Diagnosing and Treating Cardiomyopathies: A Case-Based Discussion

Moderator & Additional Panelists:

Mariko Harper, MD
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Case Example: Is it Hypertrophic Cardiomyopathy or Cardiac Amyloid or ?

Jonny Medina, DNP, ARNP

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Disclosure

- Cytokinetics, Advisory Board Attendee

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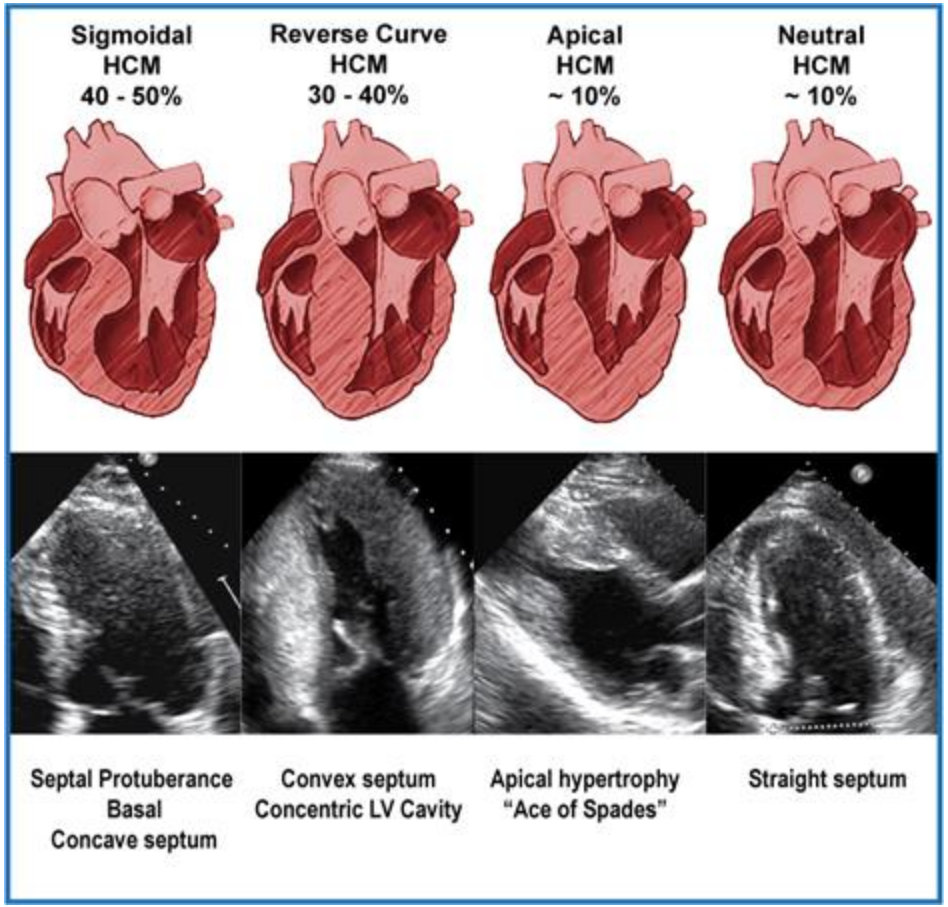
HCM Background

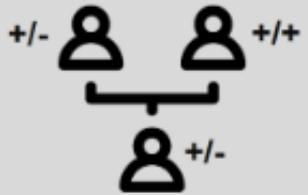


Hypertrophic cardiomyopathy (HCM):

- LVH ≥ 15mm in the absence of other conditions that could cause it
- LVH ≥ 13mm in persons with known genetic variant or first degree family history
- Diagnosis made by transthoracic echocardiogram, or with cardiac MRI in ambiguous cases.
- Often accompanied by abnormal ECG findings (increased precordial voltage, repolarization abnormalities)

HCM Background

Inheritance Pattern



Autosomal Dominant

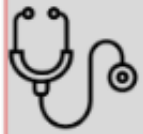
Sex Distribution

Women diagnosed less commonly

Disease Prevalence

Estimated 1:200 – 1:500

Triggers for Evaluation



Symptoms
Cardiac Event
Heart Murmur
Abnormal EKG
Cardiac Imaging
Family Studies

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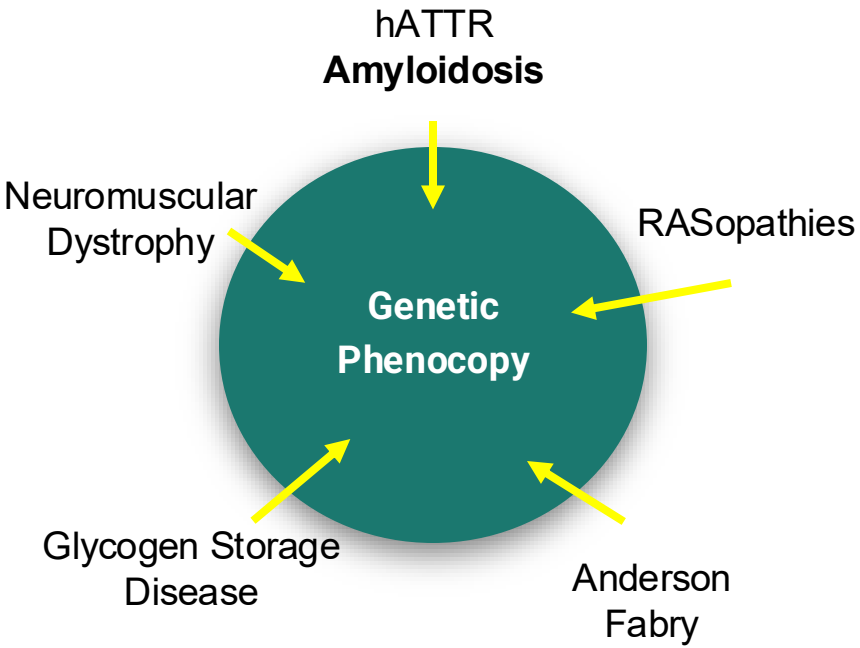
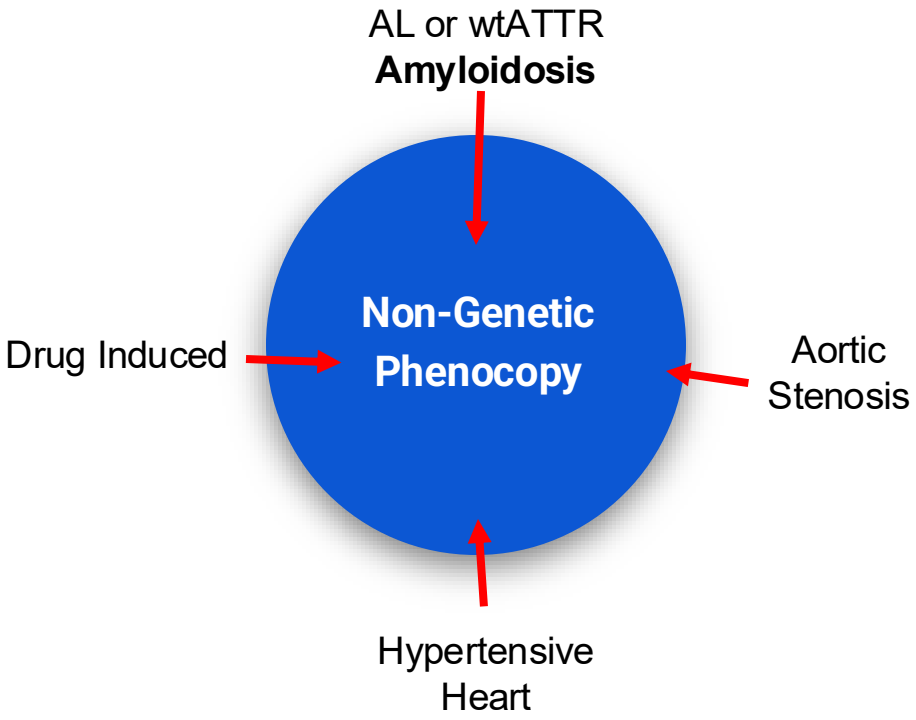
HCM and its phenocopies





Case Study - Clinical Presentation

HPI

79 y/o M with worsening exertional dyspnea over past year, persistent fatigue. Referred by PCP d/t echo findings suggestive of combined systolic and diastolic HF with marked LVH - possible infiltrative vs hypertrophic cardiomyopathy

Past Medical History

Persistent AF since 2012 s/p AFL ablation, CKD Stage 3A, bilateral carpal tunnel syndrome

Social History

He is retired. He does not smoke tobacco or drink alcohol in excess.

Family History

No SCD, CVA in 3 generation pedigree

Mother deceased age 96 “old age”

Father deceased age 88 “MI”, T2DM

Maternal GM deceases 90s

Maternal GF deceased 70s

Paternal GM deceased 80s

Paternal GF deceased 70s

No suspicious etiologies of death in any second and third-degree relatives known.

One of 8 siblings, all other siblings are living without cardiac issues

Son 57 healthy, Daughter 52 healthy

Case Study - Clinical Presentation

PHYSICAL EXAMINATION:

VITAL SIGNS: BP 132/72, pulse 56, SpO2 98% RA, weight 96 kg.

GENERAL APPEARANCE: Well-appearing Caucasian gentleman in no acute distress.

CARDIAC: **Irregularly irregular** with no significant murmurs. Nondisplaced PMI. Slightly pronounced amplitude at the apex.

NECK: No JVD. No carotid bruits.

RESPIRATORY: CTAB.

ABDOMEN: Belly with mild visceral adiposity.

LOWER EXTREMITIES: **Trace edema,** a bit more prominent on the right rather than left calf.

MEDICATIONS:

1. Carvedilol 12.5 mg p.o. b.i.d.
2. Entresto 49/51 mg p.o. b.i.d.
3. Jardiance 10 mg p.o. q.a.m.
4. Magnesium oxide.
5. Sodium bicarbonate 650 mg p.o. q.i.d.
6. Spironolactone 12.5 mg p.o. daily.
7. Vitamin D.
8. Xarelto 20 mg p.o. daily.

Case Example

Echocardiogram

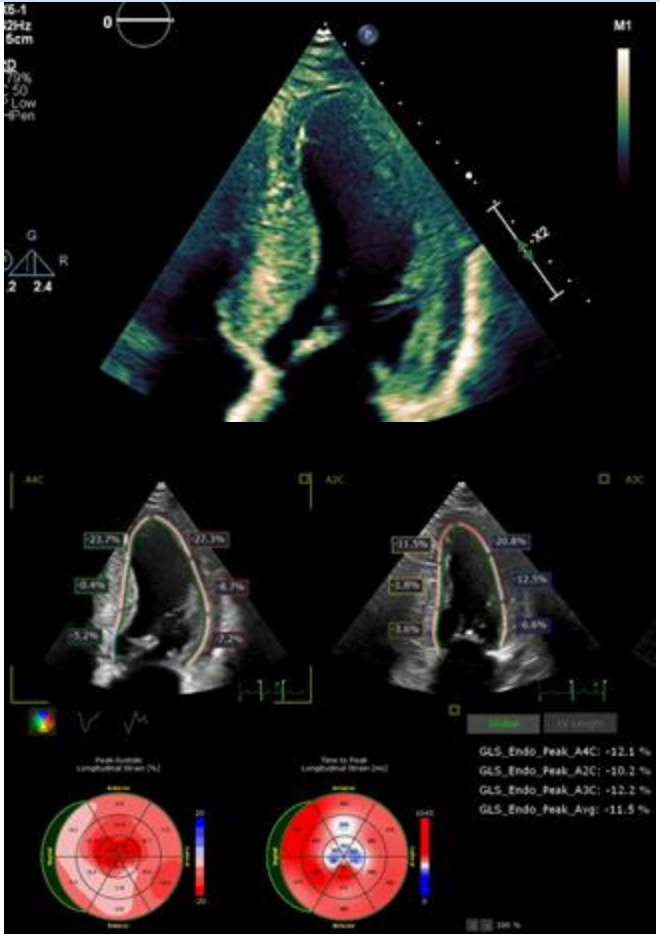
EF is visually estimated at **45-50%.**

There is mild mitral regurgitation. **No significant systolic anterior motion/SAM**

Abnormal Global Longitudinal Strain: -11.0%

There is asymmetric left ventricular hypertrophy/ASH. Septal predominance, mid septum severely increased thickness > basal septal
There is abnormal diastolic function: reduced EF, atrial fibrillation presentation

IVC size and dynamics are consistent with normal RA pressure of 3 to 8 mmHg.



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Diagnostic Workup

ECG:

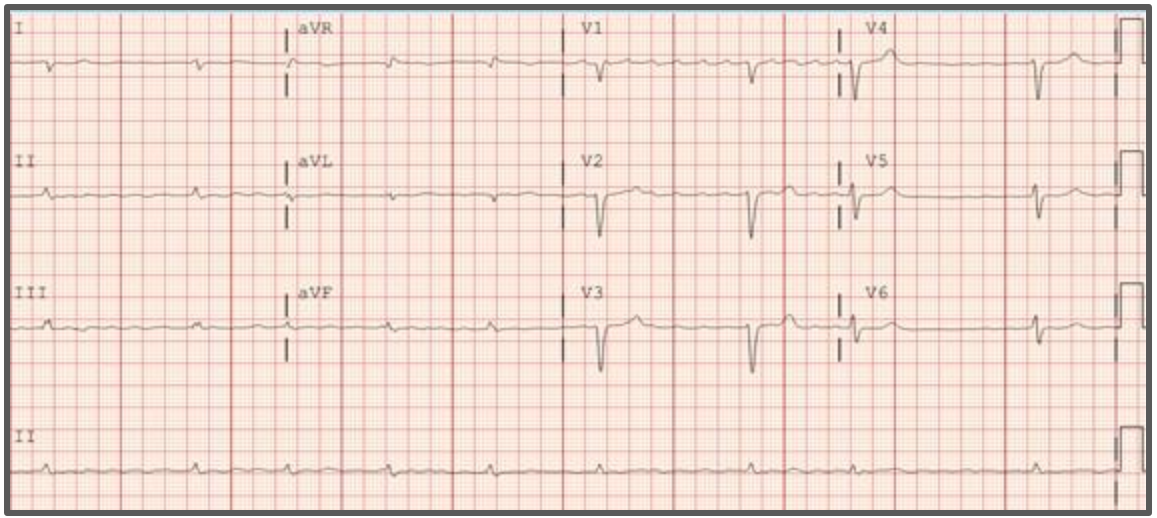
Atrial Flutter

Low voltage in frontal leads

Ventricular rate 56 bpm

QRSD 118ms

QTc 464ms



Labs:

Troponin T 55 ng/L
NT-pro BNP 14979

Serum Creatinine: 2.13

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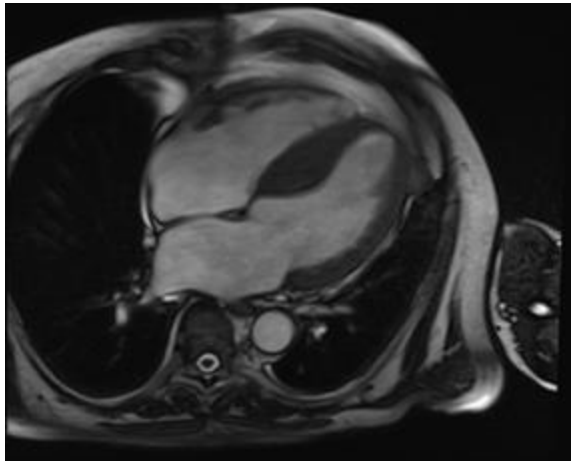
Diagnostic Workup

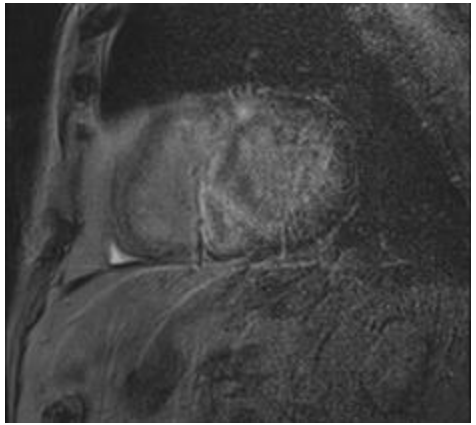
Cardiac MRI

1. There is circumferential left ventricular hypertrophy measuring up to **28mm in diastolic thickness** in the mid anteroseptal segment. Addition, there is circumferential abnormal **left ventricular mid myocardial enhancement (50%).** The combination of these findings may be seen both in the setting of **cardiac amyloidosis as well as circumferential hypertrophic cardiomyopathy.**
2. There is moderate right ventricular hypertrophy.
3. The left ventricle is moderately dilated with moderately depressed systolic function. Left ventricular ejection fraction of 36%.



Labs

Kappa Free Light Chains: 21.7 mg/L
Free Lambda Light Chains 15.1 mg/L
Kappa/Lambda Ratio: 1.44
Immunofixation UPEP: No M-Spike
Immunofixation SPEP: No Monoclonal component



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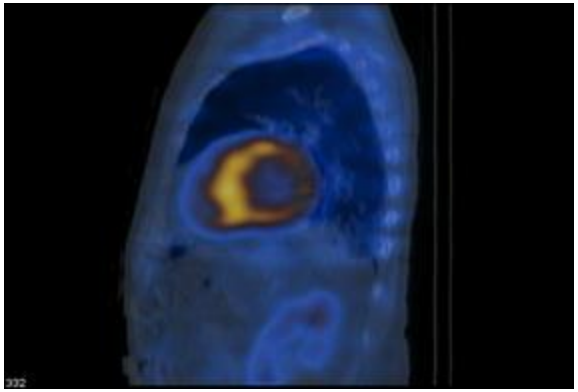
Diagnostic Workup

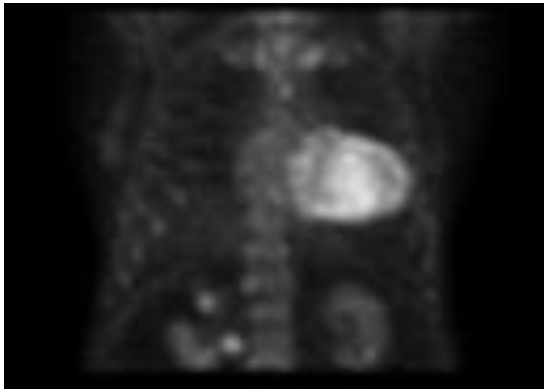
Nuclear Medicine Cardiac Technetium-99 Pyrophosphate (PYP) Scan:

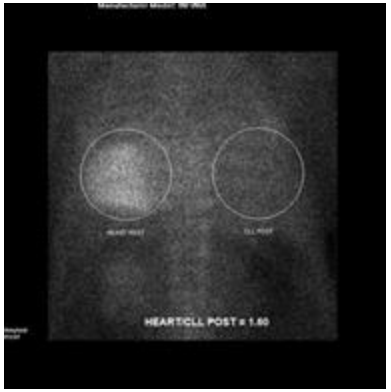
Semiquantitative (visual) criteria: Grade 3 (Myocardial uptake greater than rib uptake with mild/absent rib uptake.)

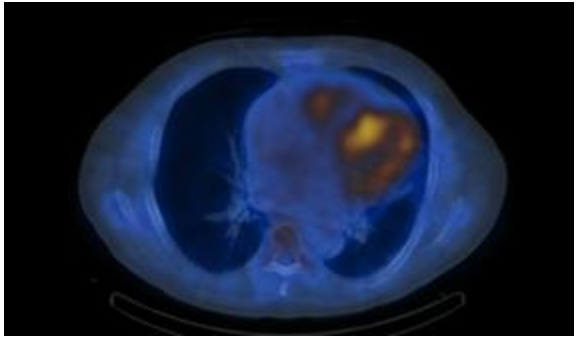
Quantitative criteria: Ratio of heart to contralateral lung uptake (H/CL ratio): 1.7.

Constellation of findings **strongly suggestive of TTR cardiac amyloid**









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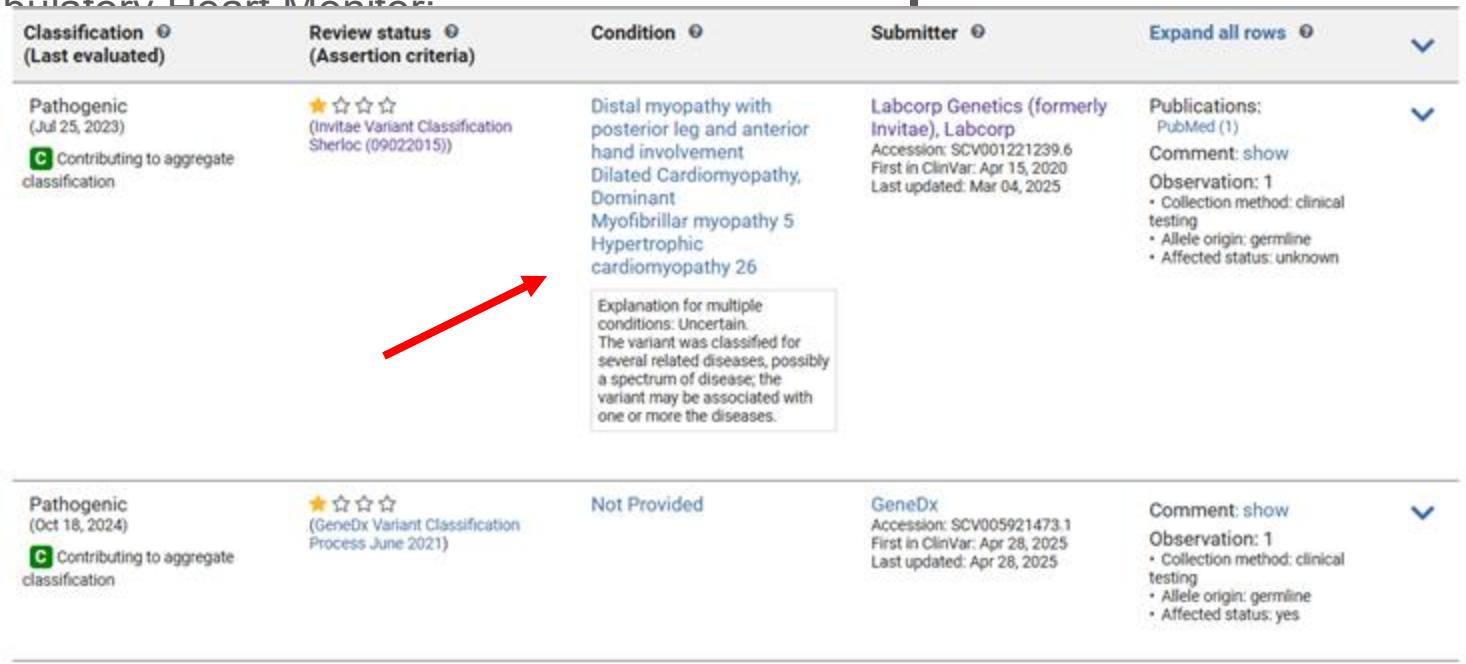
Diagnostic Workup

Am[illegible]

- Pre
- Atri
- PV(
- No

Ge

HCM
Likel



Classification (Last evaluated)	Review status (Assertion criteria)	Condition	Submitter	Expand all rows
Pathogenic (Jul 25, 2023) C Contributing to aggregate classification	★☆☆☆ (Invitae Variant Classification Sherloc (09022015))	Distal myopathy with posterior leg and anterior hand involvement Dilated Cardiomyopathy, Dominant Myofibrillar myopathy 5 Hypertrophic cardiomyopathy 26 Explanation for multiple conditions: Uncertain. The variant was classified for several related diseases, possibly a spectrum of disease; the variant may be associated with one or more the diseases.	Labcorp Genetics (formerly Invitae), Labcorp Accession: SCV001221239.6 First in ClinVar: Apr 15, 2020 Last updated: Mar 04, 2025	Publications: PubMed (1) Comment: show Observation: 1 • Collection method: clinical testing • Allele origin: germline • Affected status: unknown
Pathogenic (Oct 18, 2024) C Contributing to aggregate classification	★☆☆☆ (GeneDx Variant Classification Process June 2021)	Not Provided	GeneDx Accession: SCV005921473.1 First in ClinVar: Apr 28, 2025 Last updated: Apr 28, 2025	Comment: show Observation: 1 • Collection method: clinical testing • Allele origin: germline • Affected status: yes

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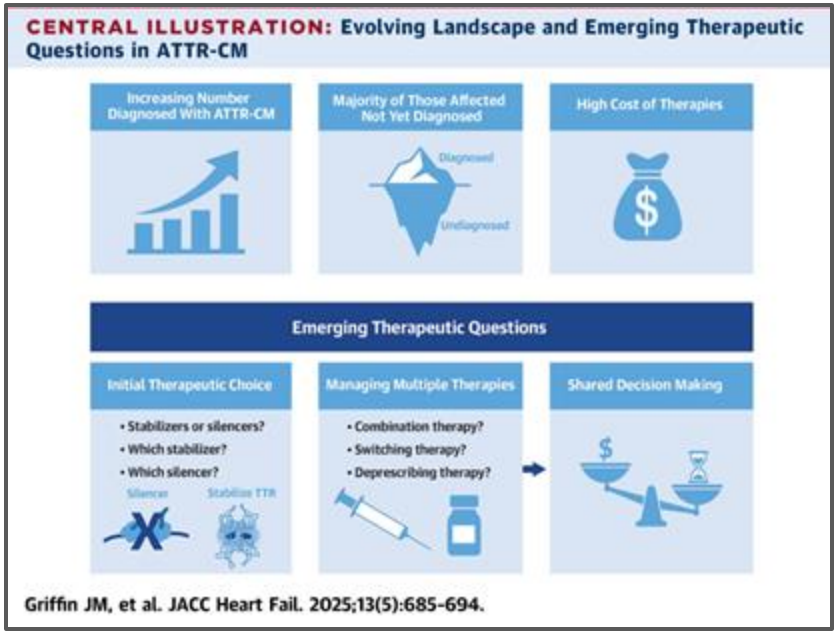
Treatment

Co-Manage HCM and ATTR Amyloidosis:

1) Cascade genetic testing for FLNC variant
2) Tafamidis for TTR stabilizer therapy
3) GDMT for HFrEF
4) Anticoagulation for AF/AFL
5) Consider Clinical Trials



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Thank You

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Cardiac Amyloidosis: Diagnosis and Novel Treatments for Transthyretin (ATTR) Cardiomyopathy

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Virginia Mason Medical Center
Seattle

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Disclosures

- Speaker for BridgeBio

Amyloidosis

- Disease of protein misfolding, aggregation, and fibril formation
- Extracellular deposition leading to organ dysfunction

Cardiac Amyloidosis

- Thick ventricle but no true myocyte hypertrophy.
- Restrictive cardiomyopathy

Highlights

1. How do we unmask and diagnose this disease

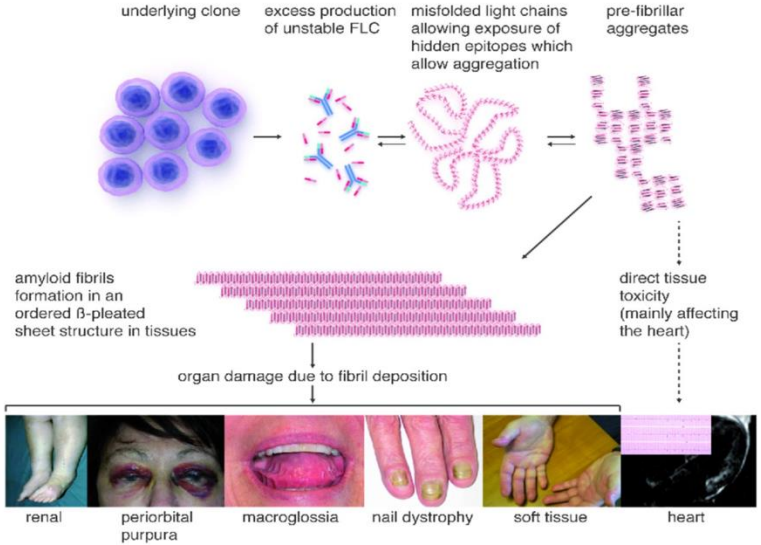
2. Discuss available disease-modifying therapies for amyloid and potential upcoming treatment options

3. Treatment of cardiac consequences

Types

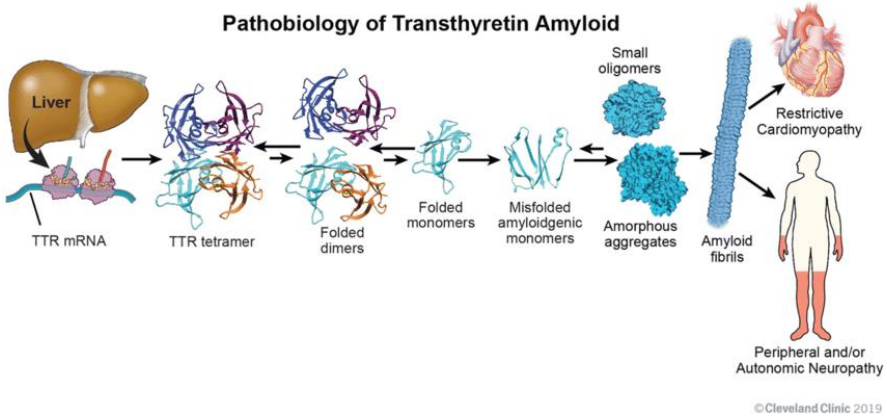
- Over 35 amyloidogenic precursor proteins identified

AL Amyloid



Update on treatment of light chain amyloidosis
S.Mehmood et al.

TTR Amyloid



Current heart Failure Reports, June 2020

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Cardiac amyloidosis pathology.

Joseph P. Donnelly, and Mazen Hanna CCJM 2017;84:12-26

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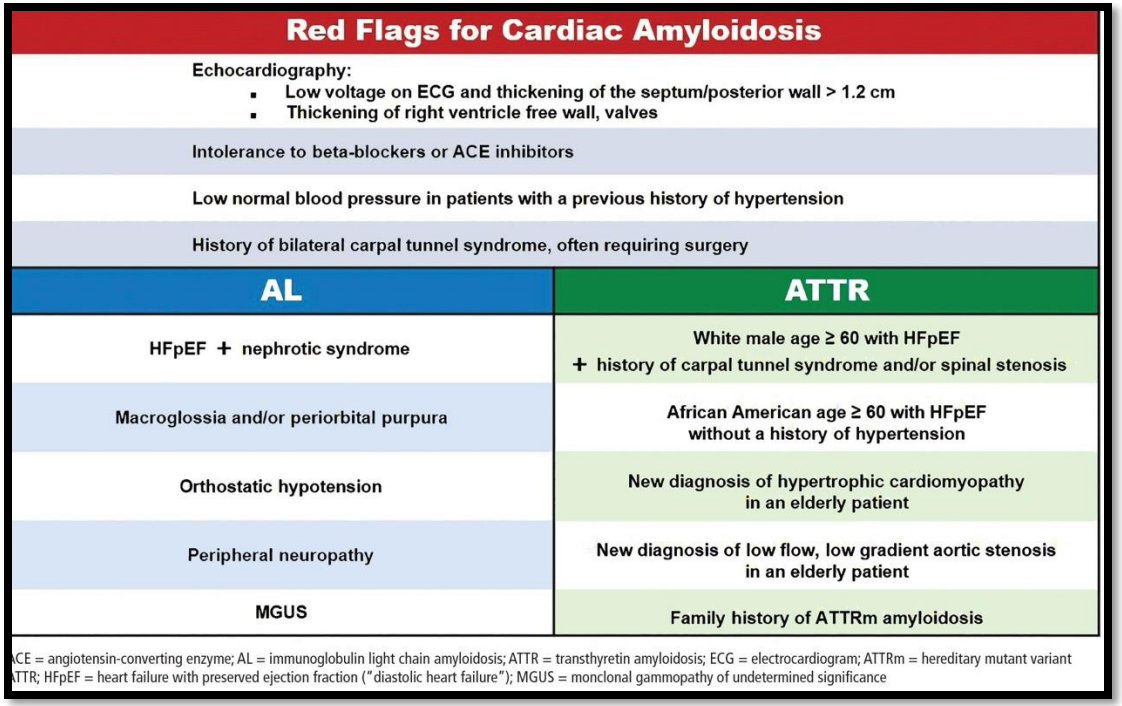
Diagnosis Requires Pattern Recognition



Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

ACE = angiotensin-converting enzyme; AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; ECG = electrocardiogram; ATTRm = hereditary mutant variant ATTR; HFpEF = heart failure with preserved ejection fraction ("diastolic heart failure"); MGUS = monclonal gammopathy of undetermined significance

Hanna M, Cleveland Clinic Journal of Medicine, 2017

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Transthyretin (TTR) Cardiac Amyloidosis

There are 2 forms of disease:

Table 1. Characteristics of Wild-Type and Common Variant Transthyretin Cardiac Amyloidosis

Mutation	Origin	Prevalence	Male:Female Ratio	Onset	Organs
SSA	Worldwide	25% >85 y	25:1 to 50:1	>60 y	Heart, ST
V122I	United States, Caribbean, Africa	4% Black	1:1 Gene (+) 3:1 Disease	>65 y	Heart, PNS, ST
V30M	Portugal, Sweden, Japan	1:1000	2:1	>50 y	PN/ANS, heart
T60A	United Kingdom, Ireland	1% Northwest Ireland	2:1	>45 y	Heart, PNS/ANS

SSA indicates senile systemic amyloidosis, wild-type (no mutation); ST, soft tissue; PNS, peripheral nervous system; and ANS, autonomic nervous system.

Ruberg FL, Berk JL, Circulation 2012

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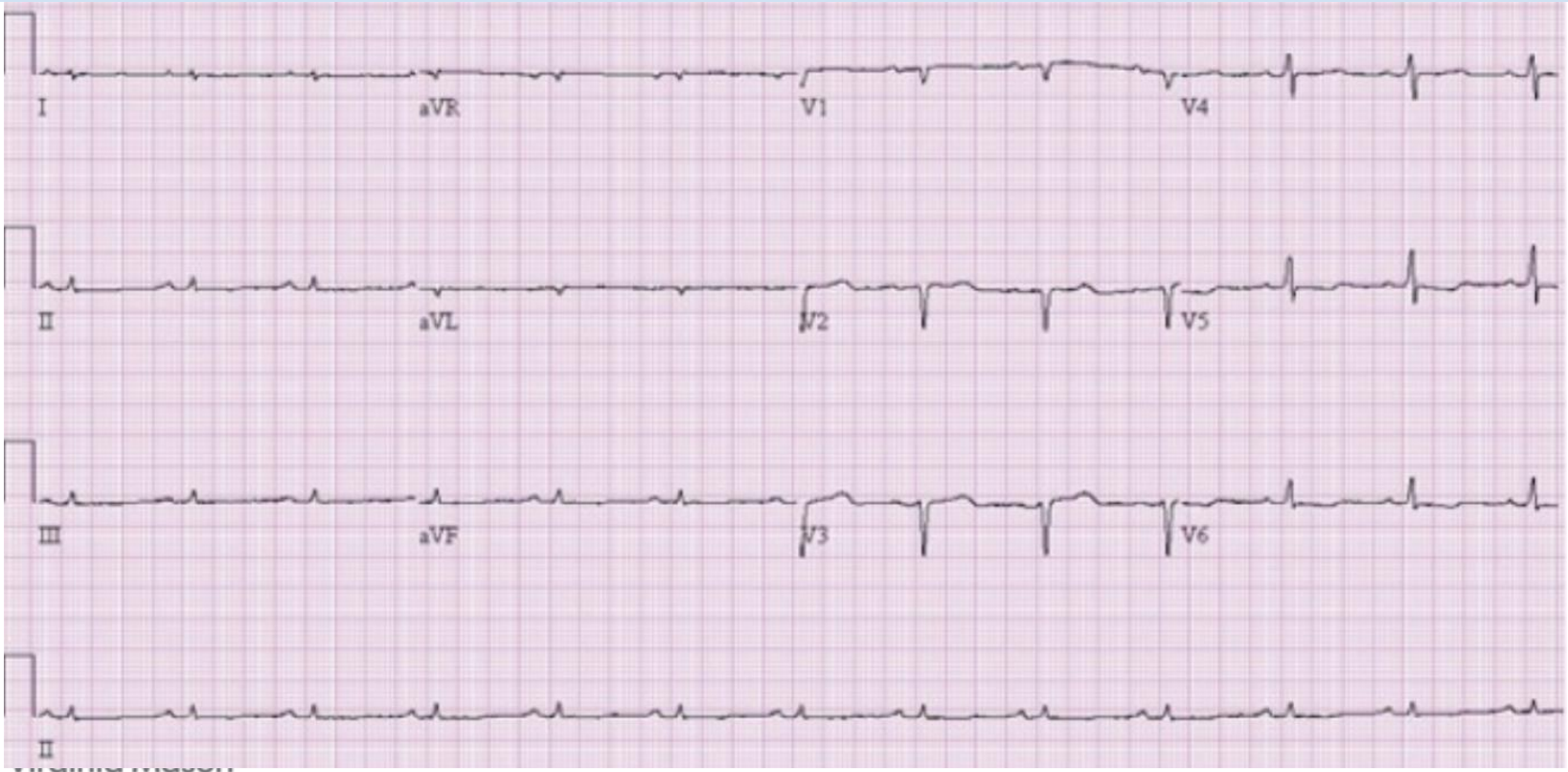

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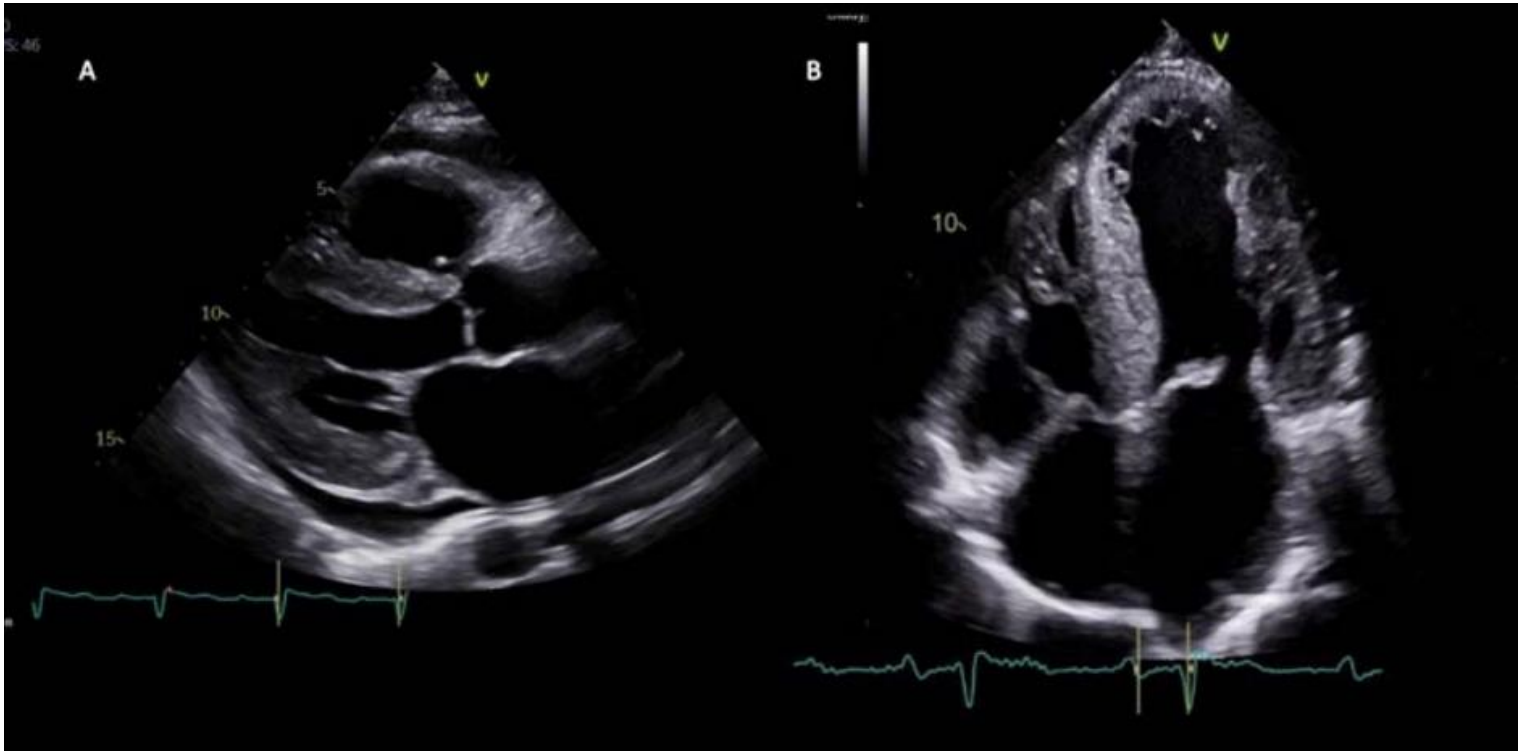

Practical Points for Echocardiography in Cardiac Amyloidosis
JASE 2022

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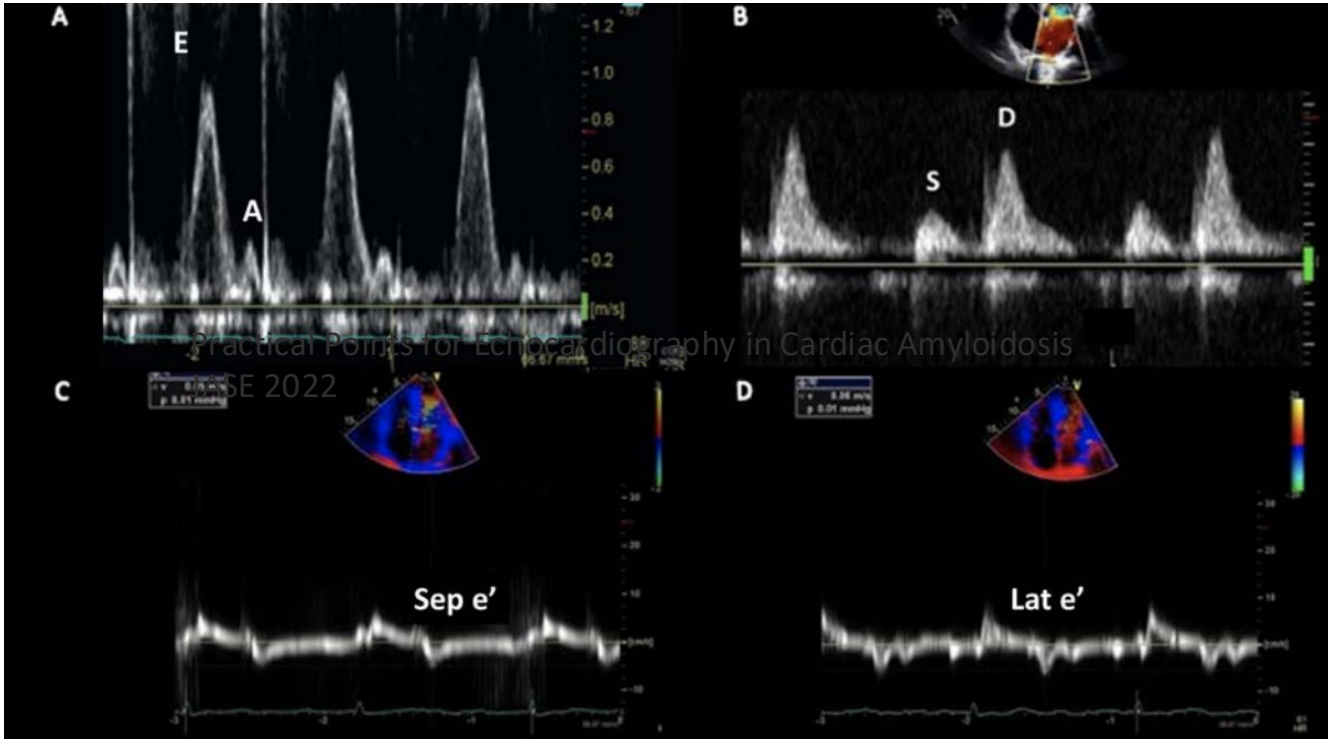

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Practical Points for Echocardiography in Cardiac Amyloidosis
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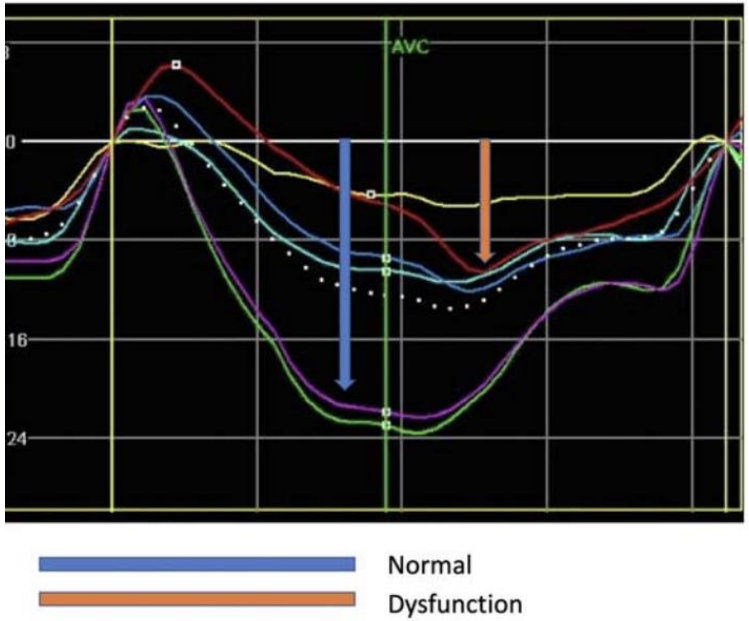

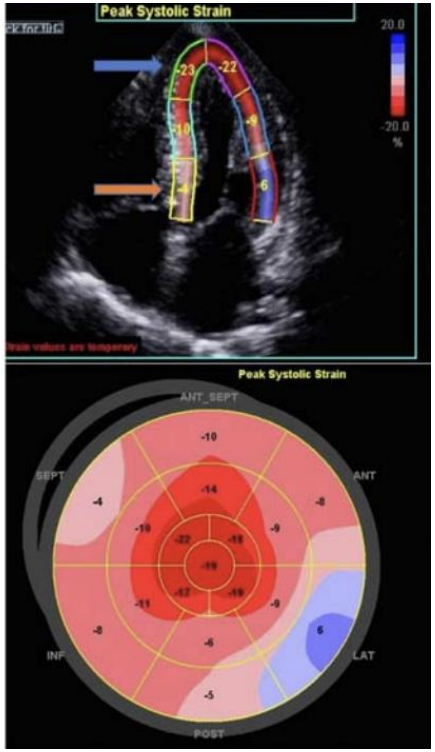

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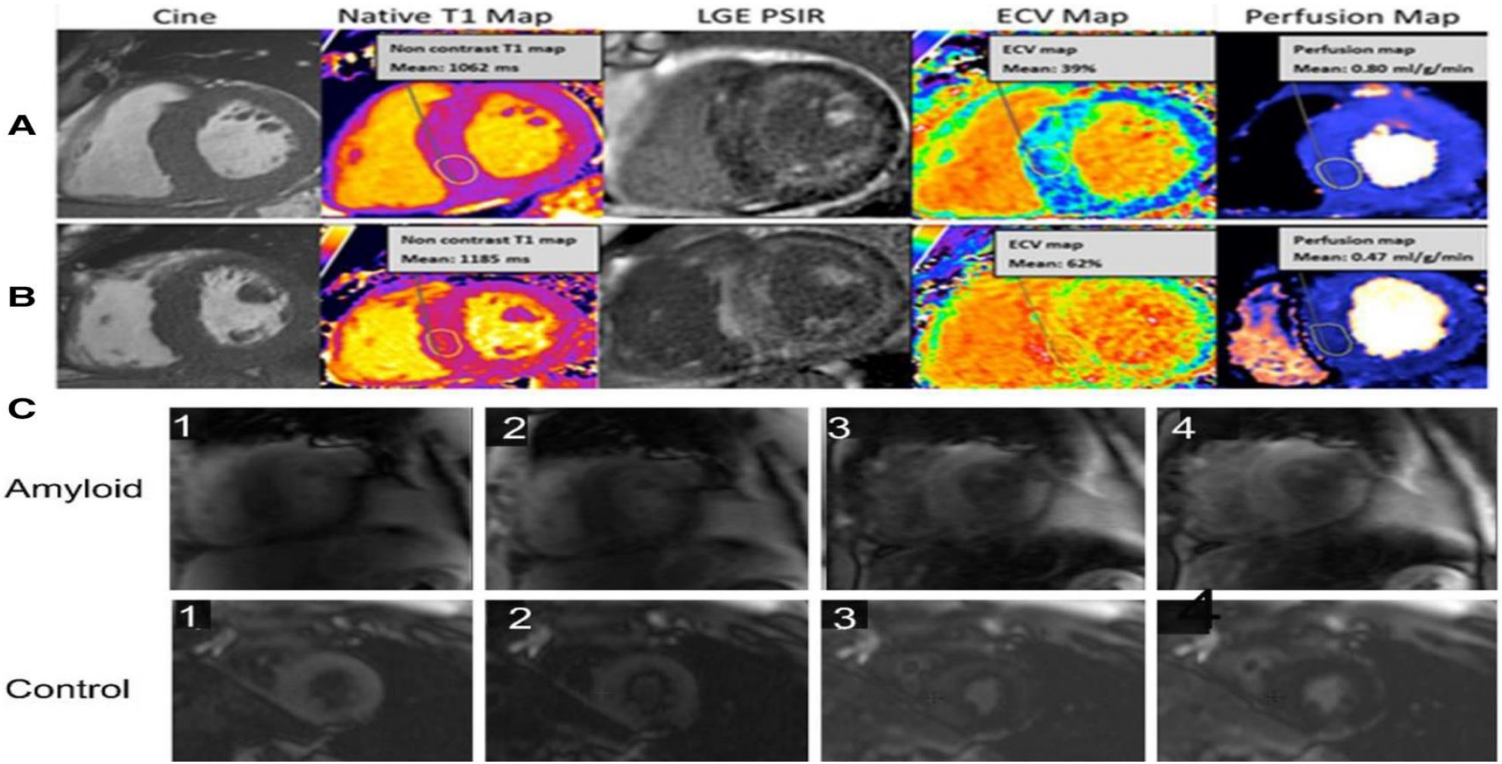
JASE 2022



Sharmila Dorbala. Circulation: Cardiovascular Imaging. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging, Volume: 14, Issue: 7, Pages: e000029, DOI: (10.1161/HCI.0000000000000029)

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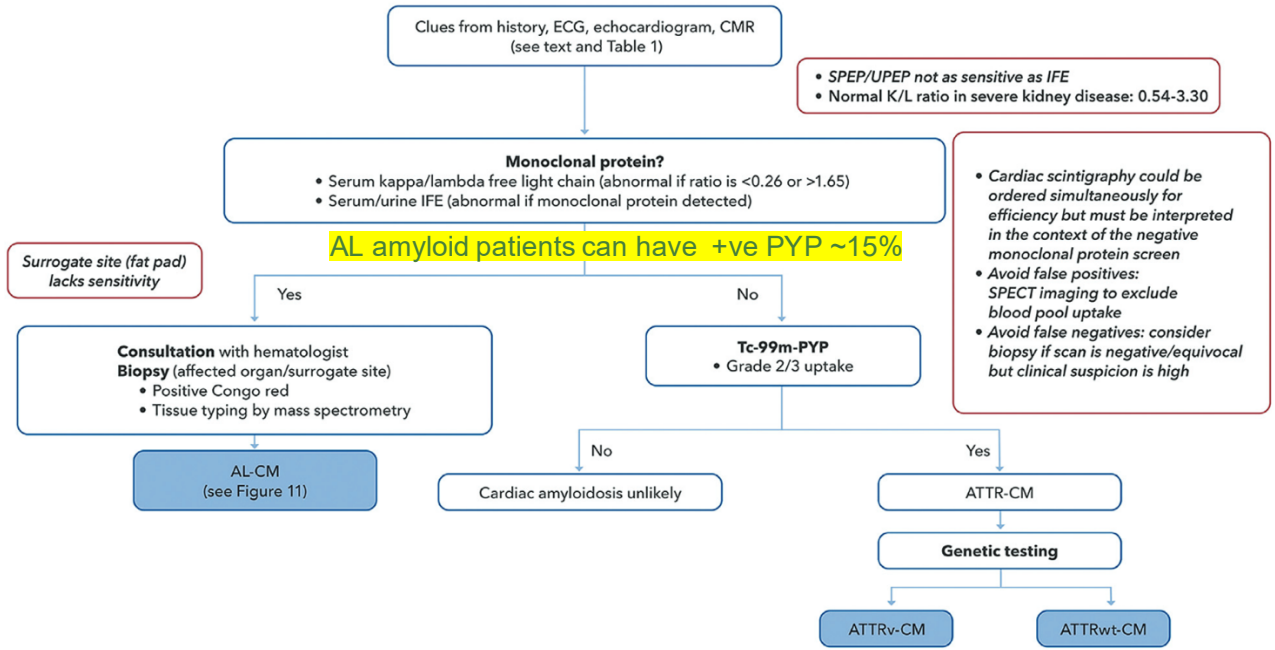
FIGURE 3 Diagnostic Algorithm for Cardiac Amyloidosis



AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM = amyloid transthyretin cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance; ECG = electrocardiogram; IFE = immunofixation electrophoresis; K/L = kappa/lambda; PYP = pyrophosphate; SPECT = single-photon emission computed tomography; SPEP/UPEP = serum/urine protein electrophoresis.

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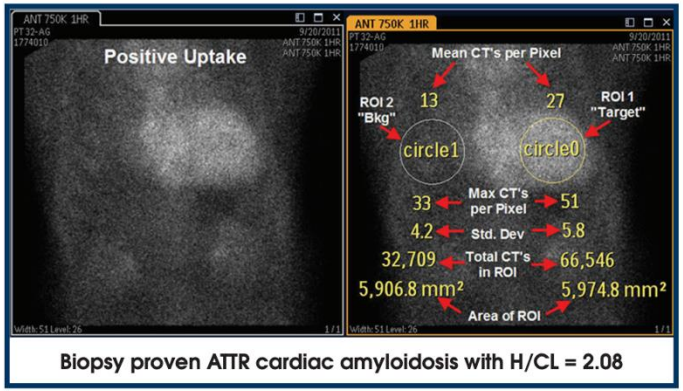
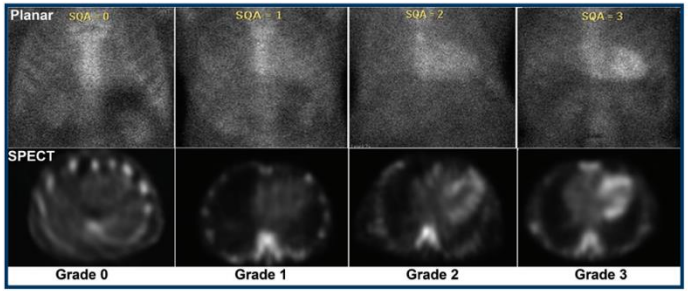
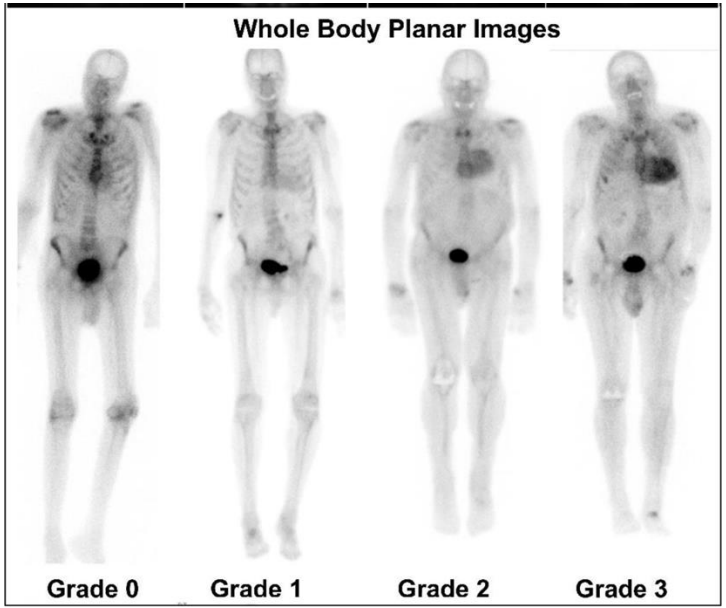
Figure 1. Quantitation of Cardiac ^{99m}Tc-PYP Uptake Using Heart-to-Contralateral Lung (H/CL) Ratio



Biopsy proven ATTR cardiac amyloidosis with H/CL = 2.08

Figure 2. Grading ^{99m}Tc-PYP Uptake on Planar and SPECT Images





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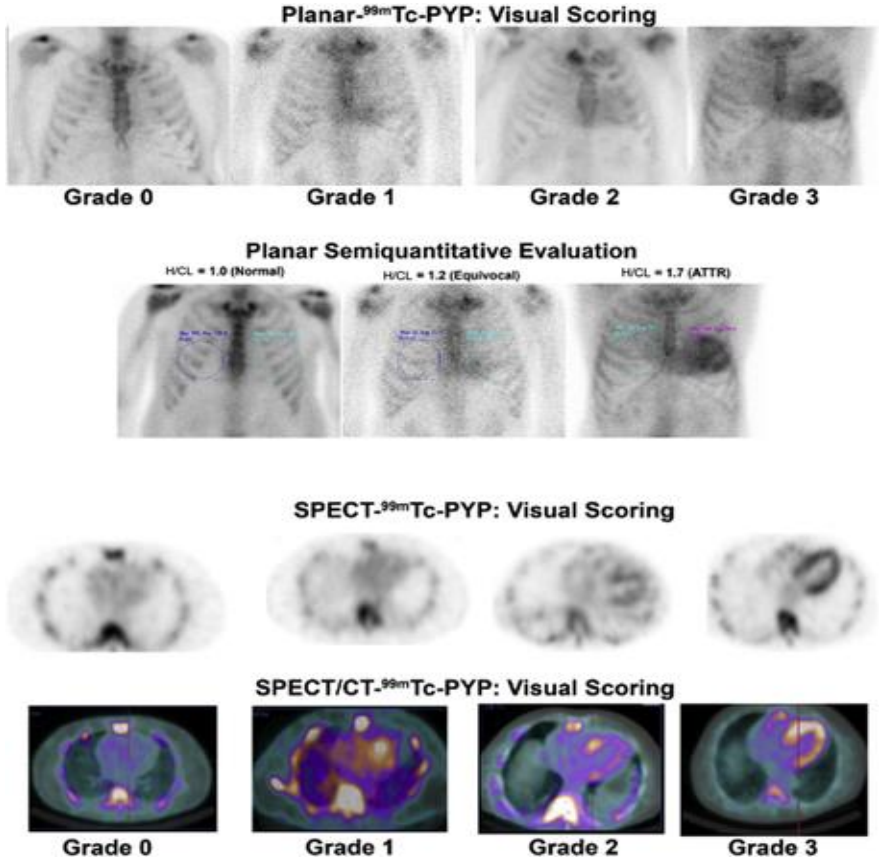
Sharmila Dorbala. Circulation: Cardiovascular Imaging. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis:



Mazen Hanna et al. *JACC* 2020; 75:2851-2862.

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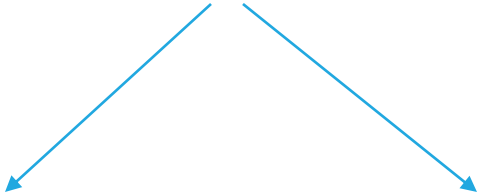
Treatment of Cardiac amyloidosis

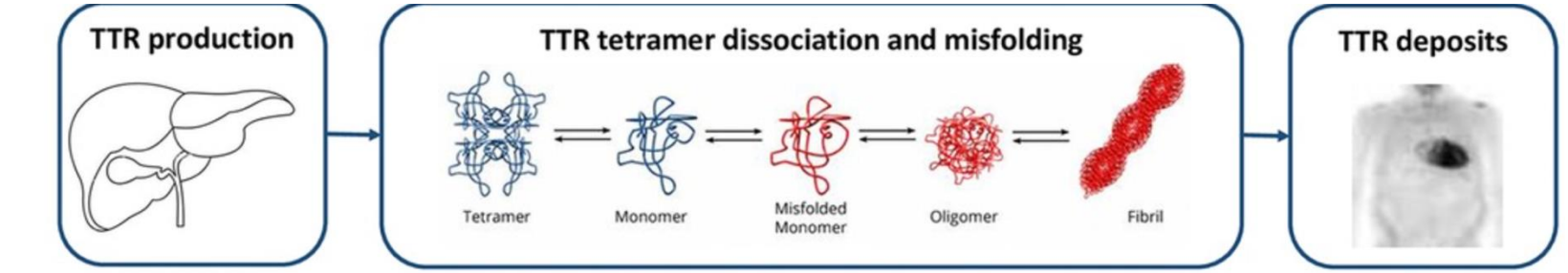


Treatment of consequences

- Heart failure
- Arrhythmia
- Conduction disease
- Orthostatic hypotension

Disease modifying Therapies

- AL amyloidosis- Chemotherapy (DaraCyborD commonly used, SCT)
- TTR cardiac amyloidosis- Stabilizers, Silencers



Inhibition of TTR synthesis

- **Liver transplantation**
- **RNA silencing**

siRNA:
- Patisiran
- Revusiran
- Vutrisiran

ASO
- Inotersen
- Eplontersen

- **Gene editing**

CRISPR–Cas9:
- NTLA-2001

TTR stabilization

Non-selective agents
- Diflusinal

Selective agents
- Tafamidis
- Acoramidis

TTR degradation

- Doxyciclin and (T)UDCA

Monclonal Ab
- PRX004
- NI006

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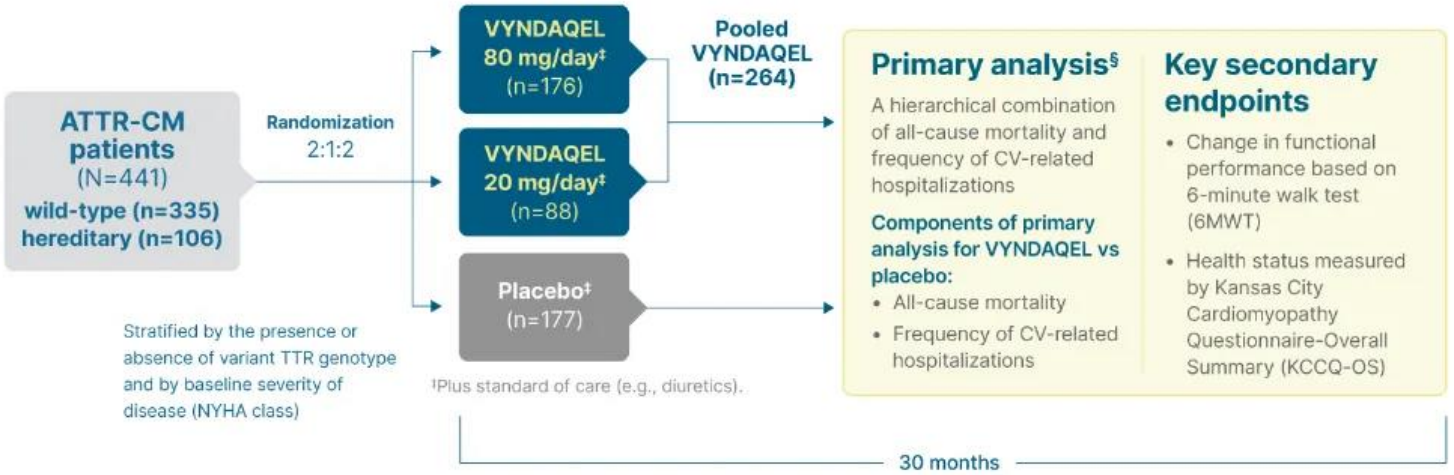
Tomasoni et al., Front. Cardiovasc. Med., 23 May 2023

ATTR-ACT Trial (TAFAMIDIS)

Inclusion criteria

- Patients between 18 and 90 years of age
- Confirmation of ATTR cardiac amyloidosis, wild-type or hereditary
- Echocardiography with an end-diastolic interventricular septal wall thickness >12 mm
- History of heart failure with at least 1 prior hospitalization for heart failure, or clinical evidence of heart failure (without hospitalization)[||]
- NT-proBNP level ≥600 pg/mL
- 6MWT >100 m



https://vyndamax.pfizerpro.com/about-vyndamax/study-design

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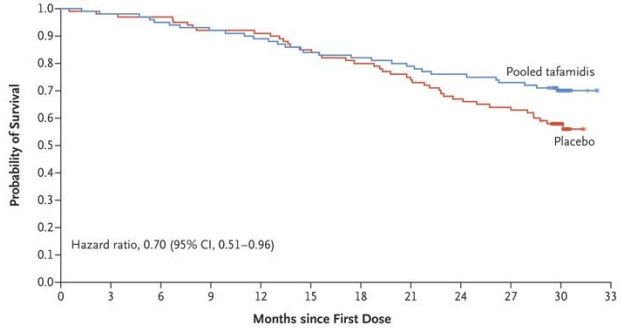
Tafamidis: ATTR-ACT Trial

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Maurer MS et al, NEJM 2018

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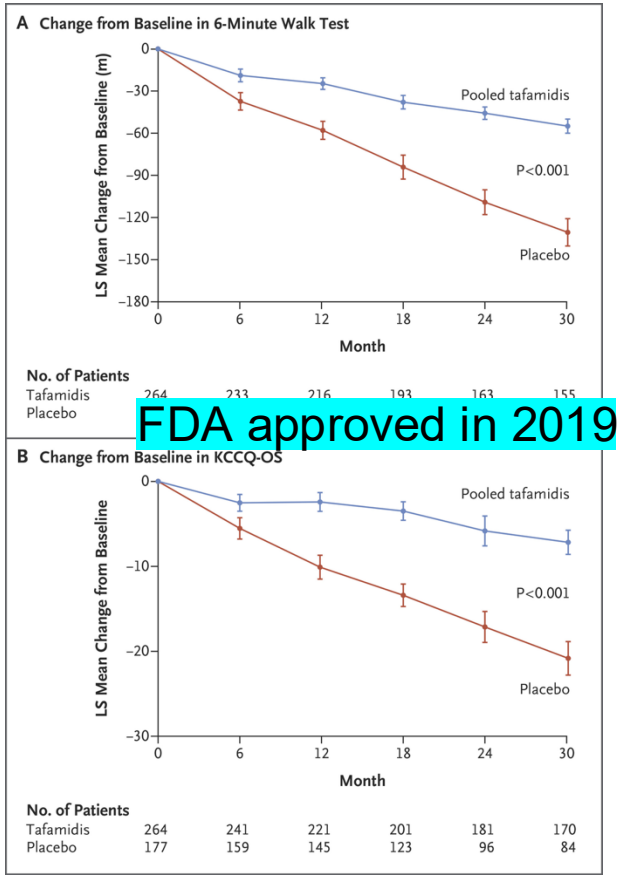

FDA approved in 2019

- **NNT to prevent 1 death=7.5**
- **NNT to prevent 1 hospitalization per year=4.5**

Maurer MS et al, NEJM 2018

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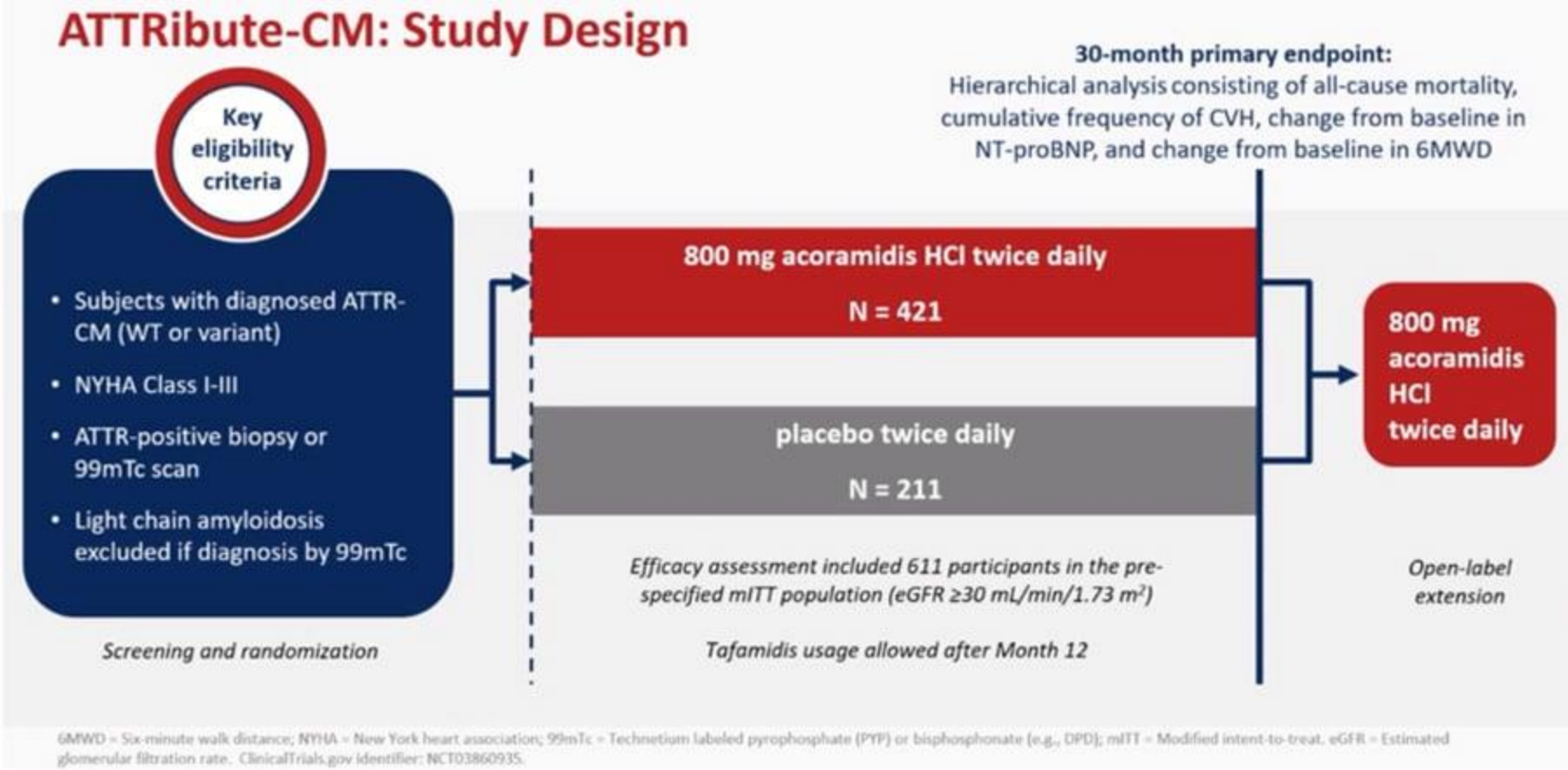
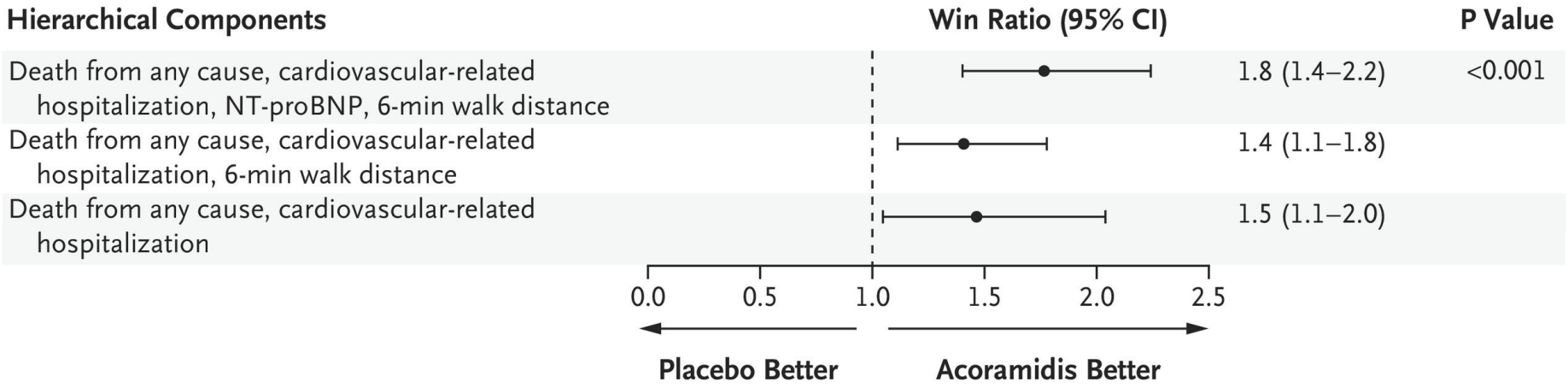
ACORAMIDIS

Replicates the stabilizing effect of the naturally occurring T119M mutation





Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy- Attribute-CM trial

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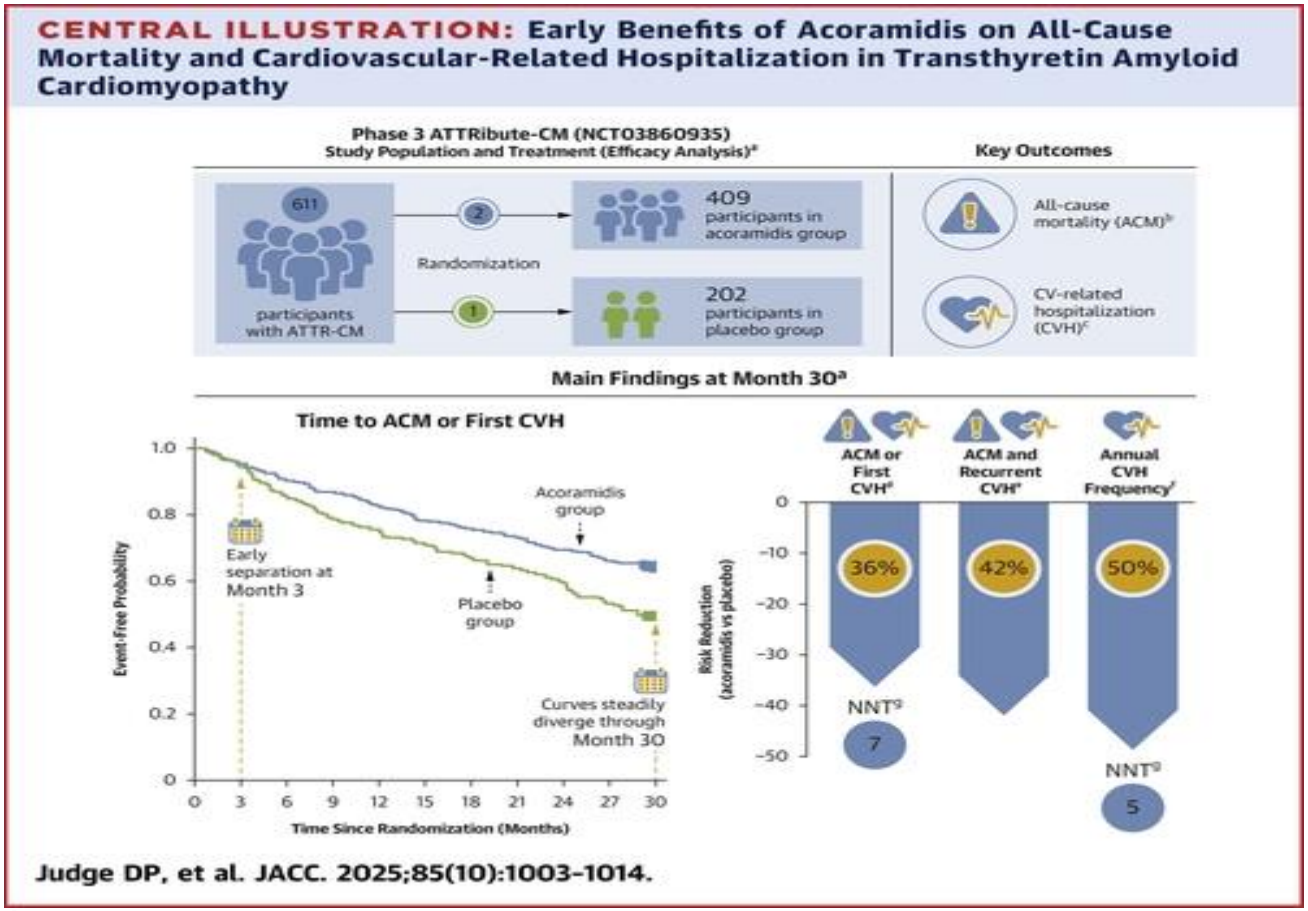

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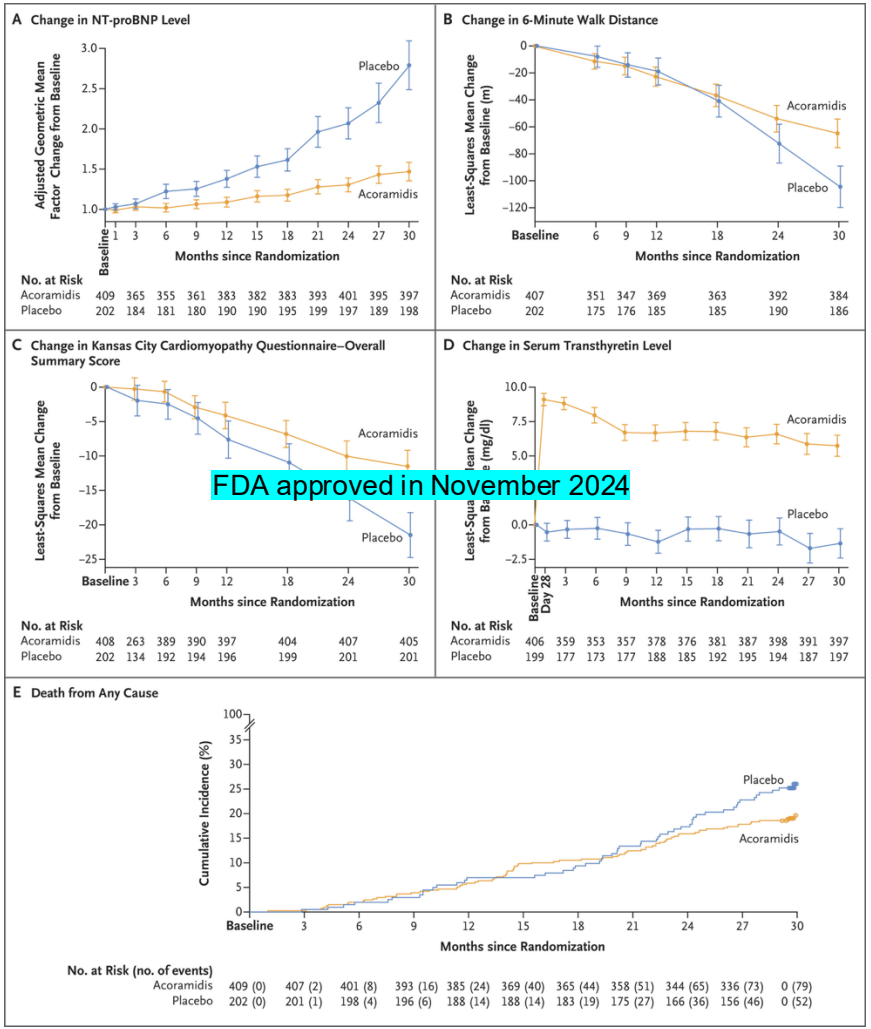
Daniel P. Judge et al. *JACC* 2025; 85:1003-1014.



FDA approved in November 2024

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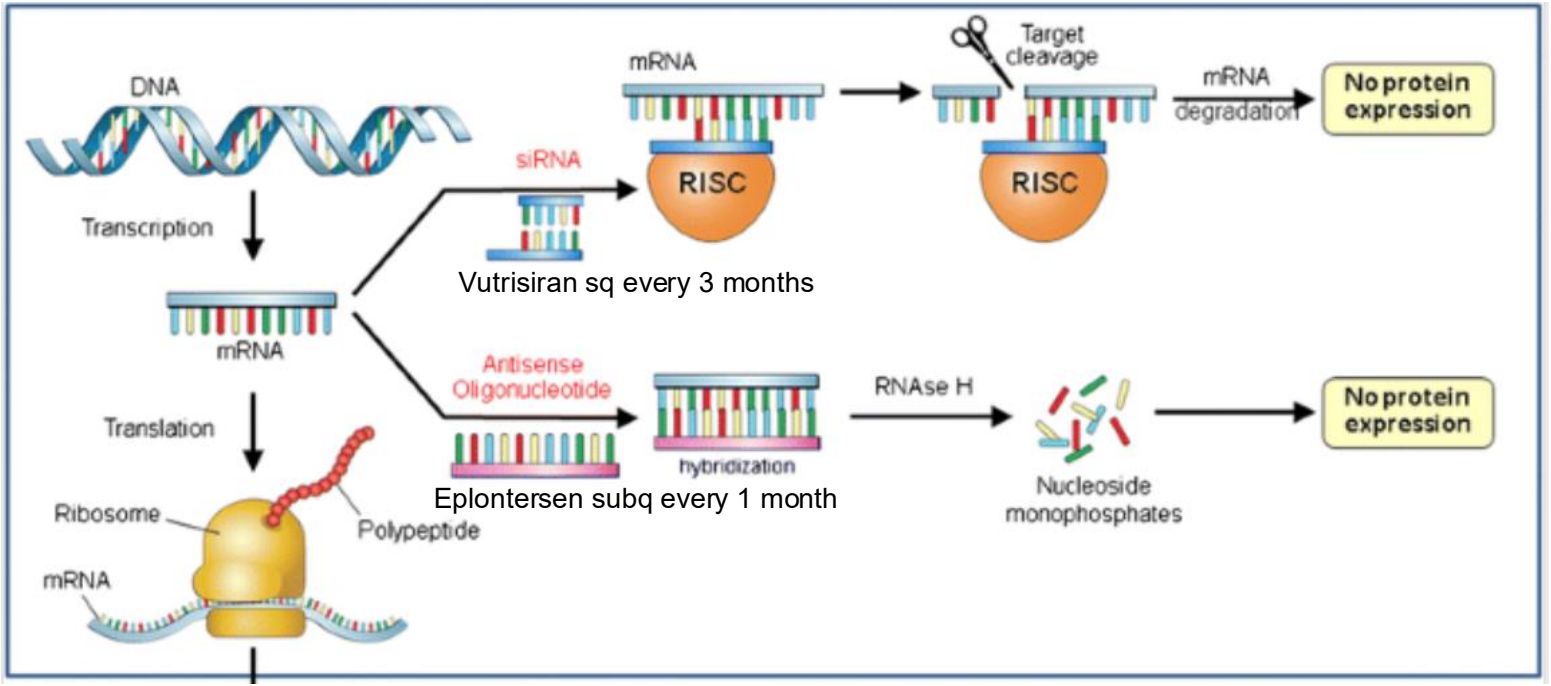
Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy- Attribute-CM trial

Silencers: Blocks translation of TTR RNA



Vranian Curr Cardiology Report 2015

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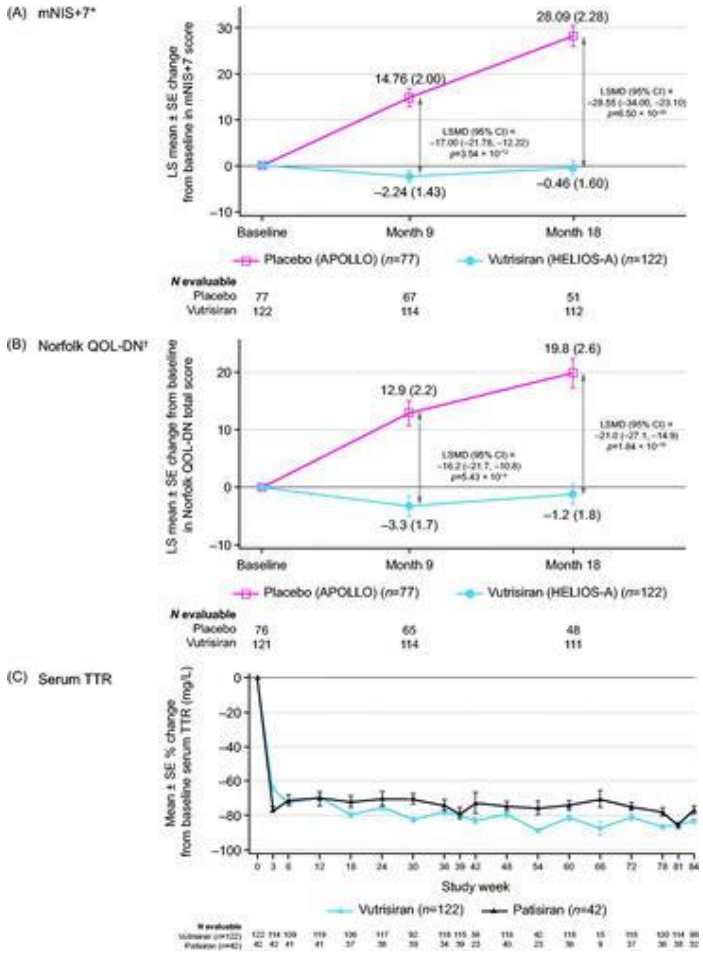
Helios A trial (vutrisiran)



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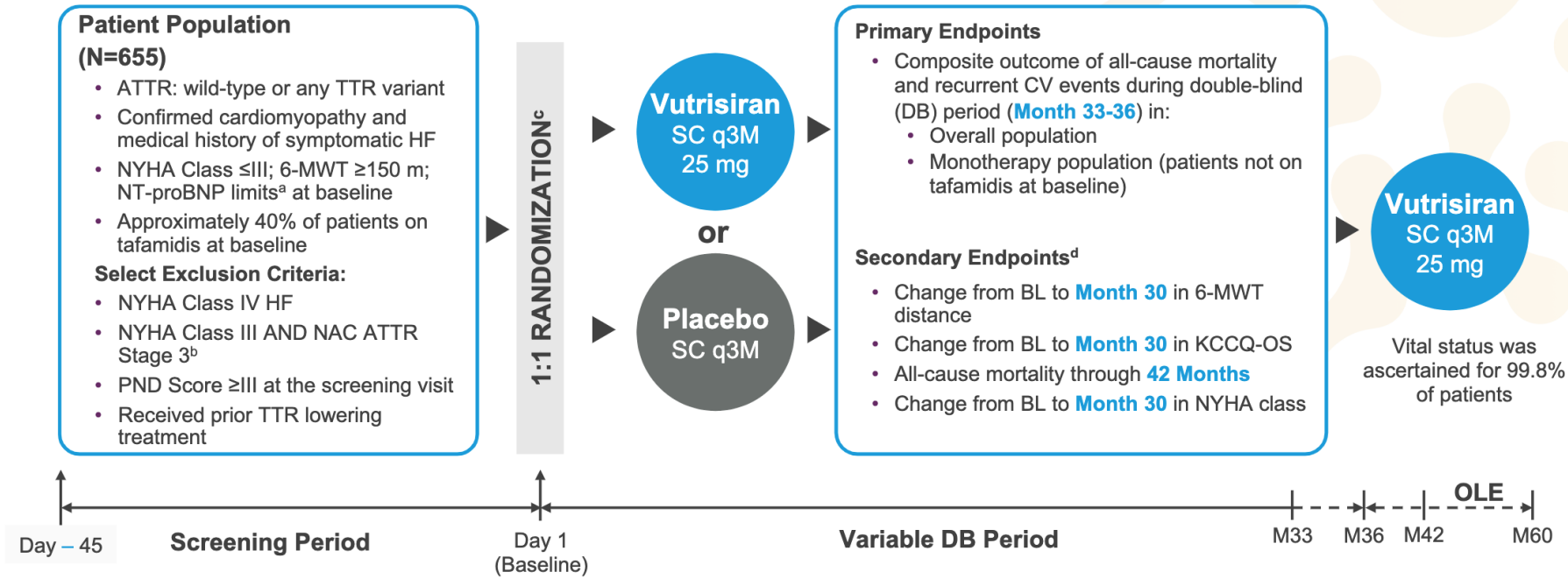
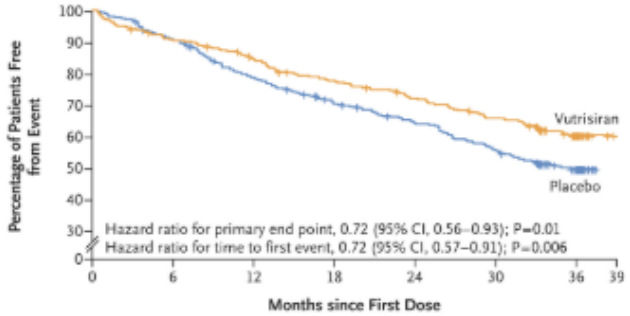
HELIOS-B Study Design

A randomized, double-blind outcomes study to evaluate vutrisiran in patients with ATTR-CM



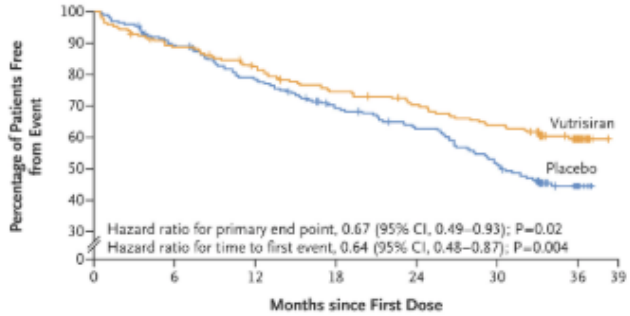
A Time to First Event in the Overall Population



No. at Risk (cumulative no. of events)

Vutrisiran	326 (0)	294 (30)	271 (50)	247 (72)	227 (90)	206 (110)	62 (125) 0 (125)
Placebo	328 (0)	295 (31)	253 (70)	221 (96)	199 (115)	172 (142)	52 (159) 0 (159)

B Time to First Event in the Monotherapy Population

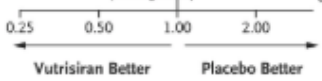


No. at Risk (cumulative no. of events)

Vutrisiran	196 (0)	172 (22)	157 (34)	141 (49)	131 (57)	119 (69)	32 (76)	0 (76)
Placebo	199 (0)	175 (22)	152 (43)	130 (60)	116 (72)	95 (93)	26 (105)	0 (105)

C Subgroup Analyses of the Primary End Point (overall population)

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Overall	654	0.72 (0.56–0.93)
Age		
<75 yr	257	0.55 (0.35–0.85)
≥75 yr	397	0.81 (0.58–1.11)
Tafamidis use at baseline		
No	395	0.67 (0.49–0.93)
Yes	259	0.79 (0.51–1.21)
ATTR disease type		
Variant	76	0.92 (0.49–1.72)
Wild type	578	0.67 (0.51–0.90)
NYHA class		
I or II	592	0.73 (0.55–0.96)
III	62	0.68 (0.33–1.41)
Baseline NT-proBNP level		
≤2000 pg/ml	342	0.53 (0.35–0.79)
>2000 pg/ml	312	0.80 (0.56–1.13)



D Subgroup Analyses of the Primary End Point (monotherapy population)

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Overall	395	0.67 (0.49–0.93)
Age		
<75 yr	153	0.53 (0.32–0.88)
≥75 yr	242	0.72 (0.47–1.10)
ATTR disease type		
Variant	48	0.67 (0.31–1.44)
Wild type	347	0.66 (0.45–0.95)
NYHA class		
I or II	368	0.73 (0.53–1.02)
III	27	0.31 (0.09–1.02)
Baseline NT-proBNP level		
≤2000 pg/ml	188	0.50 (0.28–0.92)
>2000 pg/ml	207	0.71 (0.47–1.07)

12 Month OLE Data From ESC, August 2025

Endpoint*	Overall Population (n=654)	Monotherapy Group (n=395)
Composite of all-cause mortality	Relative Risk Reduction: 37%	Relative Risk Reduction: 42%
Composite of all-cause mortality and recurrent CV events	Relative Risk Reduction: 34% p<0.01	Relative Risk Reduction: 40% p<0.01
All-cause mortality	Relative Risk Reduction: 37% p<0.01	Relative Risk Reduction: 39% p<0.01

Vutrisiran was approved for Wild type or Hereditary TTR cardiac amyloidosis in March 2025

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Questions:

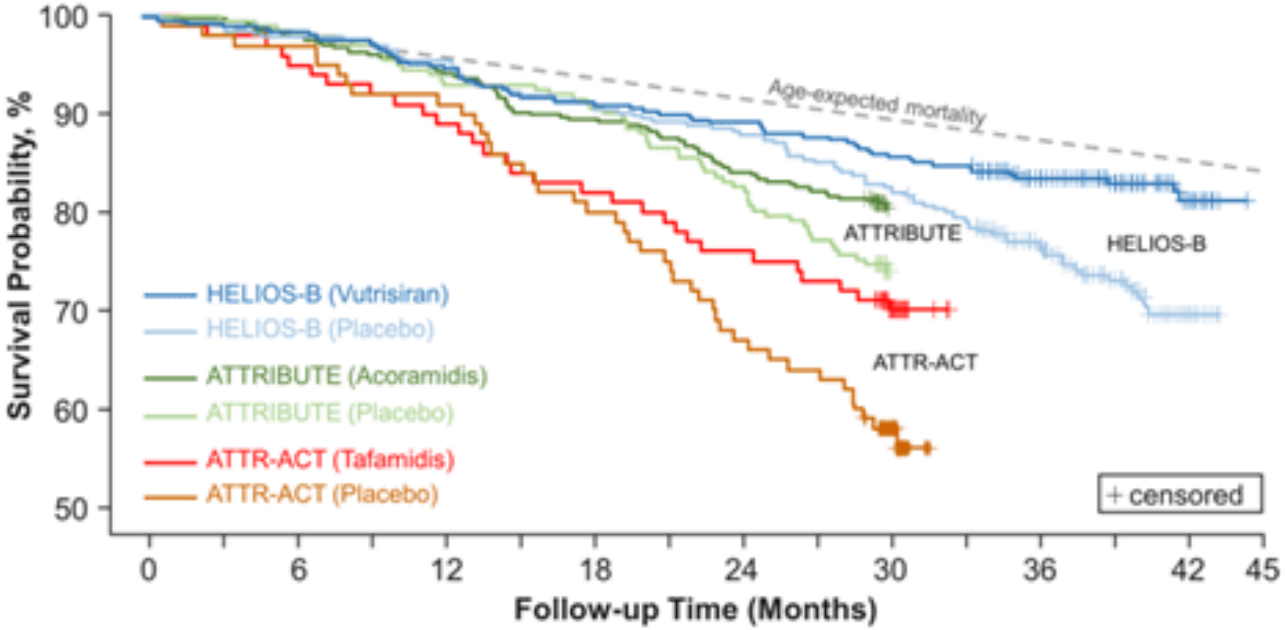
1. What is the preferred drug?
2. When do we switch?
3. Dual therapy?
4. Possible to reverse the disease?
5. How do we monitor the disease progress?

TABLE 1 Comparison of Therapies for ATTR-CM

	Tafamidis	Acoramidis	Vutrisiran
Mechanism of action	TTR stabilizer	TTR stabilizer	siRNA: gene silencer
Primary trial	ATTR-ACT (n = 441)	ATTRibute-CM (n = 632)	HELIOS-B (n = 655)
Year conducted	2013-2018	2019-2023	2019-2024
Age of participants, y	75	77	77
ATTRwt/ATTRv	335 (76)/106 (24)	574 (91)/58 (9)	578 (88)/77 (12)
Placebo mortality at 30 mo, %	43	26	18
Placebo CV event rate per year	0.70	0.45	0.288
NYHA functional class			
I	37 (8)	68 (11)	84 (13)
II	263 (60)	455 (72)	508 (78)
III	141 (32)	109 (17)	62 (9)
NT-proBNP, pg/mL, median	3,078	2,134	1,911
Mortality	0.70 (0.51-0.96)[a]	0.77 (0.54-1.10)[a]	0.69 (0.49-0.98)[b]
CV events	0.68 (0.56-0.81)	0.50 (0.36-0.70)	0.68 (0.53-0.86)
Least square mean difference in 6MWD at 30 mo	75.7 (57.6-93.8)	39.6 (21.1-58.2)	26.5 (13.4-39.6)
Least square mean difference in KCCQ-OSS at 30 mo	13.65 (9.48-17.83)	9.94 (5.97-13.91)	5.8 (2.4-9.2)
Binding site	T4 binding sites	T4 binding sites	N/A
Brand name	Vyndaqel or Vyndamax	ATTRuby	Amvuttra
Dose	80 mg or 61 mg	712 mg orally twice daily	25 mg subcutaneously every 3 mo
TTR stabilization			N/A
TTR occupancy with FPE assay, %	~65	96.6 ± 2.1	
Tetramer dissociation assay, %	>96 at 28 μm	>96 at 11 μm	
Increase in serum TTR, %	33	39	N/A
Knockdown in serum TTR, %	N/A	N/A	81
Cost[c]	$267,908	$225,108	$477,404

Values are n (%) or HR (95% CI), unless otherwise indicated. [a]Survival at 30 months. [b]Survival at 42 months. [c]Average wholesale price per year from UpToDate; notably, cost for amvuttra for ATTR-CM is unknown because it not approved for this indication.

6MWD = 6-minute walk distance; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv = variant transthyretin amyloidosis; ATTRwt = wild type transthyretin amyloidosis; CV = cardiovascular; FPE = fluorescence probe exclusion; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire—Overall Summary Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TTR = transthyretin.



Time to All-Cause Mortality Compared Among Trials in ATTR-CM. From Girard AA, Sperry BW.. *Heart Fail Rev.* 2025;30,69-73

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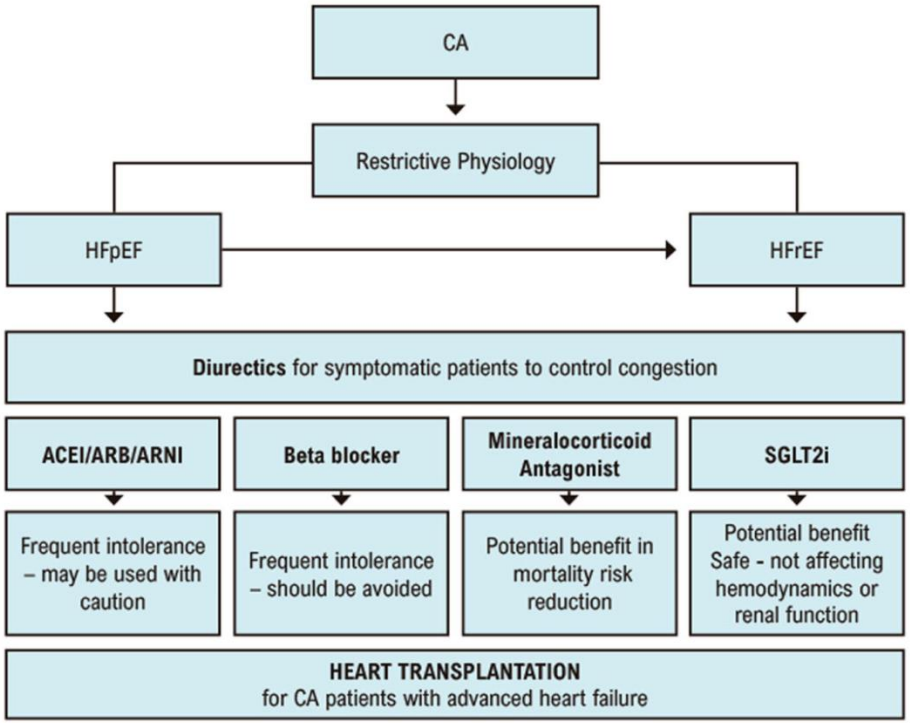
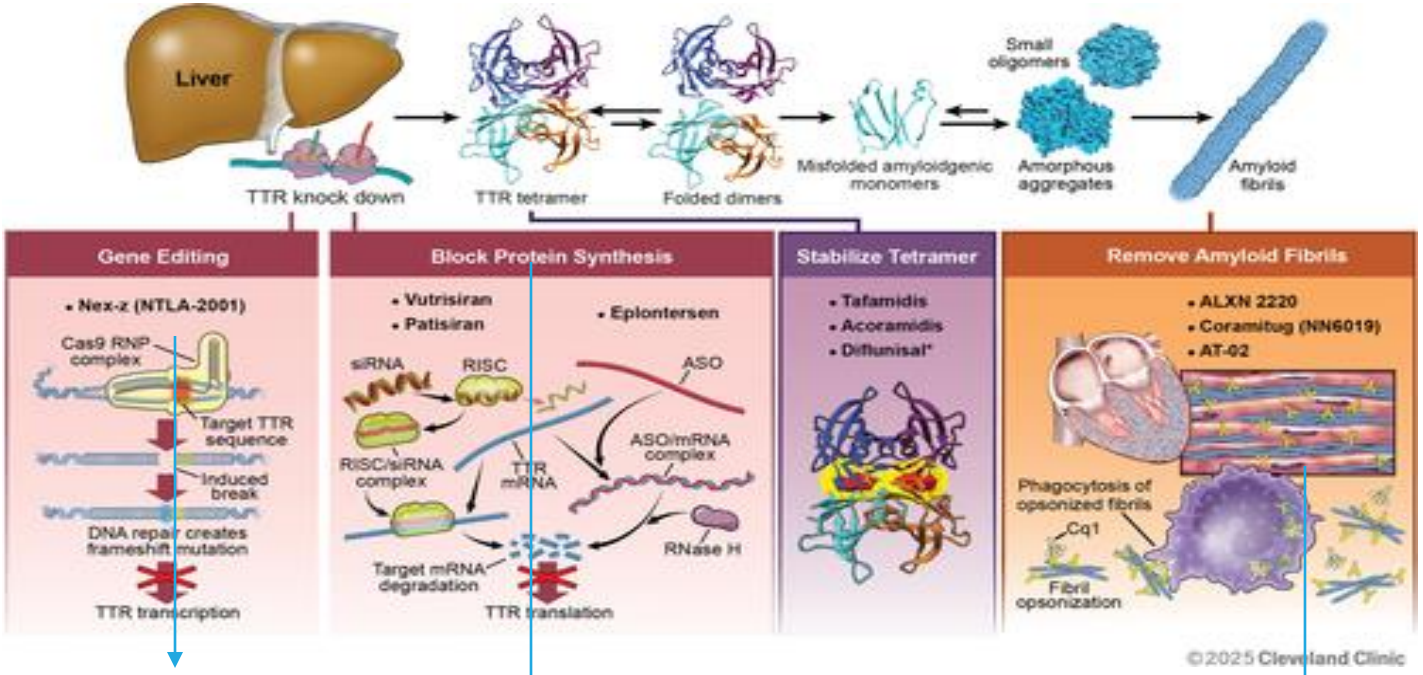
INTERNATIONAL JOURNAL OF Cardiovascular SCIENCES

Central Illustration: Heart Failure Management of Patients with Amyloid Cardiomyopathy



Int J Cardiovasc Sci. 2024; 37:e20240043



Jan M. Griffin et al. *J Am Coll Cardiol HF* 2025; 13:685-694.

Magnitude Trial-Single dose IV, Phase 3 ongoing

- Cardio TTransform trial (Eplontersen)-Largest TTR trial till date- 1400 pts, results in 2026
- Triton CM (Nucresiran)-Phase 3 ongoing

Fibril depleters
In Phase 2 and 3 trials

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Thank You

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Hypertrophic Cardiomyopathy in the Era of Cardiac Myosin Inhibitors

Lucy Lin, MD
Saint Joseph Medical Center
October 4, 2025

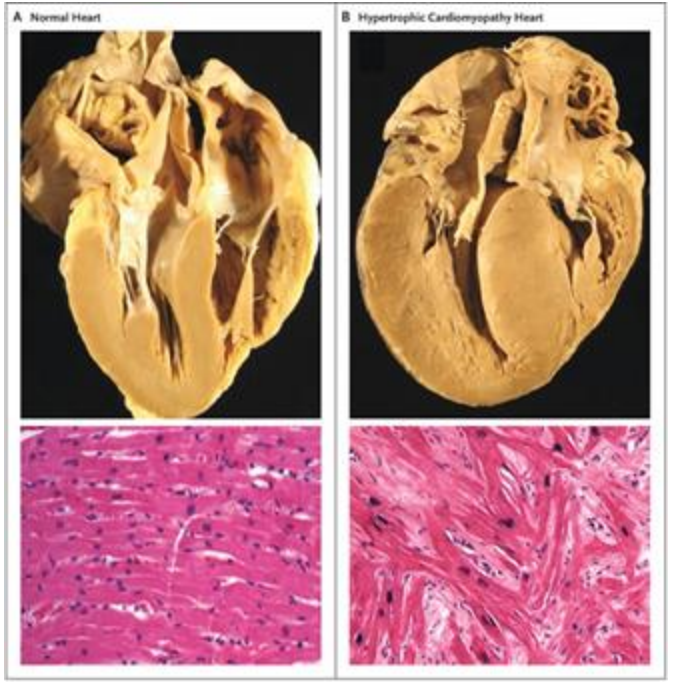
Virginia Mason Franciscan Health
Center for Cardiovascular Health

Disclosures

- NO RELEVANT DISCLOSURES

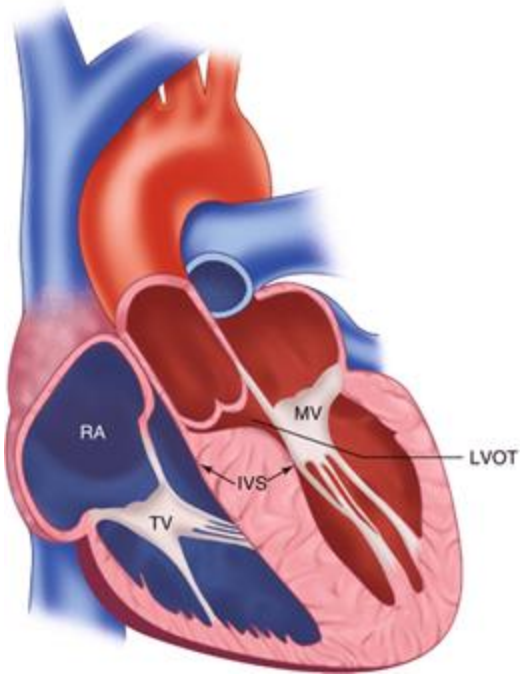
Hypertrophic Cardiomyopathy

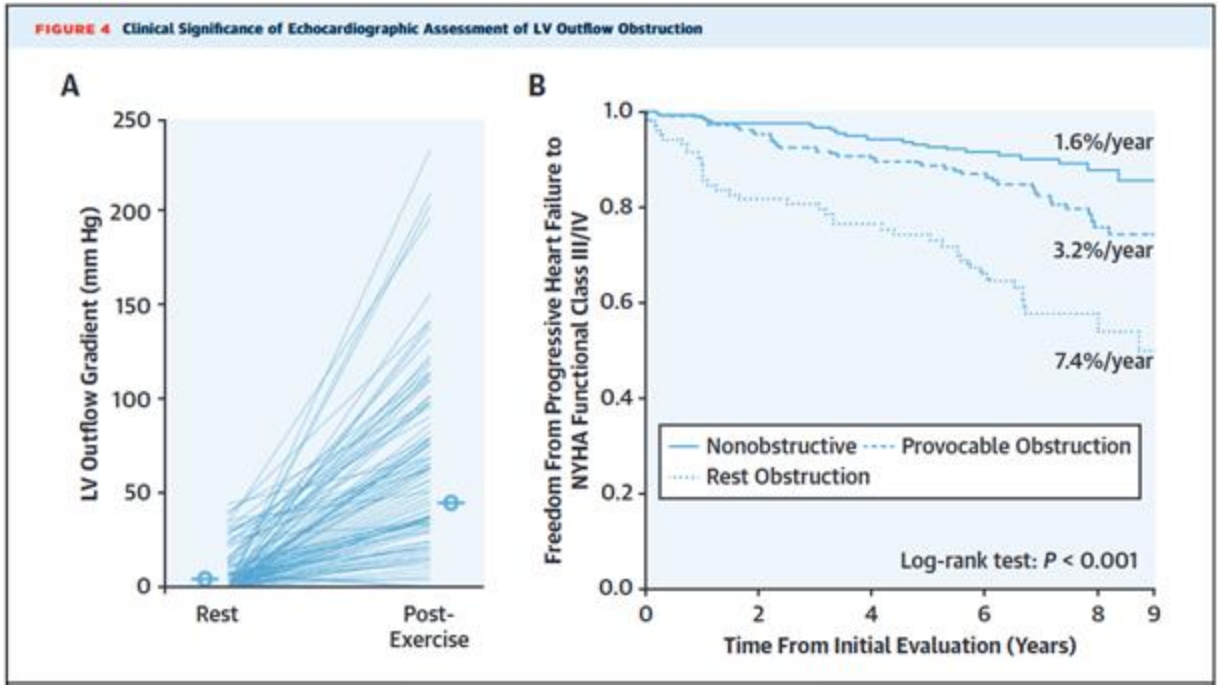
- Most common monogenic cardiac disorder - 1:200-1:500 adults
- Characteristics
  - Left ventricular hypertrophy
  - Enlarged myocytes in disarray
  - Interstitial fibrosis
  - Enhanced cardiac actin-myosin interactions
- Pathophysiological features
  - Hypercontractility
  - Diastolic dysfunction
  - Left ventricular outflow tract (LVOT) obstruction



Braunwald. NEJM 2025

LVOT Obstruction and Outcomes





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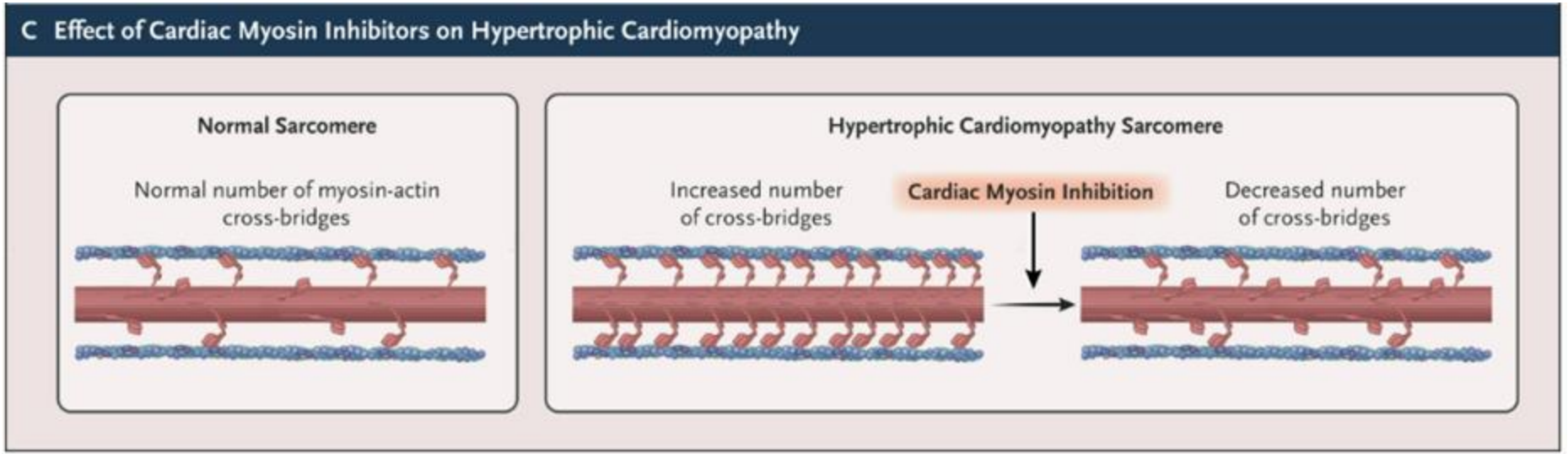
Maron et al. JACC 2022

Treatment of Symptomatic oHCM

- Conventional treatment options
  - Pharmacologic
    - Beta blockers - ↓ HR , ↓ contractility, ↑ diastolic filling time, mortality benefit
    - Calcium channel blockers - ↓ HR , ↓ contractility, ↑ diastolic filling time
    - Disopyramide - negative inotropy
  - Septal reduction therapy (SRT)
    - Surgical myectomy - gold standard
    - Alcohol septal ablation - less invasive, catheter-based
- Cardiac myosin inhibitors (CMI)
  - Mavacamten (approved 2020)
  - Aficamten (under investigation)

Cardiac Myosin Inhibitors



- Improves on/off myosin equilibrium, ATP expenditure, sarcomere force generation
  - Attenuates hypercontractility
  - Improves energetics and compliance

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Braunwald. NEJM 2025

CMI Trials - oHCM (Mavacamten)

	EXPLORER-HCM (2020)	VALOR-HCM (2022)
Drug	**Mavacamten**	**Mavacamten**
Design	P3 RDB PC	P3 RDB PC
N	251	112
Duration	30 weeks	16 weeks
NYHA	II, III	II, III, IV
Primary endpoint	Peak VO2 + NYHA class	SRT eligibility
Other endpoints	LVOT gradient (exercise)	LVOT gradient (rest/Valsalva)
	Peak VO2	NYHA, KCCQ
	KCCQ, NYHA, HCMSQ	Cardiac biomarkers
	Cardiac biomarkers	
	CMR substudy	
Conclusions	Improved exercise capacity	↓ SRT eligibility
	↓ LVOT gradient	↓ LVOT gradient
	↓ NYHA class	↓ NYHA class
	↓ NT-proBNP and hs-cTnI	↓ NT-proBNP and hs-cTnI
	Improved diastolic function	Improved health status

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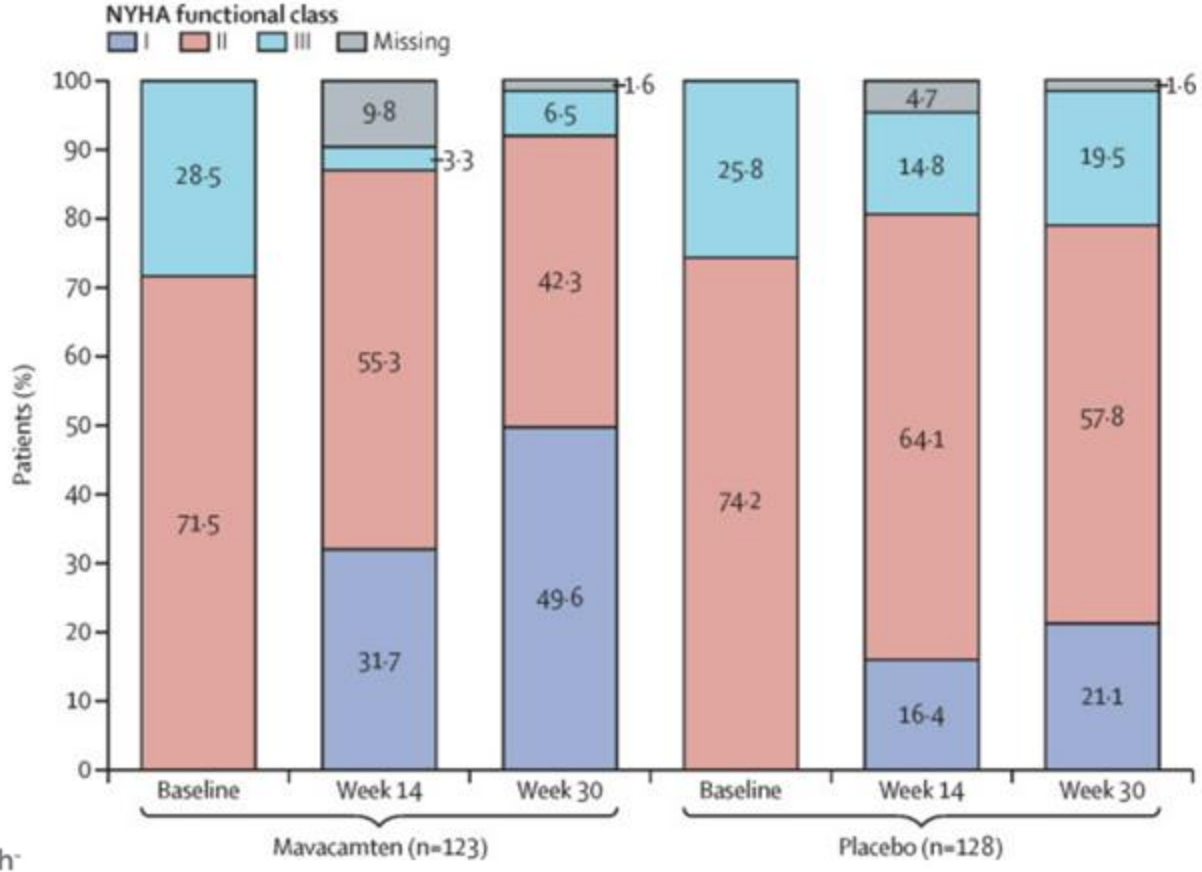
Olivotto, I, et al. Lancet 2020

Desai MY, et al. JACC 2022

EXPLORER-HCM



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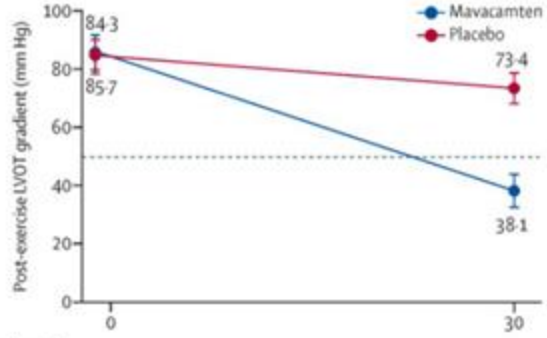
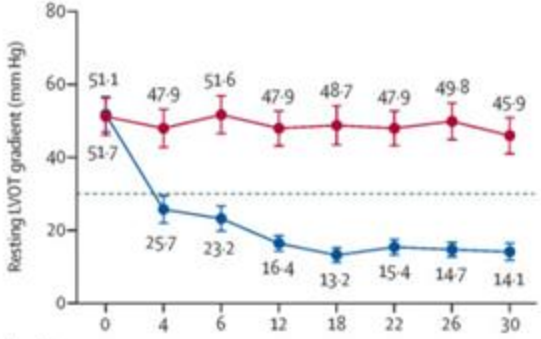
Olivotto, I, et al. Lancet 2020

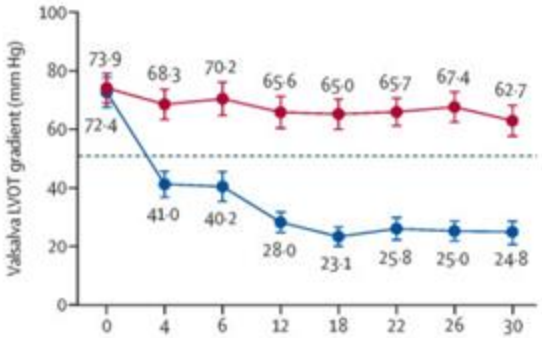
EXPLORER-HCM



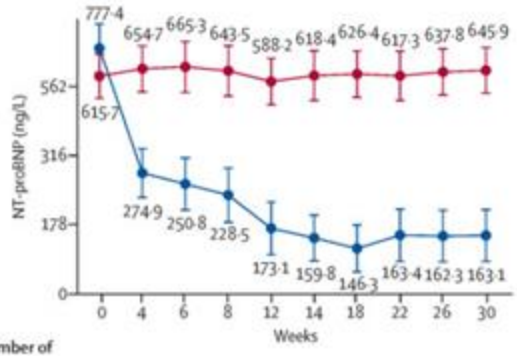
Number of patients at visit		
Mavacamten	122	118
Placebo	127	123



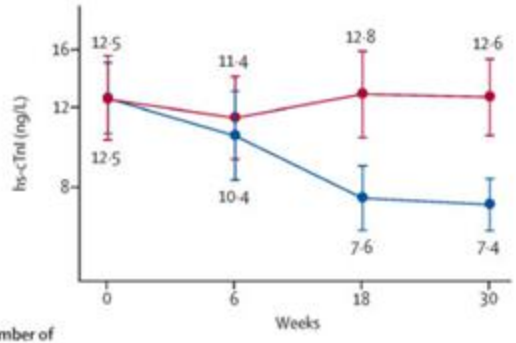
Number of patients at visit								
Mavacamten	123	119	119	118	116	118	120	117
Placebo	128	121	122	125	122	125	125	123



Number of patients at visit								
Mavacamten	123	117	118	118	116	118	120	117
Placebo	128	119	119	125	122	125	124	124



Number of patients at visit										
Mavacamten	120	115	114	115	114	109	115	115	117	119
Placebo	126	118	112	119	116	117	124	121	120	123



Number of patients at visit				
Mavacamten	120	86	102	115
Placebo	119	84	104	115

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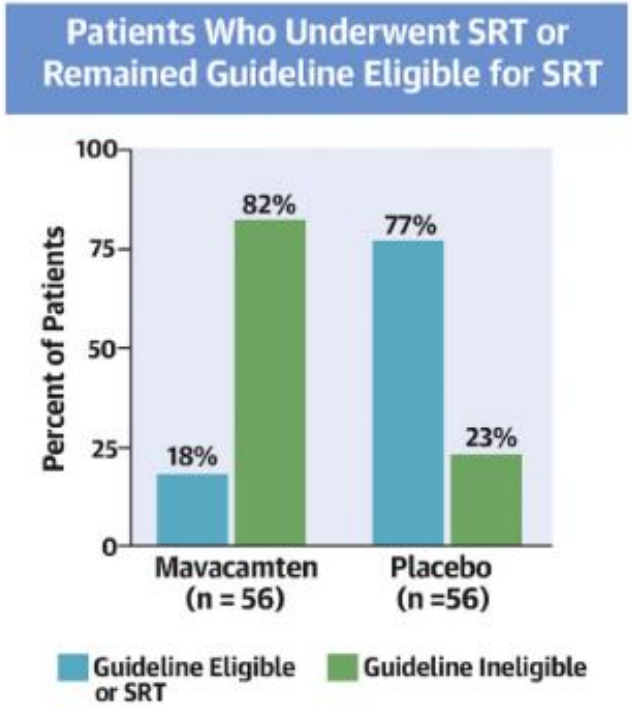
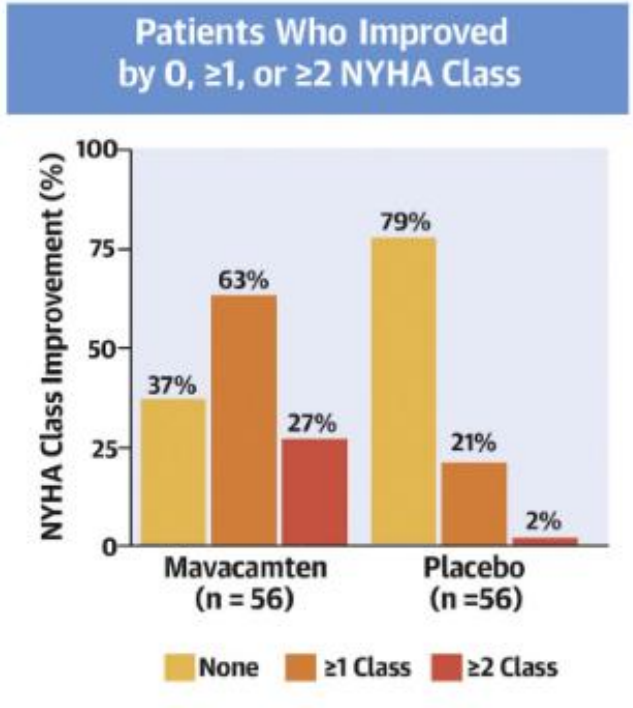
Olivotto, I, et al. Lancet 2020

VALOR-HCM





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

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2024 HCM Guidelines

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]
1	B-NR†	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]
	C-LD‡	
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]
1	C-LD	4. For patients with obstructive HCM and acute hypotension who do not respond to fluid administration, intravenous phenylephrine (or other vasoconstrictors without inotropic activity), alone or in combination with beta-blocking drugs, is recommended.[15]

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Ommen et al. Circulation 2024

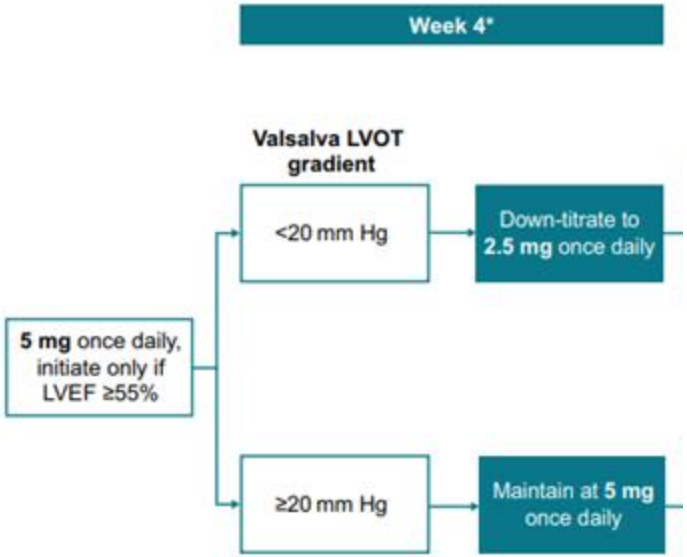
Mavacamten

- Criteria
  - Hypertrophic cardiomyopathy diagnosis
  - NYHA II-III
  - On maximally tolerated BB/CCB
  - LVEF $\geq$ 55%
  - LVOT obstruction with LVOT gradient $\geq$ 50 mmHg
- Contraindications
  - Strong CYP2C19 inhibitors, moderate-strong CYP2C19 inducers, moderate-strong CYP3A4 inducers
  - Pregnancy

Mavacamten Safety

- Adverse effects
  - Reduced LVEF/heart failure (Black Box Warning)
  - Syncope, dizziness, fatigue, dyspnea, atrial fibrillation, HTN, headache
  - Long half-life (normal CYP2C19 metabolizers: 6-9 days, poor metabolizers: up to 23 days)
- Risk Evaluation and Mitigation Strategies (REMS) program
  - Drug interactions
  - Echocardiography-guided monitoring
  - Specialty pharmacy must be enrolled in REMS
  - Prescriber must be enrolled in REMS

Mavacamten Initiation



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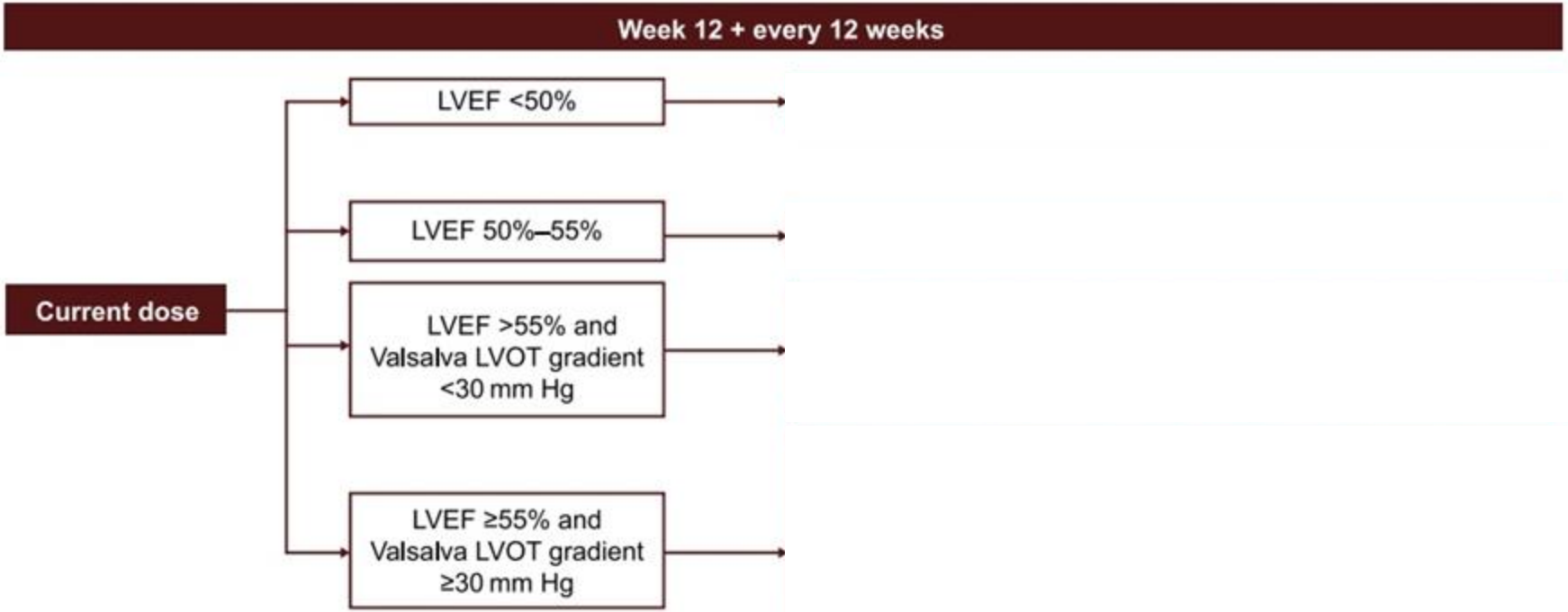
Owens, et al. JAHA 2024

Mavacamten - Maintenance



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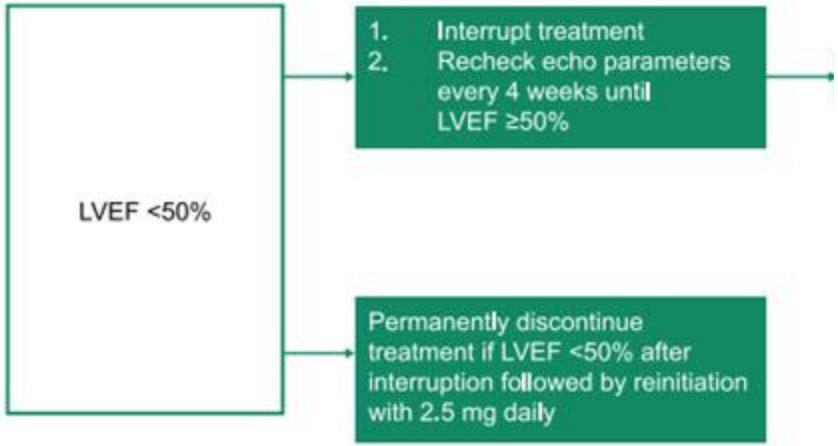
Adapted from Owens, et al. JAHA 2024

Mavacamten - LVEF < 50%



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Owens, et al. JAHA 2024

CMI Trials - nHCM (Mavacamten)

	MAVERICK-HCM (2020)	ODYSSEY-HCM (2025)
Drug	**Mavacamten**	**Mavacamten**
Design	P2 DB PC	P3 RDB PC
N	59	289
Duration	16 weeks	48 weeks
NYHA	II, III	II, III
Primary endpoint	Safety	Peak VO2, KCCQ
Other endpoints	Peak VO2 + NYHA, Peak VO2	Cardiac biomarkers
	Cardiac biomarkers	Echo parameters
	Echo parameters	
Conclusions	Well tolerated	↔ Peak VO2, ↔ KCCQ
	↓ NT-proBNP and hs-cTnI	↓ NT-proBNP and hs-cTnI
		↓ LV wall thickness*, ↓LVMI*
		Improved LA function*
		Improved diastolic function*

* directional improvement

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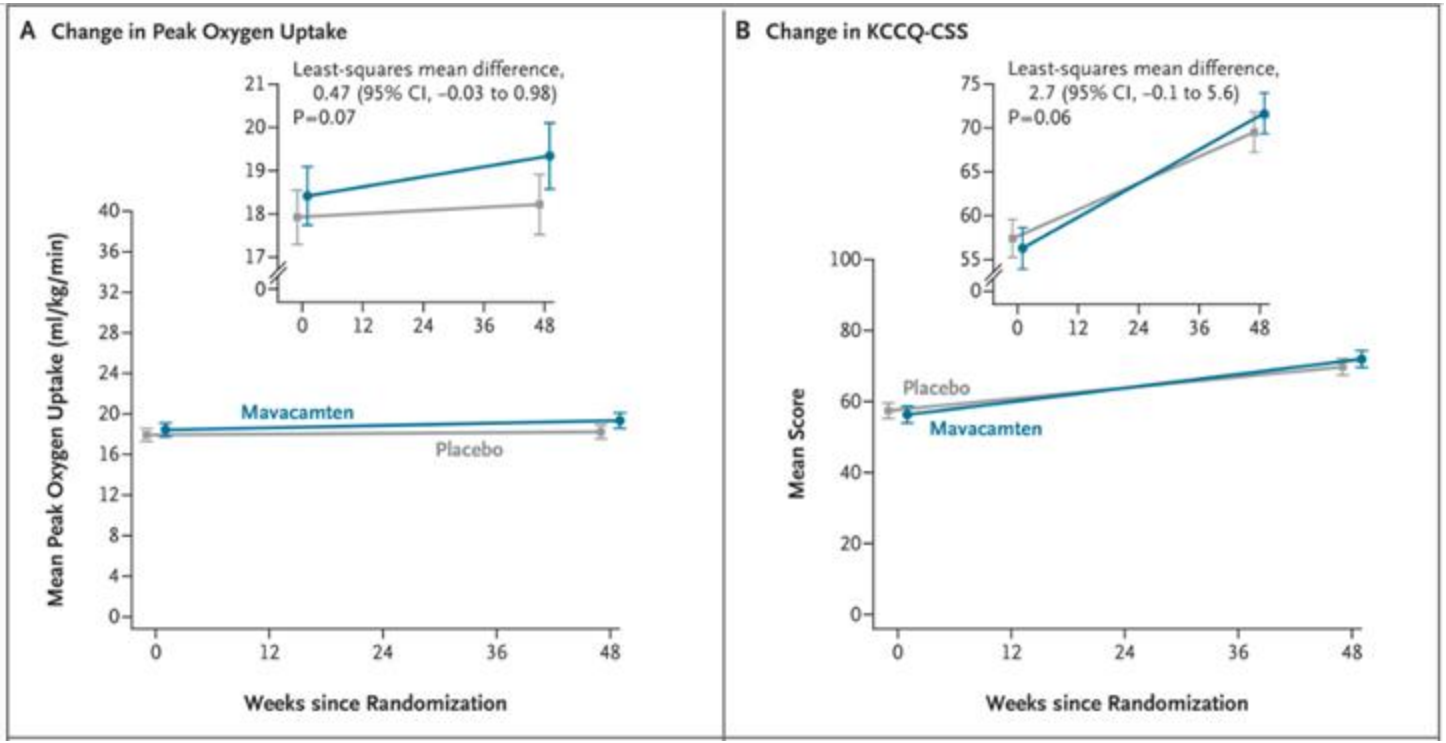
Ho CY, et al. JACC 2020

Desai MY, et al. NEJM 2025

ODYSSEY-HCM



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Desai MY, et al. NEJM 2025

Future of CMI - Aficamten

- Aficamten (under investigation)
  - Multiple metabolism pathways, consistent linear drug level to LVEF effect
  - Shorter half-life (3.5 days)
  - oHCM - SEQUOIA-HCM, MAPLE-HCM
  - nHCM - REDWOOD-HCM, ACACIA-HCM
  - Pediatric - CEDAR-HCM
  - Long-term extension - FOREST-HCM

CMI Trials - oHCM (aficamten)

	SEQUOIA-HCM (2024)	MAPLE-HCM (2025)
Drug	**Aficamten**	**Aficamten vs. Metoprolol**
Design	P3 RDB PC	P3 RDB H-H
N	282	175
Duration	24 weeks	24 weeks
NYHA	II, III	II, III
Primary endpoint	Peak VO2	Peak VO2
Other endpoints	LVOT gradient (rest/Valsalva)	LVOT gradient (rest/Valsalva)
	NYHA, KCCQ	NYHA, KCCQ
	Echo parameters	Echo parameters
	Cardiac biomarkers	Cardiac biomarkers
Conclusions	Improved exercise capacity	Improved exercise capacity
	↓ LVOT gradient	↓ LVOT gradient
	↓ NYHA, ↑ KCCQ	↓ NYHA, ↑ KCCQ
	↓ NT-proBNP and hs-cTnI	↓ NT-proBNP and hs-cTnI
	↓ LV wall thickness, ↓ LAVI	↓ LV wall thickness, ↓ LAVI
	↓ LV mass index	↔ LV mass index
	Improved diastolic function	Improved diastolic function

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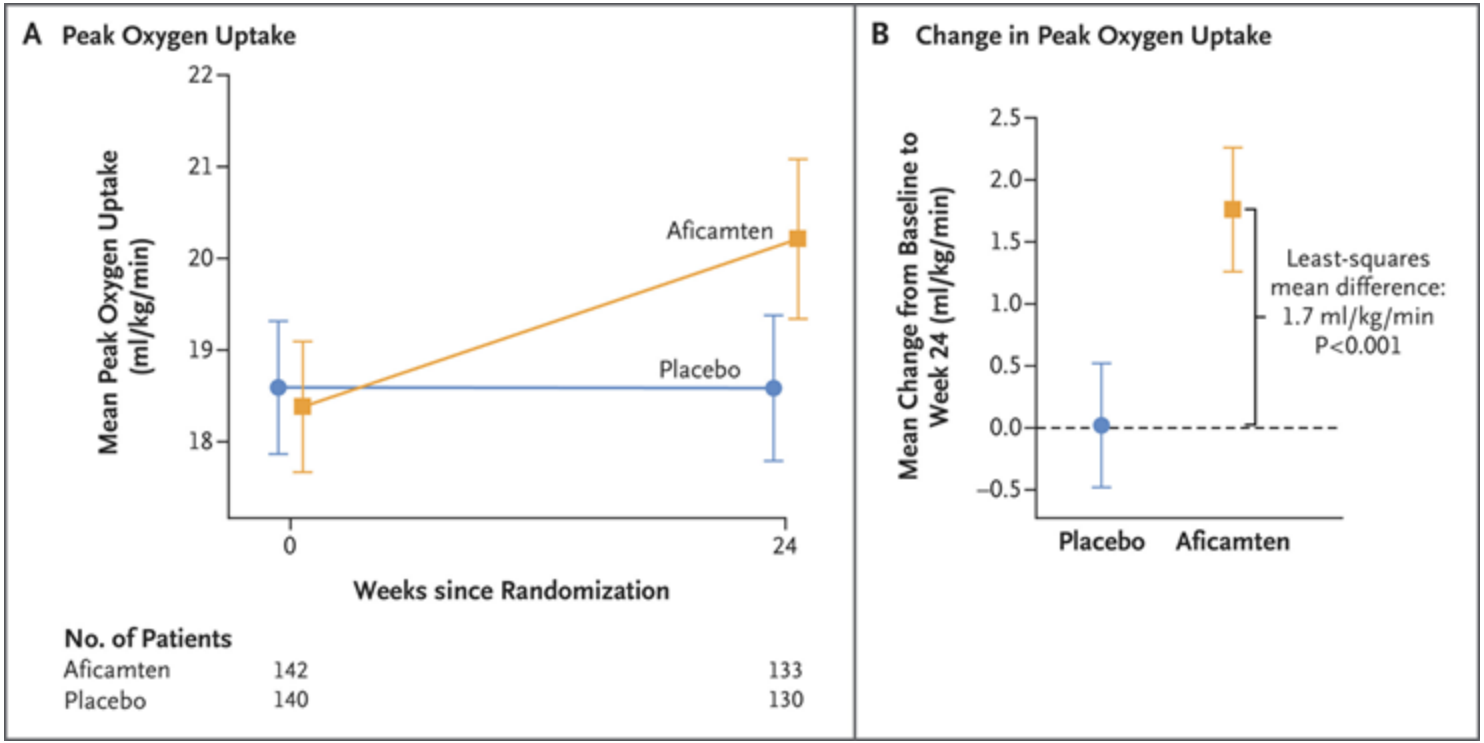
Maron MS, et al. NEJM 2024

Garcia-Pavia P, et al. NEJM 2025

SEQUOIA-HCM



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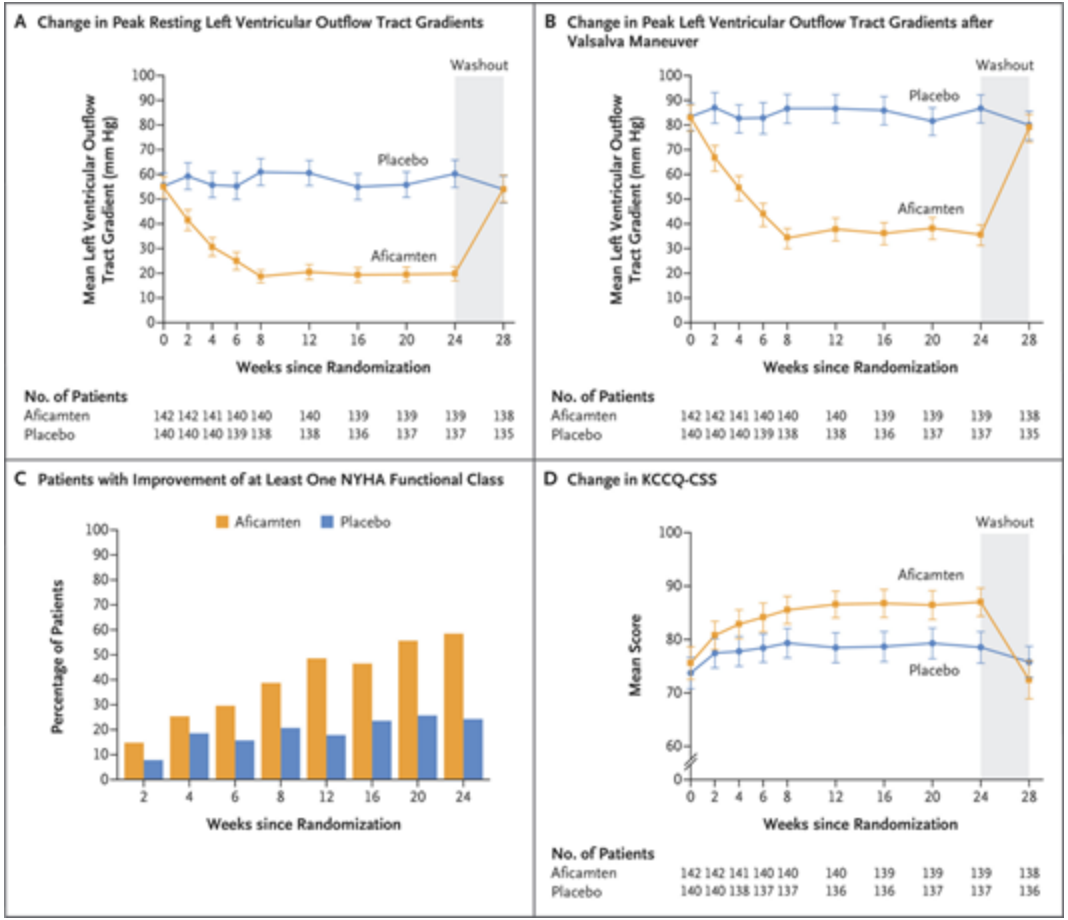
Maron MS, et al. NEJM 2024

SEQUOIA-HCM



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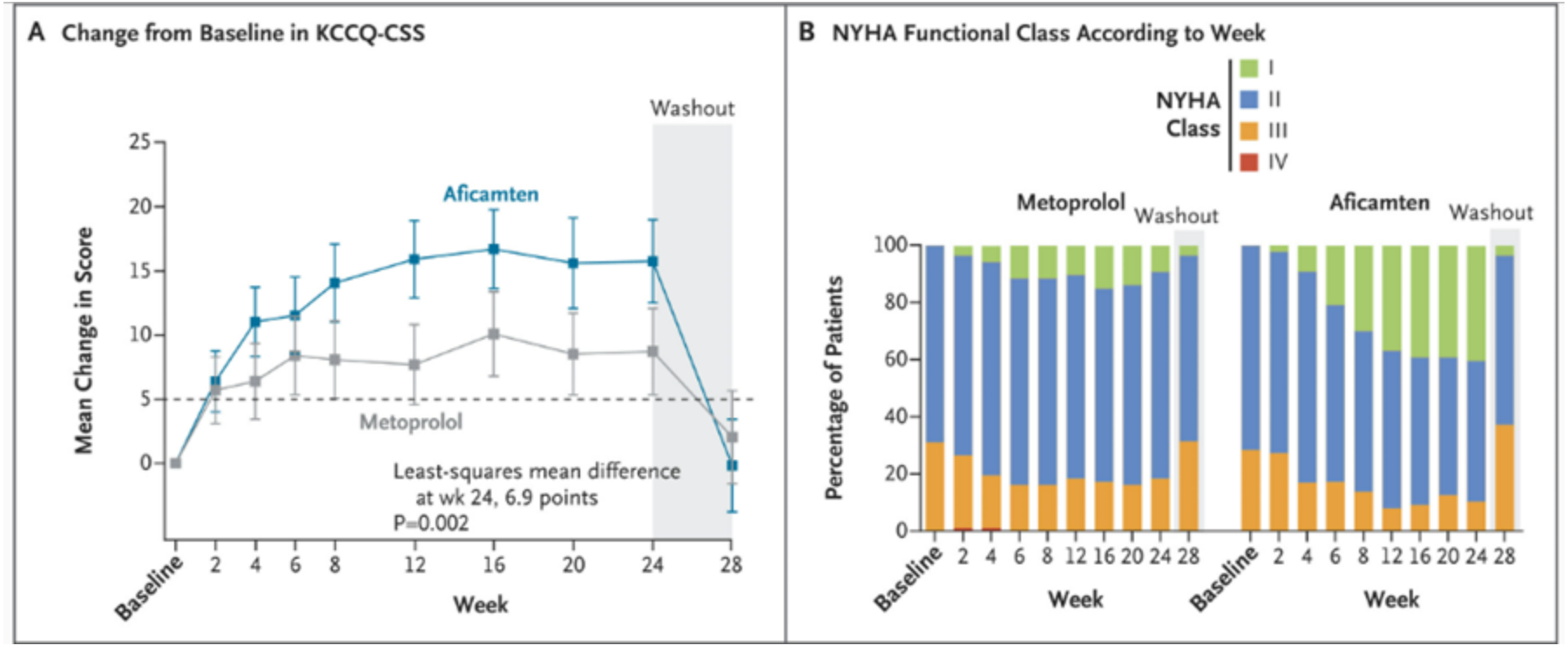
Maron MS, et al. NEJM 2024

MAPLE-HCM



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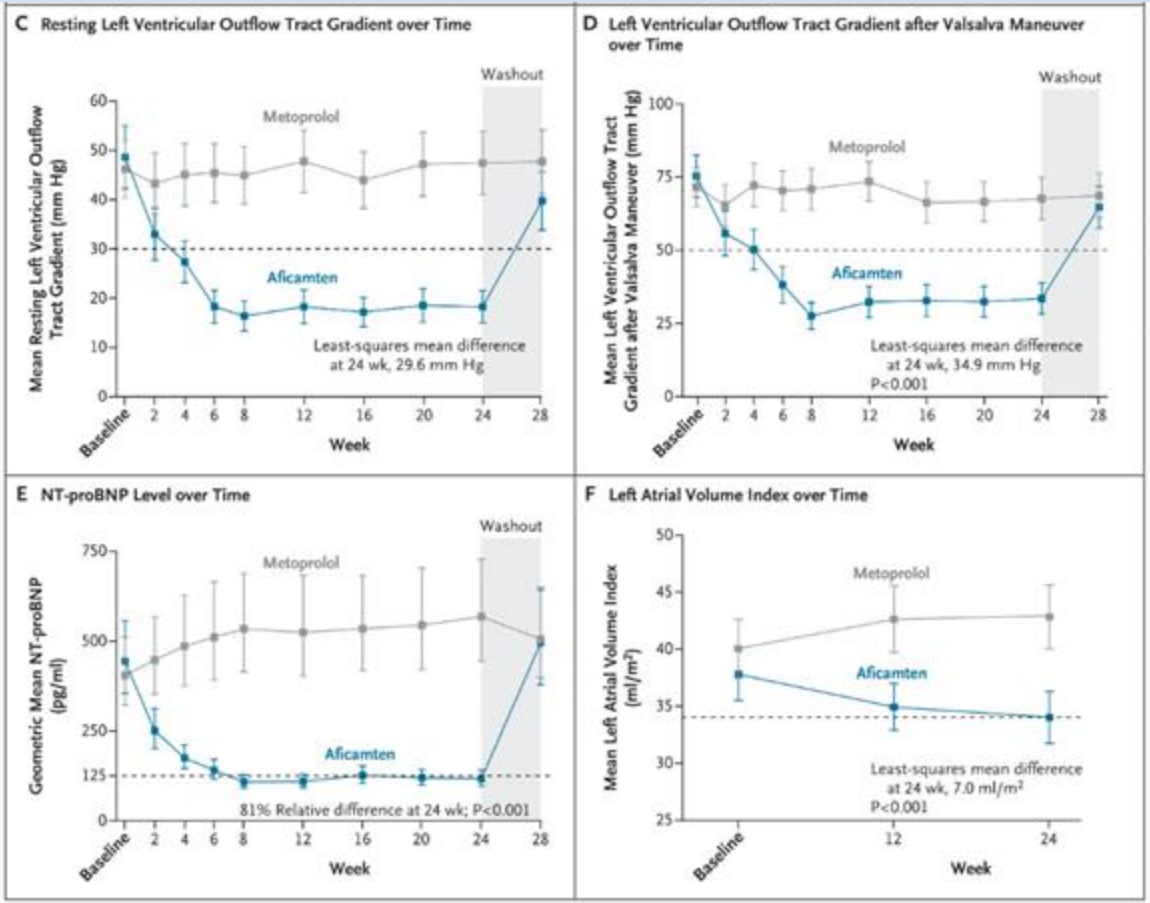
Garcia-Pavia P, et al. NEJM 2025

MAPLE-HCM



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Garcia-Pavia P, et al. NEJM 2025

Take-Home Messages

- CMIs are the first drug specifically for oHCM.
- Mavacamten is effective at improving exercise capacity and functional status while decreasing LVOT obstruction.
- Mavacamten is prescribed through a REMS program with surveillance echocardiograms and regular screening for drug-drug interactions.
- In clinical trials, aficamten also appears to be effective at decreasing LVOT gradient, improving functional status and increasing exercise capacity.
- Future studies are ongoing for non-obstructive HCM and pediatric populations.

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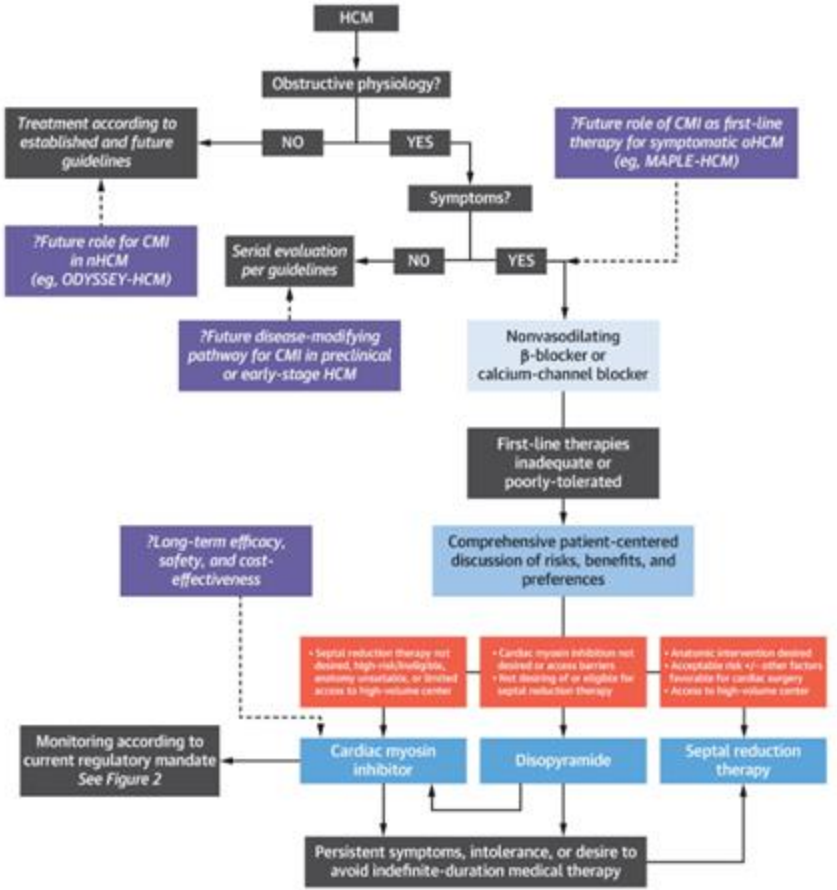
EXTRA SLIDES

Future of CMI



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