Hypertrofische cardiomyopathie
behandelmogelijkheden nu en in de toekomst

Dr. Alexander Hirsch

Cardioloog Erasmus MC

Nationale Hartfalendag, 27 september 2024

European Reference Network
for rare or low prevalence complex diseases
Network Heart Diseases (ERN GUARD-HEART)

Erasmus MC
University Medical Center Rotterdam

DISCLOSURES

(Potential) relevant company relationship	
Sponsorship	Institutional support/research grant from: GE healthcare, Siemens Healthineers, HeartFlow (Fusion study), Bracco (Patent study), BMS
Honorarium or other (financial) compensation	Medis Medical Imaging, Medical Advisory Board GE healthcare, Invited speaker Bayer SA-NV, Invited speaker BMS, Invited speaker MRI Corelab supervisor Cardialysis BV (until 2022)
Shareholder	-
Other	Erasmus MC is participating in multiple HCM trials (i.e. Explorer, Mava-LTE, Odyssey, Forest, Acacia, Sequoia, Maple)

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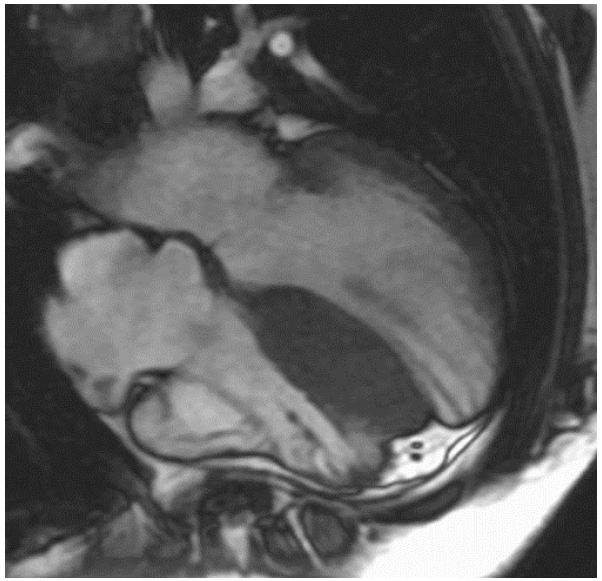
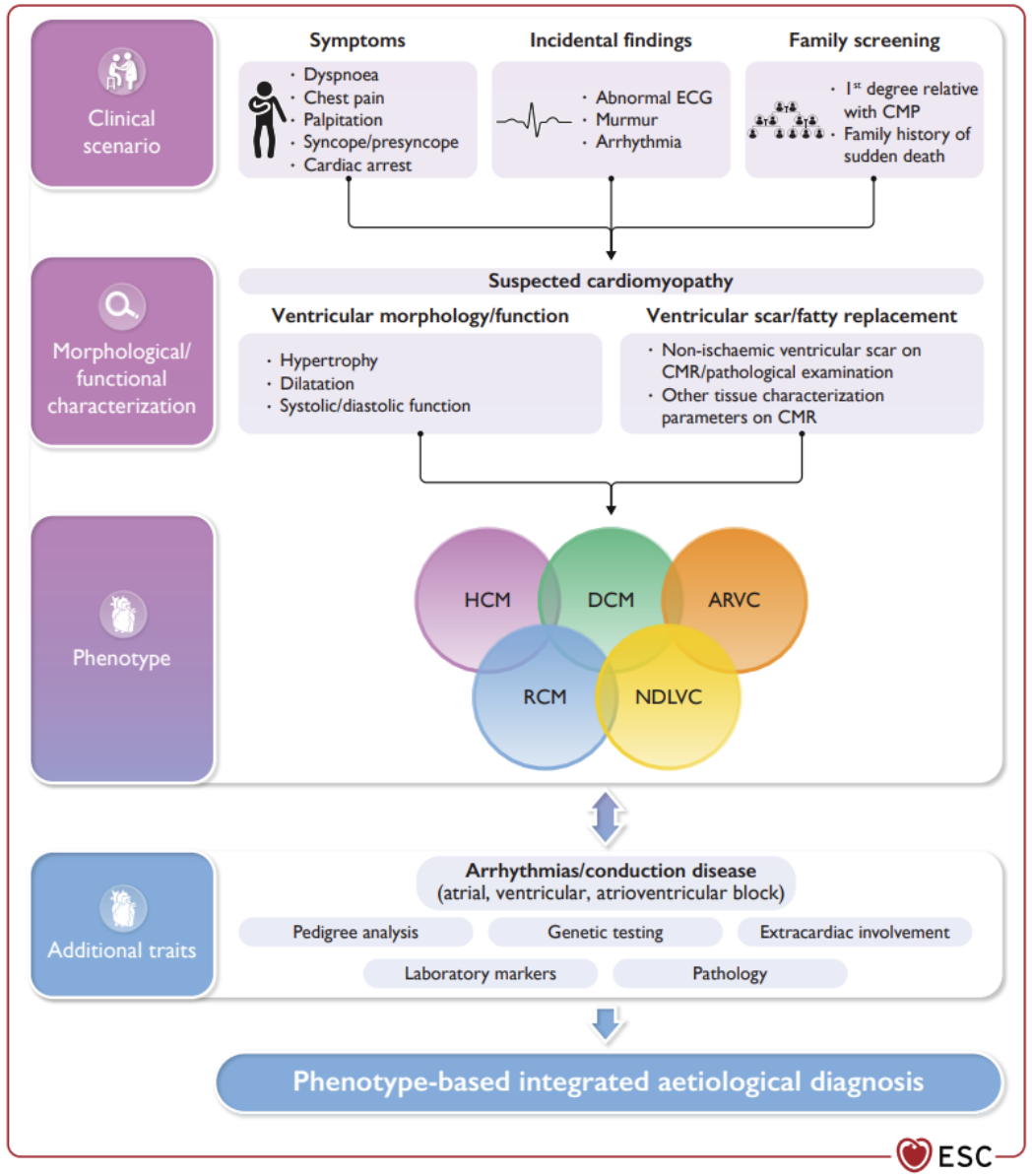
HYPERTROFISCHE CARDIOMYOPATHIE

Definitie

- Verdikking van de hartspier (≥15mm) zonder dat een andere aandoening aanwezig is, die deze verdikking kan verklaren.
- Prevalentie 0,2%





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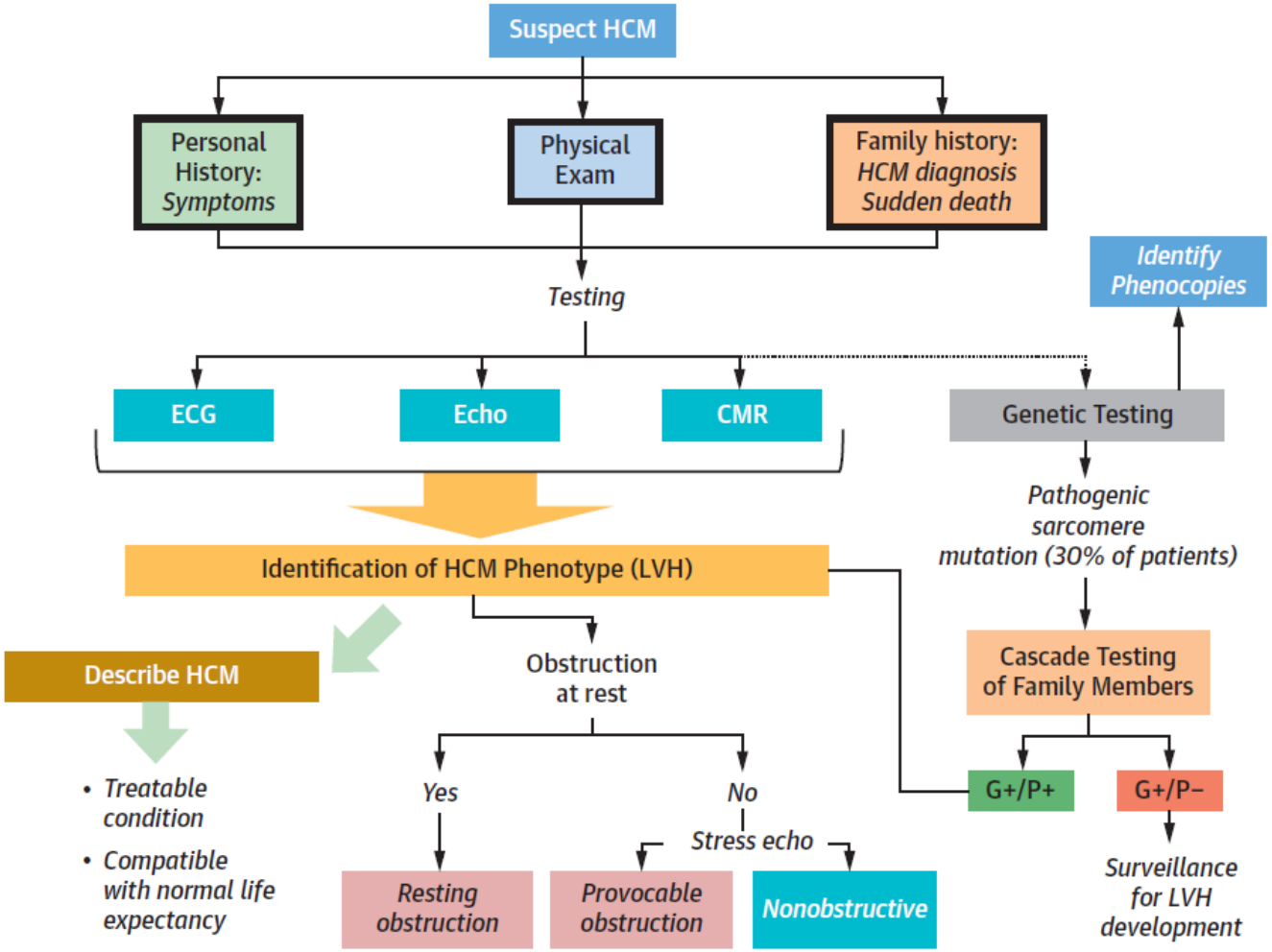
HYPERTROFISCHE CARDIOMYOPATHIE

Diagnostisch traject



Maron et al. J Am Coll Cardiol, 2022; 79: 372

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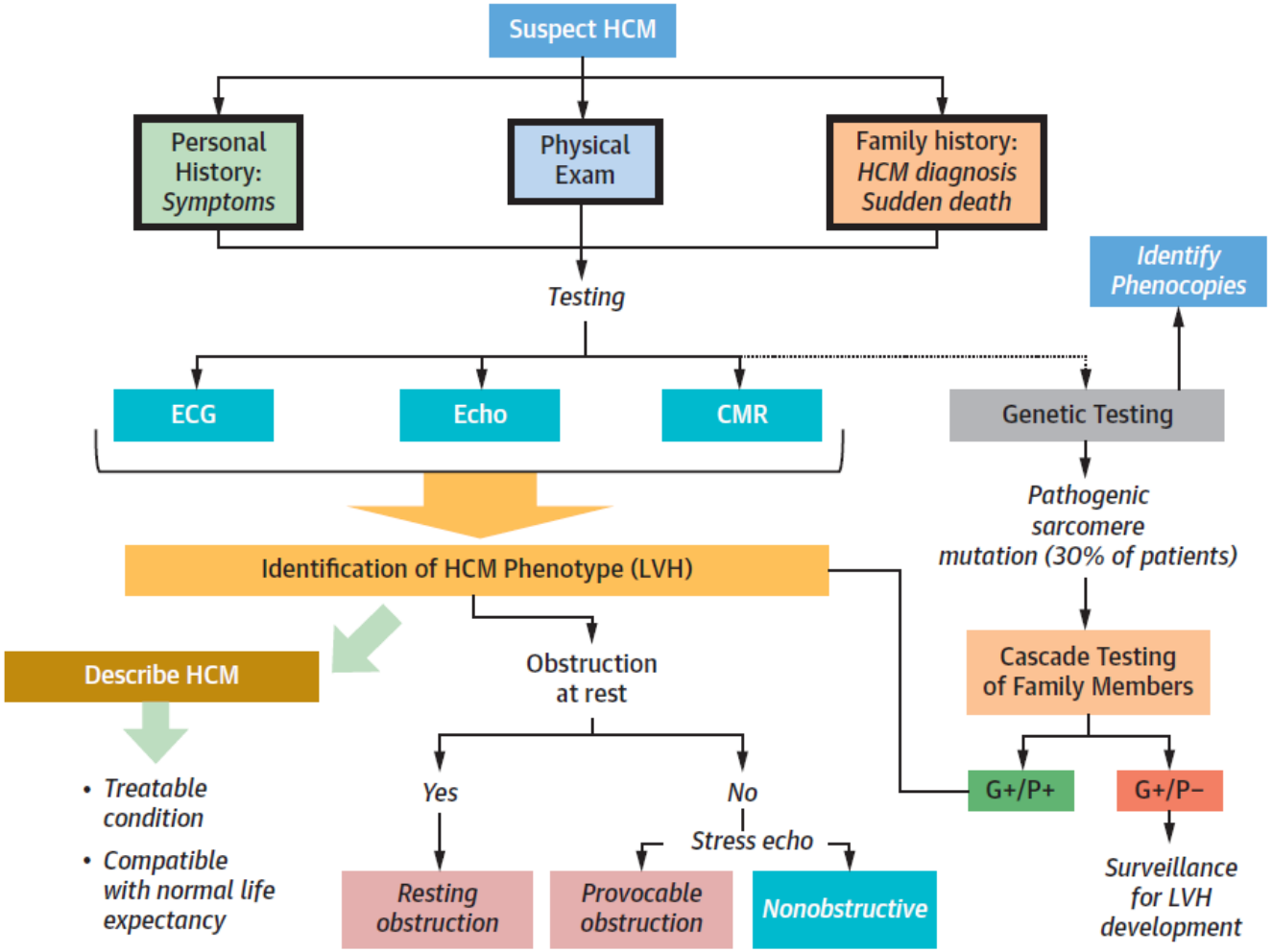
HYPERTROFISCHE CARDIOMYOPATHIE

Diagnostisch traject



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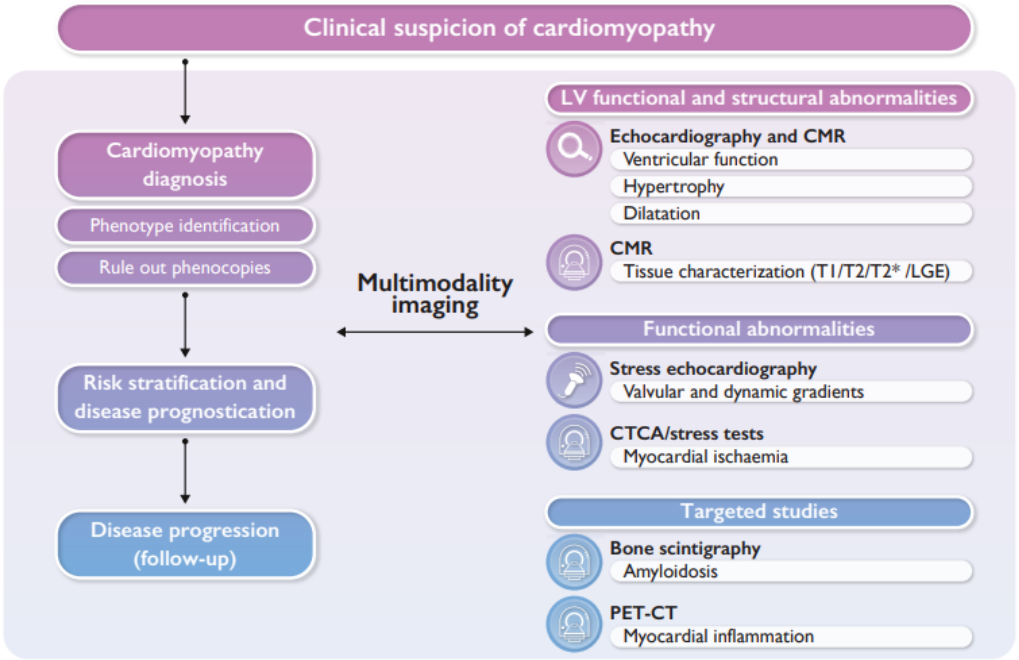

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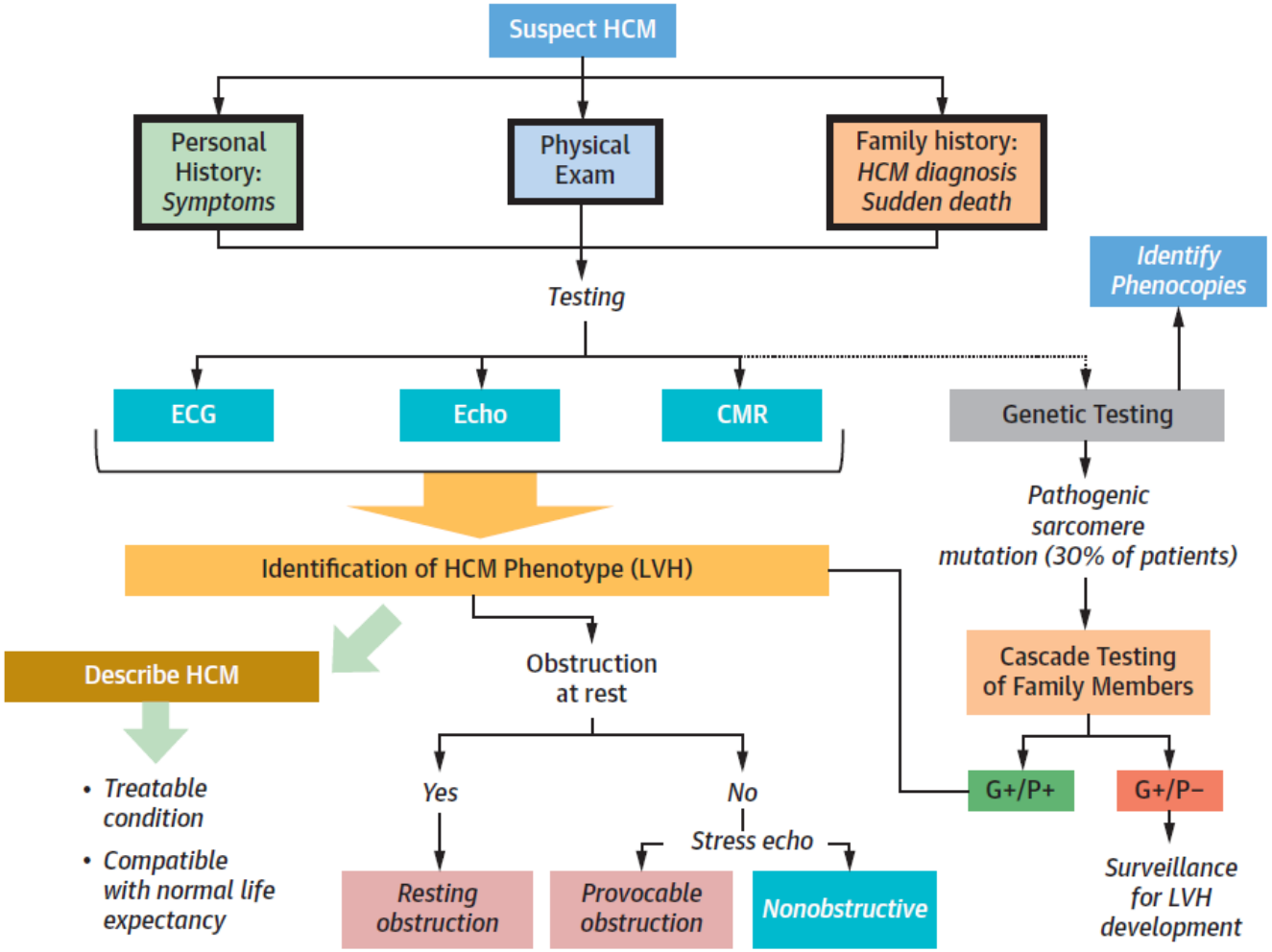
HYPERTROFISCHE CARDIOMYOPATHIE

Diagnostisch traject



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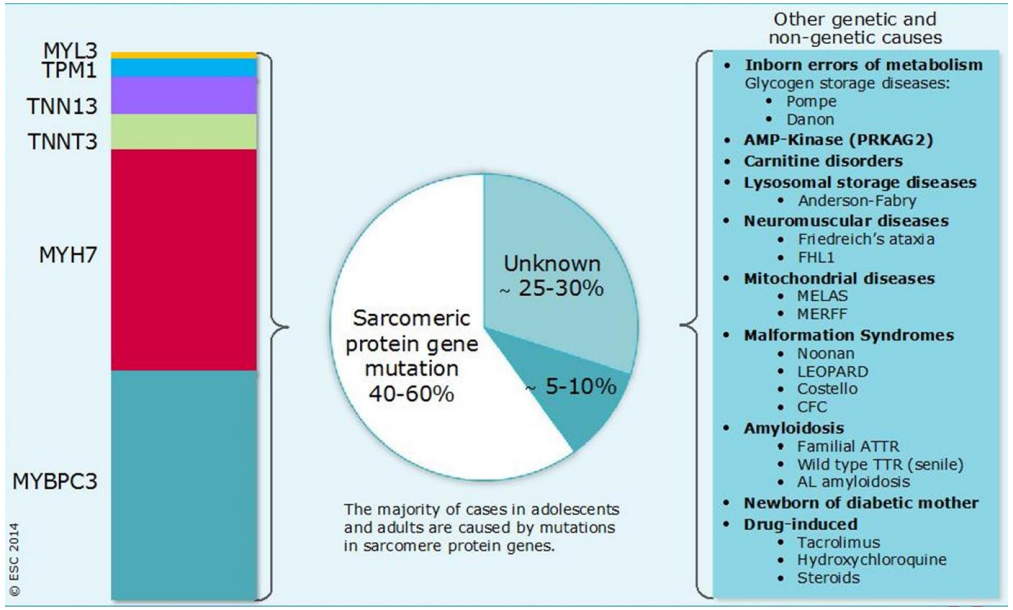

2014 ESC guidelines Hypertrophic Cardiomyopathy

- Belang goed fenotyperen o.a. vanwege ziekte specifieke behandeling

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ZIEKTE SPECIFIEKE BEHANDELING HCM

	Etiology	Novel Therapies		
Sarcomeric HCM	Mutations in Sarcomeric Genes Responsible for an Hypercontractility Phenotype	Myosin Inhibitors	→	Mavacamten Aficamten
		Gene Therapy		
RASopathy	LVH Caused by Upregulation of RAS-MAPK or PI3K-AKT-mTor Patway	MEK1 Inhibitors (in NS)	→	Trametinib
		mTor Inhibitors (in NSML)	→	Everolimus
Pompe Disease	Mutations in *GAA* Gene Responsible for Abnormal Lysosomal Glycogen Accumulation	Enzyme Replacement Therapy	→	Aglucosidase Alpha
Danon Disease	Mutations in *LAMP* Gene Responsible for Abnormal Glycogen Accumulation	Gene Therapy		
Friedreich Ataxia	LVH Caused by Mitochondria Proliferation and Iron Accumulation	NRF2 Agonists	→	Omaveloxolone
Fabry Disease	Mutations in *GLA* Gene Responsible for Gb3 and LysoGb3 Accumulation	Enzyme Replacement Therapy	→	Agalsidase Alpha Agalsidase Beta Pegunigalsidase
		Chaperone Therapy	→	Migalastat
		Substrate Reduction Therapy	→	Lucerastat Venglustat
Cardiac Amyloidosis	Abnormal Amyloid Fibrils Formation and Deposition	Antisense Oligonucleotides	→	Inotersen Eplotersen
		Small Interfering RNA	→	Patisiran Vutrisiran
		Tetramer Stabilizers	→	Tafamidis Acoramidis
		Clearance of Amyloid Deposits	→	Antibodies

Monda et al. Circ Heart Fail.2023;16:e010687

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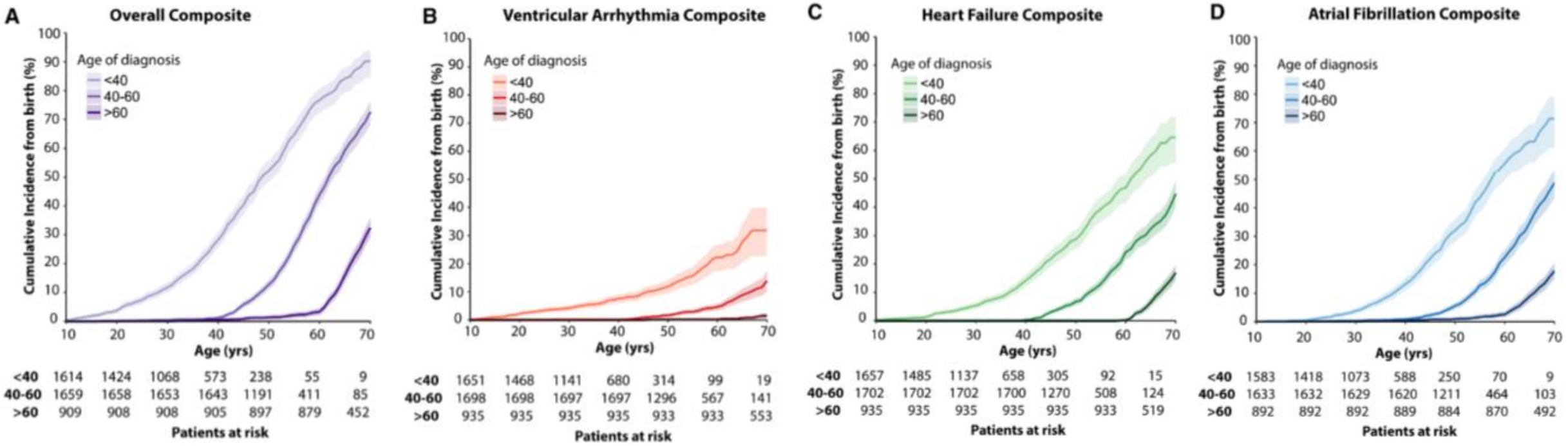
HYPERTROFISCHE CARDIOMYOPATHIE

Burden of disease



Ho et al. Circulation 2019

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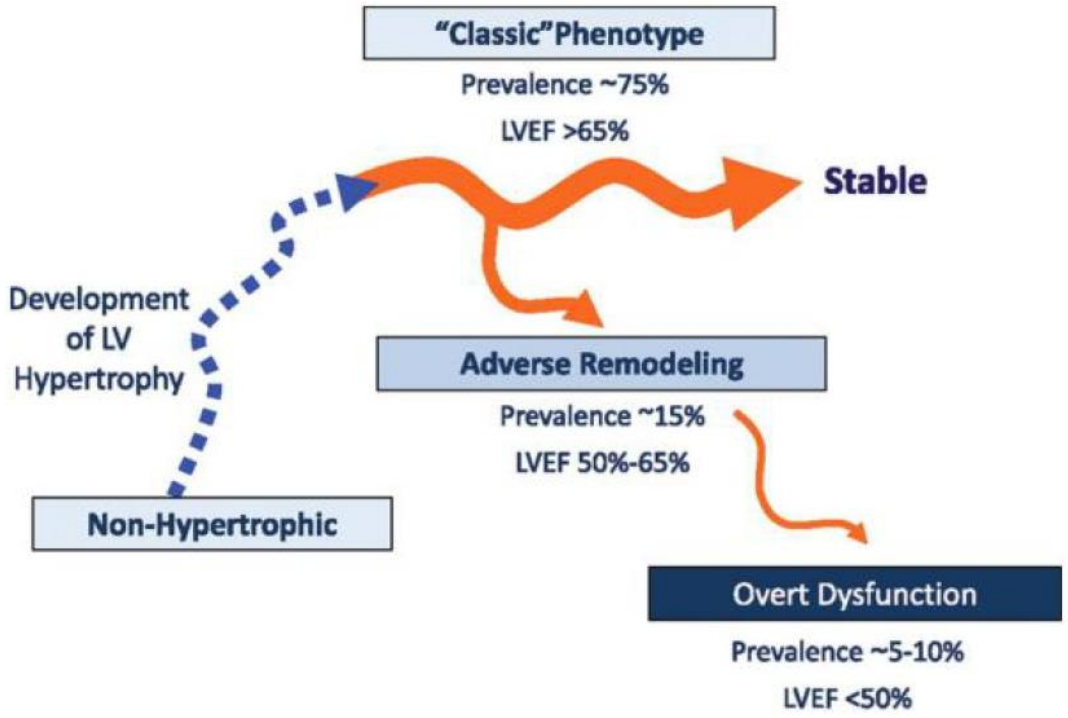
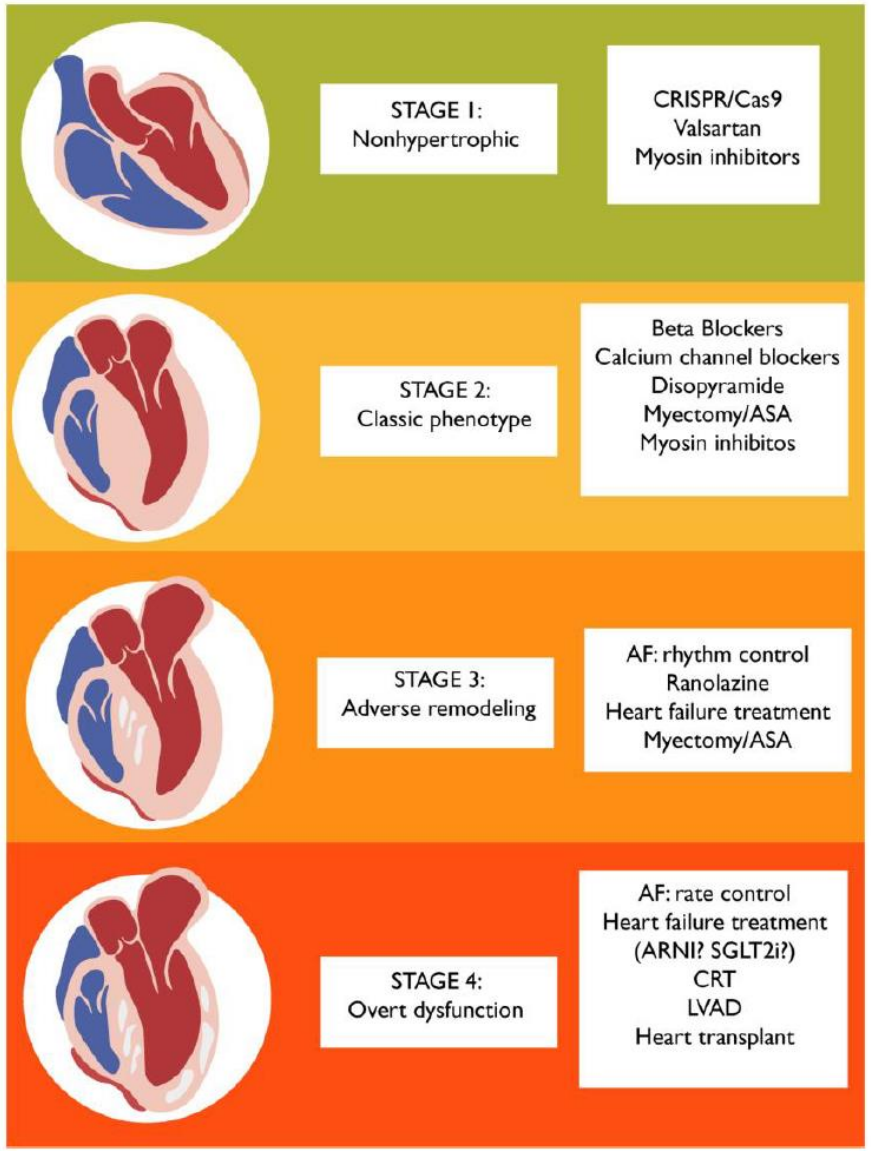
HYPERTROFISCHE CARDIOMYOPATHIE

Ziekte beloop en behandeling





Argiro et al. EHJ suppl, 2023; c155

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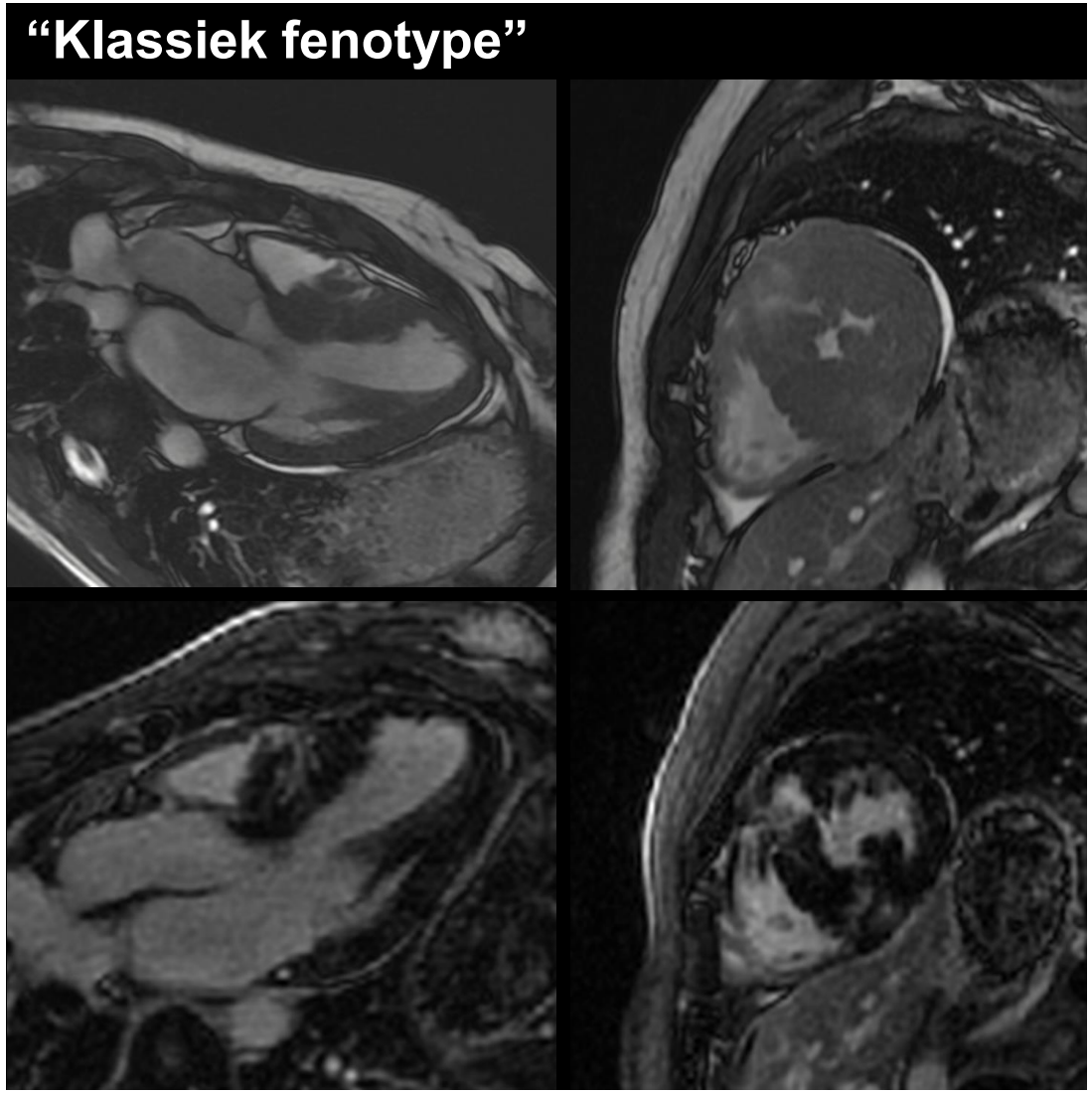
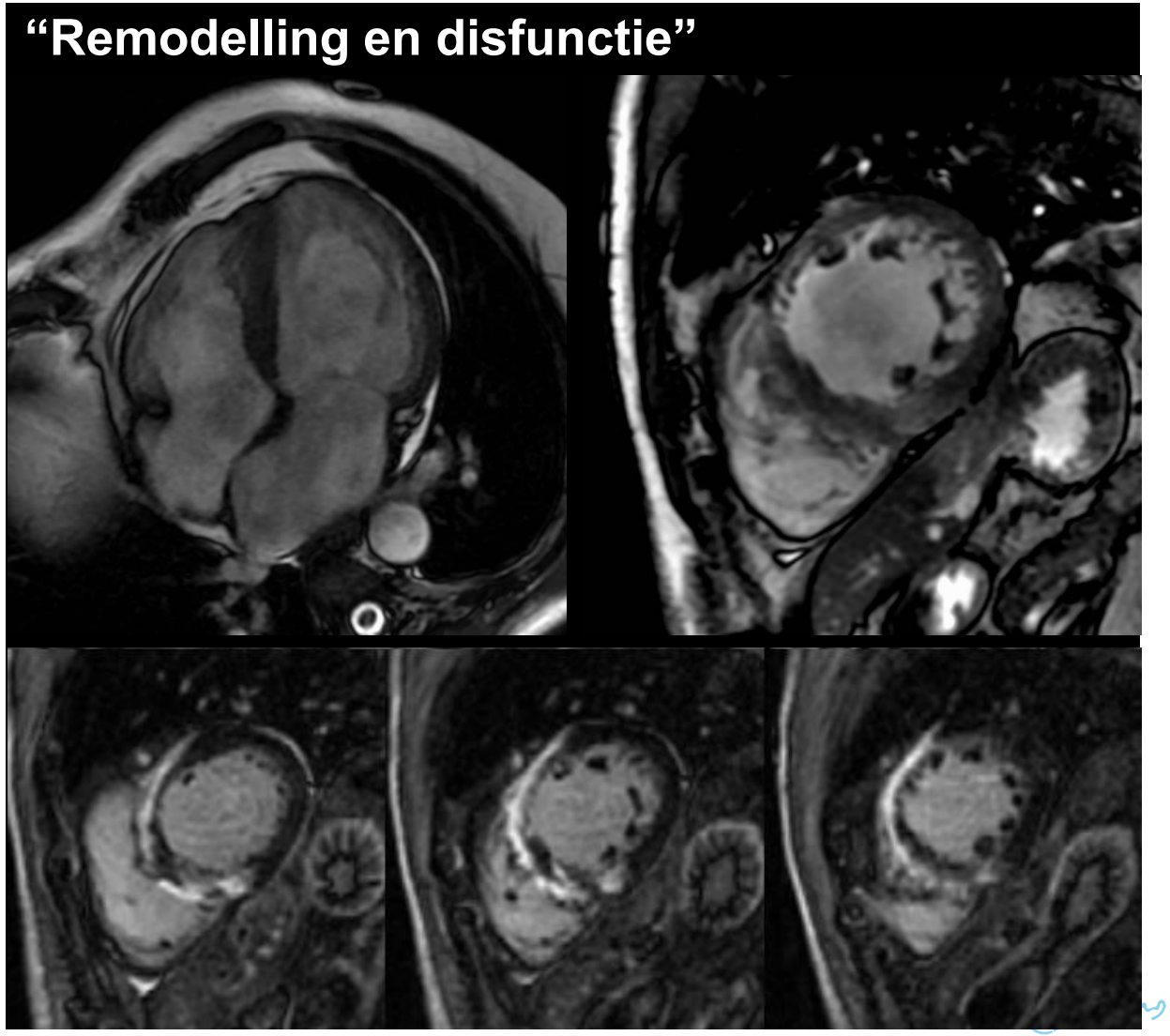
HYPERTROFISCHE CARDIOMYOPATHIE

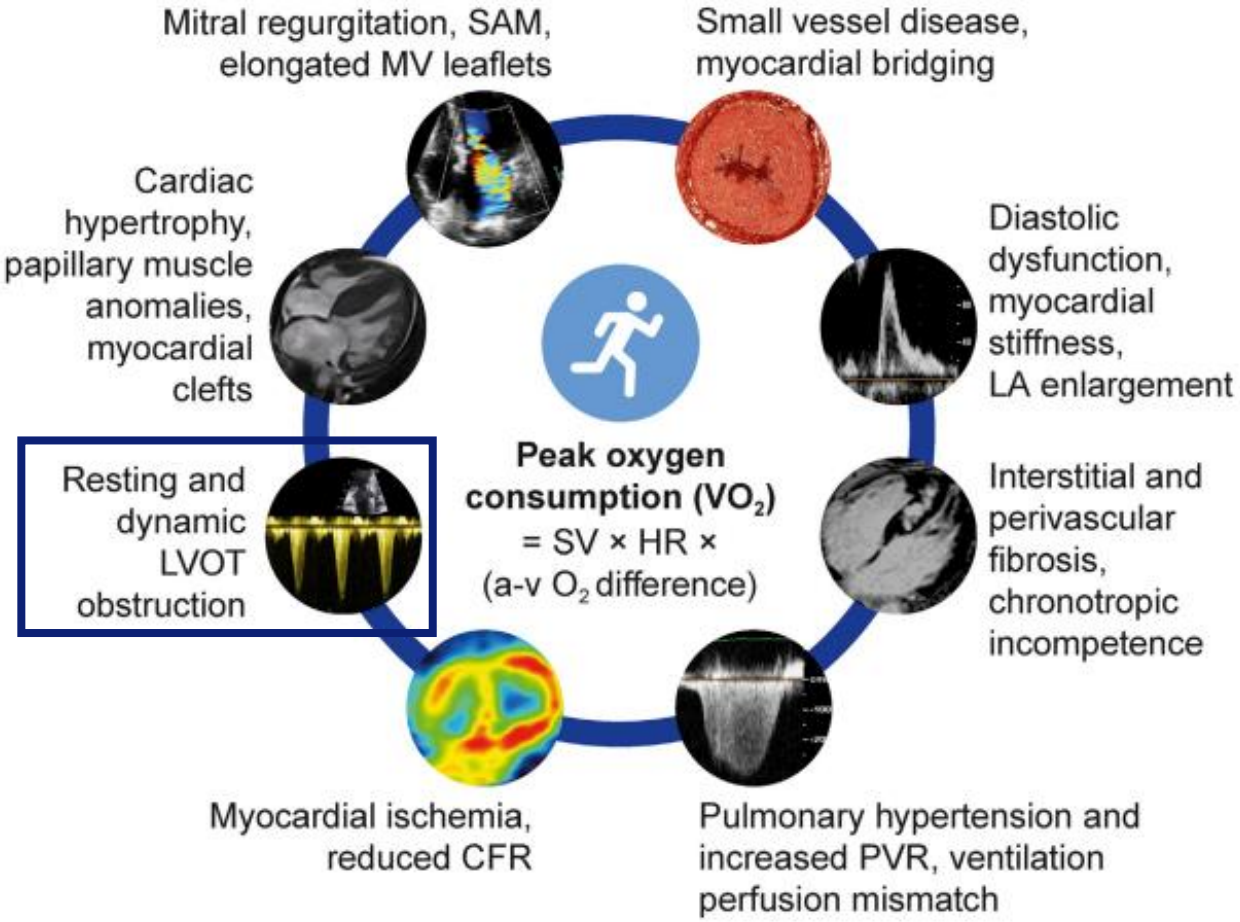
Ziektebeloop en behandeling





HYPERTROFISCHE CARDIOMYOPATHIE

Pathofysiologie



- Symptomen: oa dyspnoe d'effort, pijn op de borst, vermoeid, hartkloppingen, syncope
- Hartfalen
- Hartritmestoornissen zowel ventriculair als supraventriculair
- Plotse dood

Coats et al. JACC Heart Fail, 2024; 12: 199

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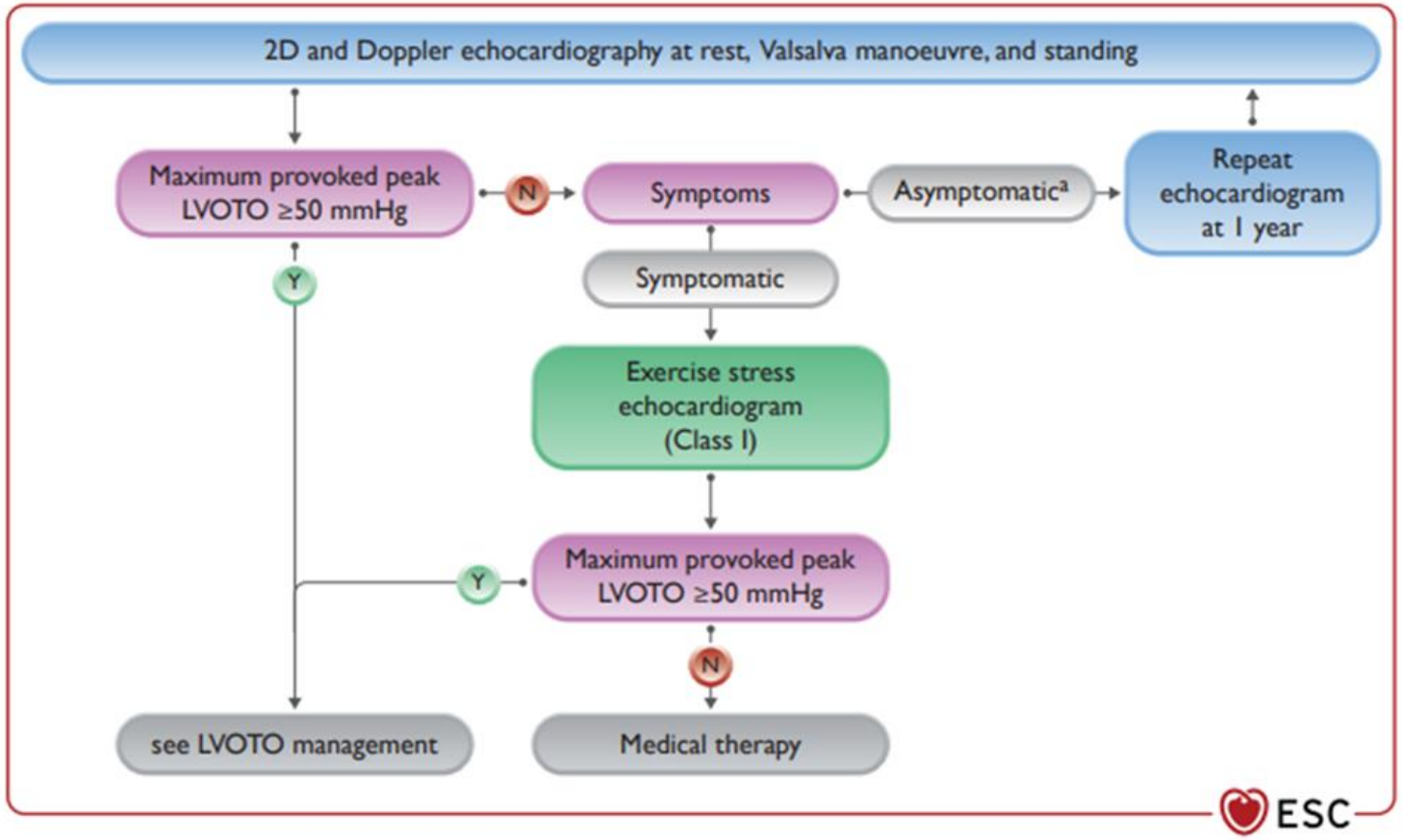
HYPERTROFISCHE CARDIOMYOPATHIE

LVOT obstructie



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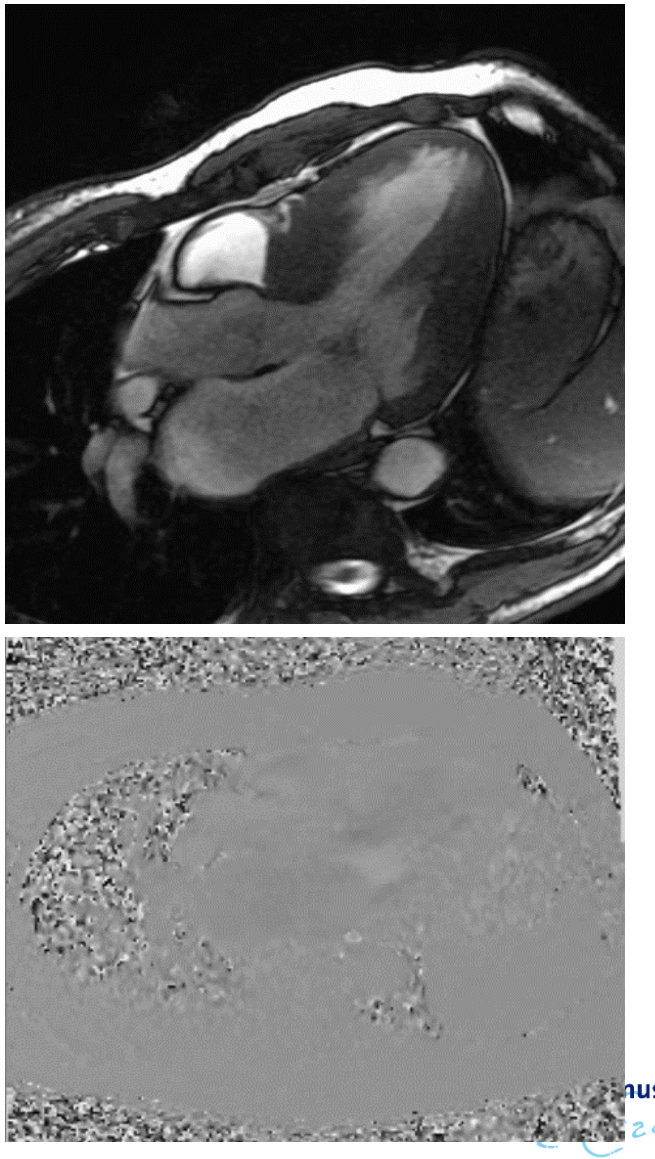

SSFP (cine)

Flow (Phase contrast)

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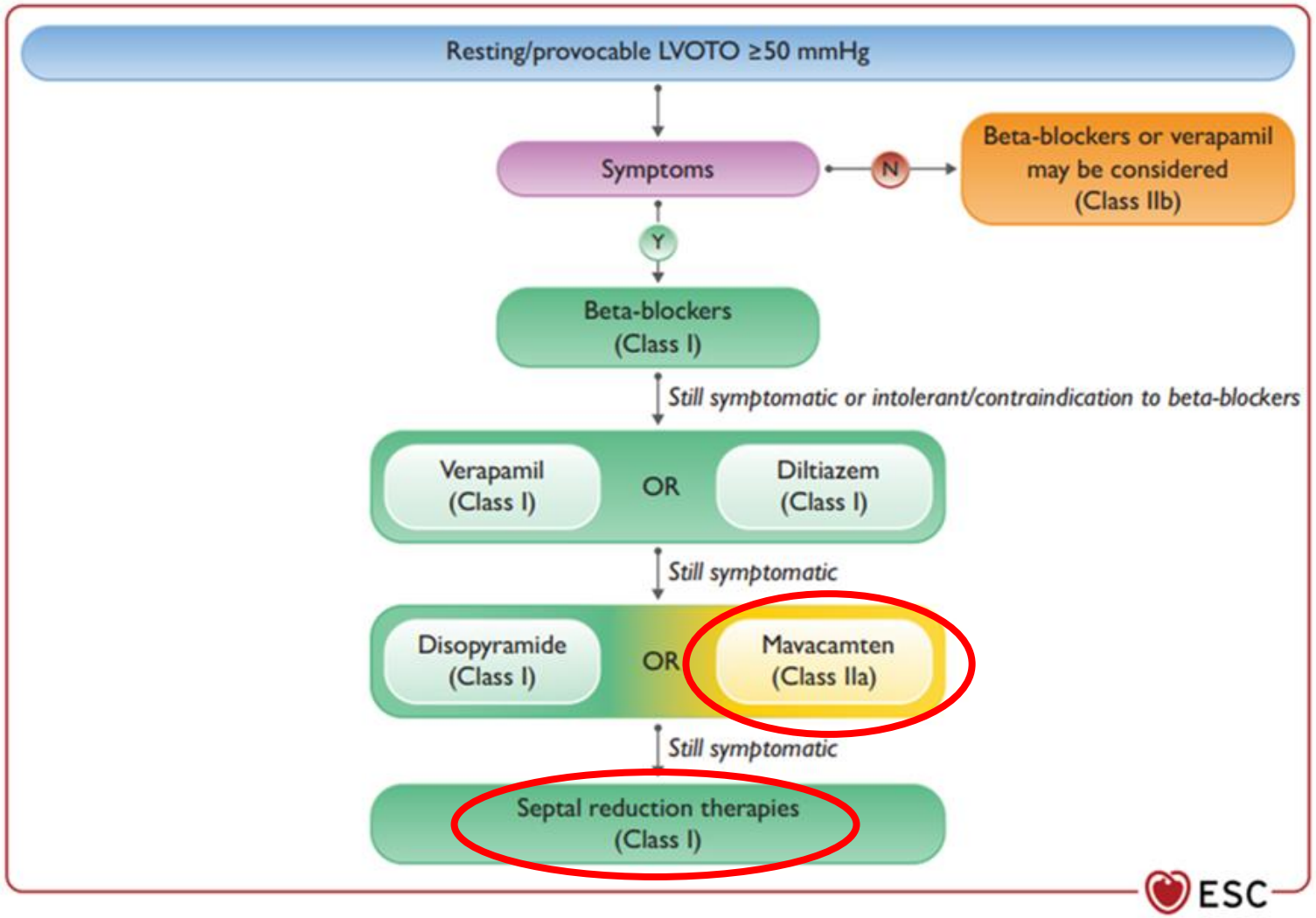
Therapie



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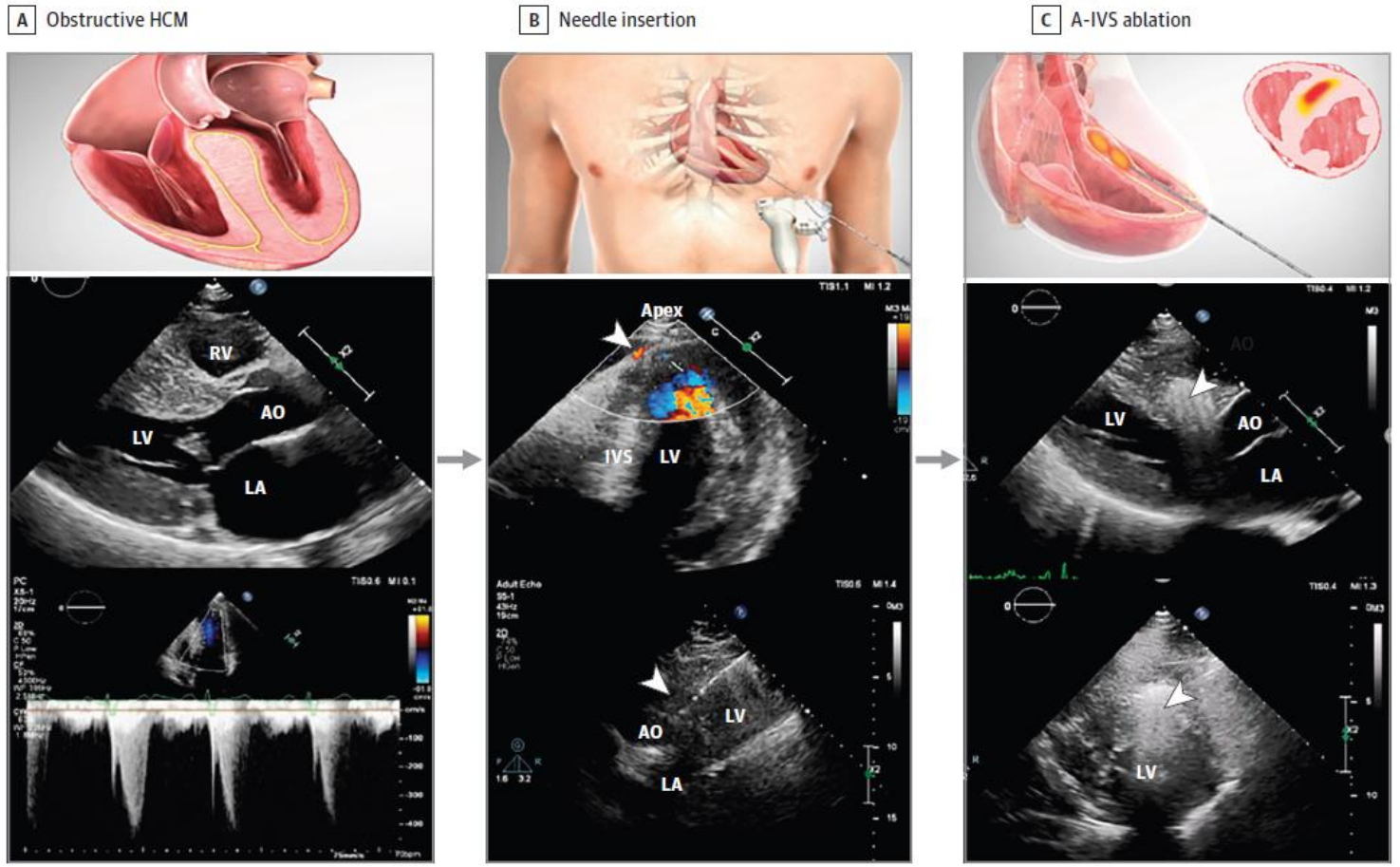
Septale reductietherapie

Figure 1. Percutaneous Intramyocardial Septal Radiofrequency Ablation (PIMSRA) Procedure Illustration and Echo Imaging



Zhou et al. JAMA Cardio 2022

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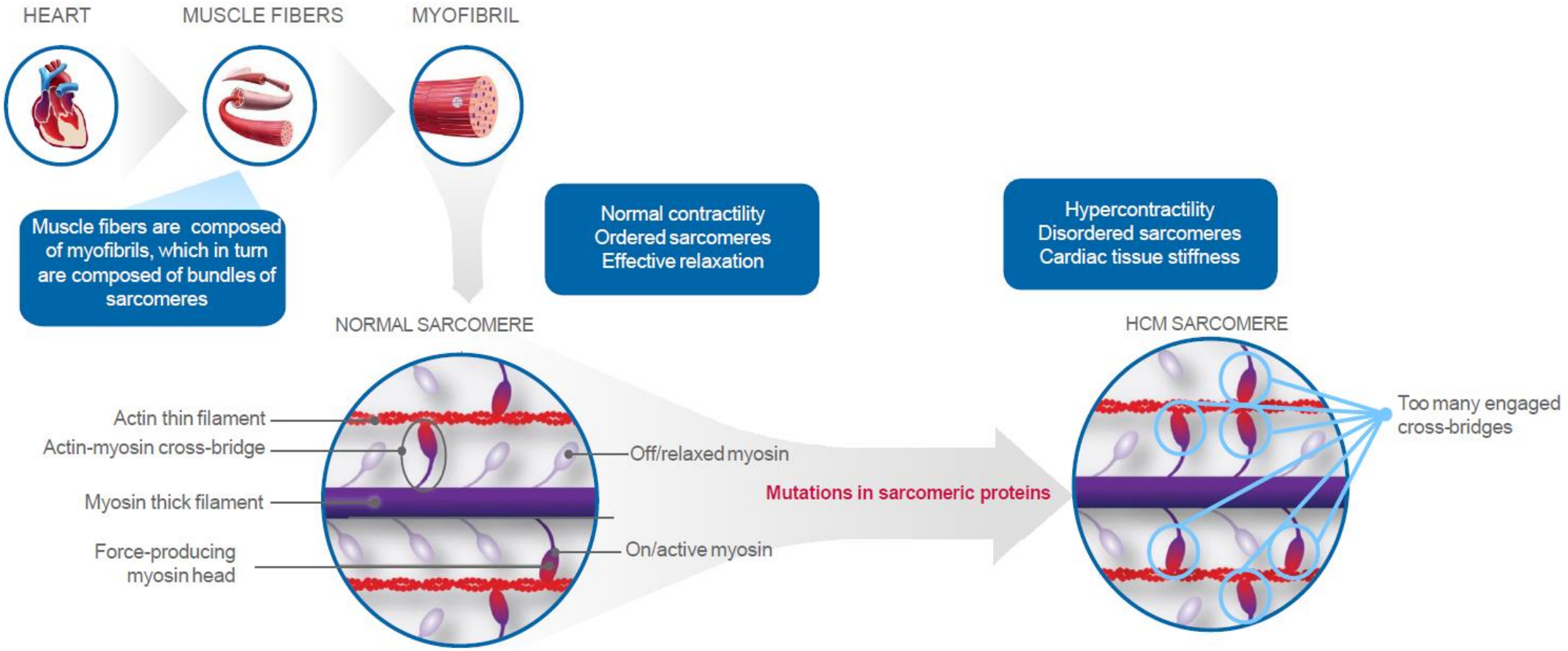
Therapie



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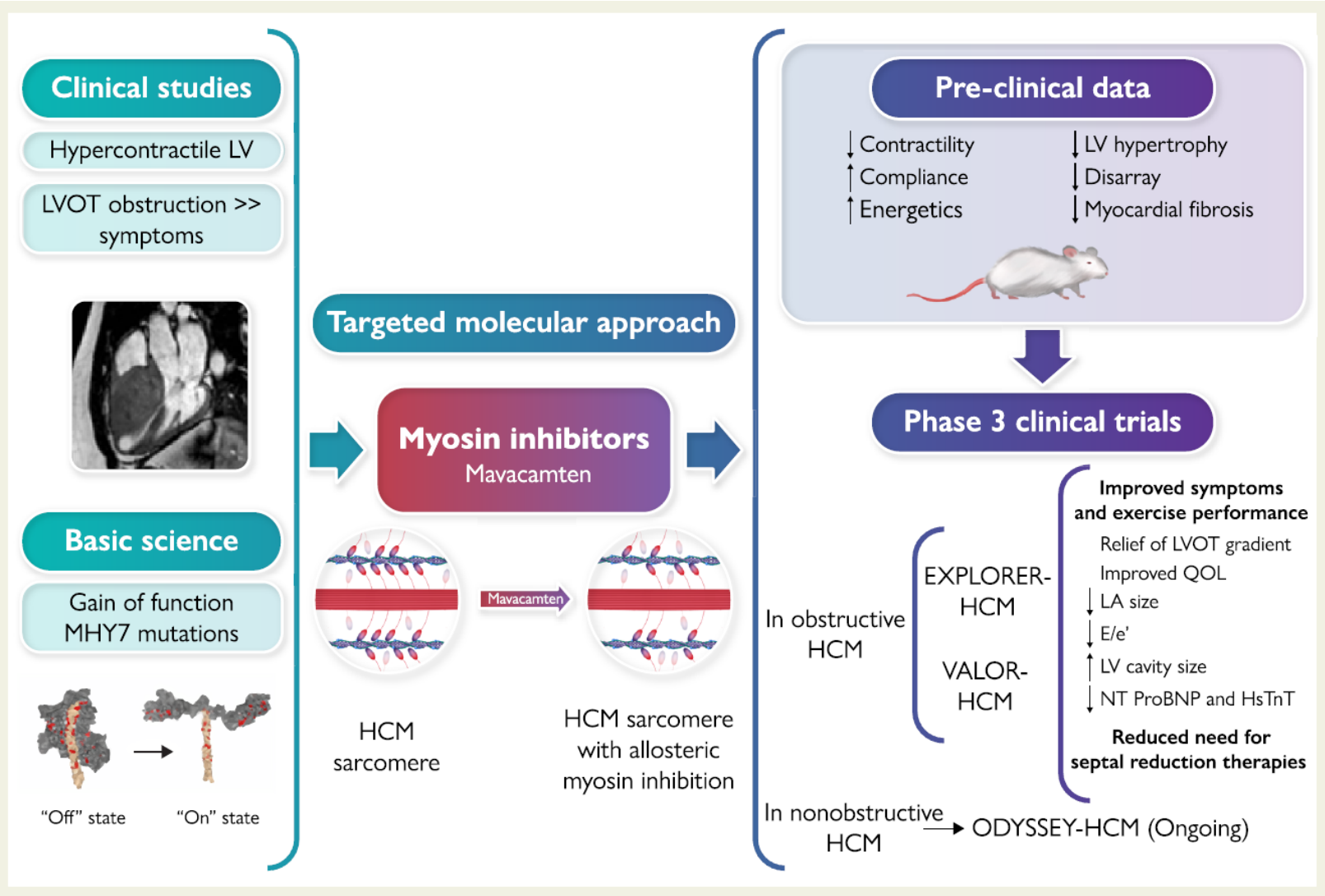
Therapie



Braunwald et al. European Heart Journal, 2023; 44: 4622

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HYPERTROFISCHE OBSTRUCTIEVE CMP

Myosine inhibitoren: Mavacamten

Title (reference)	PIONEER HCM[41,42]	EXPLORER HCM[36,37]	VALOR-ACH[43]
Design	Open-label Non-randomized	Double-blind randomized	Double-blind Randomized
N	21	251	112
Duration (weeks)	12	30	16
NYHA class	II/III	II/III	III/IV
Dose (mg/day)	2–20	2.5–15	2.5–15
Primary endpoint	Change in post-exercise LVOT gradient	Exercise capacity symptom burden	Continued eligibility for SRT
OUTCOMES	↓ LVOT gradients	↓ LVOT gradients	↓ eligibility for SRT
	Improved exercise capacity and ventilatory efficiency	Improved exercise capacity	↓ LVOT gradients
	↓ NYHA class	↓ NYHA class	↓ NYHA class
	↓ NRS dyspnoea score	↓ NT-proBNP and hs-cTnI	↓ NT-proBNP and hs-cTnI
	Improved health status	Improved diastolic function	Improved health status

hs-cTnI, high-sensitivity cardiac Troponin I; LVOT, left ventricular outflow tract; *N*, patient number; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NRS, numerical rating scale; SRT, septal reduction therapy.

Braunwald et al. European Heart Journal, 2023; 44: 4622

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HYPERTROFISCHE OBSTRUCTIEVE CMP

Mavacamten: EXPLORER-HCM

Inclusie

HCM

NYHA II-III

LVOT gradiënt ≥50 mmHg

LVEF ≥55%

	Mavacamten group (n=123)	Placebo group (n=128)	Difference* (95% CI), p value
Primary endpoint†			
Either ≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	45 (37%)	22 (17%)	19·4 (8·7 to 30·1; p=0·0005)
≥1·5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement	41 (33%)	18 (14%)	19·3 (9·0 to 29·6)
≥3·0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	29 (24%)	14 (11%)	12·6 (3·4 to 21·9)
Both ≥3·0 mL/kg per min increase in pVO_2 and ≥1 NYHA class improvement	25 (20%)	10 (8%)	12·5 (4·0 to 21·0)
Secondary endpoints‡			
Post-exercise LVOT gradient change from baseline to week 30, mm Hg	−47 (40), n=117	−10 (30), n=122	−35·6 (−43·2 to −28·1; p<0·0001)
pVO_2 change from baseline to week 30, mL/kg per min	1·4 (3·1), n=120	−0·1 (3·0), n=125	1·4 (0·6 to 2·1; p=0·0006)
≥1 NYHA class improvement from baseline to week 30§	80 (65%)	40 (31%)	34% (22 to 45; p<0·0001)
Change from baseline to week 30 in KCCQ-CSS§	13·6 (14·4), n=92	4·2 (13·7), n=88	9·1 (5·5 to 12·7; p<0·0001)
Change from baseline to week 30 in HCMSQ-SoB§	−2·8 (2·7), n=85	−0·9 (2·4), n=86	−1·8 (−2·4 to −1·2; p<0·0001)

Olivotto et al. Lancet, 2020; 396: 759

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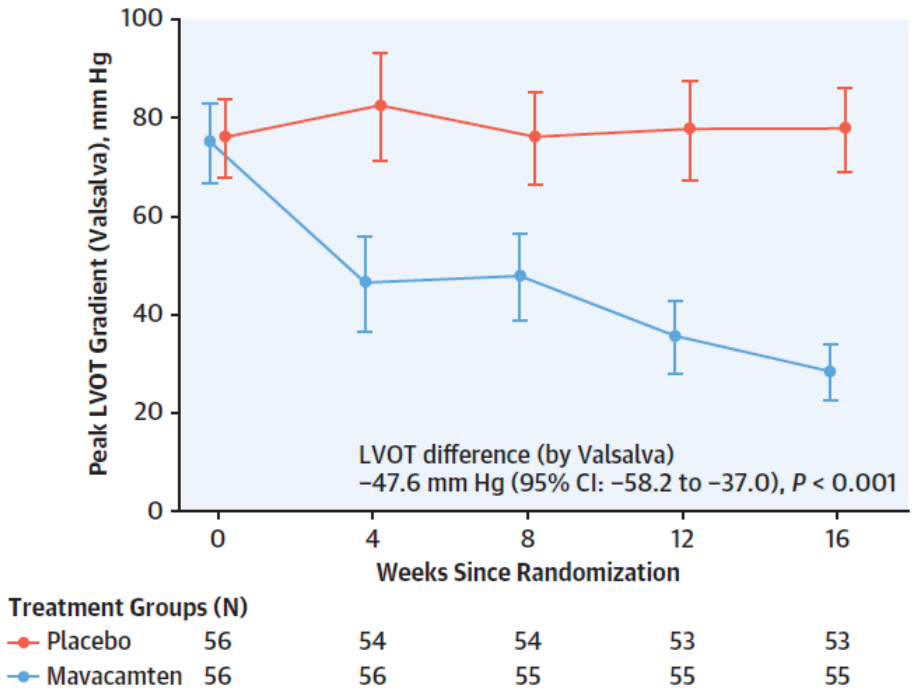
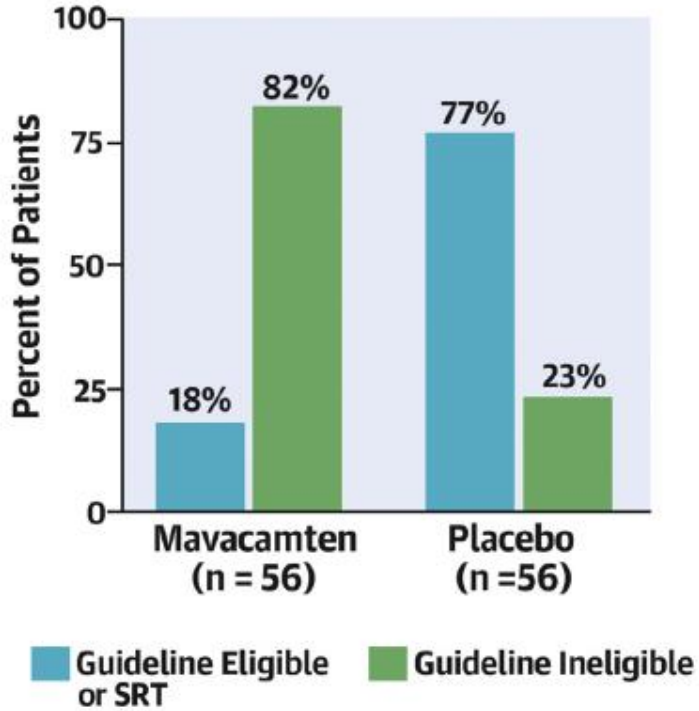
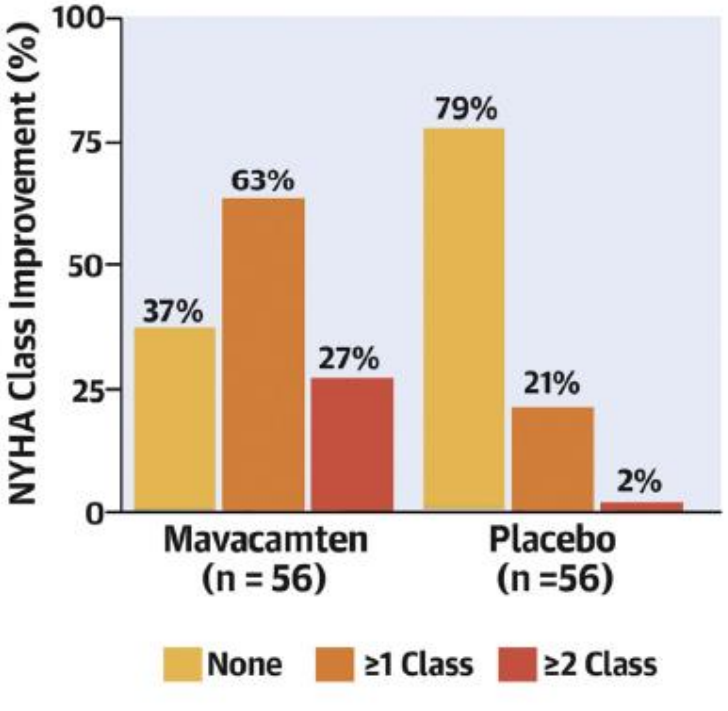
HYPERTROFISCHE OBSTRUCTIEVE CMP

Mavacamten: VALOR-HCM







Desai et al. J Am Coll Cardiol, 2022; 80: 95

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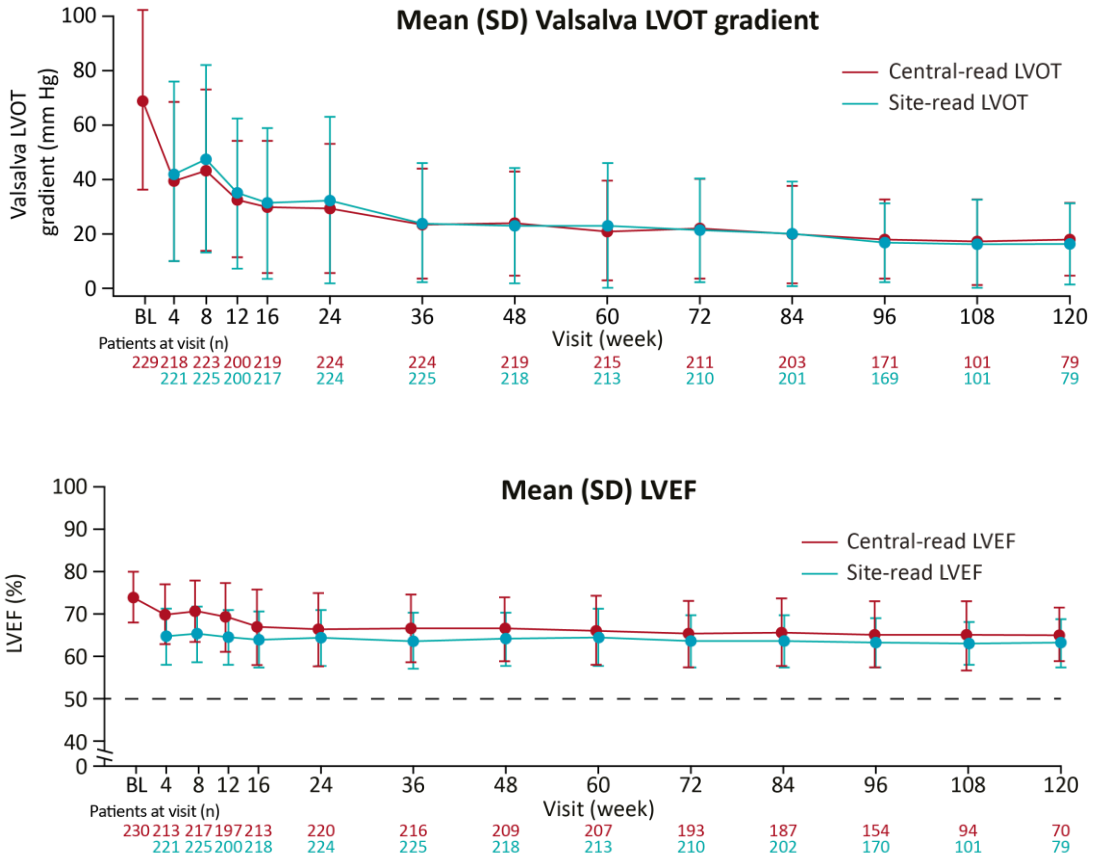
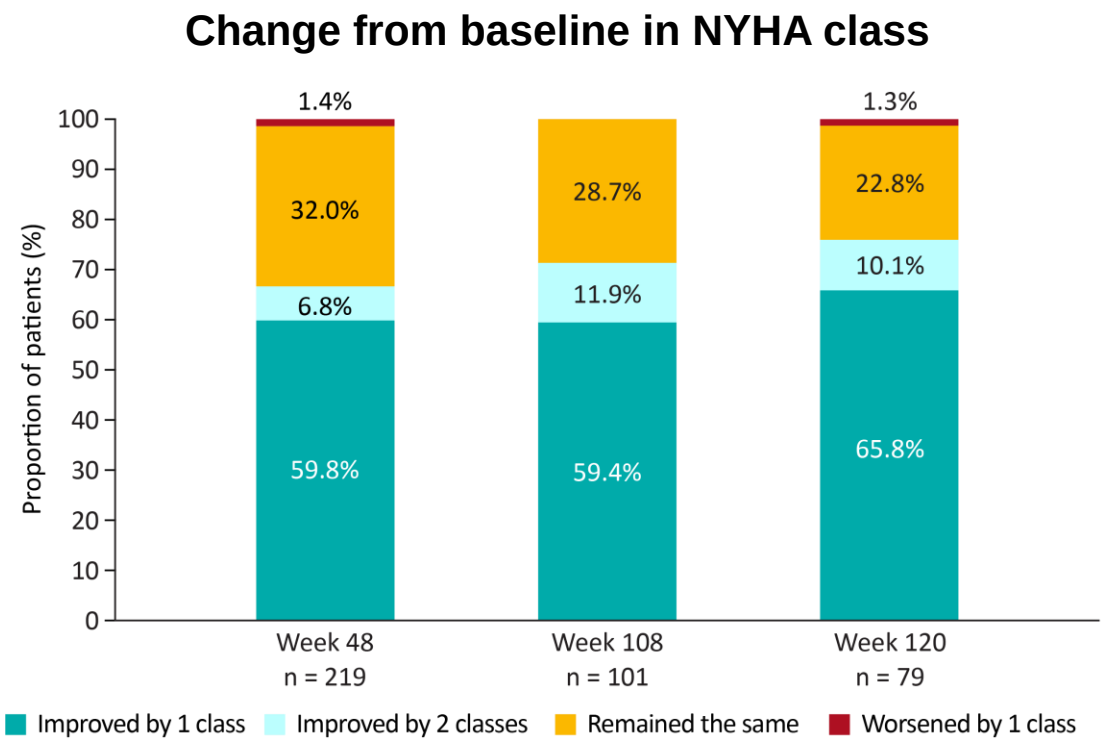
LANGE TERMIJN EFFECTEN

Mavacamten: MAVA-LTE (EXPLORER cohort)





Garcia-Pavia et al. Presented at the ESC Congress 2023

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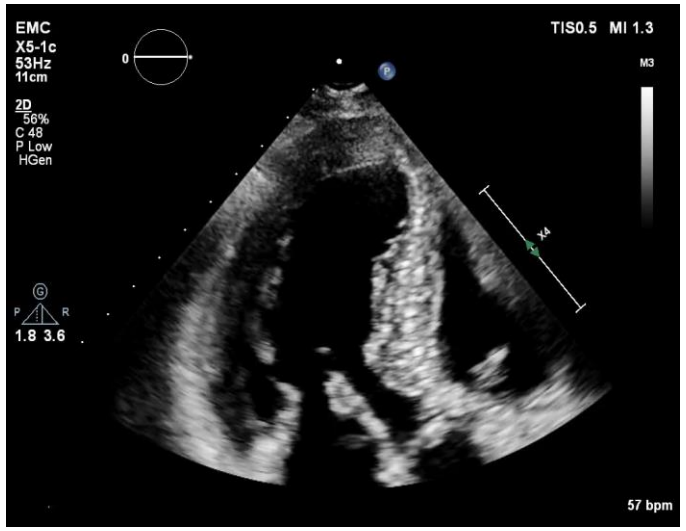
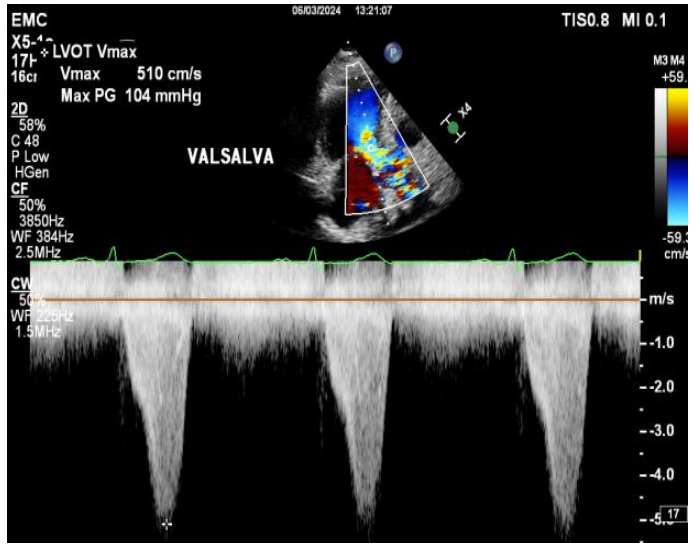
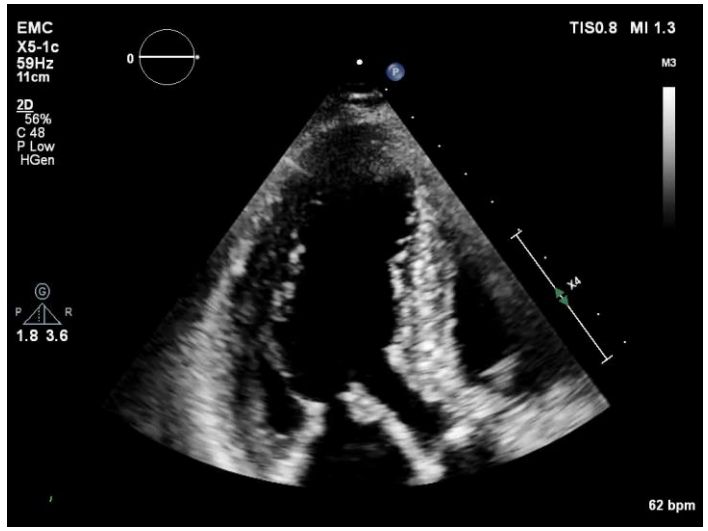
HYPERTROFISCHE OBSTRUCTIEVE CMP

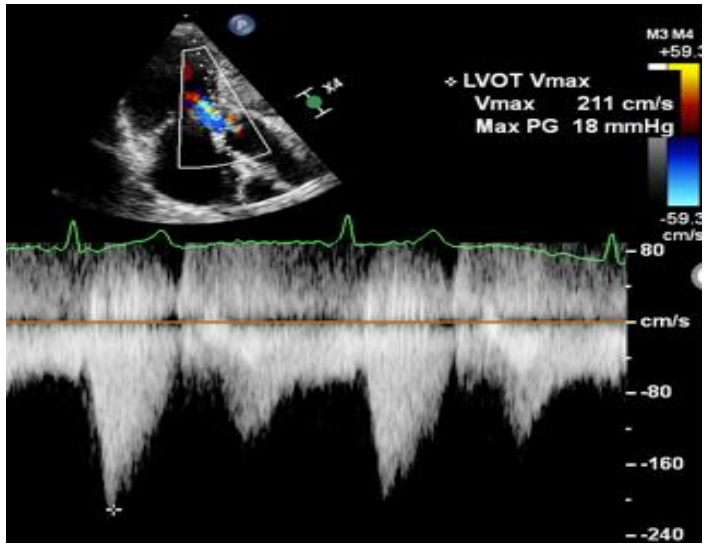
Mavacamten: ‘real word’ Erasmus experience





4 weken
Mavacamten 5 mg





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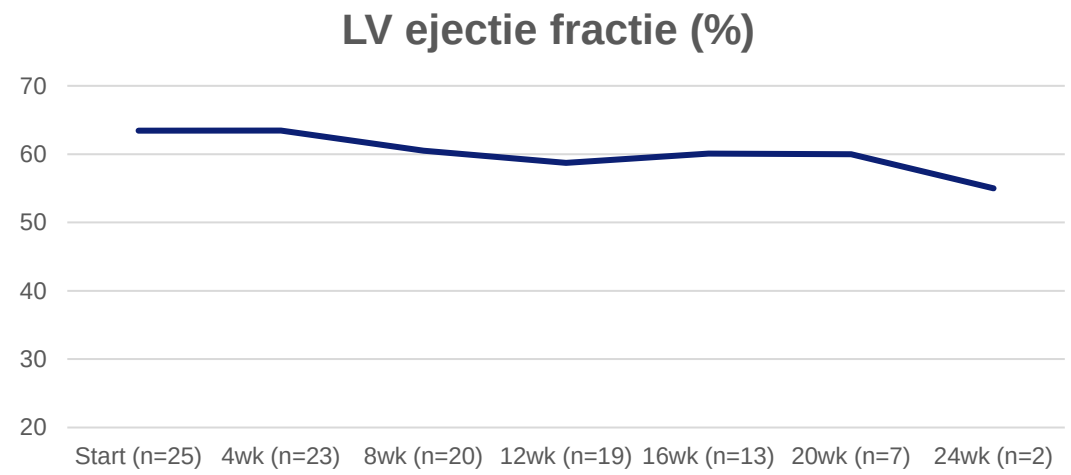
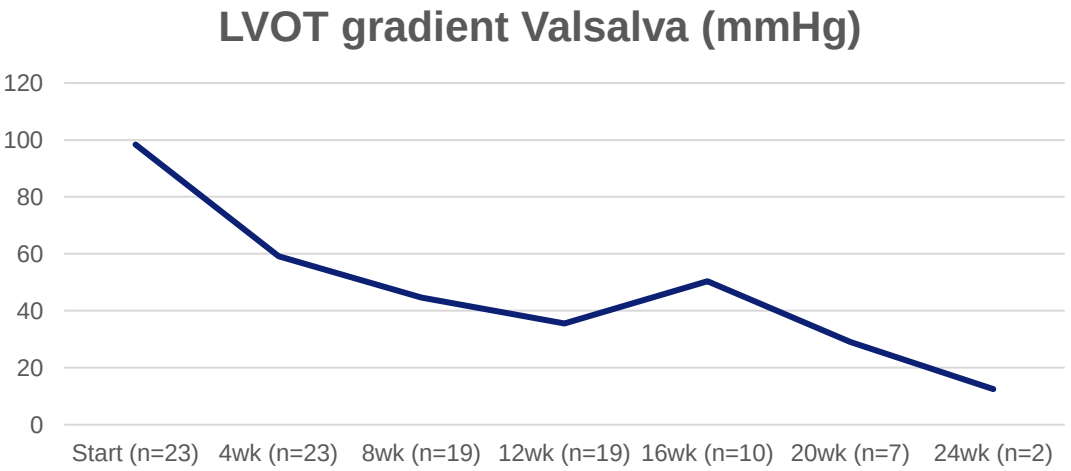
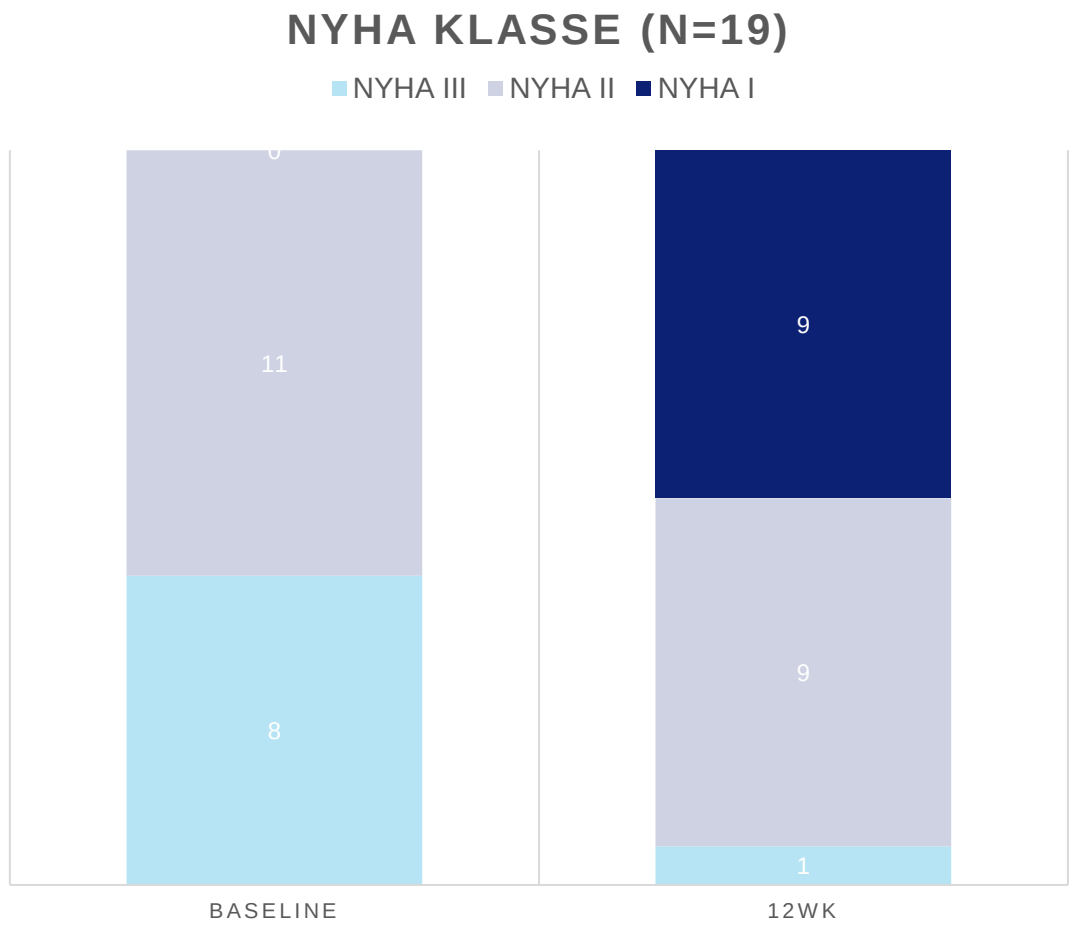
HYPERTROFISCHE OBSTRUCTIEVE CMP

Mavacamten: ‘real word’ Erasmus experience







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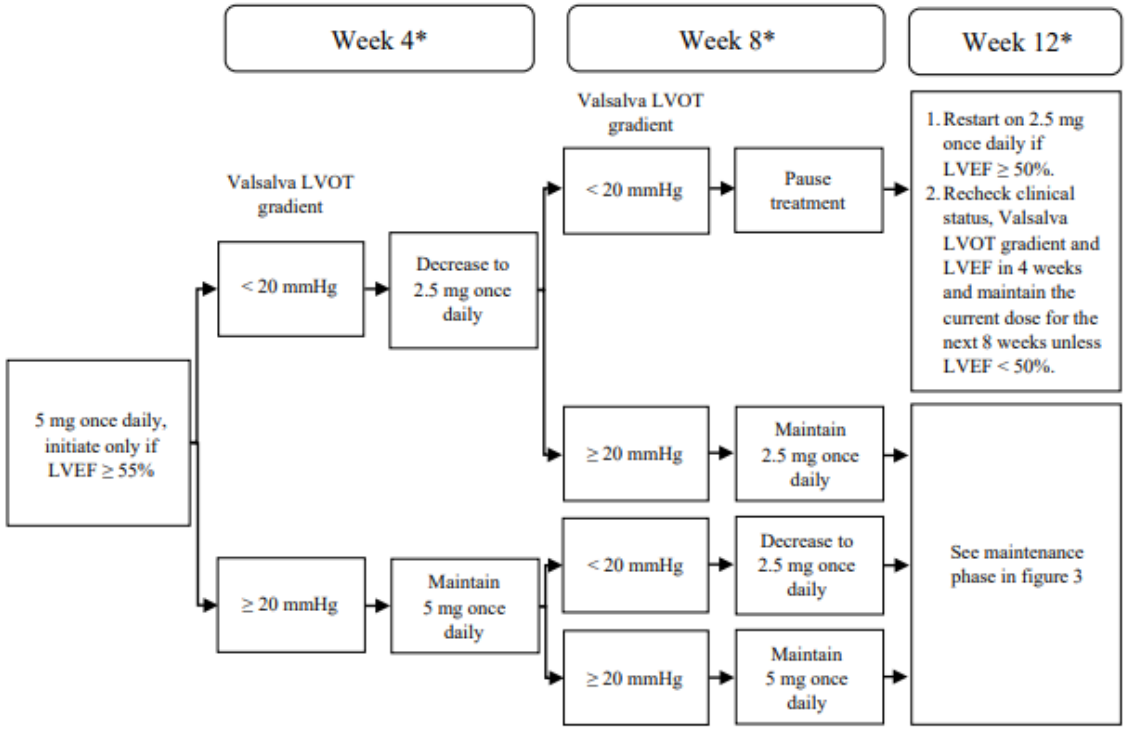
HYPERTROFISCHE OBSTRUCTIEVE CMP

Myosine inhibitoren: Mavacamten

Aandachtspunten:

- Logistiek uitdagend
- Strikte echocardiografische monitoring
- CYP2C19 genotyperen (in Europa)
- Interacties medicatie (CPY2C19 en CYP3A4 inhibitoren), onder andere PPI
- Gecontra-indiceerd in zwangerschap
- Lange half-waarde tijd (72 tot 533 uur)
- Lang tot steady state



* Interrupt treatment if LVEF is < 50% at any clinical visit; restart treatment after 4 weeks if LVEF ≥ 50% (see figure 4).
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract

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HYPERTROFISCHE OBSTRUCTIEVE CMP

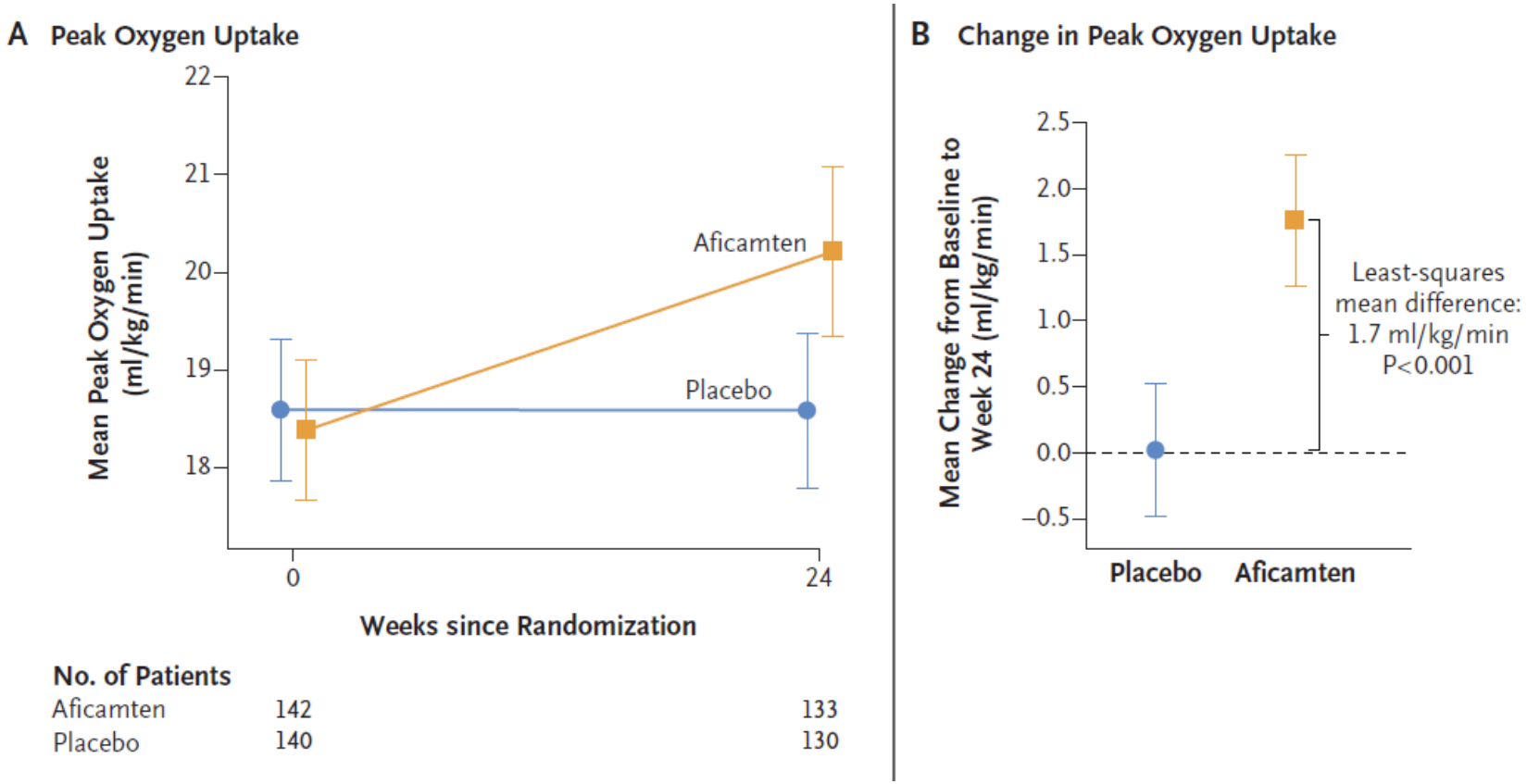
Aficamten: SEQUOIA-HCM

PATIENTS

WHO	282 patients
	18–85 years of age
	Men 59%; Women: 41%
CLINICAL STATUS	Symptomatic obstructive HCM with confirmed clinical diagnosis of HCM

TRIAL DESIGN

- PHASE 3
- INTERNATIONAL
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- TREATMENT DURATION: 24 WEEKS



Maron et al. NEJM, 2024; 80: 95

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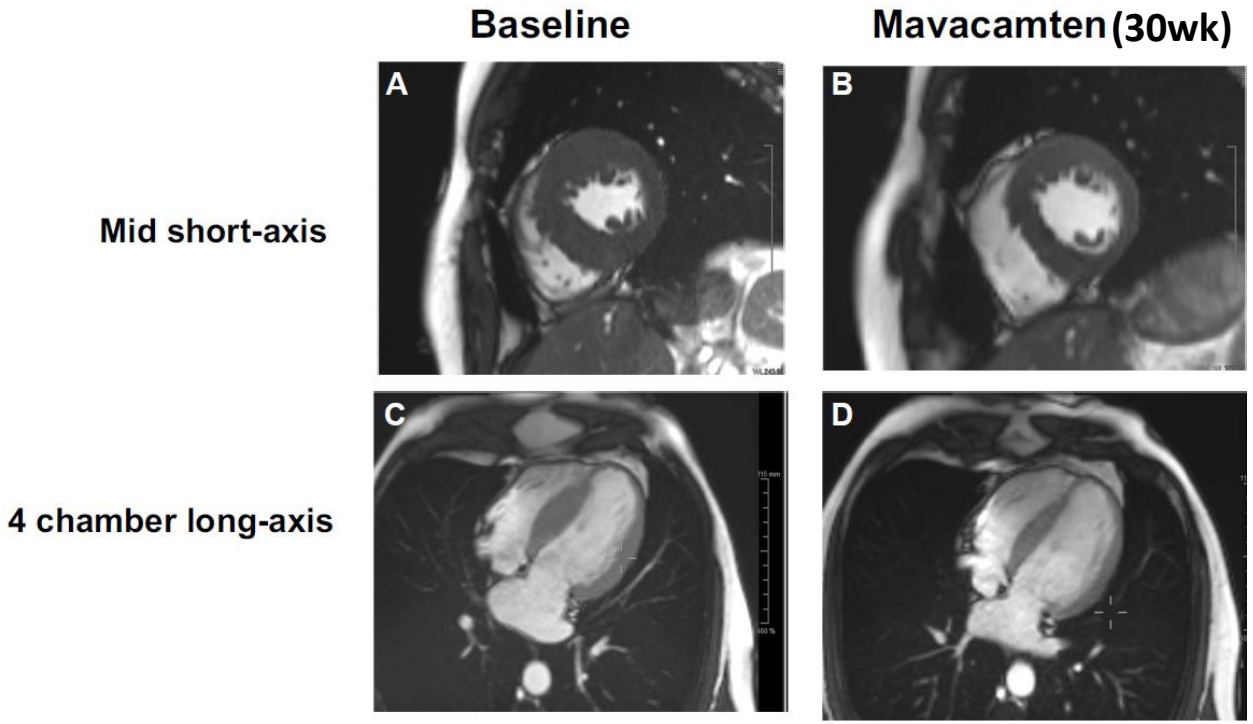
HYPERTROFISCHE (OBSTRUCTIEVE) CMP

Myosine inhibitoren: effect op morfologie en functie

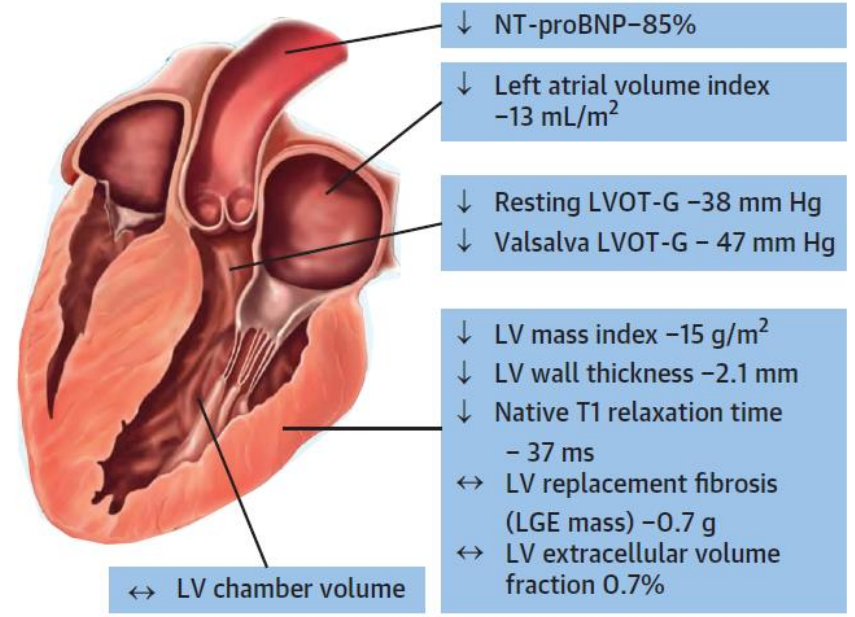


MWT ↓, LV massa ↓, LAVI ↓,
LA emptying fraction ↑

Braunwald et al. EHJ, 2023; 44: 4622

SEQUOIA CMR substudy (n=50)

Placebo-Corrected Changes From Baseline to Week 24 in Patients Receiving Aficamten



Down arrows indicate a statistically significant reduction from baseline.
Data are the least squares mean.

Masri et al. JACC, 2024; in press

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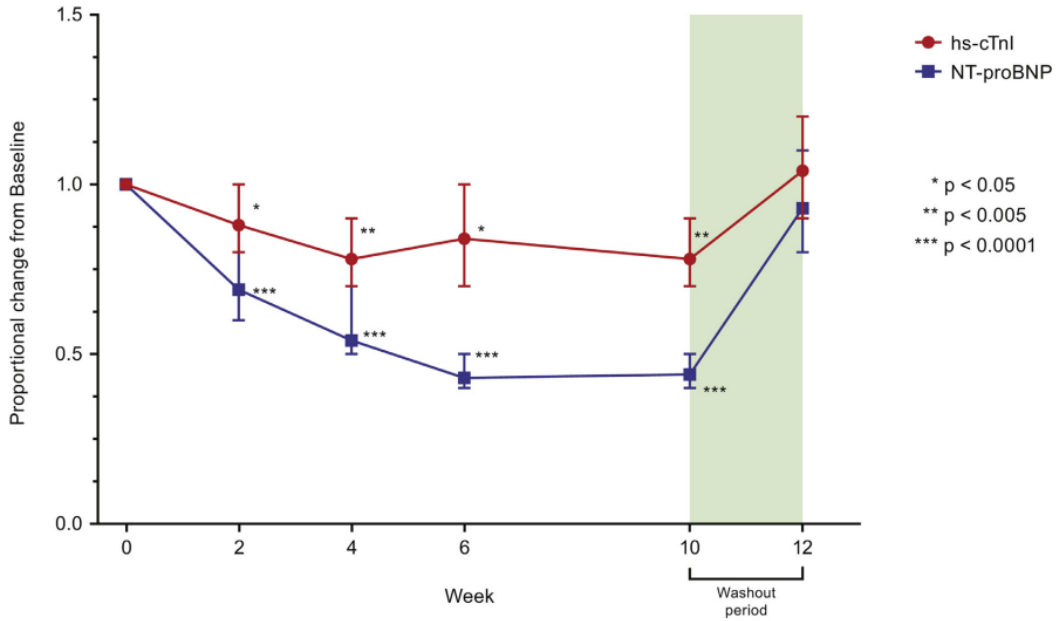
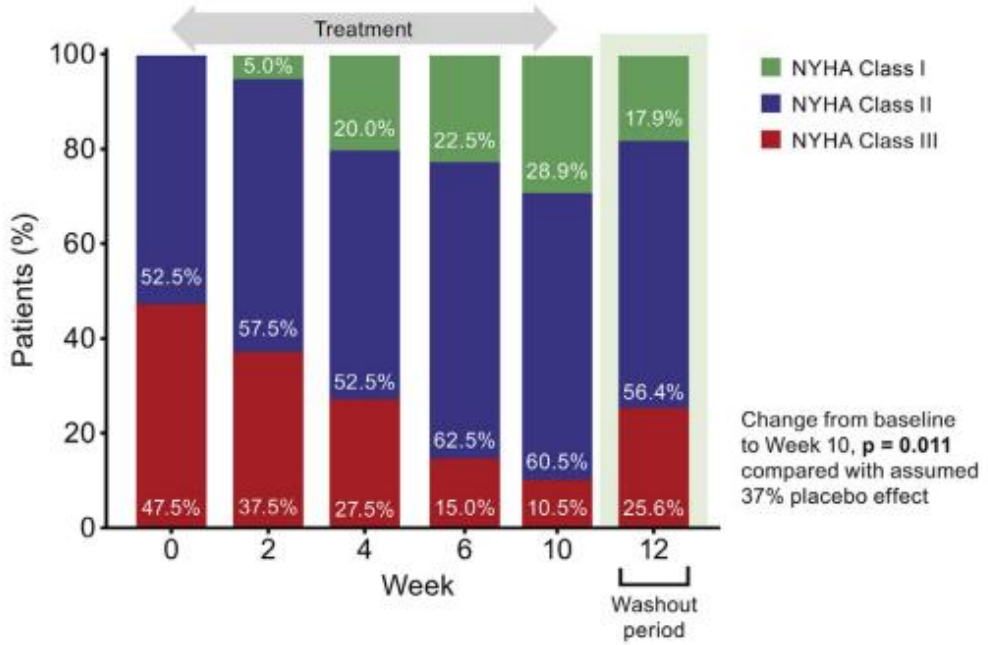
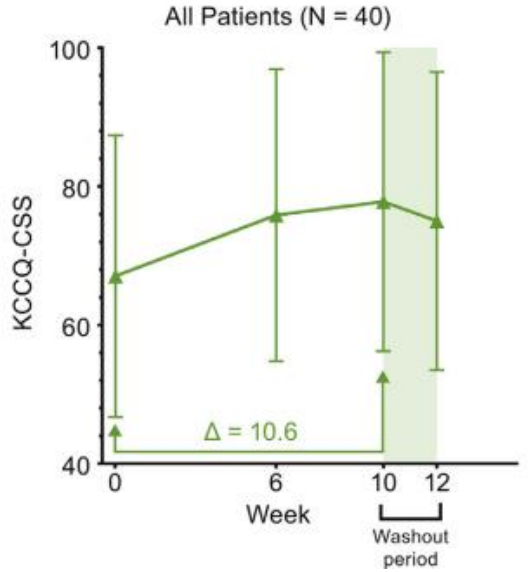
NIET OBSTRUCTIEVE HCM

Aficamten: REDWOOD-HCM







Masri et al. J Card Failure, 2024; in press

Erasmus MC

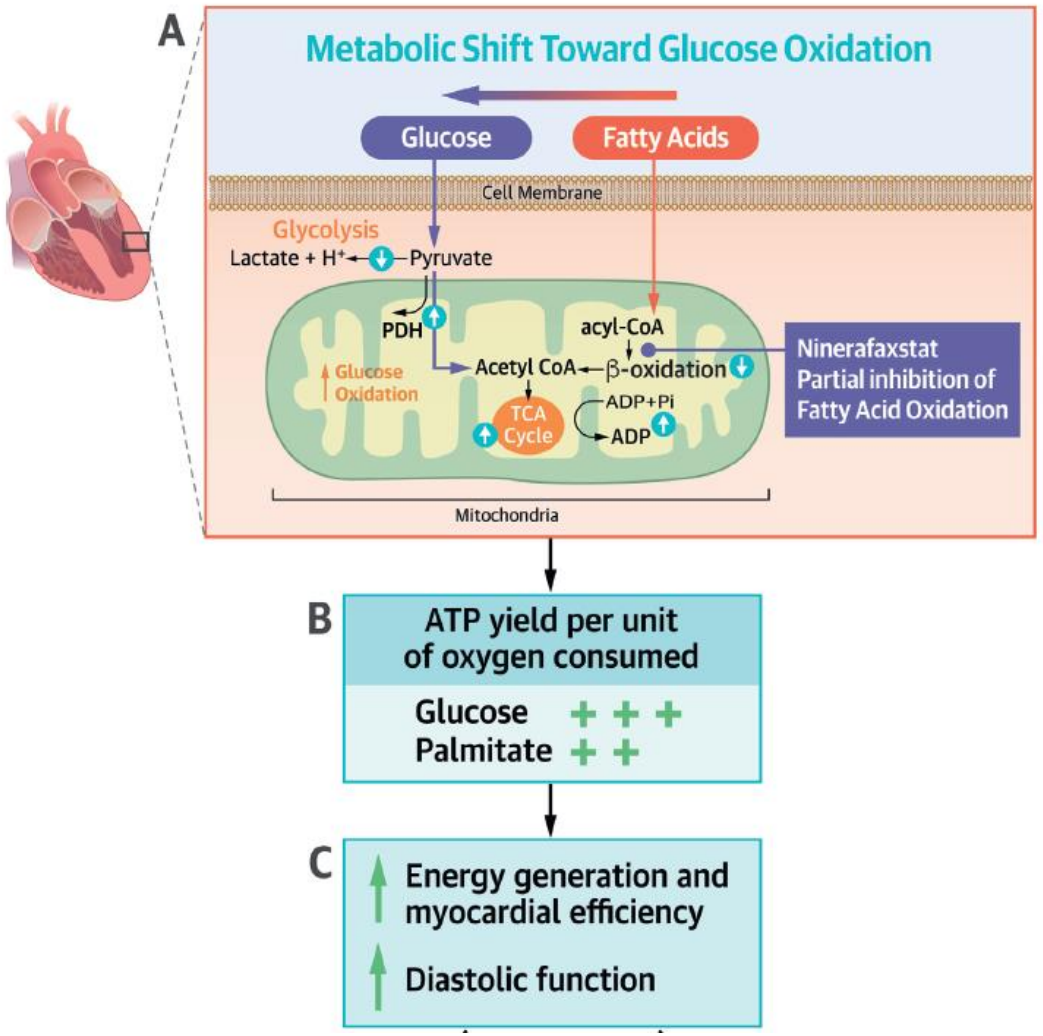
HYPERTROFISCHE (OBSTRUCTIEVE) CMP

Myosine inhibitoren

- Eerste myosine inhibitor momenteel beschikbaar
- Alleen in obstructieve HCM patiënten met goede LVEF en NYHA ≥2
- Effect op morfologie/functie veelbelovend maar meer data nodig
- Geen data mbt risico op ventriculaire ritmestoornissen/plotse dood
- Veel studies volgen nog:
  - MAVA-LTE: mavacamten in oHCM
  - SEQUOIA-LTE: aficamten in oHCM
  - ODYSSEY: mavacamten in HCM zonder obstructie
  - MAPLE-HCM: aficamten head-to-head metoprolol in oHCM
  - ACACIA: aficamten in HCM zonder obstructie
  - HCM op kinderleeftijd

NIET OBSTRUCTIEVE HCM

Metabole modulatie middels Ninerafaxstat

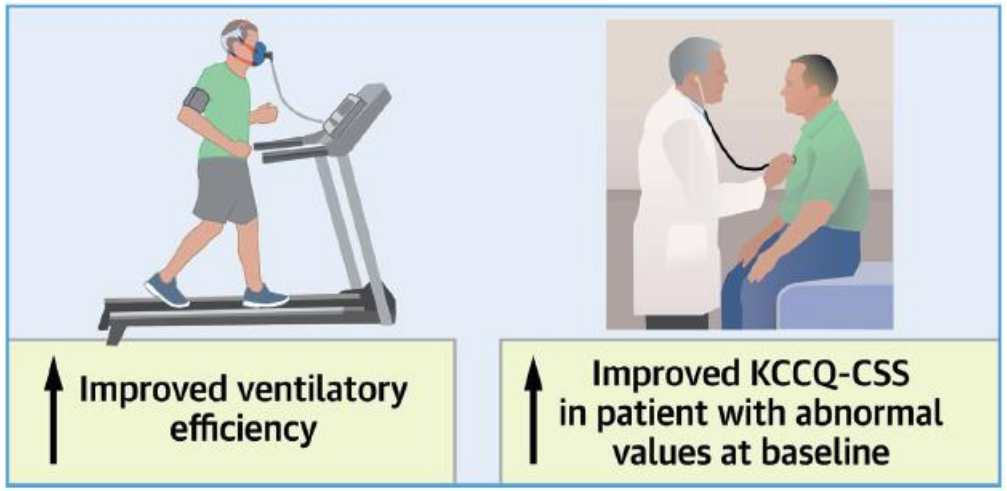


BACKGROUND In nonobstructive hypertrophic cardiomyopathy (nHCM), there are no approved medical therapies. Impaired myocardial energetics is a potential cause of symptoms and exercise limitation. Ninerafaxstat, a novel cardiac mitotrope, enhances cardiac energetics.

OBJECTIVES This study sought to evaluate the safety and efficacy of ninerafaxstat in nHCM.

METHODS Patients with hypertrophic cardiomyopathy and left ventricular outflow tract gradient <30 mm Hg, ejection fraction ≥50%, and peak oxygen consumption <80% predicted were randomized to ninerafaxstat 200 mg twice daily or placebo (1:1) for 12 weeks. The primary endpoint was safety and tolerability, with efficacy outcomes also assessed as secondary endpoints.

RESULTS A total of 67 patients with nHCM were enrolled at 12 centers (57 ± 11.8 years of age; 55% women). Serious adverse events occurred in 11.8% (n = 4 of 34) in the ninerafaxstat group and 6.1% (n = 2 of 33) of patients in the placebo group. From baseline to 12 weeks, ninerafaxstat was associated with significantly better V_E/V_{CO_2} (ventilatory efficiency) slope compared with placebo with a least-squares (LS) mean difference between the groups of −2.1 (95% CI: −3.6 to −0.6; $P = 0.006$), with no significant difference in peak VO_2 ($P = 0.90$). The Kansas City Cardiomyopathy Questionnaire Clinical Summary Score was directionally, though not significantly, improved with ninerafaxstat vs placebo (LS mean 3.2; 95% CI: −2.9 to 9.2; $P = 0.30$); however, it was statistically significant when analyzed post hoc in the 35 patients with baseline Kansas City Cardiomyopathy Questionnaire Clinical Summary Score ≤80 (LS mean 9.4; 95% CI: 0.3-18.5; $P = 0.04$).



Maron MS, et al. J Am Coll Cardiol. 2024;83(21):2037-2048.

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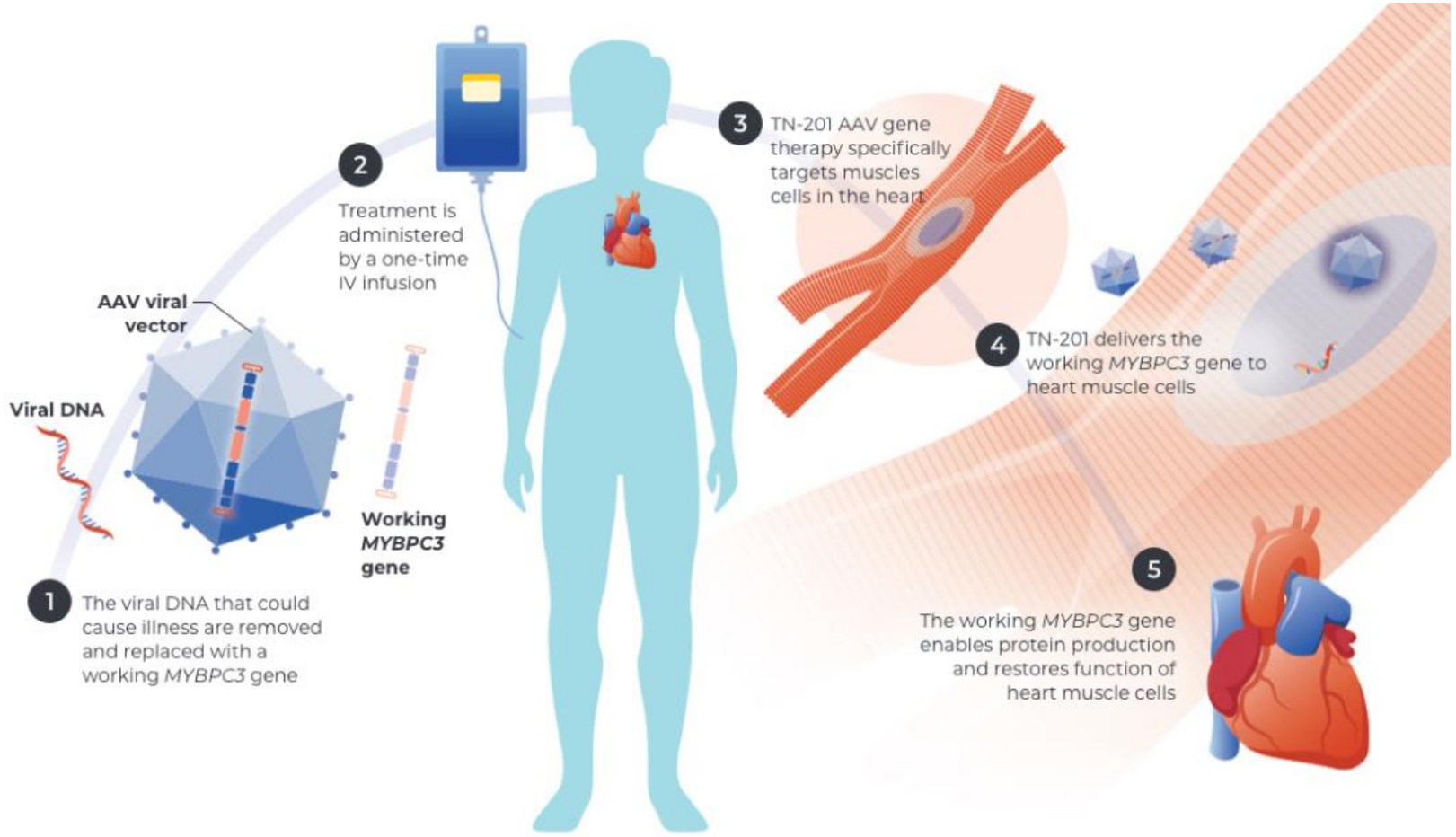
HYPERTROFISCHE CARDIOMYOPATHIE

Gen therapie (voor sarcomeer gerelateerde HCM)



[Phase 1b clinical trial: MyPeak-1](https://hcmstudies.com/our-studies/mypeak-1/)
https://hcmstudies.com/our-studies/mypeak-1/

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HYPERTROFISCHE CARDIOMYOPATHIE

Behandelmogelijkheden nu en in de toekomst

- Specifieke behandelingen voor specifieke oorzaken en daarom is goede fenotypering en genotypering nog belangrijker
- Eerste myosine inhibitor, Mavacamten, in Nederland geregistreerd voor HCM patiënten met LVOT obstructie. Ook veelbelovende resultaten voor myosine inhibitor Aficamten.
- Momenteel zijn er veel lopende studies ook in niet-obstructive HCM patiënten
- Nieuwe behandelingen in onderzoek zowel medicamenteus, invasief als gentherapie

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Bedankt voor u aandacht