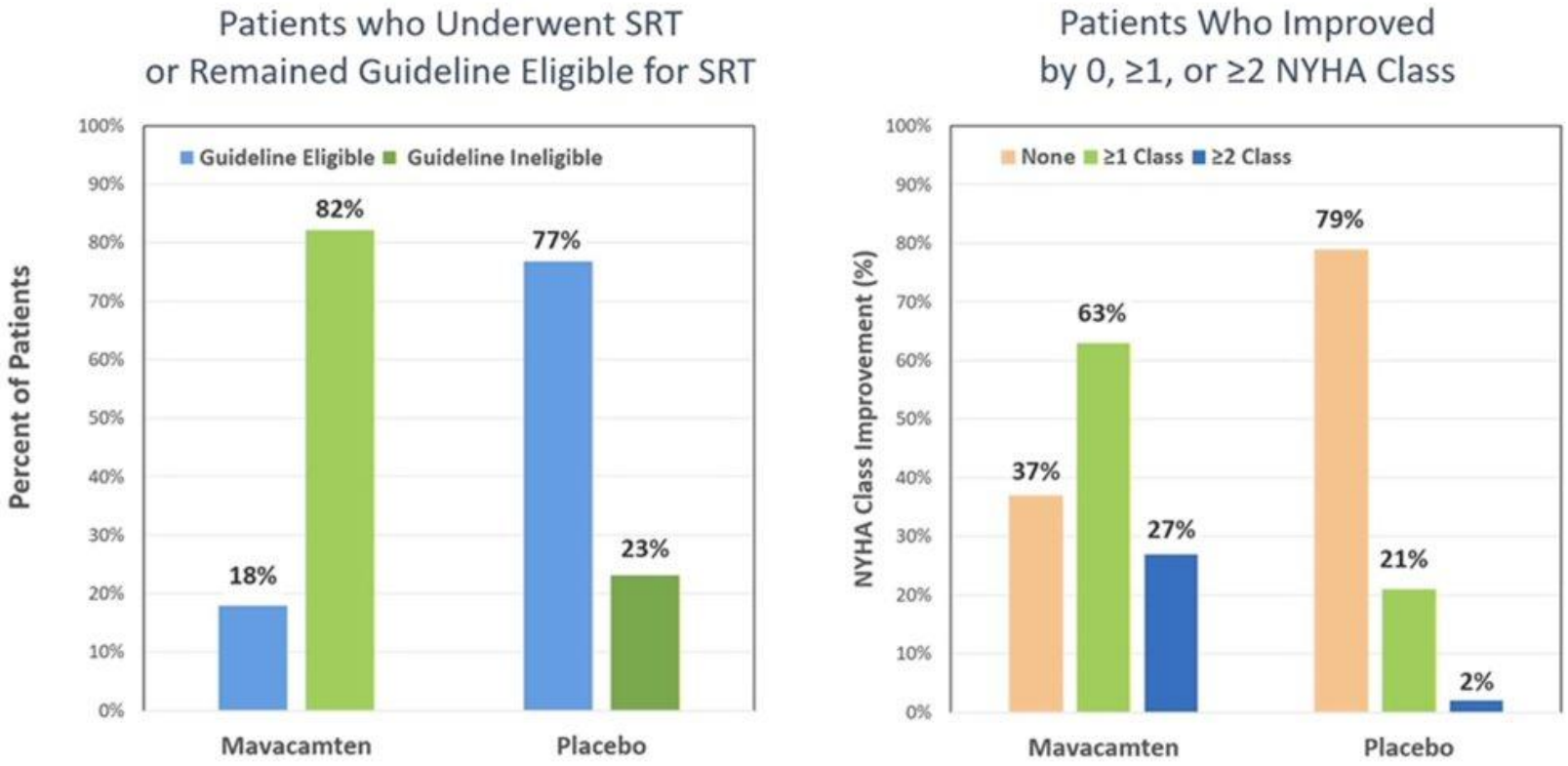
VALOR-HCM Study Design (19 US HCM Centers)



Desai M et al. Am Heart J 2021 Sep;239:80-89

Valor HCM

Primary Endpoint and NYHA Class Improvement



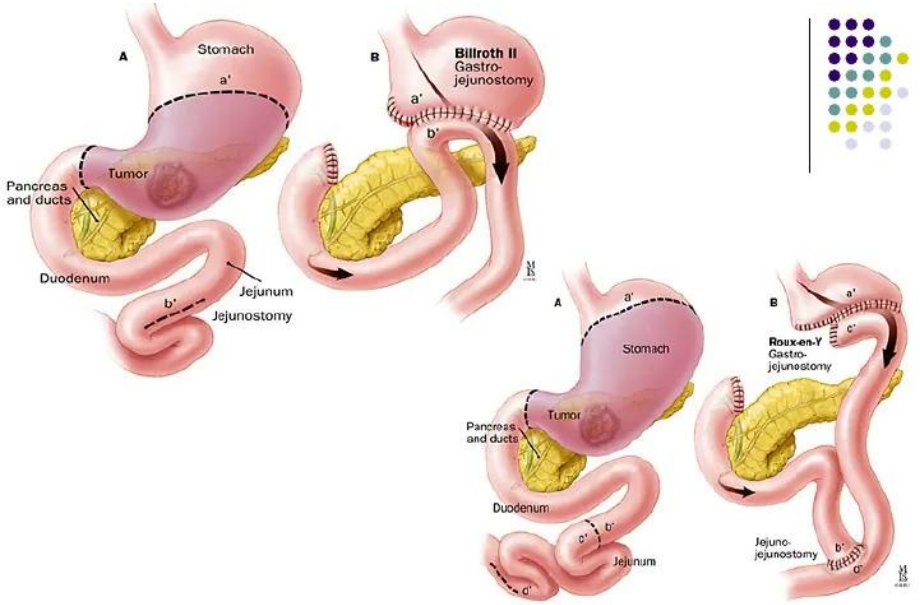
Meyer

Desai M et al ACC 2022

Mavacamten for symptomatic HCM: Holy grail or downgrade of care for surgical candidates?

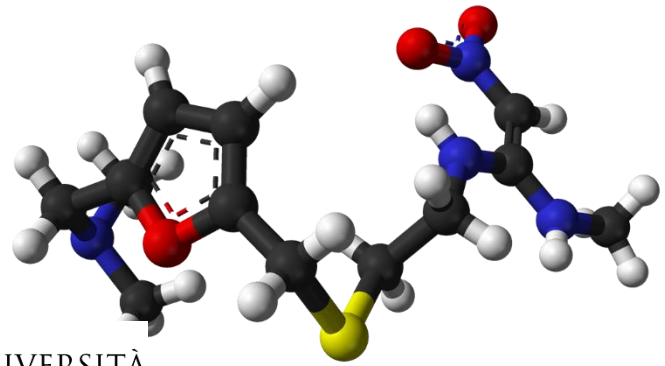
“We fear that unmeasured enthusiasm may lead to acceptance of inferior outcomes for surgical HOCM candidates. Septal myectomy is a low risk therapy proven to abolish obstruction, return to normal lifestyle and life span, and reduce arrhythmias»

Eduard Quintana, Pietro Bajona, Patrick O. Myers, The Lancet, 2020



Gastrojejunostomy : Billroth II

Gastritis



Ranitidine came into commercial use in 1981.
In 2018, it was the 41st most commonly prescribed medication in the United States, with more than 18 million prescriptions.

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OPEN QUESTIONS

- Long term safety ?
- Efficacy in nonobstructive HCM ?
- Role in HCM patients with advanced disease ?
- Antiarrhyhmic effects ?
- Pediatric patients?
- Non sarcomeric HCM ?
- Sustainability ?

National Library of Medicine
National Center for Biotechnology Information

PRS Login

ClinicalTrials.gov BETA

Resources About

Home > Search Results > Study Record

NOT YET RECRUITING

ClinicalTrials.gov Identifier: NCT05582395

A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy (ODYSSEY_HCM)

Information provided by Bristol-Myers Squibb (Responsible Party)

Last Updated: October 25, 2022

UNIVERSITÀ DEGLI STUDI FIRENZE

Meyer

Conclusions

A molecular approach targeting the specific pathophysiological mechanisms of the disease has emerged, and will hopefully change the HCM panorama in the next few years.

Optimal treatment will require evidence-based positioning of each available options, in a tailored perspective which, after 60 years, finally looks at hand.

Major challenges remain and further data are needed, to validate this molecular approaches the whole HCM spectrum.

HCM is a heterogeneous, complex disease with low hard event rates: establishing convincing end-points for clinical trials is challenging. Dedicated efforts in the field are urgently needed.