USZ Universitäts Spital Zürich

Fokus Herz Bern 2025

Eine neue Ära der Behandlung der hypertrophen Kardiomyopathie

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UniversitätsSpital Zürich, Schweiz
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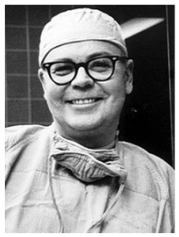
Disclosures

Speaking and consulting honoraria Bristol Myers Squibb

Speaking and consulting honoraria Cytokinetics

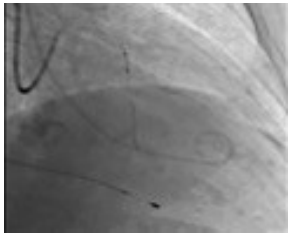
Hypertrophic cardiomyopathy – mile stones

1869, Henri Liouville – subaortic stenosis

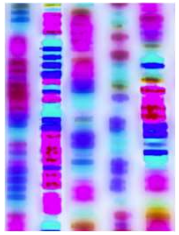


1961, Glenn Morrow - Surgery

1980, Implantation of the first defibrillator



1994, Ulrich Sigwart – septal alcohol ablation



2005, commercially available genetic tests

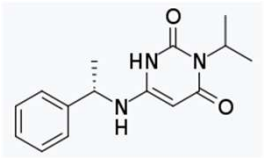
1958, Donald Teare - ‘Asymmetrical Hypertrophy of the Heart’

1971, Inge Edler and Hellmuth Hertz - 2D-echocardiography

1990, first HCM-Gene (MYH7)

2000, cardiac MRI

2022, Myosin inhibitors?



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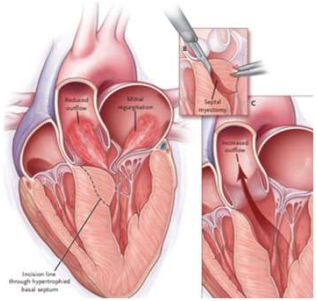
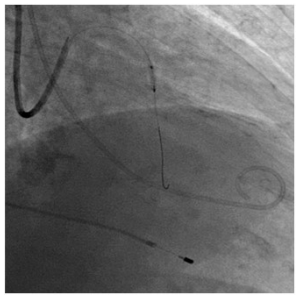
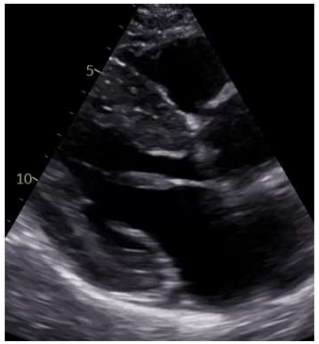
Braunwald E, Global Cardiology Science and Practice 2012;5:2-5
Feigenbaum H, Circulation 1996; 93:1321-1327

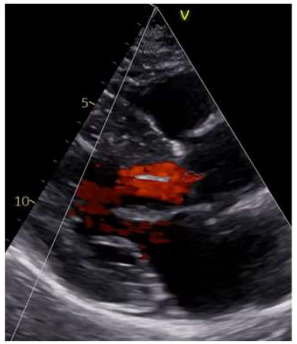
Hypertrophic cardiomyopathy – treatment development

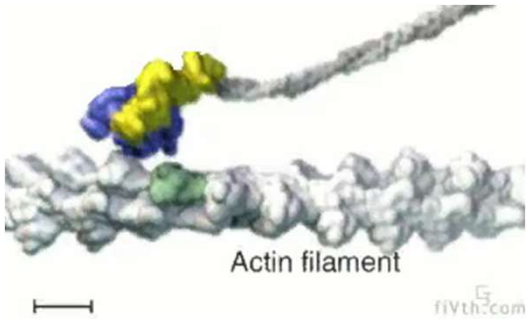
PAST **PRESENT** **FUTURE**

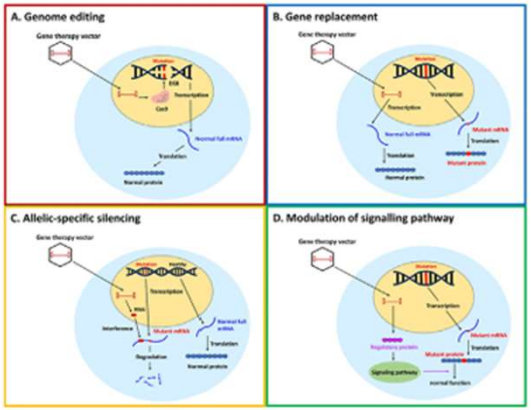












MORPHOLOGY **MOLECULAR LEVEL** **GENE THERAPY / IMMUNOLOGY**

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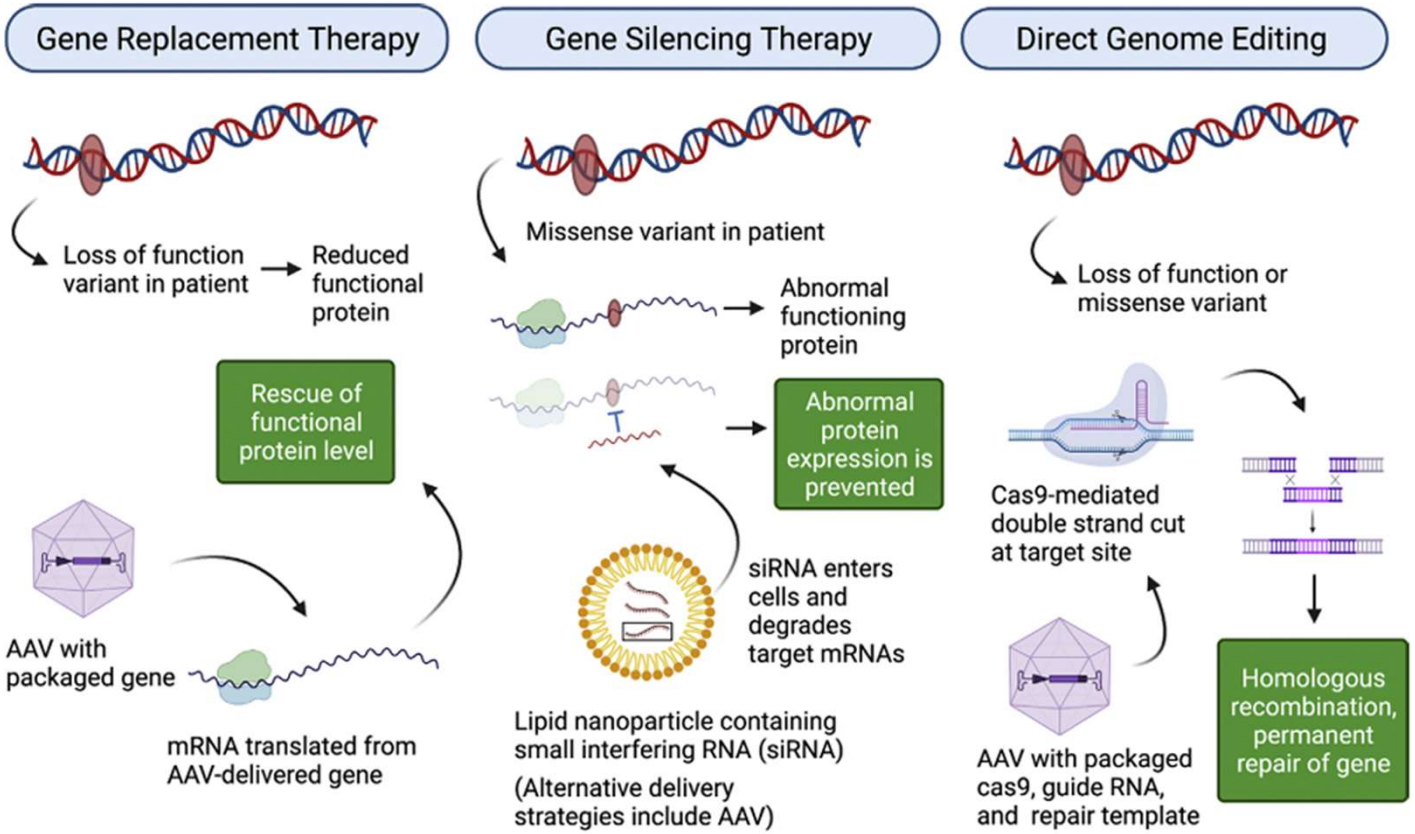
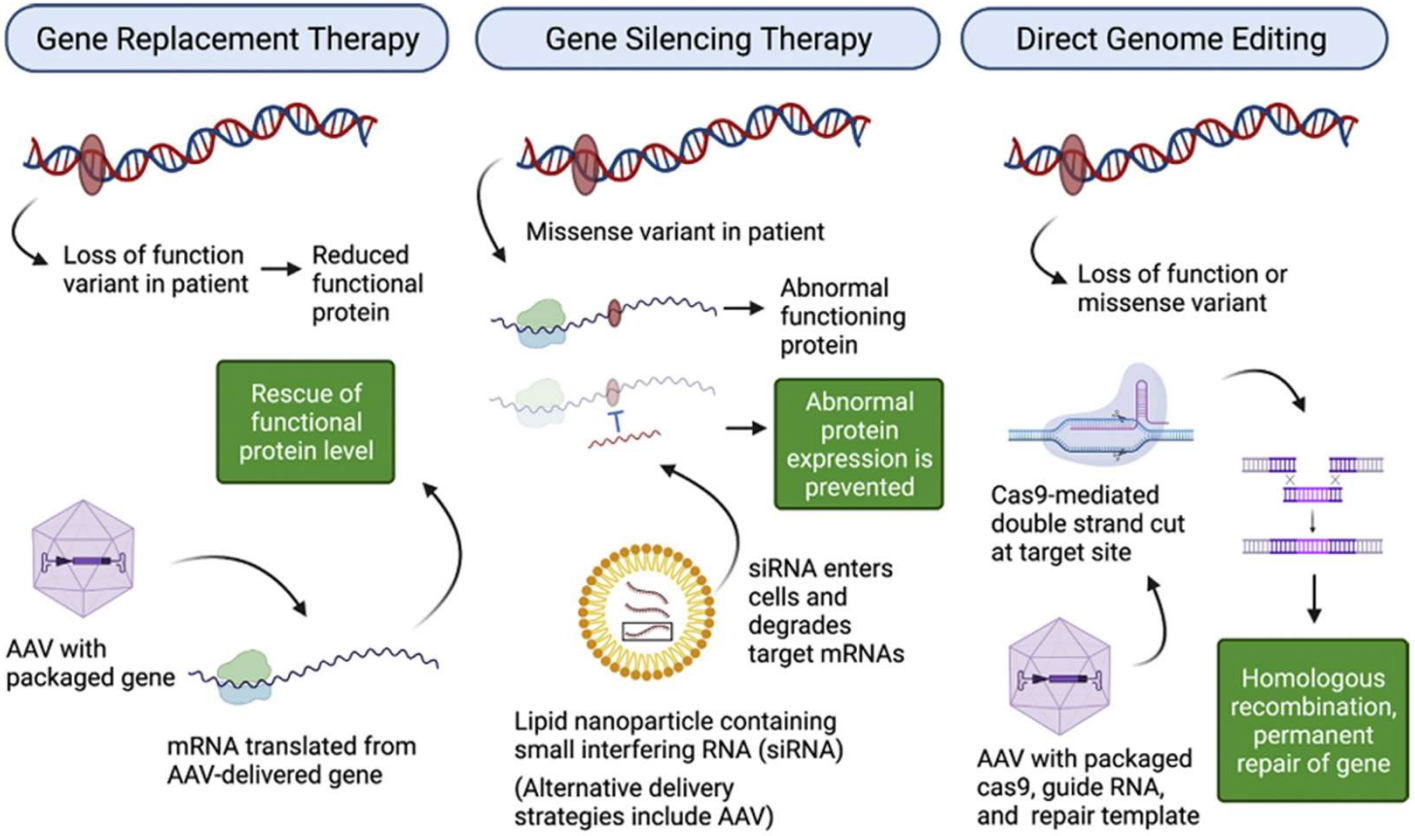
Gene therapy



Helms et al, JACC:Basic to Tranlsation Science 2022; 7(1):70-83
Maurer MS et al, NEJM 2023: 398(17):1553-65
Greenberg et al; NEJM 2025;392:972-83

Gene therapy



Danon disease, phase 1; NEJM 2025	ATTR, Patisiran, phase 3; NEJM 2023

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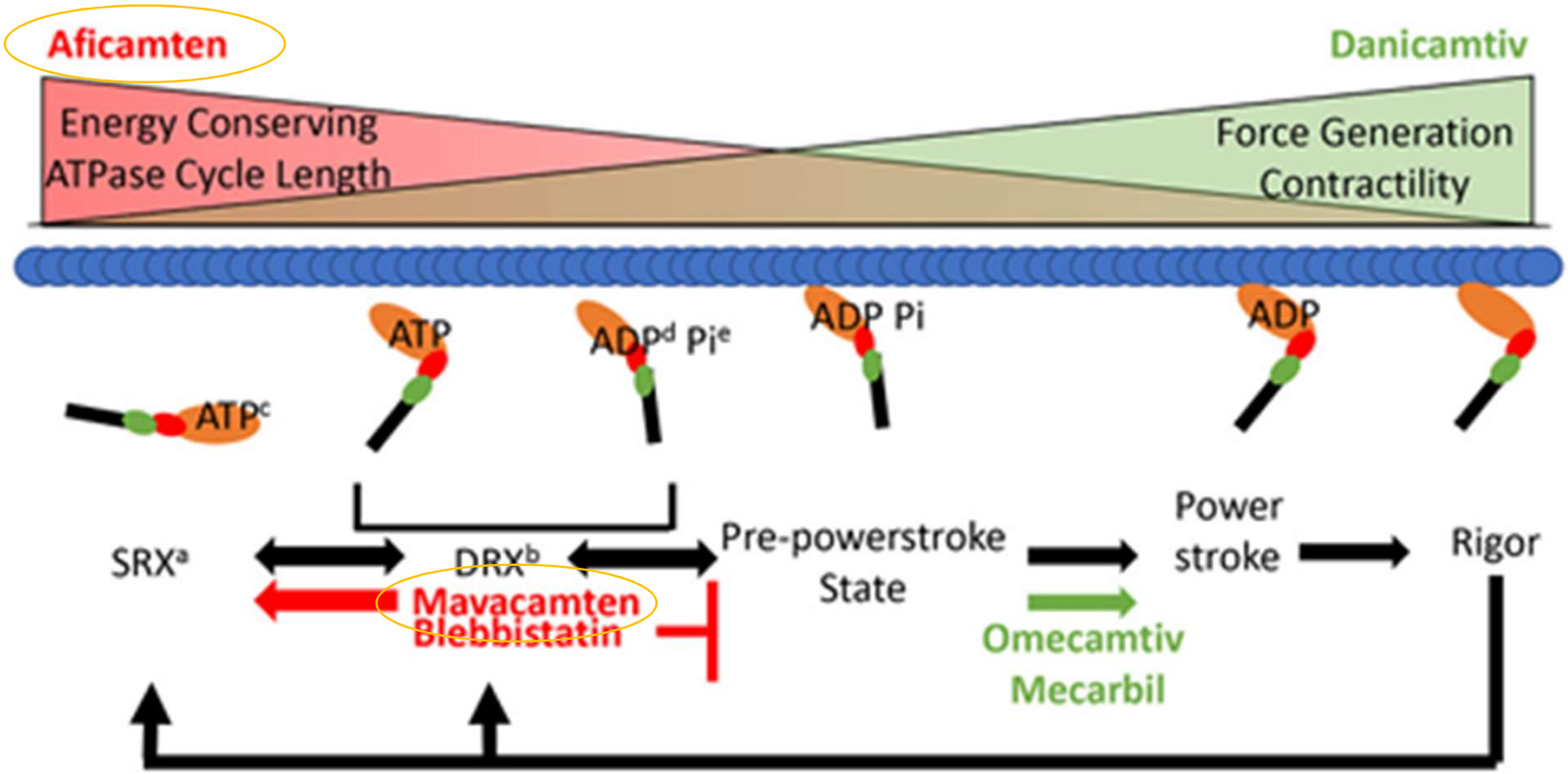
(Hypertrophic) cardiomyopathy – myosin modulators



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Lehman et al, Nat Rev Cardiol 2022; 19(6):353-363

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**

Dose-Blinded Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy: Outcomes Through 32 Weeks

Milind Y. Desai, MD, MBA; Anjali Owens, MD; Jeffrey B. Geske, MD; Kathy Wolski, MPH; Sara Saberi, MD, MS; Andrew Wang, MD; Mark Sherrid, MD; Paul C. Cremer, MD, MS; Srihari S. Naidu, MD; Nicholas G. Smedira, MD, MBA; Hartzell Schaff, MD; Ellen McErlean, RN, MSN; Christina Sewell, RN; Aarthi Balasubramanyam; Kathy Lampl, MD; Amy J. Sehnert, MD; Steven E. Nissen, MD

The NEW ENGLAND JOURNAL of MEDICINE

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

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

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

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	Mavacamten	Aficamten
T1/2	6-9 days	3-4 days
CYP2C19	yes	no
Approved	yes	not yet

Table 1. Key characteristics of all phase 3 trials on cardiac myosin inhibitors for patients with symptomatic obstructive hypertrophic cardiomyopathy

	Mavacamten[a]			Aficamten[b]
	EXPLORER-HCM	VALOR-HCM	EXPLORER-CN	SEQUOIA-HCM
Phase 3 trials (number of patients)	30 weeks (n = 251)	16 weeks (n = 112)	30 weeks (n = 81)	24 weeks (n = 282)
Key inclusion criteria	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥55% • NYHA class II or III	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥60% • NYHA class III/IV or class II with exertional syncope • referred for and actively considering SRT • on maximally tolerated background HCM therapy	• peak LVOT gradient of ≥50 mm Hg at rest or after Valsalva • LVEF of ≥55% • NYHA class II or III	• LVEF ≥60% • LVOT gradient ≥30 mm Hg at rest and ≥50 mm Hg after Valsalva • NYHA class II or III • decreased exercise capacity, defined by a predicted peak oxygen uptake of 90% or less based on age and sex
Key patient characteristics	• mean age 59 years • 59% men • 73% NYHA class II, 27% class III/IV • 75% on beta blockers	• mean age 60 years • 51% men • 93% NYHA class III/IV, 7% class II • 75% on beta blockers (36% on combination therapy, including disopyramide)	• mean age 52 years • 72% men • 82% NYHA class II, 18% class III • 89% on beta blockers	• mean age 59 years • 59% men • 76% NYHA class II, 24% class III/IV • 61% on beta blockers (11% on disopyramide) • 15% not on background HCM therapy
Starting dose and dose titration	5 mg/day with dose titration at 8 and 12 weeks		2.5 mg/day with dose titration at 8, 14, and 20 weeks	5 mg/day with dose titration at 2, 4, and 6 weeks
Key primary endpoint(s)	1.5 mL/kg/min or greater increase in pVO_2 and at least one NYHA class reduction or 3.0 mL/kg/min or greater increase in pVO_2 without NYHA class worsening	patient deciding to proceed with SRT or continuing to meet guideline eligibility for SRT	change in Valsalva LVOT peak gradient from baseline to week 30	change in pVO_2 from baseline to week 24
Key secondary endpoints	change from baseline to week 30: • post-exercise LVOT gradient • pVO_2 • proportion of patients with at least one NYHA class improvement • KCCQ-23 CSS • HCMSQ subscore	change from baseline to week 16: • post-exercise LVOT gradient • NYHA functional class • KCCQ-23 CSS • NT-proBNP • cardiac troponin I	proportion of patients at week 30 with • Valsalva LVOT peak gradient <30 mm Hg • Valsalva LVOT peak gradient <50 mm Hg • at least 1 NYHA class improvement change from baseline to week 30: • resting LVOT peak gradient • KCCQ-23 CSS • NT-proBNP • high-sensitivity cardiac troponin I • LVMI evaluated by cardiac magnetic resonance	change from baseline to week 24: • KCCQ-23 CSS • NYHA class • LVOT Valsalva gradient • Valsalva LVOT gradient < 30 mm Hg • duration of eligibility for SRT • total workload on CPET change from baseline to week 12: • KCCQ-23 CSS • NYHA functional class • LVOT Valsalva gradient • Valsalva LVOT gradient <30 mm Hg
Criteria for therapy interruption	LVEF <50% for temporary interruption or <30% for permanent discontinuation			LVEF <40%
Dose adjustments and therapy interruptions	core-lab			site-read
Drug dosages	last dose at end of double-blind period: • 2.5 mg = 6% • 5 mg = 49% • 10 mg = 33% • 15 mg = 11%	last dose at end of double-blind period: • 2.5 mg = 21% • 5 mg = 23% • 10 mg = 34% • 15 mg = 21%	last dose at end of double-blind period: • 2.5 mg = 6% • 5 mg = 59% • 10 mg = 30% • 15 mg = 4%	dose at end of escalation phase: • 5 mg = 3% • 10 mg = 13% • 15 mg = 35% • 20 mg = 49%
Primary findings	37% of patients on mavacamten vs. 17% on placebo met the primary endpoint (difference +19.4%, 95% CI, 8.7 to 30.1; p = 0.0005)	76.8% of patients assigned to placebo and 17.9% assigned to mavacamten met guideline criteria or underwent SRT (difference 58.9%, 95% CI, 44.0 to 73.9; p < 0.001)	LSM difference in post-Valsalva LVOT gradient between mavacamten and placebo was −70.3 mm Hg (95% CI, −89.6 to −50.9 mm Hg; one-sided p < 0.001)	LSM difference in pVO_2 between aficamten and placebo was 1.7 mL/kg/min (95% CI, 1.0 to 2.4; p < 0.001)
Key secondary findings	all key secondary endpoints were significantly positive in favor of mavacamten vs. placebo			all key secondary endpoints were significantly positive in favor of aficamten vs. placebo
LVEF reduction during trial	−4.0%; 95% CI, −5.5 to −2.5		LSM change, 3.7% in mavacamten vs. 3.0% in placebo	−4.8%; 95% CI, −6.3 to −3.2
LVEF <50%	total of 9 patients through week 30 (5 during the study at week 26 [3 on mavacamten and 2 on placebo] and an additional 4 on mavacamten at week 30)	total of 2 patients on mavacamten through week 16	0 patients through week 30	total of 5 patients on aficamten through week 24 and 1 on placebo

Desai and Braunwald, Med July 2024: 655-659

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4/5 patients improvement of:

- NYHA functional class
- Peak VO2
- LVOT obstruction
- Cardiac biomarkers

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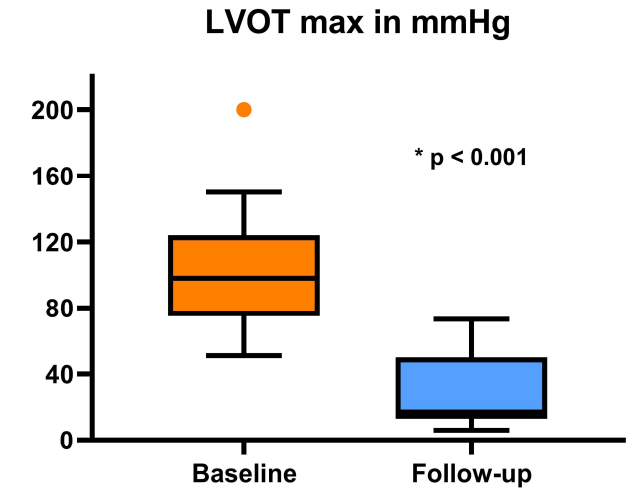
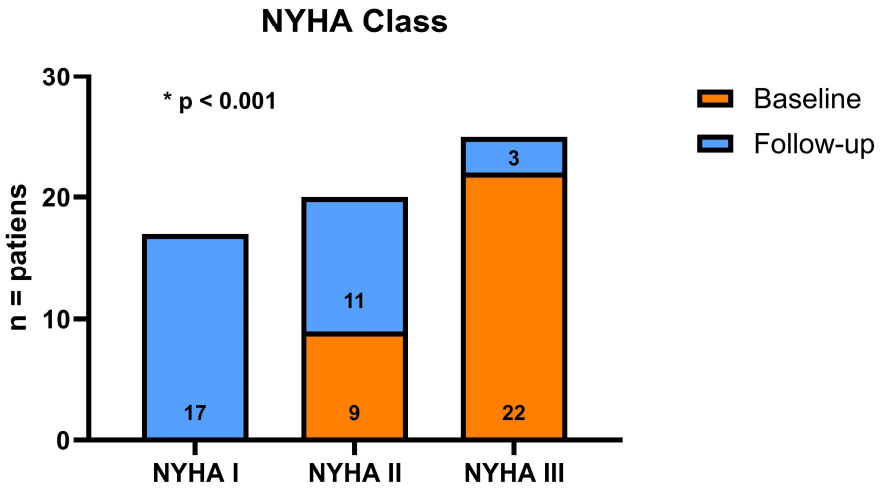
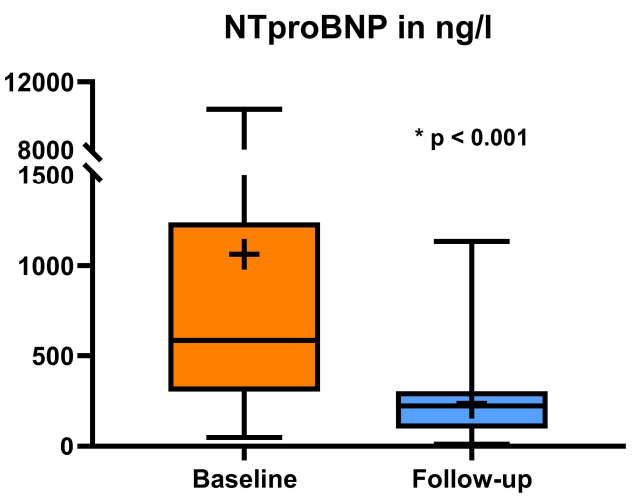
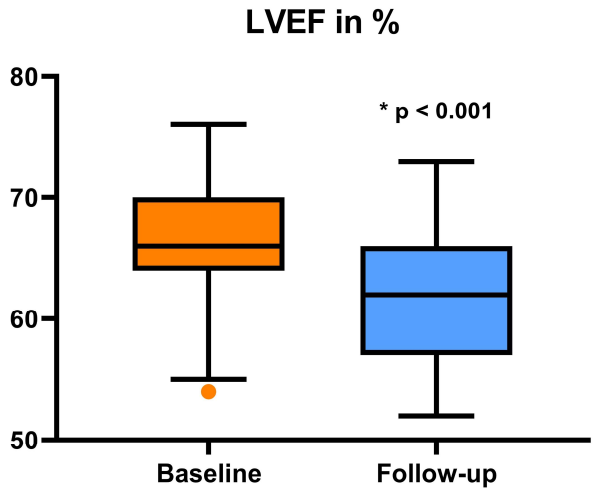
Desai and Braunwald, Med July 2024: 655-659

USZ cohort, Dec 2024: n = 31, mean FU 8.6 months (3 – 16 months)



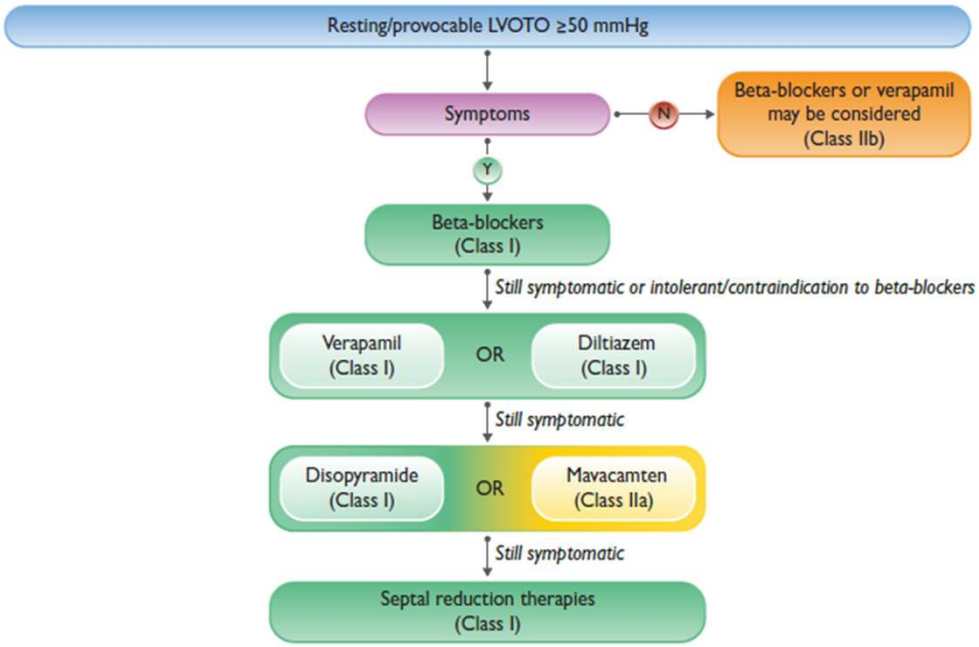




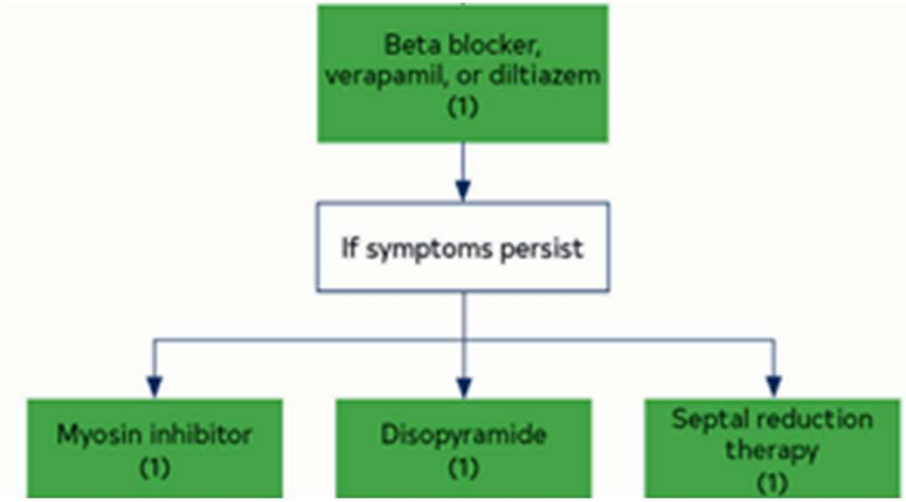


Hypertrophic cardiomyopathy – myosin inhibitors - myectomy

EUROPE



NORTH AMERICA



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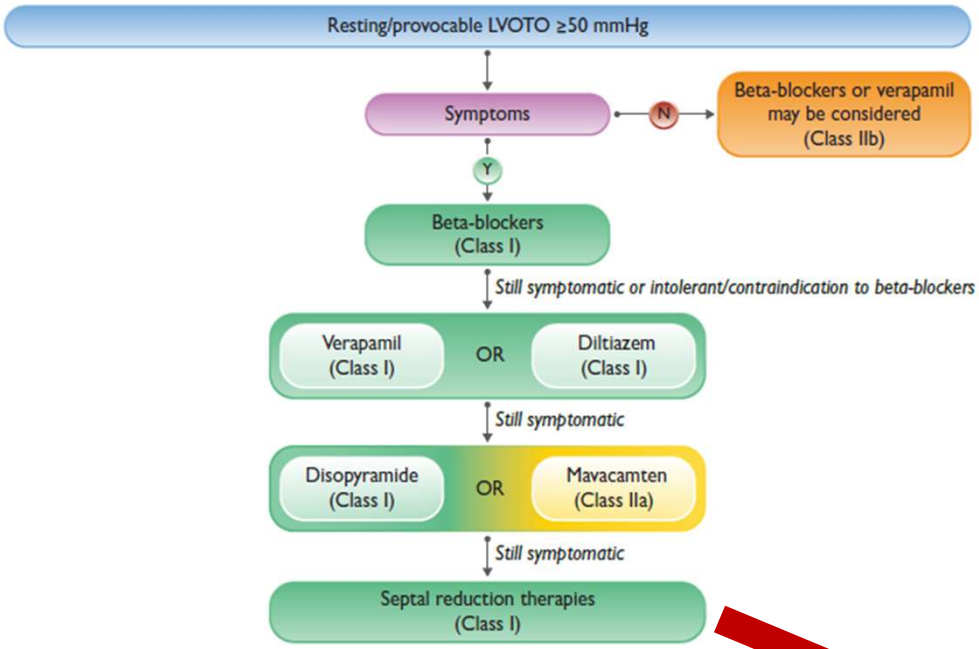
2023 Guidelines for the managament of cardiomyopathies, EHJ (2023):00, 1-124
2024 Guideline for the managament of hypertrophic cardiomyopathy, JACC (2024):83:2324-2405

Hypertrophic cardiomyopathy – myosin inhibitors - myectomy

EUROPE



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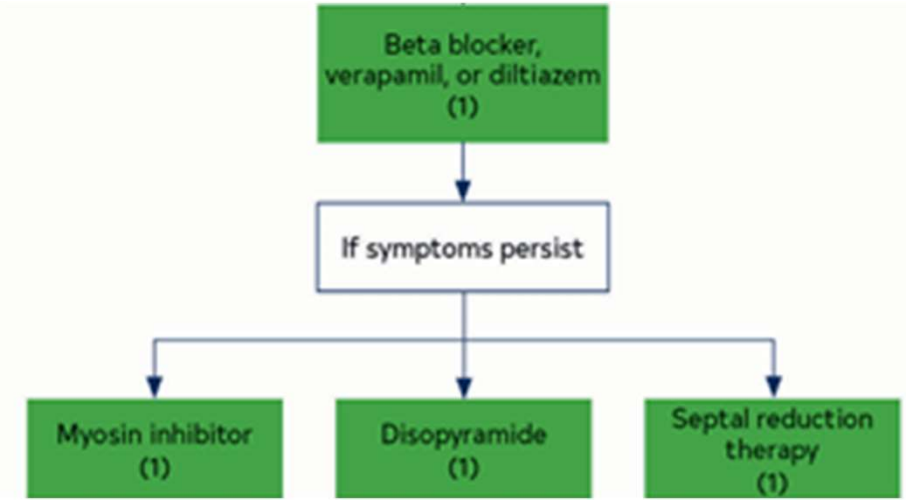

- Pregnancy
- Concomittant intrinsic mitral valve disease
- Syndromic HCM
- Storage diseases / infiltrative disorders

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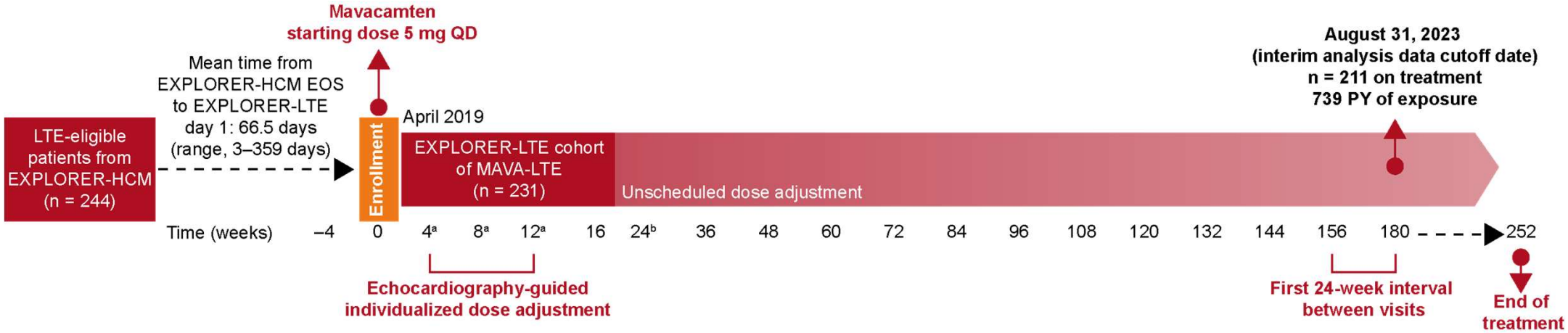
Study design: MAVA-LTE (EXPLORER cohort)



After titration, patients were assessed at 12-week intervals between weeks 24 and 156; week 180 was the first visit after a 24-week interval

Mavacamten was temporarily discontinued if site-read LVEF was < 50% at any visit; patients could resume treatment at 1 dose level lower than the previous dose if LVEF was ≥ 50% at the follow-up visit 4–6 weeks later

Titration scheme differs from CAMZYOS® (Mavacamten) Product information. For details see www.swissmedicinfo.ch.
Patients completed an 8-week washout period after treatment in EXPLORER-HCM before enrollment in MAVA-LTE. Owing to the COVID-19 pandemic, patients had variable time without receiving treatment after completing the parent study. [a]Dose adjustments were based on site-read echocardiography measures of Valsalva LVOT gradient and LVEF. [b]Dose adjustment was also possible at week 24 after site-read echocardiography assessment of postexercise LVOT gradient. Subsequent to week 24, dose adjustment was possible if site-read Valsalva LVOT gradient was > 30 mm Hg and LVEF was ≥ 50%
EOS, end of study; HCM, hypertrophic cardiomyopathy; LTE, Long-Term Extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; PY, patient-years; QD, once daily

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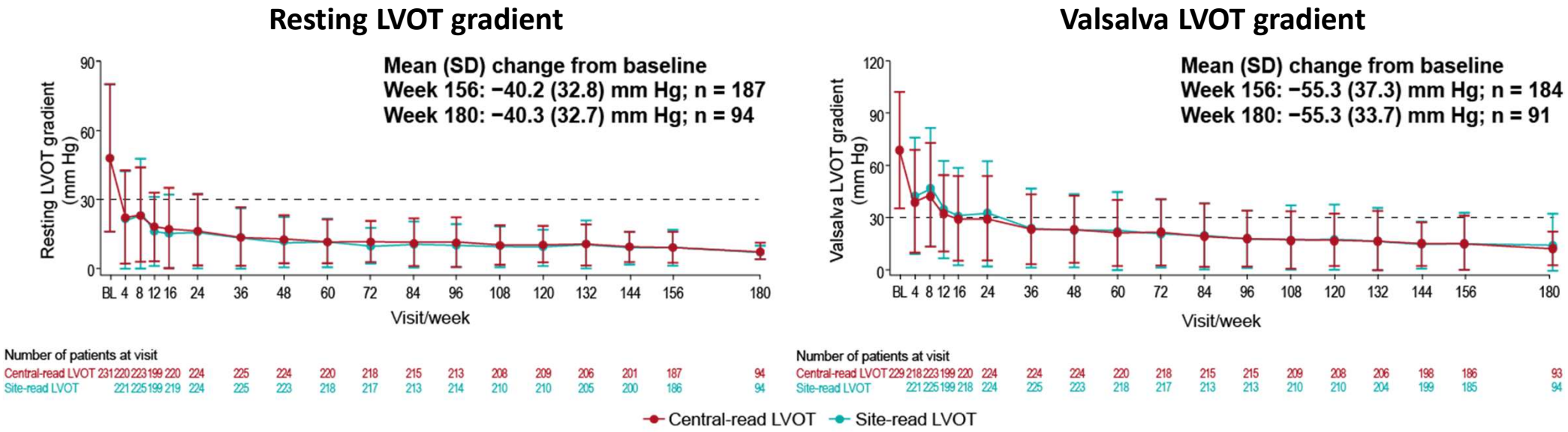
Garcia-Pavia et al, EHJ 2024; 45:5071-5083

Sustained improvements in LVOT gradients over 3.5 years of treatment



- Improvements in resting and Valsalva LVOT gradients with mavacamten treatment were sustained through weeks 156 and 180, as confirmed by both site-read and central-read echocardiograms
- Overall, 191 patients (82.7%) achieved a central-read Valsalva LVOT gradient of ≤ 30 mm Hg – indicative of no obstruction – during the study and remained at or below the 30 mm Hg threshold until the data cutoff

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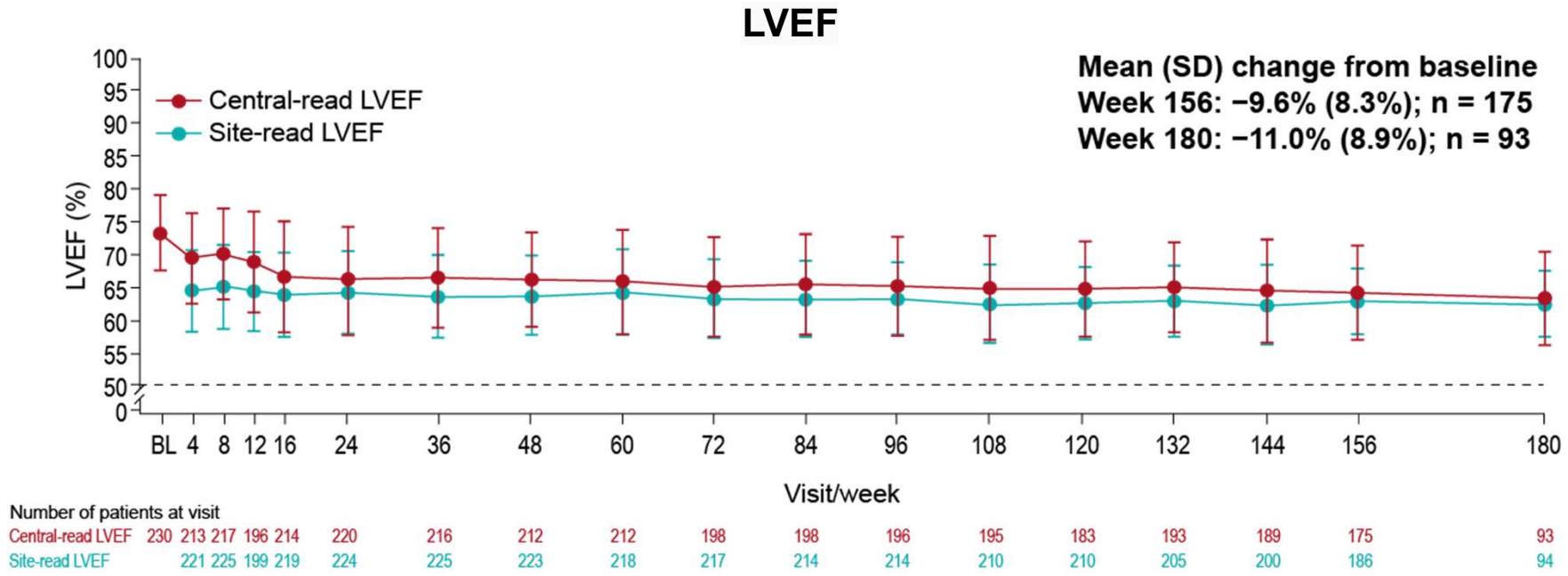
Garcia-Pavia et al, EHJ 2024; 45:5071-5083

Change in LVEF from baseline through week 180



After an initial reduction in mean LVEF from baseline during the dose titration period, no further clinically meaningful reduction in LVEF through week 180 was observed

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Garcia-Pavia et al, EHJ 2024; 45:5071-5083

Safety: TEAEs

	Patients, n (%)	Events, n	Exposure-adjusted incidence per 100 PY (PY)	
			Day 1 to week 60	Day 1 to week 252
TEAEs	228 (98.7)	1870	187.7 (108.2)	174.6 (130.6)
Events of clinical interest	161 (69.7)	433	50.53 (213.7)	39.55 (402.0)
Atrial fibrillation	33 (14.3)	68	6.57 (274.1)	4.50 (689.2)
Cardiac failure	14 (6.1)	15	3.55 (282.0)	1.94 (721.7)
Ejection fraction decreased	13 (5.6)	15	2.12 (282.9)	1.51 (729.0)
Serious TEAEs	63 (27.3)	117	11.09 (270.5)	9.13 (657.3)
CV serious events of clinical interest[a]	28 (12.1)	40	–	–
Atrial fibrillation	14 (6.1)	20	2.12 (283.3)	1.64 (730.0)
Cardiac failure	5 (2.2)	5	1.40 (284.9)	0.68 (737.7)
Ejection fraction decreased	5 (2.2)	5	0.70 (286.1)	0.67 (741.0)
Drug-related serious TEAEs	10 (4.3)	10[b]	–	–
TEAEs resulting in permanent treatment discontinuation	13 (5.6)	17	–	–
Death	5 (2.2)	5[c]	–	–

- The exposure-adjusted incidence per 100 PY of all TEAEs was lower for the day 1 to week 252 period than for the day 1 to week 60 period (174.6 vs 187.7)
- Of the 33 patients who experienced TEAEs of atrial fibrillation, 15 (45.5%) had a medical history of atrial fibrillation
- Of the 10 patients who experienced drug-related serious TEAEs, 6 (60.0%) remained on treatment at the data cutoff date
- All 5 deaths that occurred during the study were considered to be unrelated to mavacamten treatment

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Garcia-Pavia et al, EHJ 2024; 45:5071-5083

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Garcia-Pavia et al, EHJ 2024; 45:5071-5083

Mavacamten – atrial fibrillation

HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

Heart Rhythm Society SM

Research Letter

Check for updates

Incidence of newly recognized atrial fibrillation in patients with obstructive hypertrophic cardiomyopathy treated with Mavacamten

Matteo Castrichini, MD,[1,2] Said Alsidawi, MD,[3] Jeffrey B. Geske, MD,[1] Darrell B. Newman, MD,[1] Adelaide M. Arruda-Olson, MD, PhD,[1] J. Martijn Bos, MD, PhD,[2] Steve R. Ommen, MD,[1] Konstantinos C. Siontis, MD,[1] Michael J. Ackerman, MD, PhD,[1,2,4] John R. Giudicessi, MD, PhD[1,2]

Philadelphia – real world

- N = 96
- 23 (24%) history of AF
- 11 (11%) with AF episodes since start Mavacamten (6 pts new onset, 5 pts recurrent)

Mayo – real world

- N = 63
- 17 (27%) history of AF
- 20 (32%) with AF episodes since start Mavacamten (7 pts new onset, 13 pts recurrent)

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Atrial Fibrillation in Patients Receiving Mavacamten for Obstructive Hypertrophic Cardiomyopathy

Real-World Incidence, Management, and Outcomes

Thomas A. Boyle, MD,* Nosheen Reza, MD,* Matthew Hyman, MD, PhD, Gregory Supple, MD, Vincent Y. See, MD, MS, Amy Marzolf, CRNP, Nicole Hornsby, CRNP, Alejandro de Feria, MD, Teresa Wang, MD, Kenneth B. Margulies, MD, Anjali Tiku Owens, MD,† David S. Frankel, MD†

Boyle et al, JACC Clinical EP 2025; 2:411-413
Castrachini et al, HeartRhythm2024; 21: 2065-2067

Mavacamten – atrial fibrillation

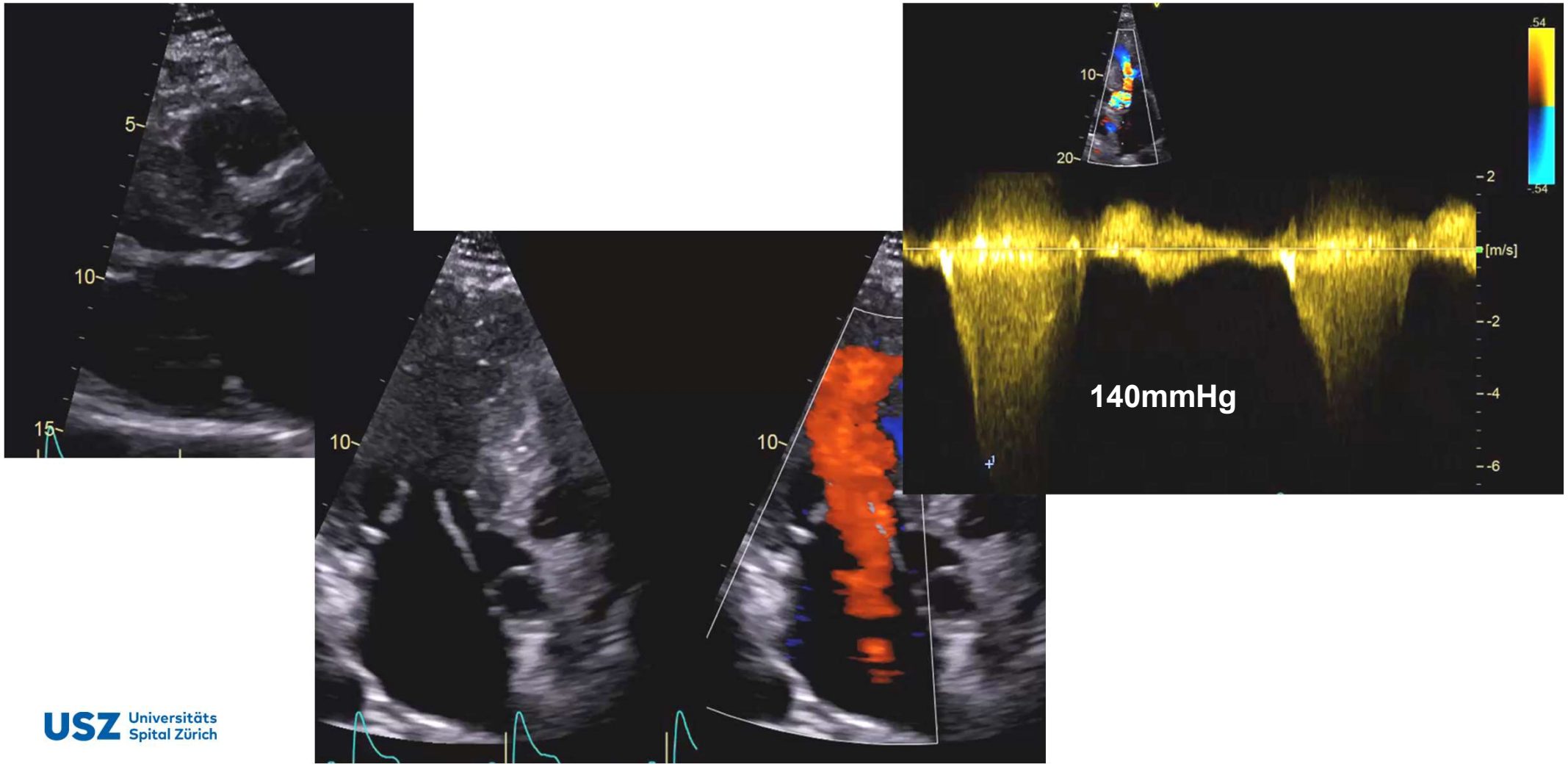
Study	N	Mean age	% Male	History of AF	LVEF	LVOT rest	LAVi	New onset AF
Mava-LTE	228	60	61	41/18%	74%	48mmHg	38ml/m^2	18/8%
Valor – 128 weeks	108	60	54	16/17%	68%	50mmHg	41ml/ml^2	11/10%
Real-world-Philadelphia	96	63	46	23/24%	68%	56mmHg	?	6/6%
Real-world-Mayo	63	60	56	17/27%	70%	?	44ml/ml^2	7/11%

Mavacamten – atrial fibrillation

Study	N	Mean age	% Male	History of AF	LVEF	LVOT rest	LAVi	New onset AF
Mava-LTE Median FU-time 166 weeks	228	60	61	41/18%	74%	48mmHg	38ml/m^2	18/8%/2.5%
Valor – 128 weeks FU-time 120	108	60	54	16/17%	68%	50mmHg	41ml/ml^2	11/10%/4.3%
Real-world-Philadelphia Median FU-time 47 weeks	96	63	46	23/24%	68%	56mmHg	?	6/6% ≈
Real-world-Mayo Median FU-time 32 weeks	63	60	56	17/27%	70%	?	44ml/ml^2	7/11%/14%

Annual incidence of atrial fibrillation in HCM 2-7%

11/2023 – 45 ♂, genotype negative, proBNP 920ng/l, Bisoprolol 7.5mg



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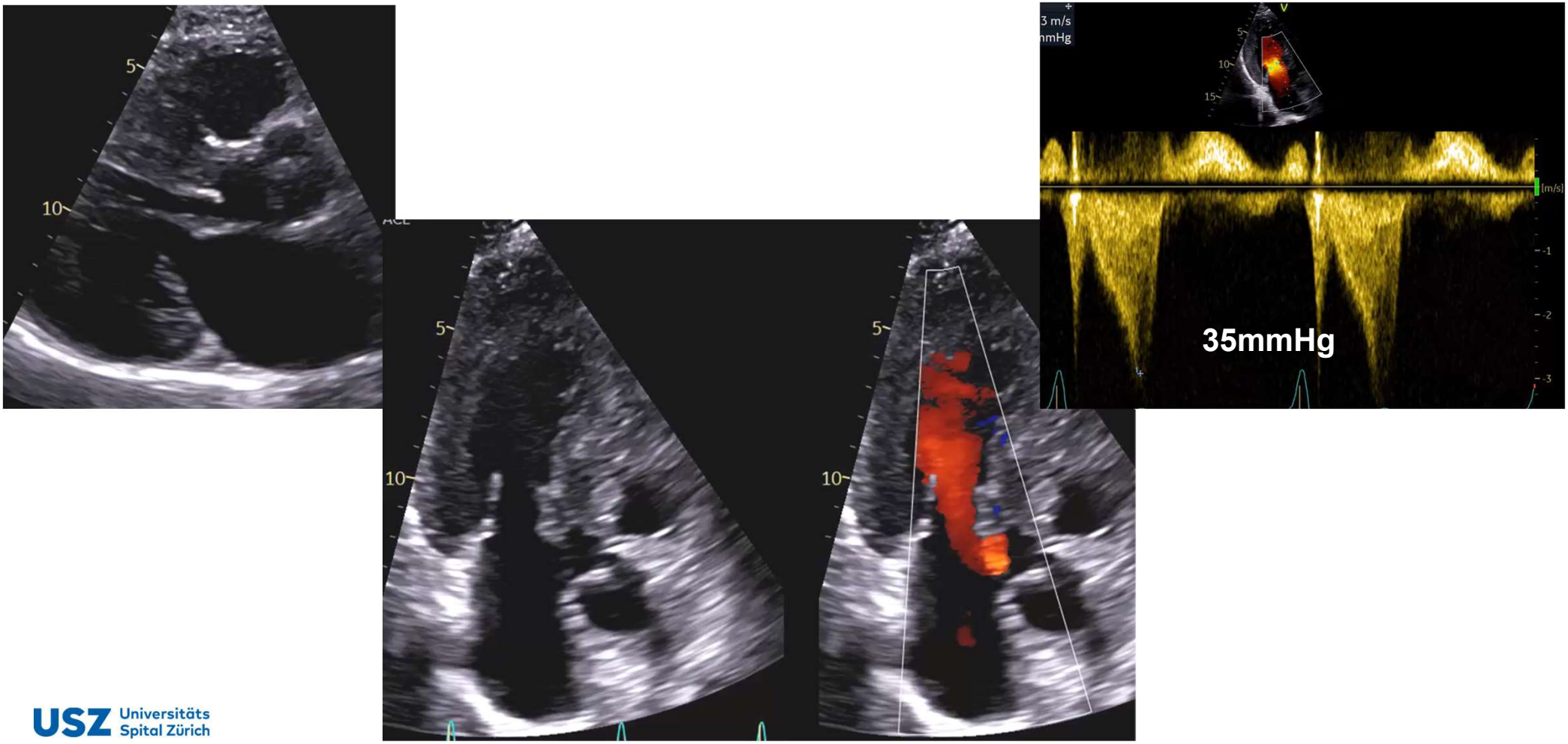
01/2025 – 46 ♂, proBNP 120ng/l, Bisoprolol 7.5mg + Mavacamten 15mg



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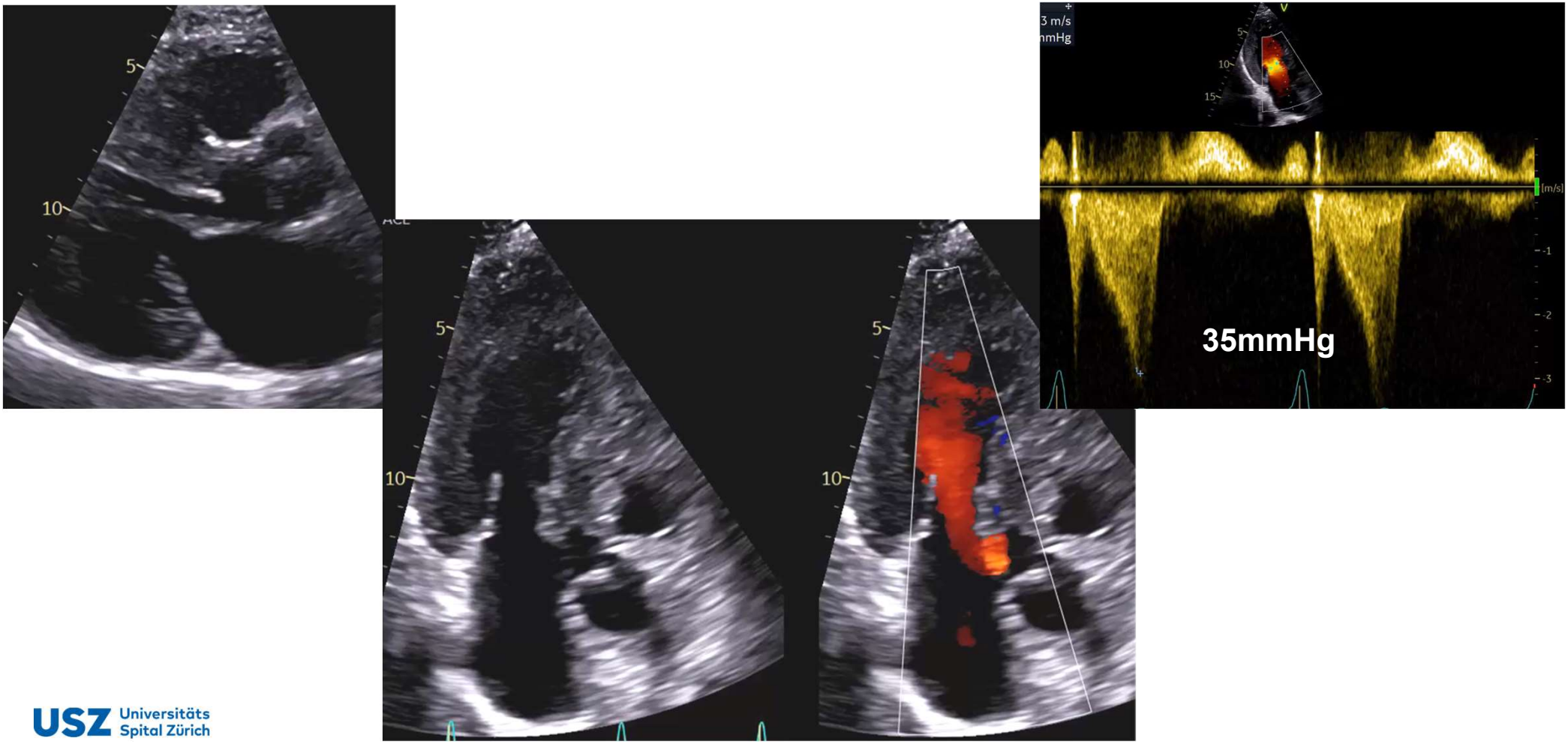

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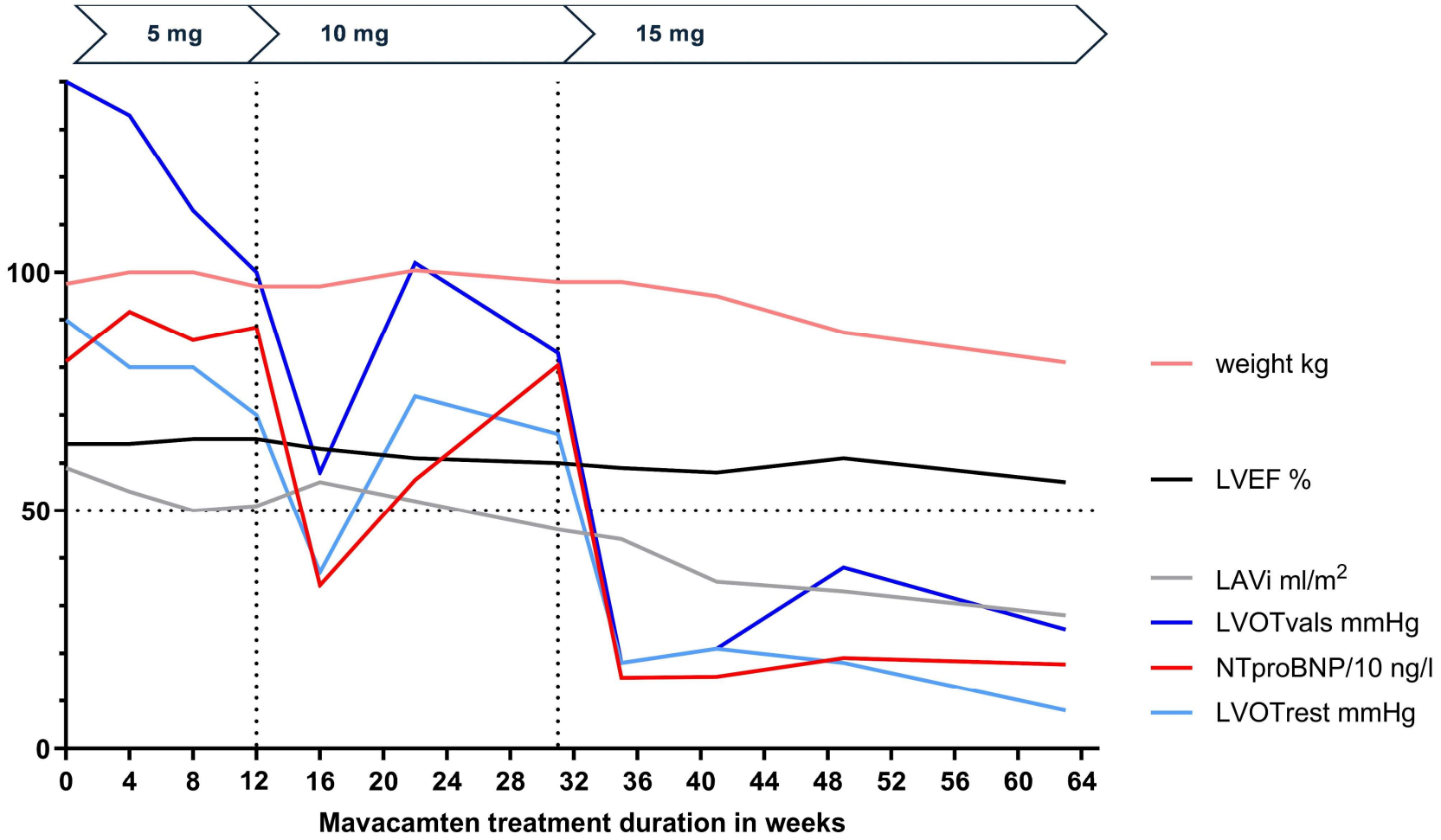

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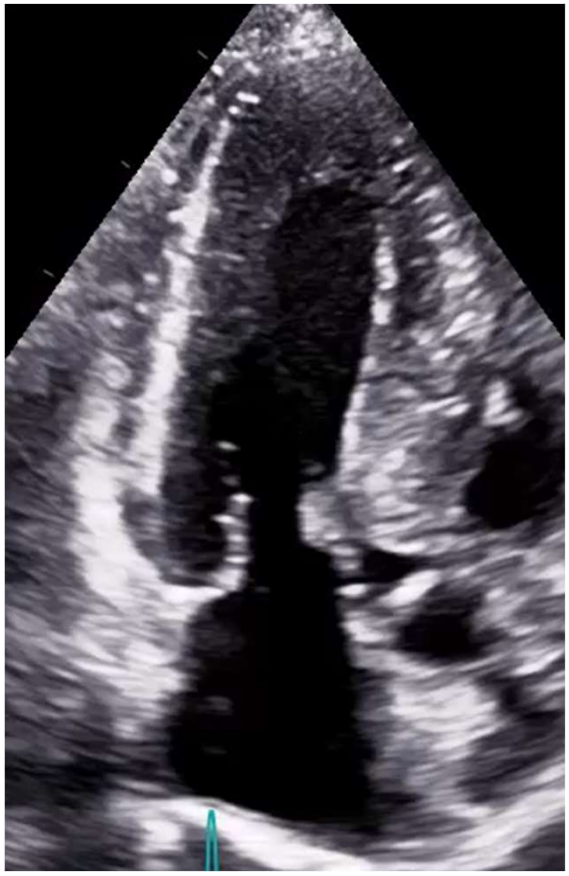
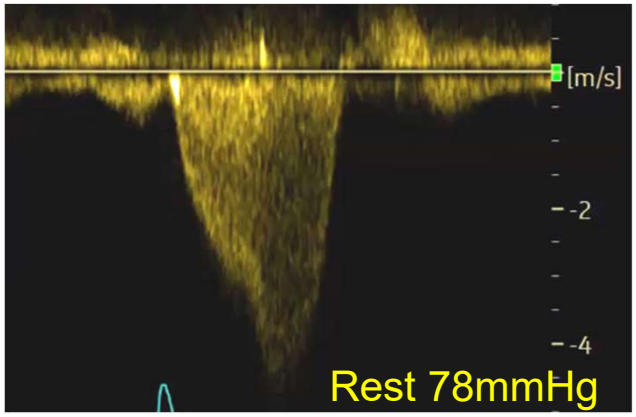
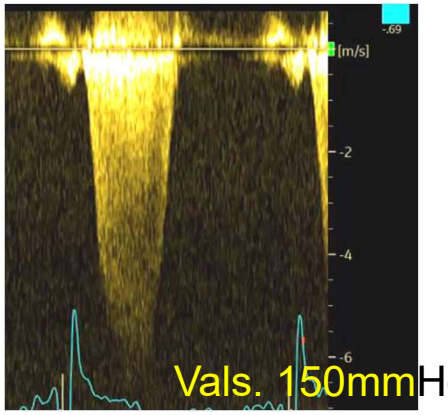
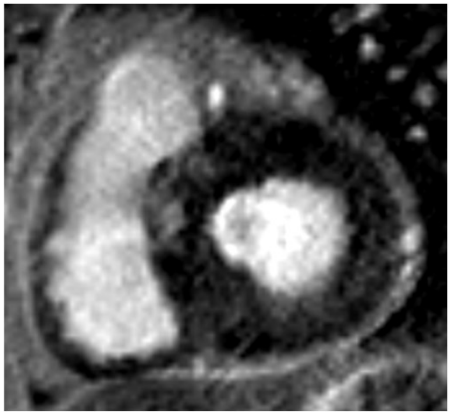
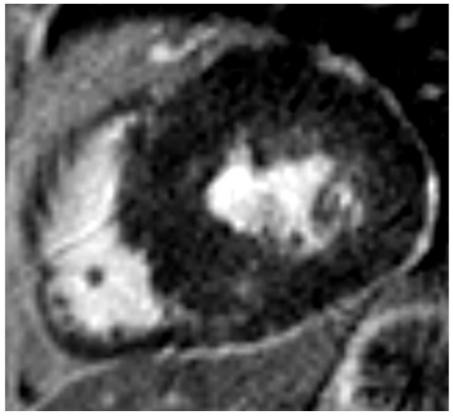
04/2024 – 77♀, diabetes, chronic kidney disease, BMI 34kg/m2, NHYA III

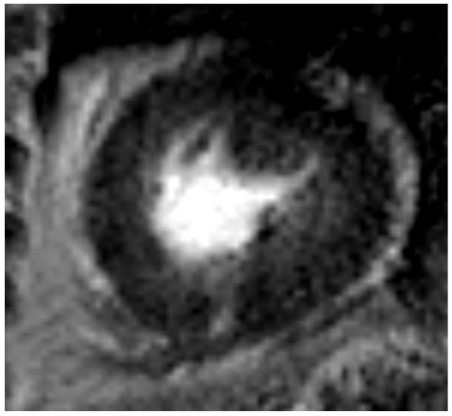












MWTH 21mm basal septum, LVEF 68%, LVEDVi 39ml/m2, 9% LGE, no evidence for infiltrative disease

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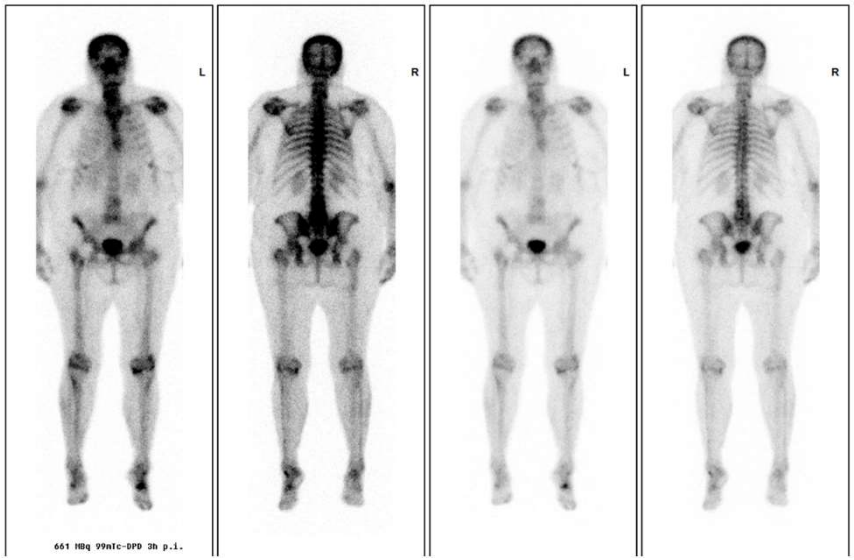

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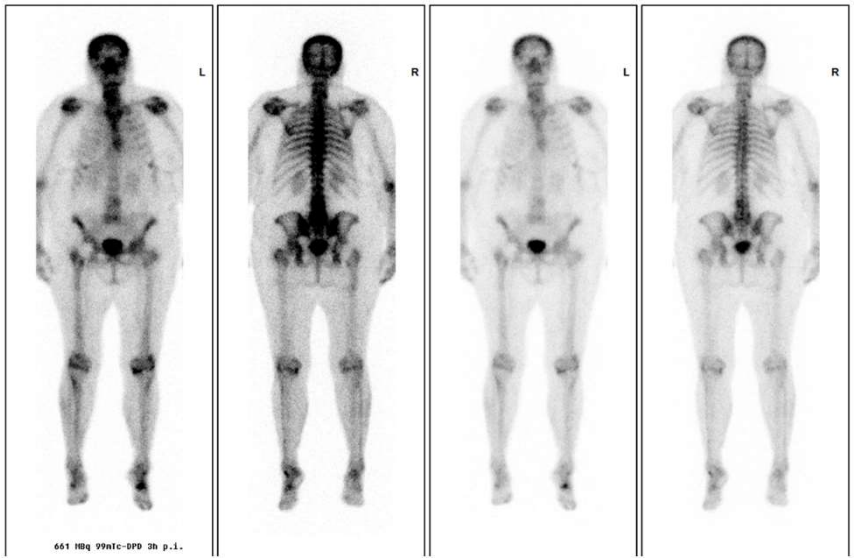

Start Mavacamten

		Entnahme Eingang Befund-Nr.	07.10.2024-09:00 07.10.2024-11:43 J410070926	24.06.2024-12:03 24.06.2024-13:33 J406241229	30.04.2024-14:00 30.04.2024-14:40 J404301488	05.04.2024-08:15 05.04.2024-08:50 J404050410	27.02.2024-09:15 27.02.2024-10:42 J402270734
Kreatinin	44 - 80	µmol/l	109 H	111 H	101 H	139 H	159 H
eGFR(Krea) CKD-EPI 2009		ml/min	42 (1)	41 (1)	46 (1)	32 (1)	27 (1)
eGFR(Krea) BIS1-Formel		ml/min	41 (2)	41 (2)	44 (2)	33 (2)	30 (2)
CK, total	< 170	U/l	42	48	56		67
Troponin T, High Sensitive	< 14	ng/l	19 H	21 H	30 H		45 H
NT-proBNP (Roche)	< 738	ng/l	312	386	646	8502 H	10424 H

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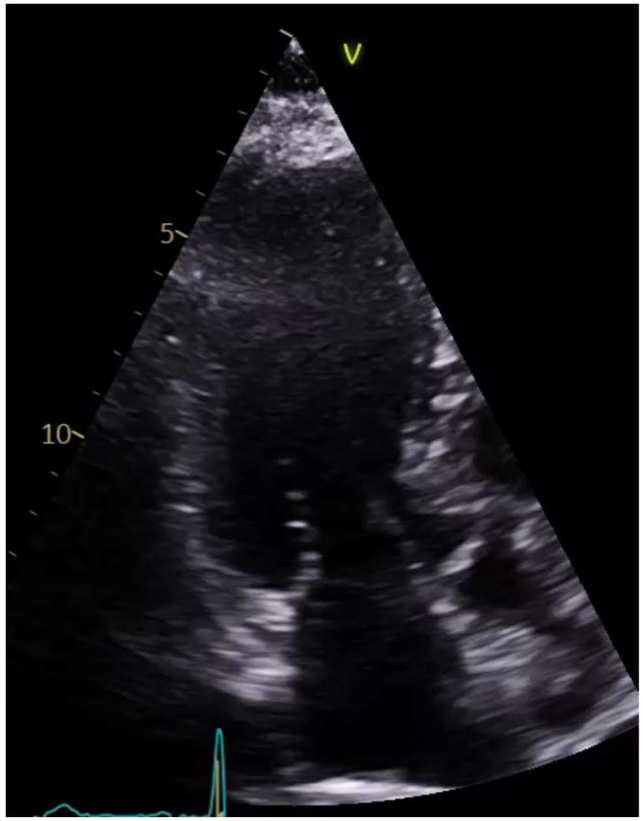
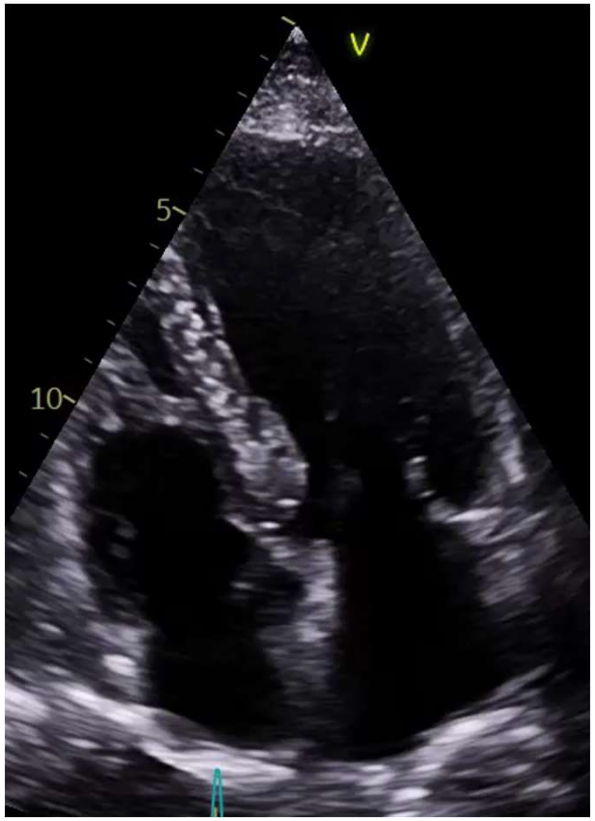
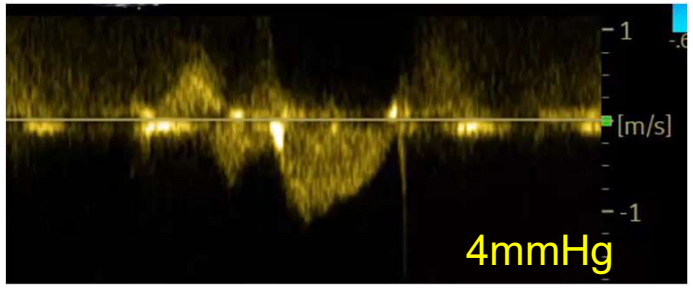
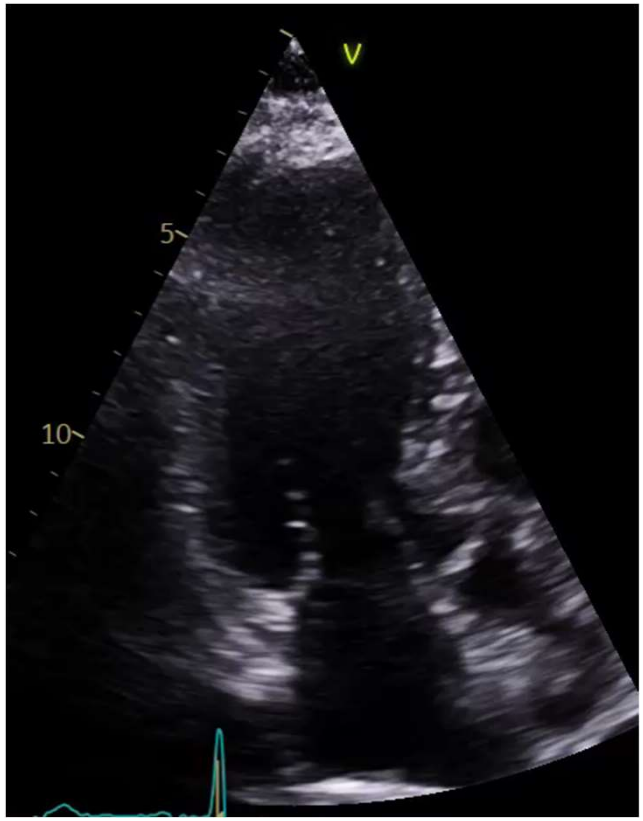
1 year later

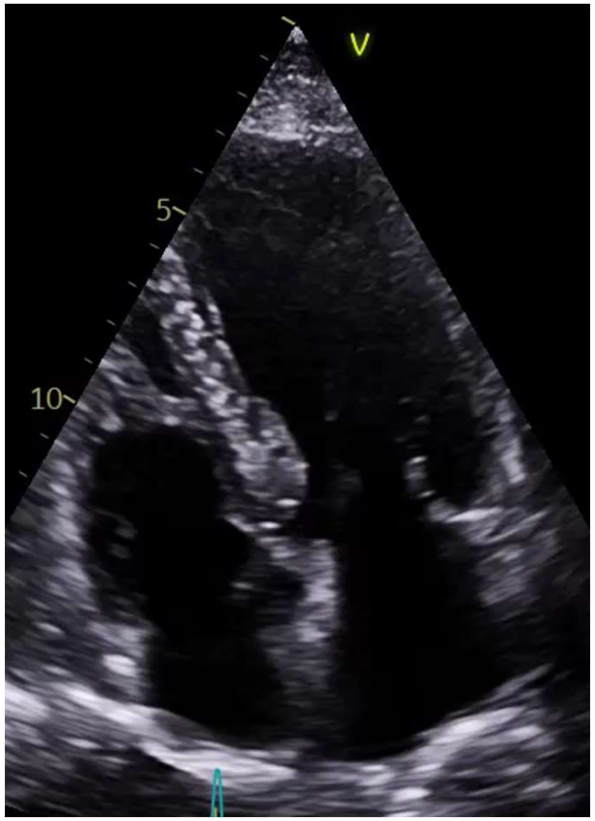


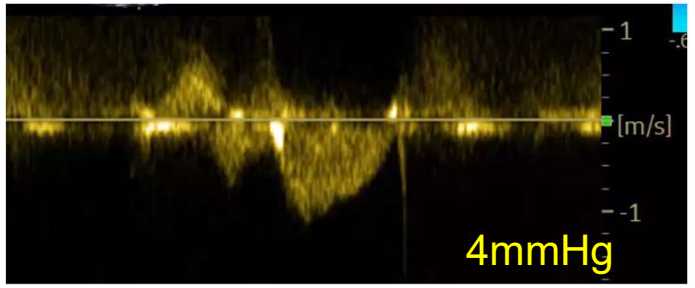




1 year later

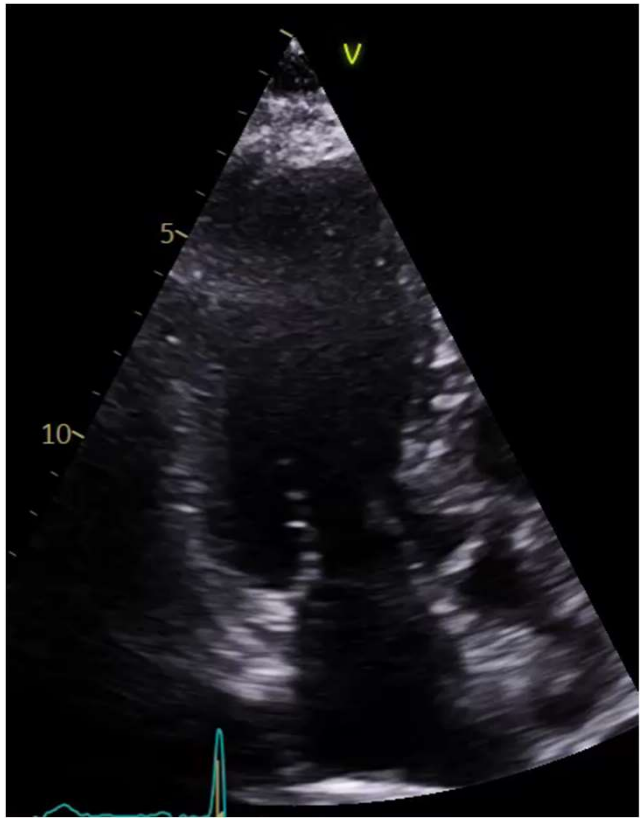


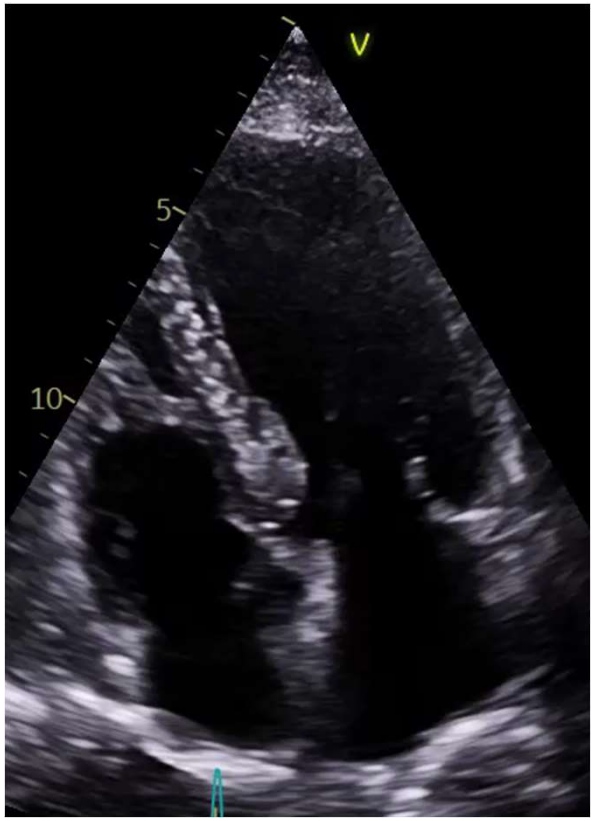


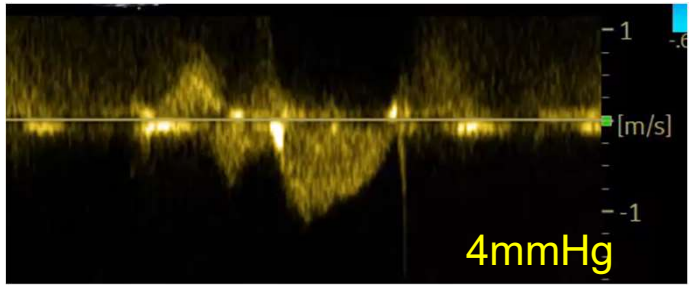


	Pre	Latest FU
MWTH	21	15
LVEDVi	35	53
LVOT_prov	150	4
LVEF	68	52

1 year later







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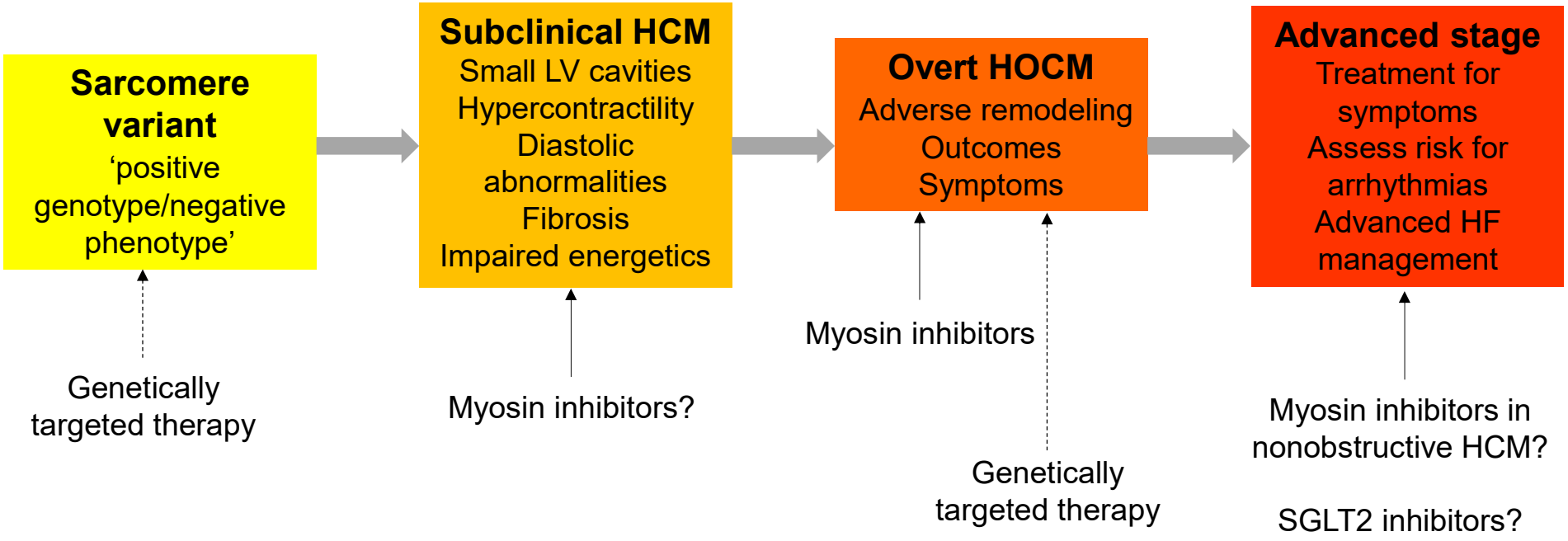
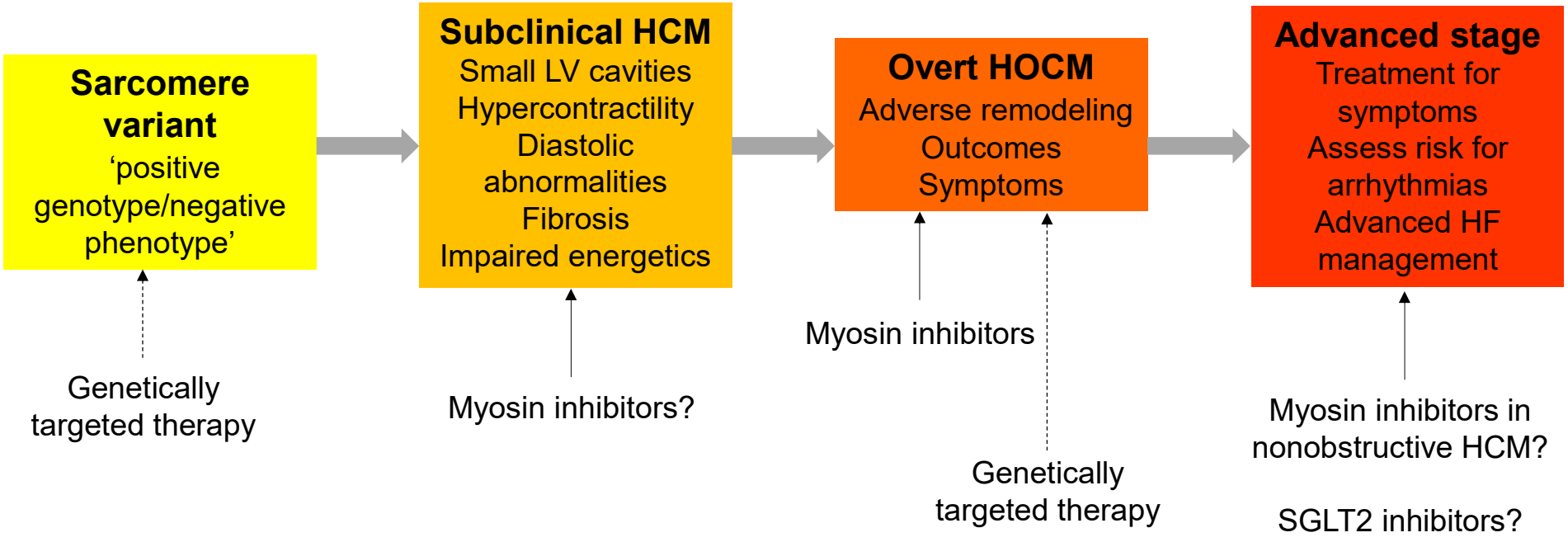
NYHA III; Myalgias; most likely not statin-associated – Pause Mavacamten

Hypertrophic cardiomyopathy – (future) therapies



Adapted from Carolyn Ho

Hypertrophic cardiomyopathy – (future) therapies



Bristol Myers Squibb Provides Update on Phase 3 ODYSSEY-HCM Trial April 14, 2025

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced the Phase 3 ODYSSEY-HCM trial evaluating *Camzyos* (mavacamten) for the treatment of adult patients with symptomatic New York Heart Association (NYHA) class II-III non-obstructive hypertrophic cardiomyopathy (nHCM) did not meet its dual primary endpoints of changes from baseline to Week 48 compared to placebo in the Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-23 CSS) and peak oxygen consumption (pVO2). No new safety signals were observed.

Herzlichen Dank für Ihre Aufmerksamkeit

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