ST. MICHAEL'S
UNITY HEALTH TORONTO

Cardiology for the Practitioner
Saturday, May 4, 2024

New Standards in the Management of Heart Failure and Cardiomyopathy

Gordon Moe, MD, FRCP(C), FACC, FAHA

ST. MICHAEL'S
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Presenter Disclosure

Dr. Gordon Moe

New standards in the management of heart failure and cardiomyopathy

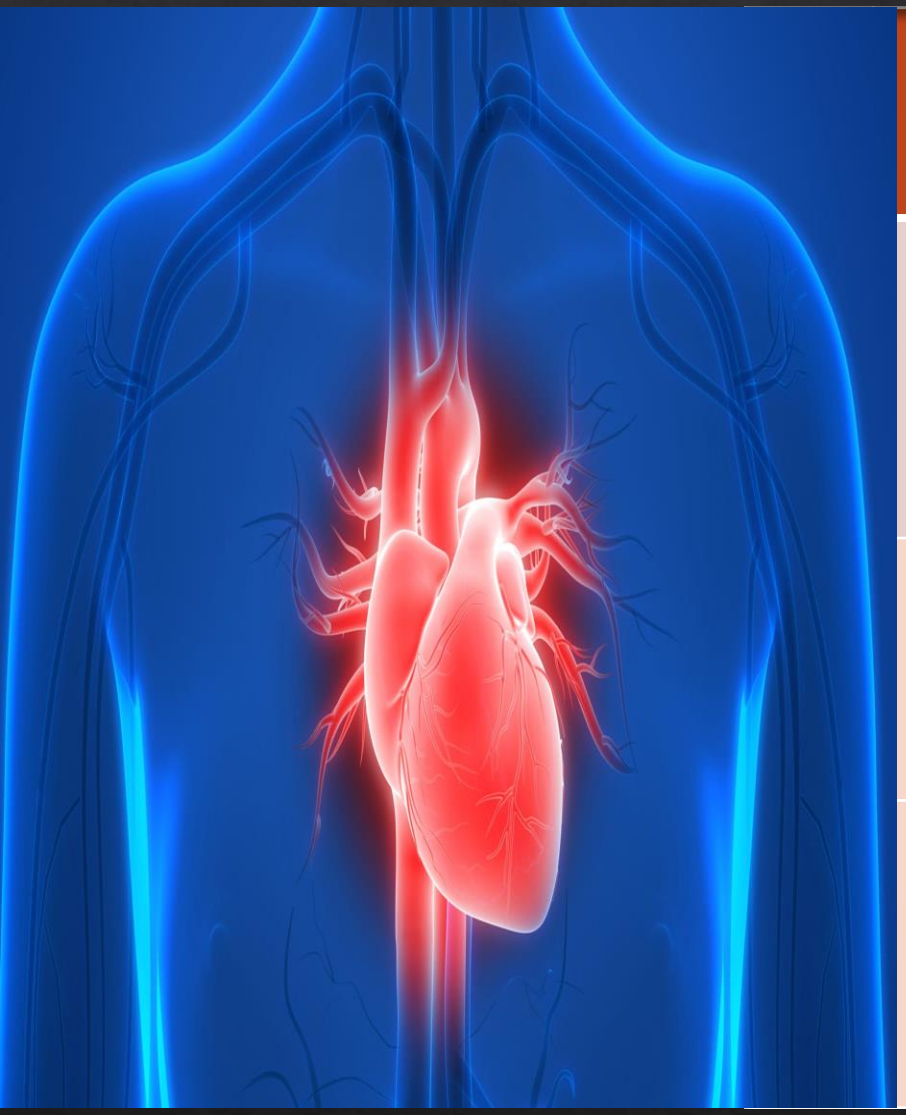
Relationships with financial sponsors:

- **Grants/Research Support:** BridgeBio Pharma
- **Speakers Bureau/Honoraria:** CHRC
- **Consulting Fees:** Bristol Myers Squibb, Pfizer
- **Patents:** N/A
- **Other:** N/A

Learning Objects

- Review recent game-changing clinical trial data and new standards in the management of heart failure (HF) – *Practical application*
- Review recent data and new standards in the management of selected cardiomyopathy – *Clinical application*

HF Phenotypes and Left Ventricular Ejection Fraction



LVEF < 40%	*HFrEF*
LVEF = 41-50%	*HFmrEF*
LVEF > 50%	*HFpEF*
Baseline LVEF ≤40%, ↑≥10 % points to LVEF >40% on 2nd measurement	*HFimpEF*

Two “Game Changing” Clinical Trials!

1st Trial: $SGLT_2i$ in Chronic + Acute HFmrEF and HFpEF

LVEF 41-50% LVEF >50%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

ABSTRACT

**Solomon SD et al . DOI: 10.1056/NEJMoa2206286

DELIVER, largest and broadest trial to date in patients HFmrEF and HFpEF[1]

N=6263

LVEF >40% and evidence of structural heart disease
Elevated NT-proBNP
Ambulatory or hospitalized
eGFR ≥25 mL/min/1.73 m²

1:1 randomization

DAPA 10 mg | **Placebo**

Median follow-up: 2.3 years

Primary endpoint[2]

Composite of CV death or worsening HF (hHF or an urgent HF visit):

- **Full patient population**
- **Patients with LVEF <60%**

Secondary endpoints[2]

- **Total # of hHF (first and recurrent) and CV death**
- **Change in KCCQ-TSS to 32 weeks**
- **CV death**
- **All-cause mortality**

Baseline characteristics[1,2]

1011 pg/mL
Median NT-proBNP

54%
Average LVEF

55%
Without T2D

50%
With an eGFR <60 mL/min/1.73 m²

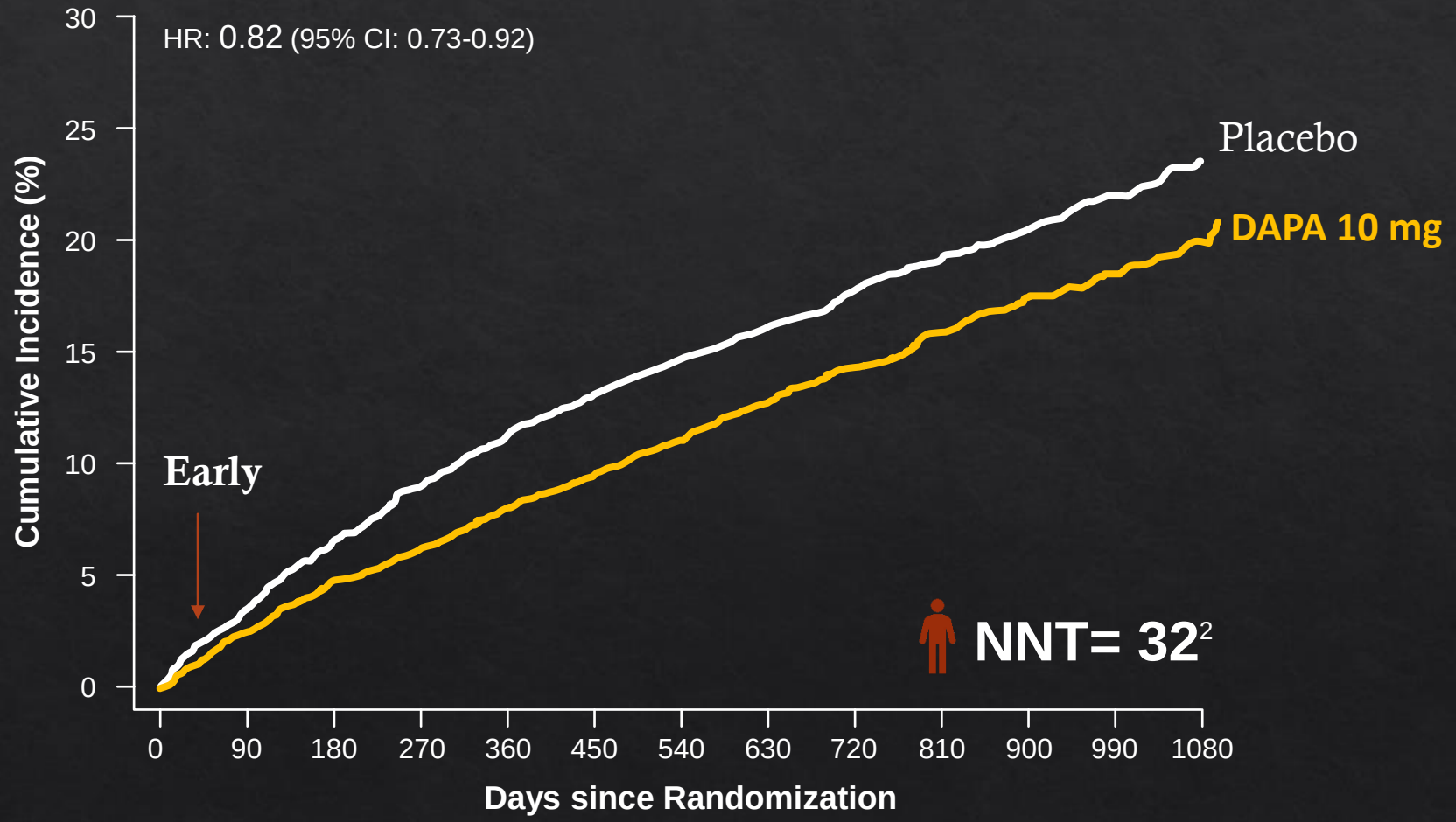
10%
Hospitalized or recently discharged

~18%
With prior LVEF ≤40%

1. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 2. Solomon SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med*. 2022.

Primary Endpoint

Composite of CV Death or Worsening HF[a]



18 % RRR

3.1% ARR
p=0.0008[2]

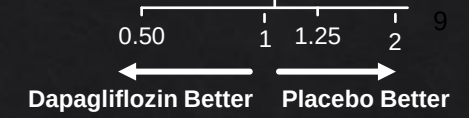
[a] HF hospitalization an urgent HF visit.

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Treatment effect sustained across prespecified subgroups

Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
Age, year	≤72	247/1545	306/1604	0.82 (0.69-0.97)
	>72	265/1586	304/1528	0.81 (0.69-0.96)
Sex	Female	195/1364	243/1383	0.81 (0.67-0.97)
	Male	317/1767	367/1749	0.82 (0.71-0.96)
Race	Asian	97/630	106/644	0.91 (0.69-1.20)
	Black	21/81	19/78	1.08 (0.58-2.01)
	White	372/2214	461/2225	0.79 (0.69-0.90)
	Other	22/206	24/185	0.83 (0.46-1.48)
Region	Europe/ Saudi Arabia	261/1494	309/1511	0.83 (0.70-0.98)
	Asia	92/607	103/619	0.89 (0.67-1.18)
	Latin America	70/602	87/579	0.78 (0.57-1.07)
	North America	89/428	111/423	0.75 (0.57-1.00)
T2D	Yes	270/1401	317/1405	0.83 (0.70-0.97)
	No	242/1730	293/1727	0.81 (0.68-0.96)
AF/AFL on ECG	Yes	227/1327	271/1317	0.81 (0.68-0.97)
	No	285/1803	339/1814	0.82 (0.70-0.96)
BMI, kg/m²	<30	275/1734	302/1736	0.89 (0.75-1.04)
	≥30	236/1395	308/1392	0.74 (0.63-0.88)

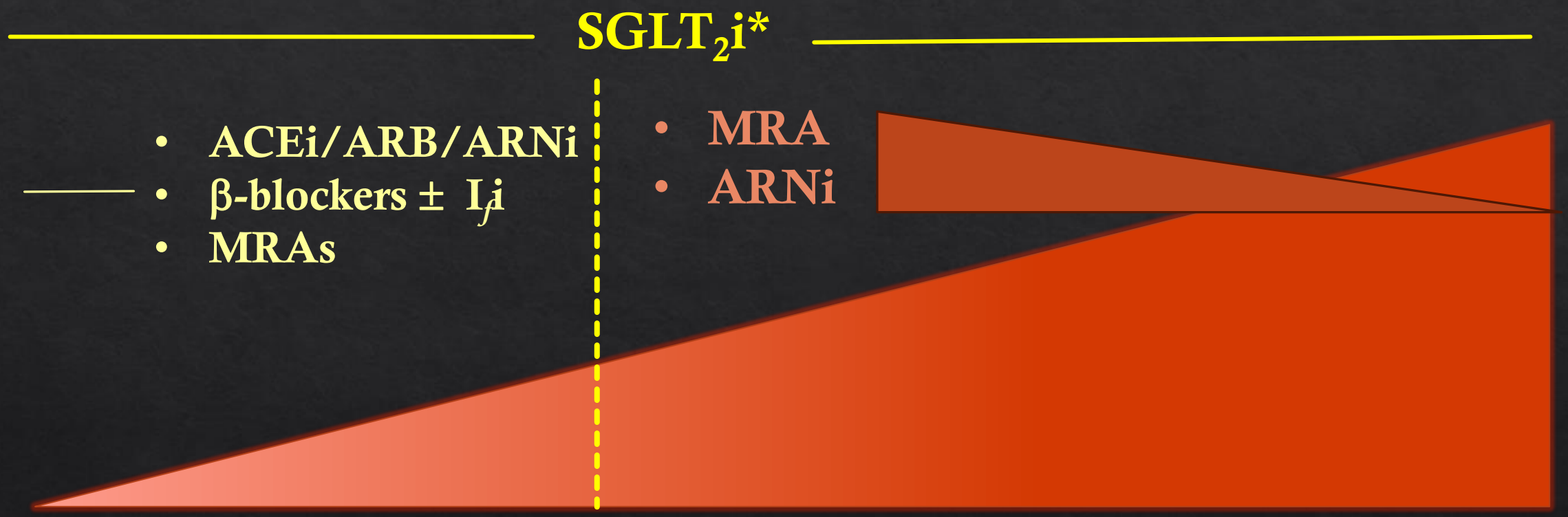
Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
NYHA class	II	331/2314	411/2399	0.81 (0.70-0.94)
	III or IV	181/817	198/732	0.80 (0.65-0.98)
LVEF, %	≤49	207/1067	229/1049	0.87 (0.72-1.04)
	50-59	174/1133	211/1123	0.79 (0.65-0.97)
	≥60	131/931	170/960	0.78 (0.62-0.98)
NT-proBNP, pg/mL	≤1011	173/1555	208/1578	0.84 (0.68-1.02)
	>1011	339/1576	402/1553	0.79 (0.69-0.92)
Enrollment during or within 30 days of hHF	Yes	93/328	113/326	0.78 (0.60-1.03)
	No	419/2803	497/2806	0.82 (0.72-0.94)
Prior LVEF ≤40% (HFimpEF)	Yes	92/572	119/579	0.74 (0.56-0.97)
	No	420/2559	491/2553	0.84 (0.73-0.95)
eGFR, mL/min/1.73 m²	<60	289/1516	355/1554	0.81 (0.69-0.94)
	≥60	223/1615	255/1577	0.84 (0.70-1.00)
SBP, mmHg	≤128	280/1568	300/1590	0.93 (0.79-1.10)
	>128	232/1563	310/1542	0.71 (0.60-0.85)



Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

What is the practical implications?

Foundational Therapy for Treatment of All Heart Failure 2024



* also includes in HF*imp*EF

ARNi, angiotensin receptor neprilysin inhibitor
MRA, mineralocorticoid receptor antagonist

2. A strategy of rapid up-titration of GDMT in hospitalized patients

Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

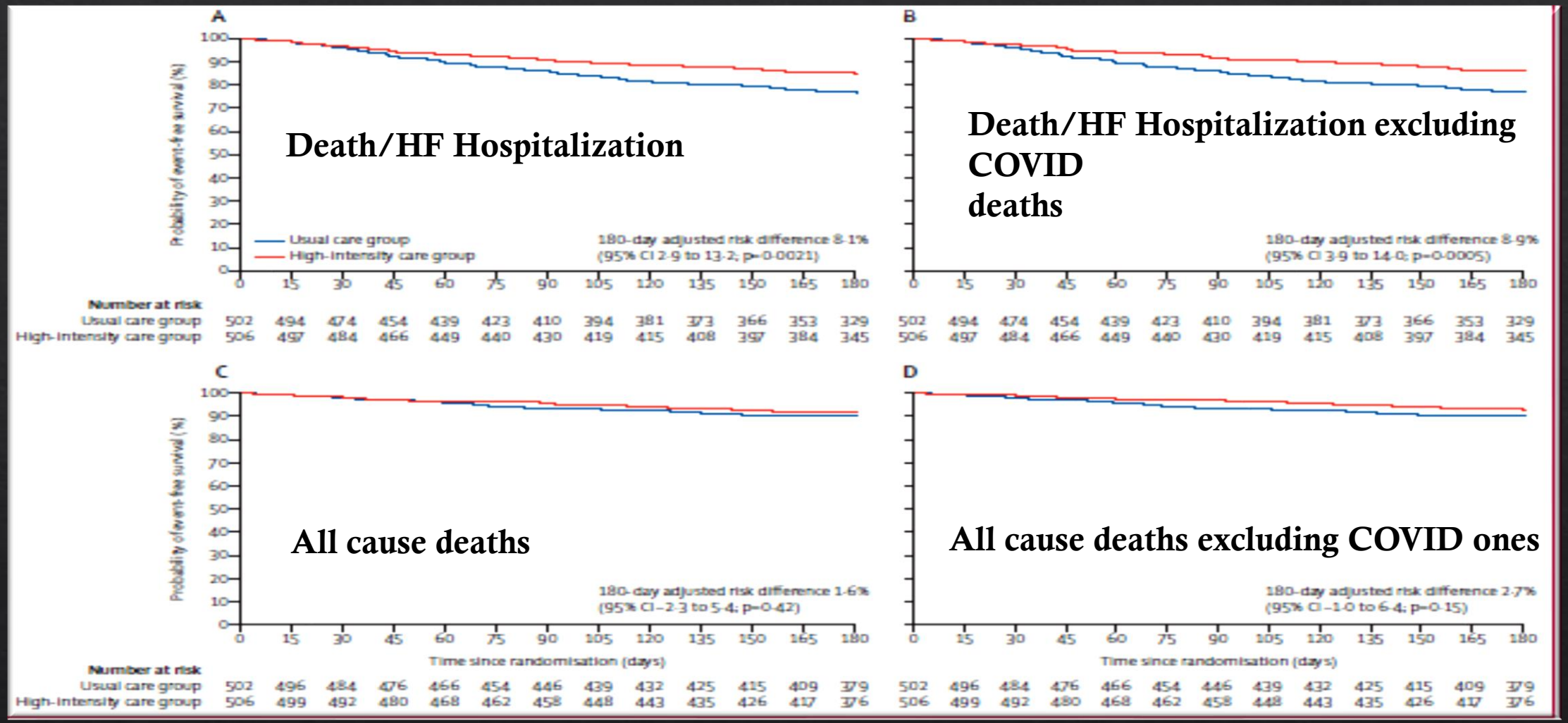
Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

1800 admitted patients, randomized open-label to rapid up-titration of treatments to 100% of recommended doses of GDMT within 2 weeks of discharge, or usual care with 4 scheduled outpatient visits over the 2 months after discharge

Published November 07, 2022DOI:https://doi.org/10.1016/S0140-6736(22)02076-1

Primary Endpoint: 180-day Death/HF Hospitalization

Trial terminated early



- BP, pulse, body wt. and NT-proBNP declined more in high-intensity care group
- More adverse events, but serious and fatal adverse events similar

What is the clinical implications of STRONG-HF?

- An intensive treatment strategy of rapid up-titration of guideline-directed medication during acute HF admission with close follow up after admission reduces symptoms, improved quality of life, and reduced the risk of 180-day all-cause death or heart failure readmission.
- This should now be standard therapy.

Case

- 64 year old male
- No HF history. History of poorly controlled hypertension and diabetes
- On Ramipril, Metformin, Sitagliptin
- Admitted with 2 weeks history of dyspnea and edema
- HF diagnosed (clinically) for the first time

- BP 158/99 mmHg, HR 99 bpm, coarse lung crackles, marked ankle edema
- Echo on hospital waiting list
- CXR, marked congestion
- ECG, sinus rhythm HR@106 bpm
- Creatinine, 116 mmol/l; eGFR, 40 ml/min/1.73 m^2; K, 4.3 mmol/l, NT-proBNP 5768 pg/ml

Question for you

What therapy will you initiate?

- Start a $SGLT_2$ inhibitor?
- Switch Ramipril to Sacubitril/Valsartan?
- Start Spironolactone?
- Start Ivabradine?

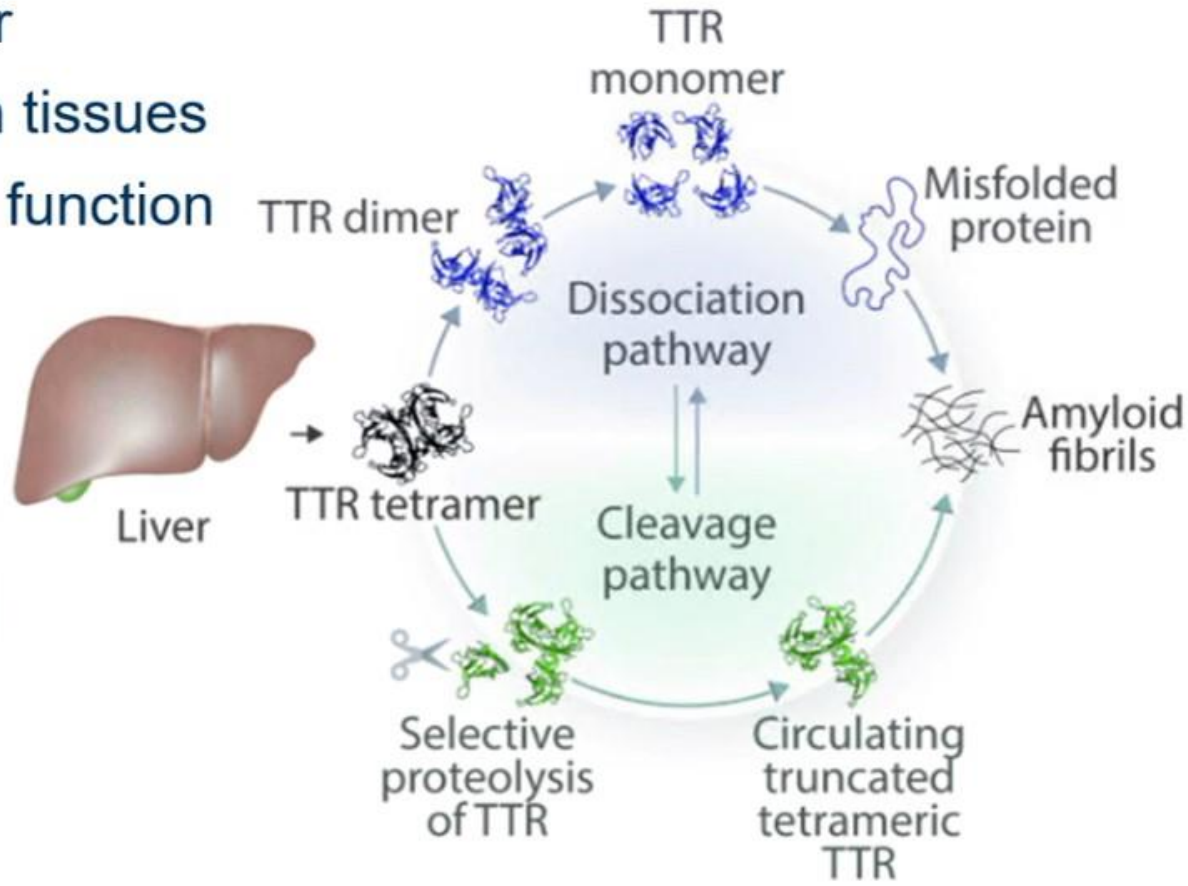
Learning Objects

- Review recent clinical trial data and new standards in the management of heart failure (HF)
- **Review recent data and new standards in the management of selected cardiomyopathy**
  1. Transthyretin Amyloidosis cardiomyopathy (ATTR-CM)
  2. Obstructive hypertrophic cardiomyopathy (oHCM)

What is amyloidosis?

- Amyloidosis is a protein misfolding disorder
- Extracellular deposition of fibrillar protein in tissues
- Disruption of tissue architecture and organ function
- Pathognomonic green birefringence on Congo red staining
- >30 different types of amyloidosis

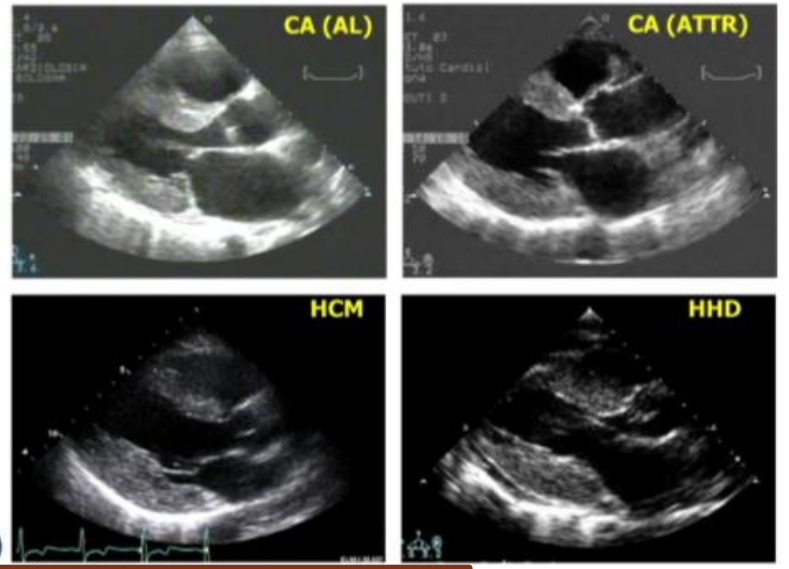
Amyloid type	Amyloid Fibril Protein
AL	Immunoglobulin light chain
AA	Serum amyloid A protein
ATTR	Transthyretin (TTR)



Amyloidosis: Diagnostic Challenges

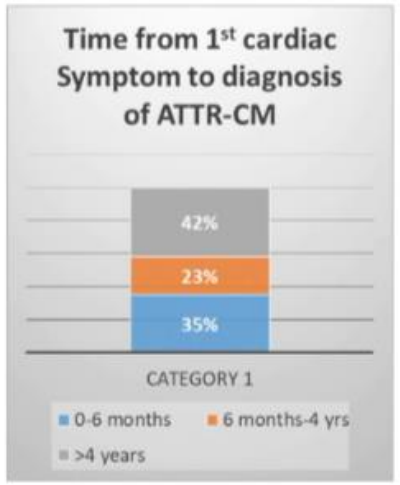
Suspicion

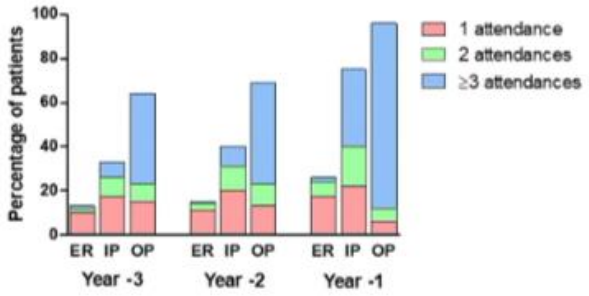
- Echocardiography poorly sensitive and specific in cardiac amyloidosis
- Need to consider 'Red Flags'



Amyloid was until recently a biopsy diagnosis

- Heart biopsy – is not routinely performed by cardiologists to investigate heart failure
- nerve biopsy – is not routinely performed by neurologists to investigate polyneuropathy
- Screening biopsies (fat, rectal) are poorly sensitive in ATTR amyloidosis
- Histology is challenging (false positive/negative Congo red, amyloid typing – AL v ATTR)
- Bone scintigraphy capable to diagnose ATTR amyloidosis non-invasively after exclusion of monoclonal gammopathy





Median 17 hospital attendances prior to diagnosis!
Median 3 hospital IP episodes prior to diagnosis

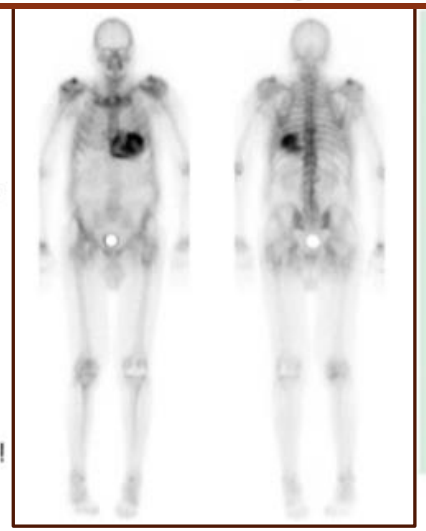


Table 1 Alternative diagnosis for patients with hereditary ATTR amyloidosis and variables associated with misdiagnosis of hereditary ATTR amyloidosis

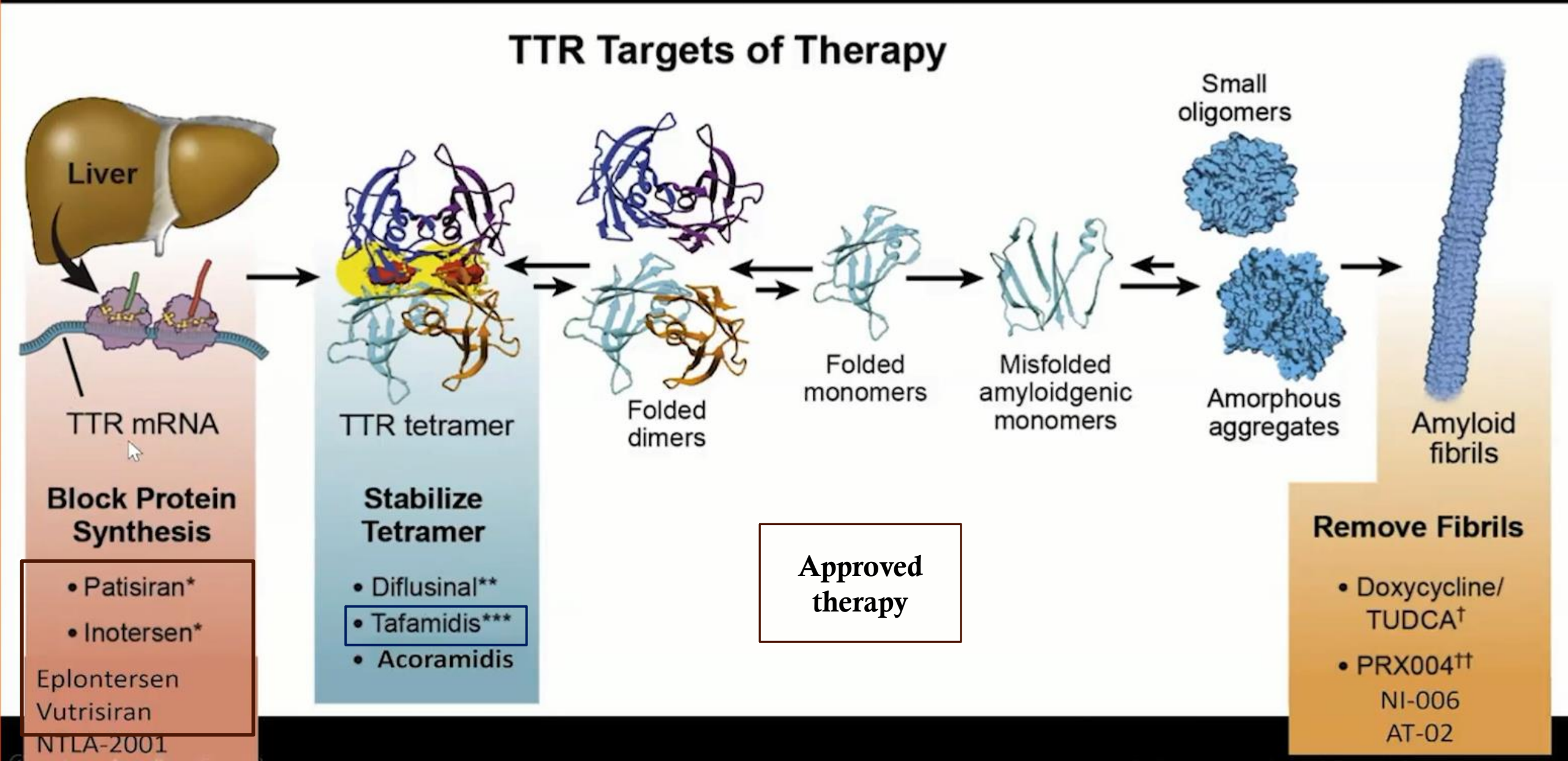
Misdiagnoses	n=49 (%)
Chronic inflammatory demyelinating polyneuropathy	30 (61)
Lumbar and sacral radiculopathy and lumbar canal stenosis	11 (22)
Paraproteinaemic peripheral neuropathy	3 (6)
AL amyloidosis	3 (6)
Wild-type ATTR amyloidosis	1 (2)
Toxic peripheral neuropathy	4 (8)
Vasculitic peripheral neuropathy	1 (2)
Motor neuron disease	1 (2)
Fibromyalgia	2 (4)
Other diagnosis	2 (4)
Multiple misdiagnosis	9 (18)

Lane T *et al*, Circulation 2019;140:16-26
Cortese A *et al*, J Neurol Neurosurg Psych 2017;88:457-458

Common Types of Transthyretin Amyloidosis with Cardiac Involvement

Transthyretin Cardiomyopathy, Wild Type (ATTRwt-CM)	Cardiomyopathy
Transthyretin Cardiomyopathy, Hereditary/Variant Type (ATTRv-CM)	Cardiomyopathy Peripheral neuropathy Autonomic neuropathy
Light Chain Amyloidosis Cardiomyopathy (AL-CM)	Multiorgan involvement

Treatments of ATTR Amyloidosis based on disease mechanisms



TTR Stabilizers for ATTRv-CM (hATTR) and ATTRwt-CM
The ATTR-ACT trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

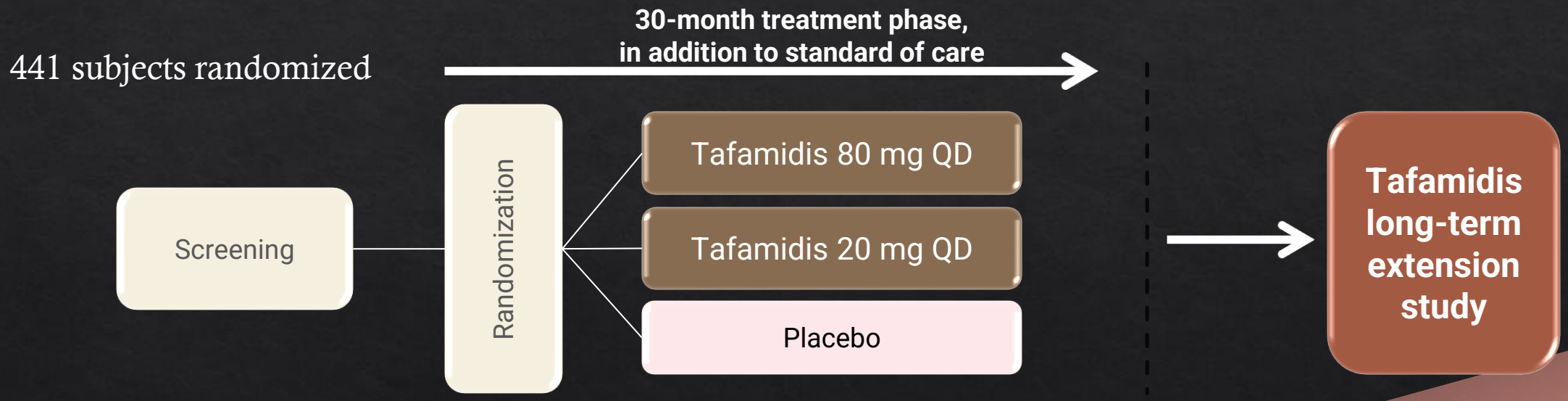
Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

Maurer MS, et al. N Engl J Med 2018;379:1007-16

ATTR-ACT Trial design

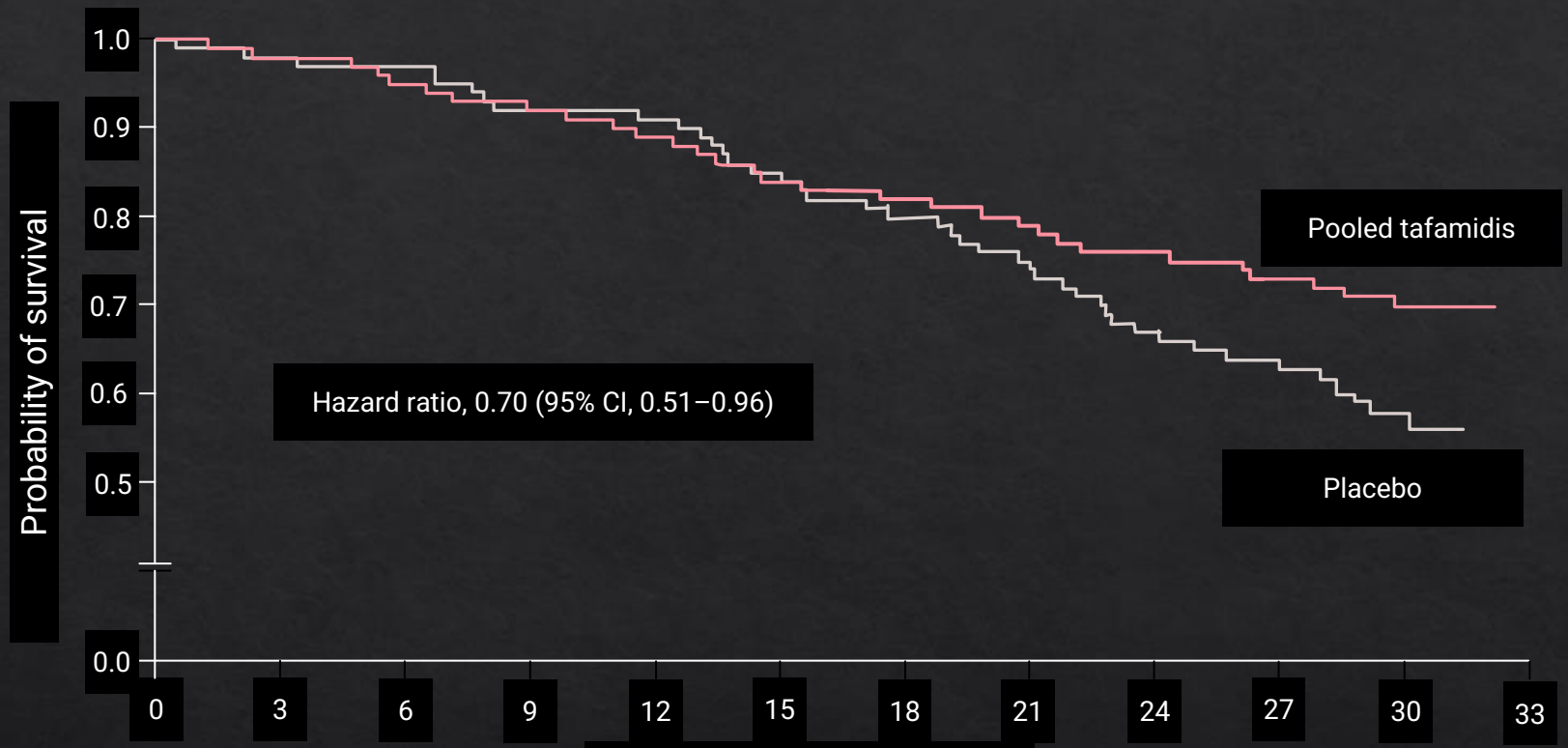
Randomized, double-blind, placebo-controlled, multicentre, international Phase III trial to evaluate the efficacy, safety and tolerability of tafamidis (20 or 80 mg orally daily) compared with placebo in patients with hereditary or wild-type ATTR-CM



- ✓ Patients were stratified by genotype (wild-type or variant) and disease severity (NYHA functional classification)
- ✓ Patients were randomized to receive tafamidis 80 mg or 20 mg, or placebo in a 2:1:2 ratio

1. Maurer MS, et al. *New Engl J Med* 2018;379(11):1007–16;
2. https://clinicaltrials.gov/ct2/show/NCT01994889?term=NCT01994889&rank=1 (October 2018)

Primary Endpoint: All-Cause Mortality*



Number at risk (cumulative number 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)

In primary analysis, hierarchically evaluated all-cause mortality, followed by CV-related hospitalizations according to the Finkelstein–Schoenfeld method.

30% reduction in the risk of all-cause mortality with tafamidis vs. placebo (P=0.0259)†

*These secondary endpoints are not multiplicity protected against type 1 error.
†Heart transplant and implantation of a CMAD were treated as death for this analysis.

Maurer MS, et al. *New Engl J Med* 2018;379(11):1007–16.

CV-related hospitalizations*

	Pooled tafamidis (n=264)	Placebo (n=177)
No. (%) of patients with CV-related hospitalizations	138 (52.3)	107 (60.5)
CV-related hospitalizations per year	0.4750	0.7025
Pooled tafamidis vs placebo treatment difference (relative risk ratio)	0.6761	
P-value	<0.0001	

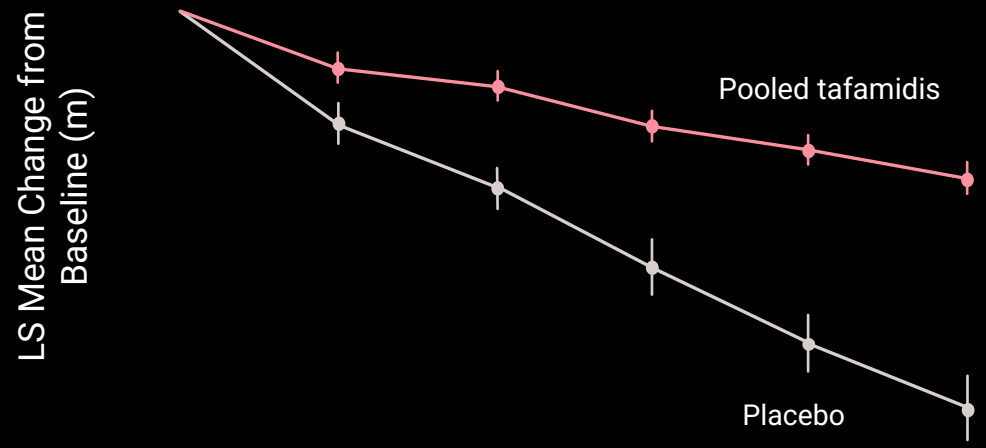
32% reduction in CV-related hospitalization with tafamidis compared with placebo (P<0.0001)

*These secondary endpoints are not multiplicity protected against type 1 error.

1. Maurer MS, et al. *New Engl J Med* 2018;379(11):1007–16.

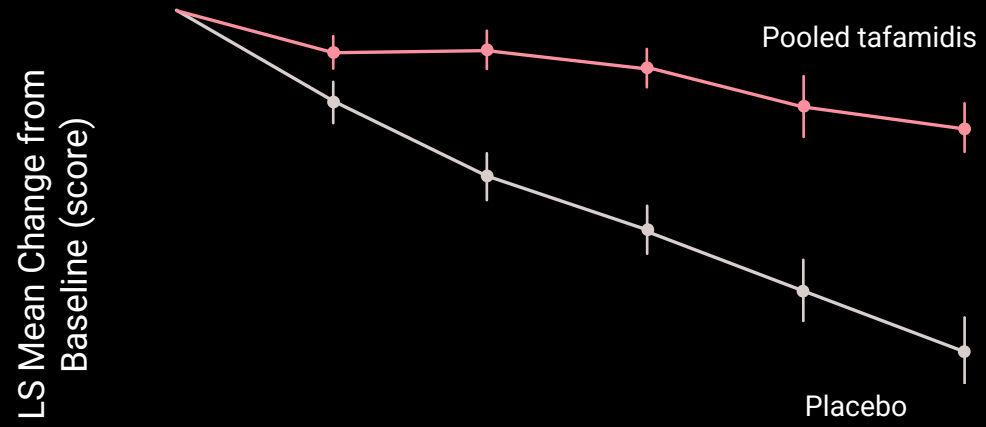
Key secondary endpoints: 6-minute walk test and the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)

Change from baseline in 6-minute walk test



Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70

Change from baseline in KCCQ-OS



Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

LS, Least Squares

1. Maurer MS, et al. *New Engl J Med* 2018;379(11):1007–16

Another Stabilizer: Acoramidis*

ORIGINAL ARTICLE

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

J.D. Gillmore, D.P. Judge, F. Cappelli, M. Fontana, P. Garcia-Pavia, S. Gibbs, M. Grogan, M. Hanna, J. Hoffman, A. Masri, M.S. Maurer, J. Nativi-Nicolau, L. Obici, S.H. Poulsen, F. Rockhold, K.B. Shah, P. Soman, J. Garg, K. Chiswell, H. Xu, X. Cao, T. Lystig, U. Sinha, and J.C. Fox, for the ATTRibute-CM Investigators*

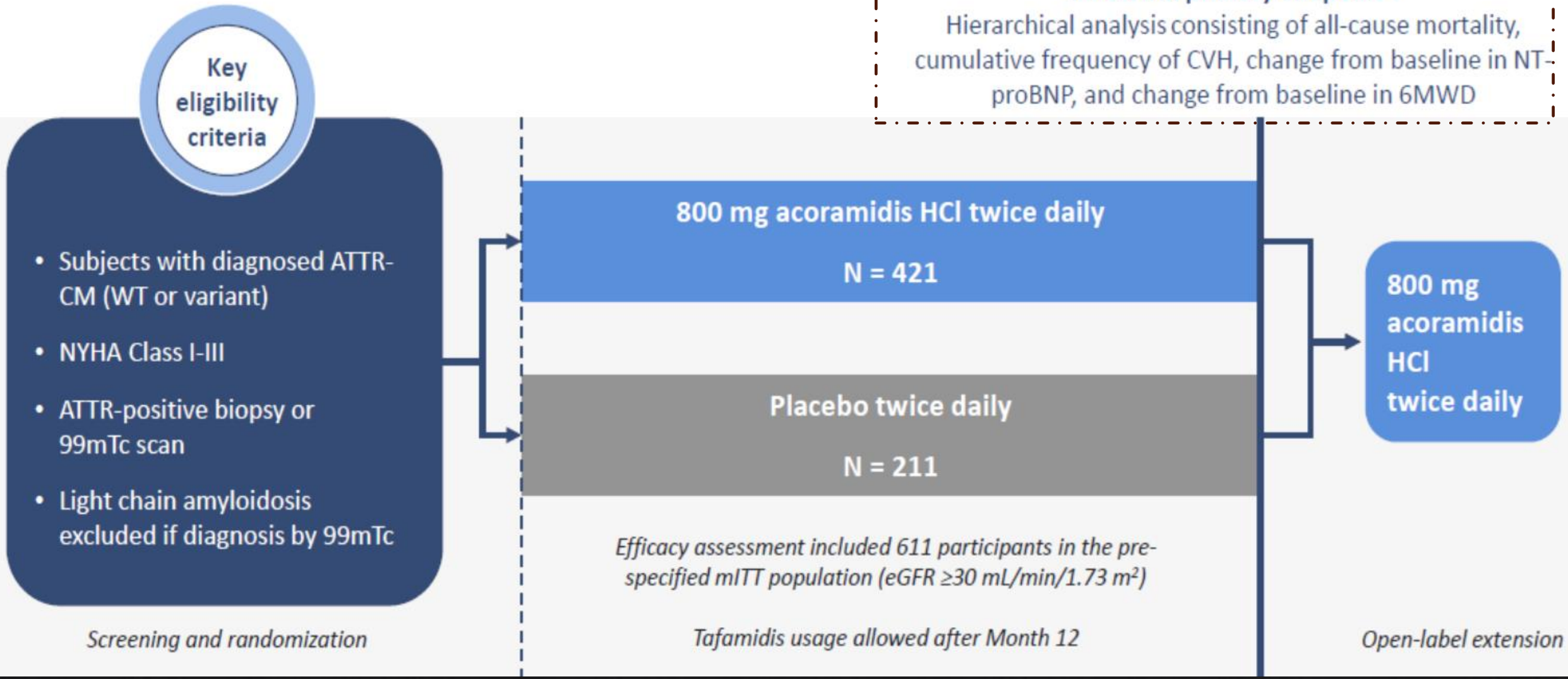
Acoramidis (AG-10) is a high-affinity TTR stabilizer that inhibits dissociation of tetrameric TTR resulting in >90% stabilization

* Not yet FDA- or Health Canada approved

Gilmore, JD , et al. N Engl J Med 2024;390:132-42

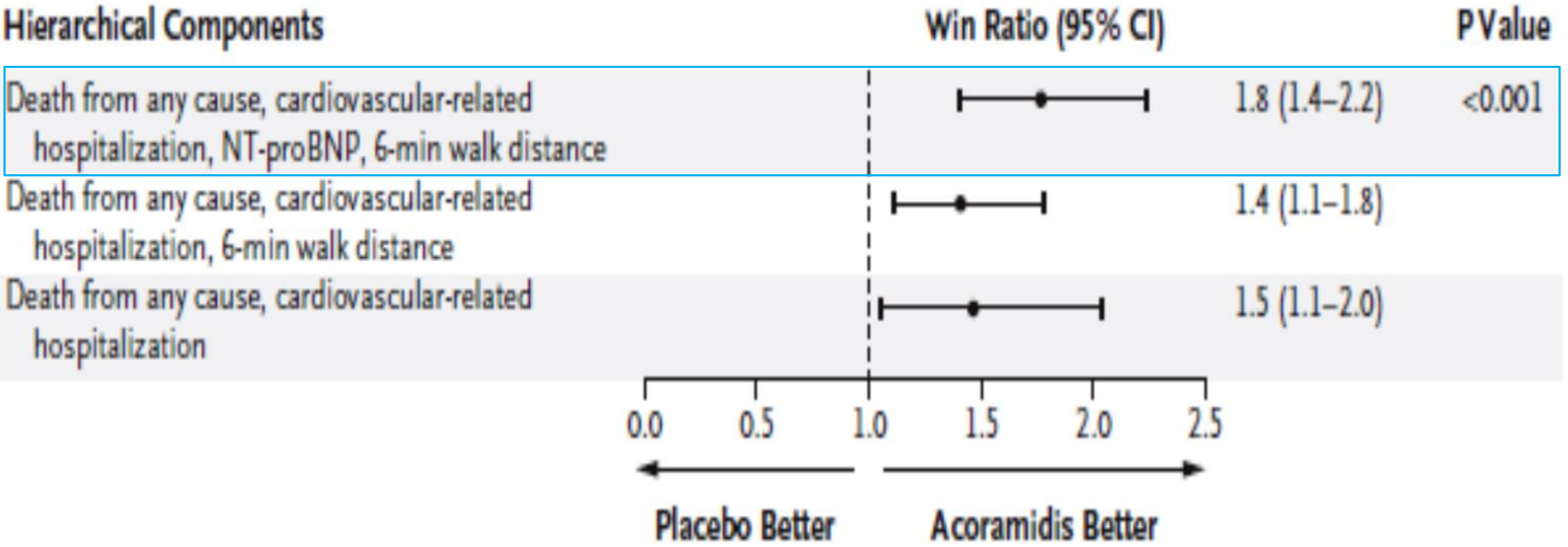
ATTRibute-CM study design[1,2]

30-month primary endpoint[3]:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD



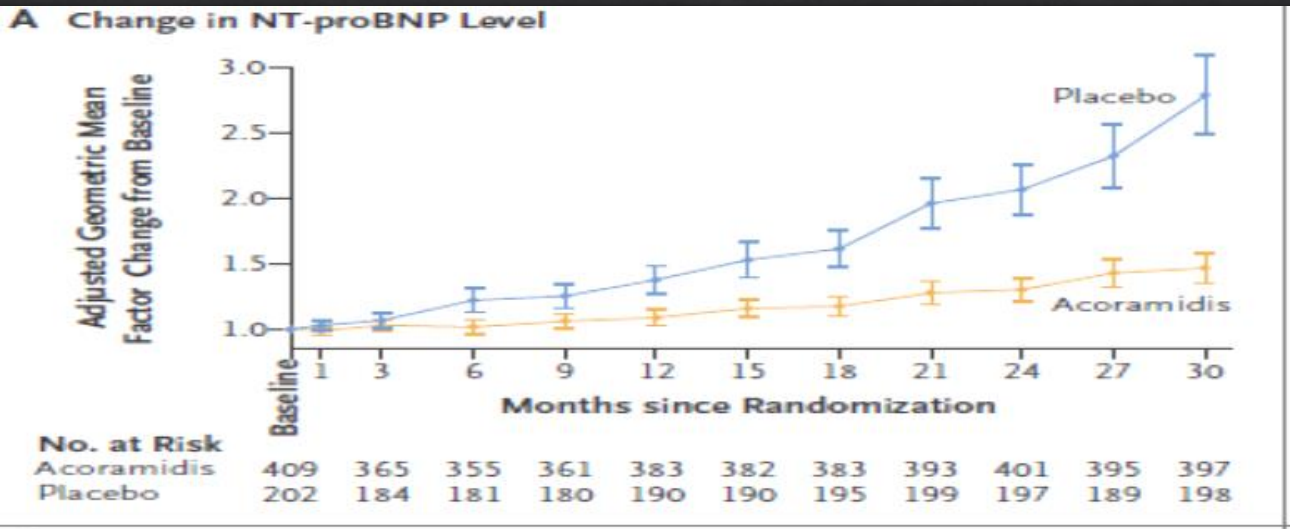
Gilmore, JD , et al. N Engl J Med 2024;390:132-42

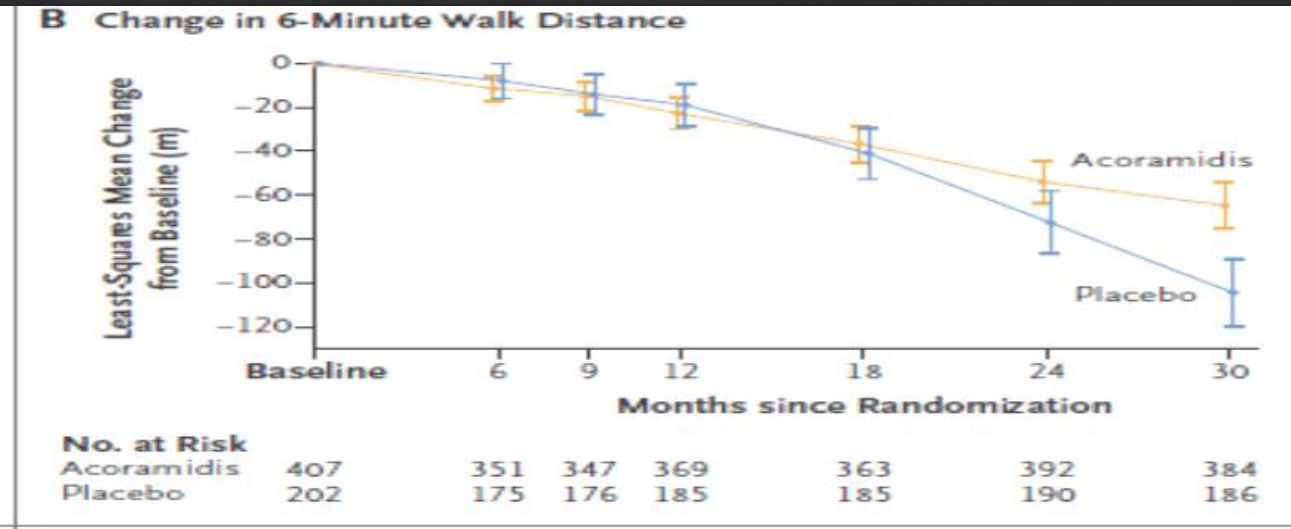
Primary Efficacy Analysis and Prespecified Secondary Analyses: Win Ratios from Finkelstein-Schoenfeld Method

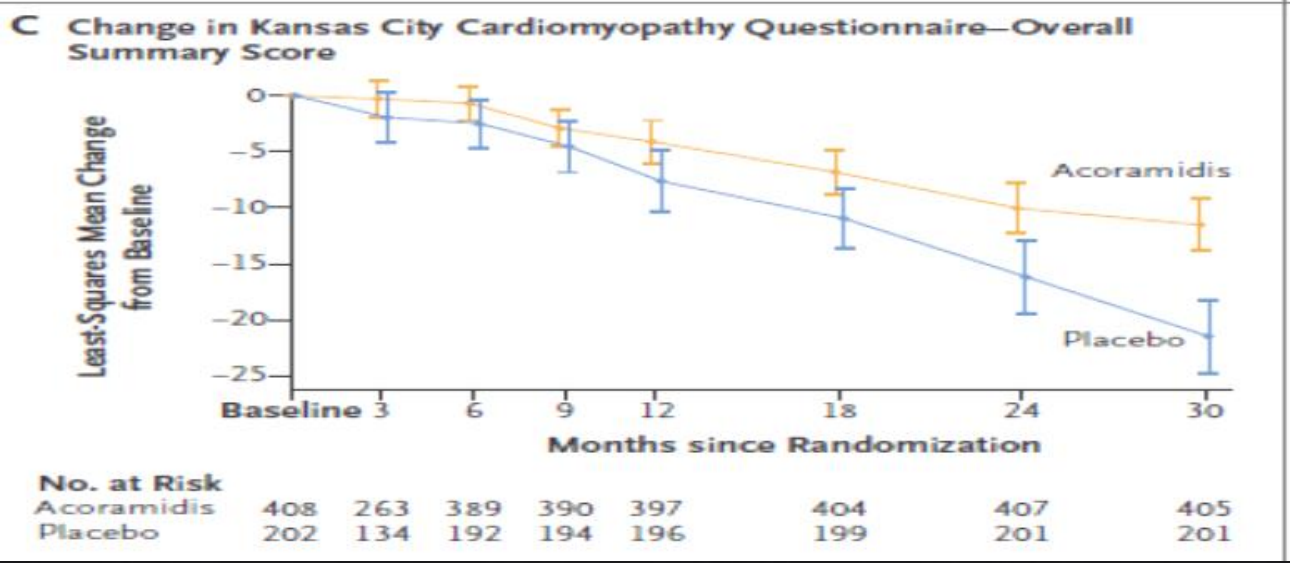


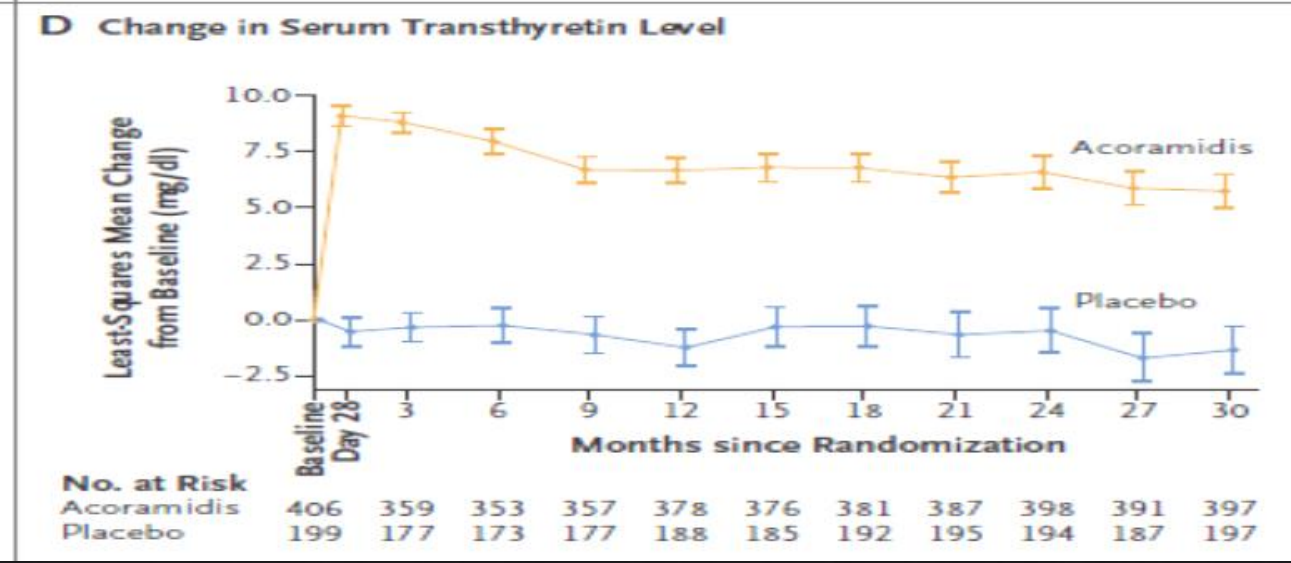
Gilmore, JD , et al. N Engl J Med 2024;390:132-42

ATTRibute-CM: Key secondary outcomes









Gilmore, JD , et al. N Engl J Med 2024;390:132-42

ATTRibute-CM: Clinical Implications

- Improves the composite outcomes of total mortality, CV hospitalization, NT-proBNP and 6-min walk: win ratio 1.8 p<0001
- Preserves functional capacity (6-min walk) and quality of life (KCCQ-OS)]
- 81% survival rate of acoramidis approaches that of the age-matched U.S. population!
- Reassuring safety profile
- Acoramidis is pending approval

What is the status of treatment of ATTR-CM?

- Major development in the treatment of ATTR-CM
  - Supportive therapy
  - Targeted therapy

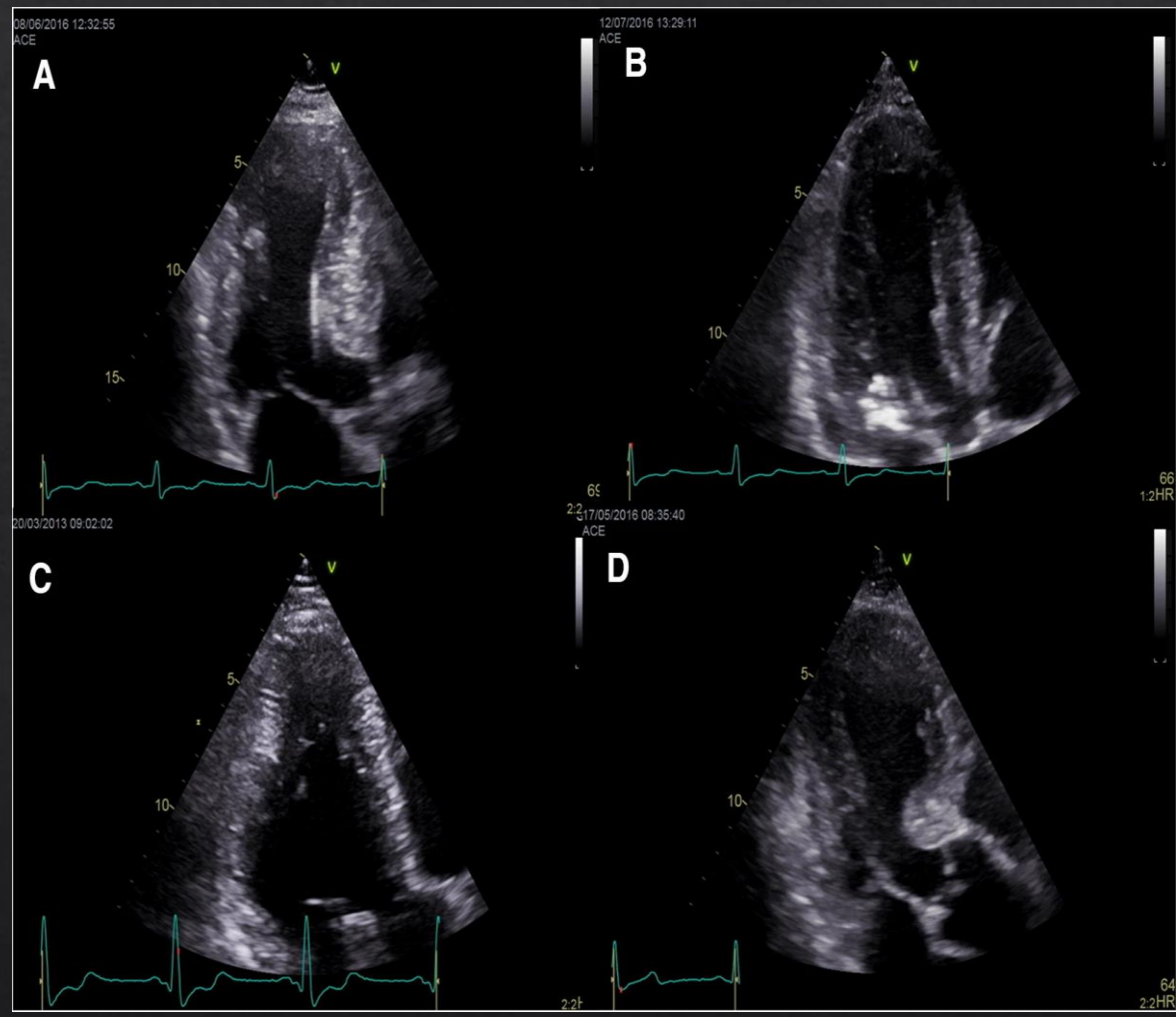
- Newer targeted therapies: stabilizers (Acoramidis), silencers (Eplontersen, Vutrisiran), gene editing and anti-fibril therapy hold promise.

Learning Objects

- Review recent clinical trial data and new standards in the management of heart failure (HF)
- **Review recent data and new standards in the management of selected cardiomyopathy**
  - Transthyretin Amyloidosis cardiomyopathy (ATTR-CM)
  - **Obstructive hypertrophic cardiomyopathy (oHCM)**

HCM is a chronic, progressive disease of the heart muscle[1–3]

- Characterized by a progressive thickening of the left ventricular (LV) wall[1-4]
- Hallmarks: LV hypertrophy (LVH), hypercontractility, impaired relaxation, excess energy consumption, and reduced compliance
- In >60% of HCM cases, thickened LV wall obstructs blood flow out of the heart, a condition known as **obstructive HCM (oHCM)**[,4–6]
  - **Key abnormality in oHCM is hypercontractility,** a major determinant of dynamic LV outflow tract obstruction[7,8]
  - oHCM is associated with downstream conditions: HF and atrial fibrillation[7]



[a]LVOT obstruction is defined by a peak LVOT gradient of ≥ 30 mmHg.
HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy.

1. Ommen SR et al. *Circulation*. 2020;142(25):e558–e631. 2. Elliott PM et al. *Eur Heart J*. 2014;35(39):2733–2779. 3. Maron MS et al. *Circulation*. 2006;114(21):2232–2239. 4. Data on file. BMS-REF-MAVA-0025. Princeton, NJ: Bristol-Myers Squibb; 2022. 5. Tuohy CV et al. *Eur J Heart Fail.* 2020;22(2):228-240. 6. Lu D-Y et al. *J Am Heart Assoc.* 2018;7(5):e006657. 7. Maron BJ. *N Engl J Med.* 2018;379(7):655–668. 8. Seferović PM et al. *Eur J Heart Fail.* 2019;21(5):553–576.

Current treatment for oHCM and unmet needs

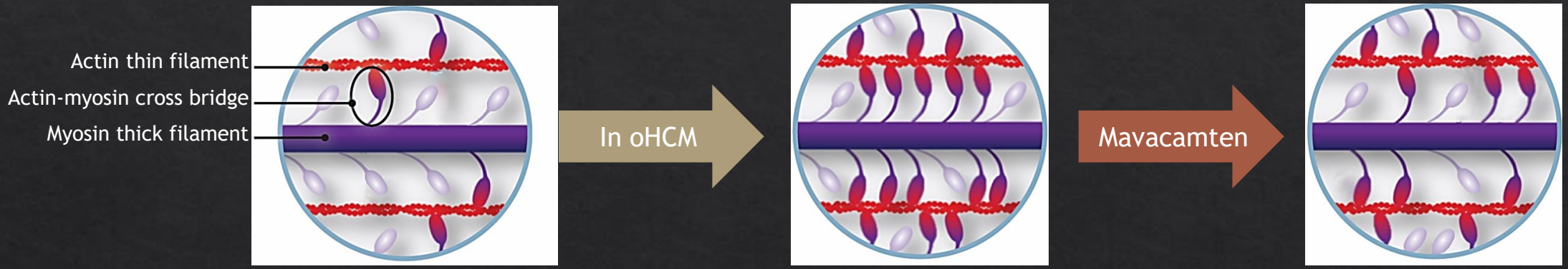
- **Current management for oHCM** include:[1,2]
  - **Pharmacotherapies:** β-blockers, calcium channel blockers, and disopyramide
  - **Procedures:** septal reduction therapy, including alcohol septal ablation and septal myectomy and heart transplant
  - **Medical devices:** implantable cardioverter-defibrillator and pacemaker
- Due to **limited randomized controlled data,** management of symptomatic oHCM is often based on nonrandomized data or on expert opinion[2]
- **Current recommended pharmacologic treatment options, may provide symptomatic relief in oHCM but are not designed to target the underlying mechanism of disease[2]**

BB, beta-blocker; CCB, calcium-channel blocker; ICD, implantable cardioverter-defibrillator; oHCM, obstructive hypertrophic cardiomyopathy; SRT, septal reduction therapy.

1. Gersh BJ et al. *Circulation*. 2011;124(24):2761–2796. 2. Ommen SR et al. *Circulation*. 2020;142(25):e558–e631.

Mavacamten inhibits the excessive myosin-actin cross-bridging and to reduce excessive contractility in HCM[a,1-6]

- **In oHCM, there is excessive myosin-actin cross-bridging[1]**



Normal sarcomere[1]	HCM sarcomere[1]	HCM sarcomere with mavacamten[1-5]
Normal contractility Effective relaxation	Hypercontractility Impaired relaxation Altered myocardial energetics	Reduces myosin-actin cross bridges Attenuates hypercontractility and improved compliance and energetics

Mavacamten is now indicated for the treatment of symptomatic oHCM with NYHA class II-III symptom

HCM, hypertrophic cardiomyopathy; MoA, mechanism of action; oHCM, obstructive hypertrophic cardiomyopathy; NYHA, New York Heart Association.

1. Ho CY et al. *Circ Heart Fail.* 2020;13(6):e006853. 2. Bristol Myers Squibb. Accessed March 2021. https://news.bms.com/news/corporate-financial/2021/U.S.-Food-and-Drug-Administration-FDA-Accepts-Bristol-Myers-Squibbs-Application-for-Mavacamten-in-Symptomatic-Obstructive-Hypertrophic-Cardiomyopathy-oHCM/default.aspx 3. Heitner SB et al. *Ann Intern Med.* 2019;170(11):741–748. 4. Green EM et al. *Science.* 2016;351(6273):617–621. 5. Olivotto I et al. *Lancet.* 2020;396(10253):759–769. 6. Desai MY et al. Oral presentation at the ACC22; Apr 2–4, 2022. 7. CAMZYOS [product monograph].

Trials Evaluating Mavacamten in oHCM:
Eligibility Criteria

Eligibility Criteria	*EXPLORER-HCM*[1]	*VALOR-HCM*[2]
Age	≥18 years	
LV wall thickness	≥15 mm (≥13 mm if familial)	
NYHA class	II-III	II[a] -IV
Peak LVOT gradient	Resting, Valsalva or exercise ≥50 mm Hg	Resting or Valsalva ≥50 mm Hg
LVEF	≥55%	≥60%
Background therapy	Combination therapy and disopyramide not allowed	Combination therapy and disopyramide allowed
Other criteria	None	**Patients referred for SRT; actively considering scheduling the procedure**

[a]Class II with exertional symptoms of syncope or near syncope.

1. Olivotto I et al. Lancet. 2020;396:759-769; 2. Desai MY et al. Am Heart J. 2021;239:80-89.

EXPLORER-HCM: Phase III RCT in symptomatic oHCM

STUDY DESIGN

- **N=251** pts with LVOT gradient ≥ 50 mm Hg and NYHA class II, III
- Randomized 1:1, placebo-controlled
- Oral mavacamten (5 mg with a 2-step dose titration) 30 weeks

STUDY ENDPOINTS

Change from baseline to Week 30:

Primary endpoint

Composite 1

≥ 1.5 mL/kg/min increase in pVO_2 with ≥ 1 NYHA class improvement

Composite 2

≥ 3.0 mL/kg/min increase in pVO_2 with no worsening of NYHA class

Secondary efficacy endpoints

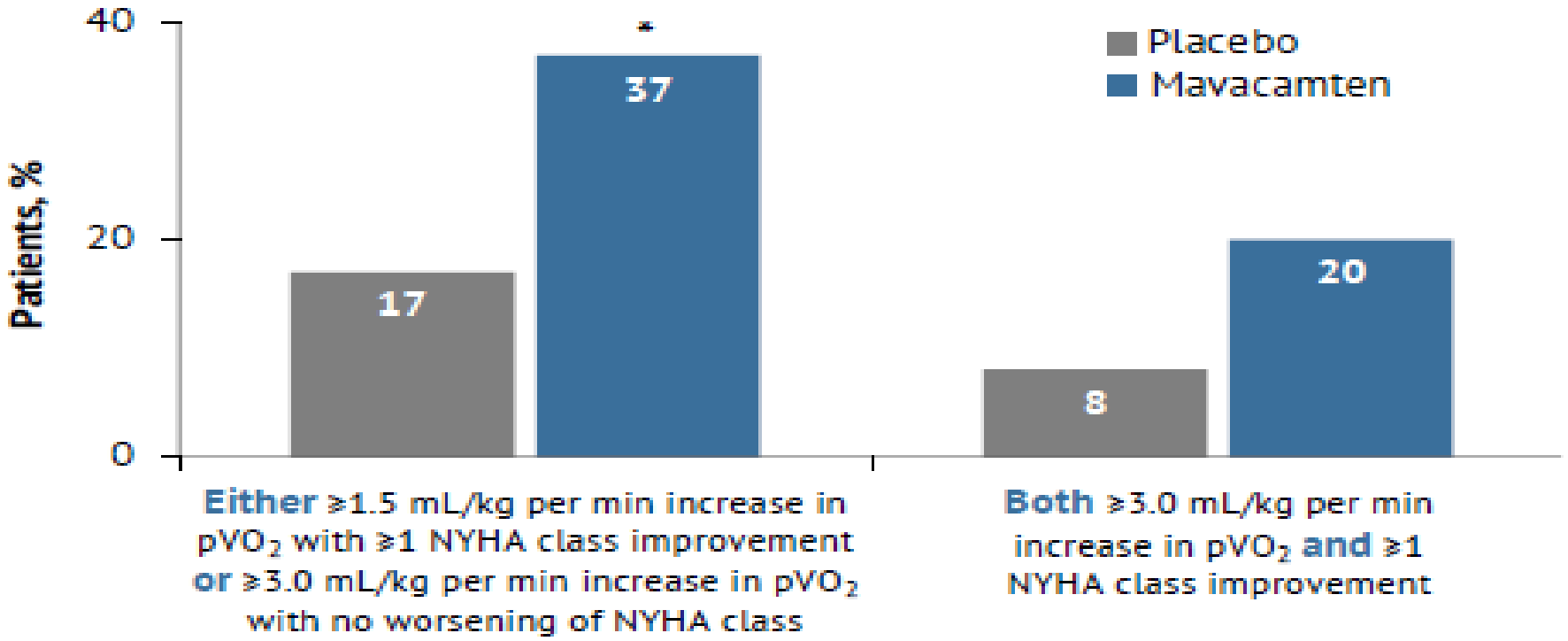
- Postexercise LVOT gradient
- Peak VO_2
- Pts with ≥ 1 NYHA class improvement
- Health status

Olivotto I et al. Lancet 2020;396:759-769

EXPLORER-HCM Trial: Primary Endpoint

Efficacy of Cardiac Myosin Inhibitor Mavacamten: EXPLORER-HCM

Phase 3, double-blind RCT: Primary composite functional endpoint (N = 251)



* *P* = .0005.

Abbreviation(s): pVO_2: peak oxygen uptake; RCT: randomized controlled trial.
Reference(s): Olivotto I et al. *Lancet*. 2020;396:759-769.

EMPEROR-HCM: LVOT, NT-proBNP and hs-troponin

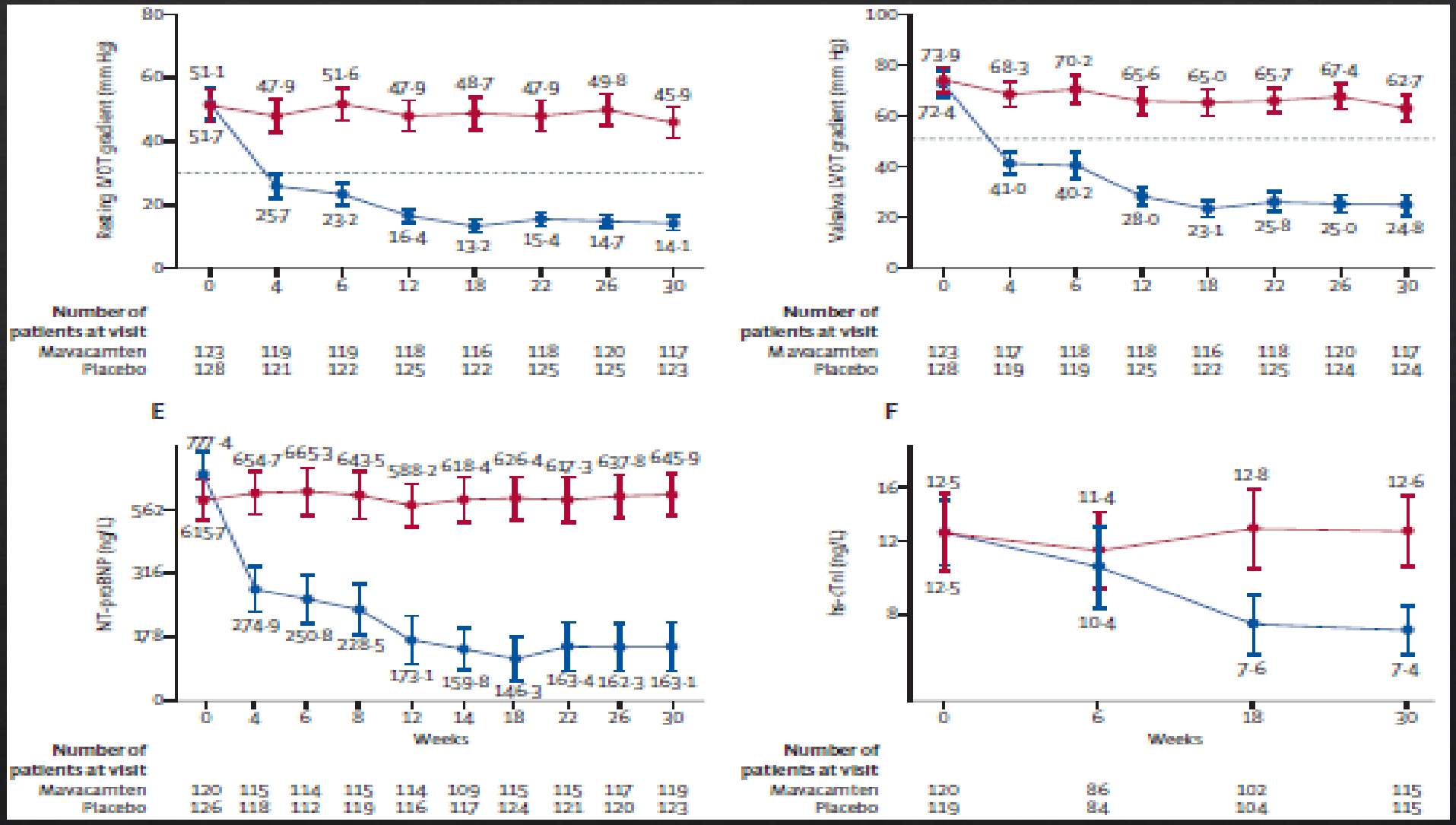
Resting LVOT

Valsalva LVOT

N=429
LVOT≥50 mmHg
NYHA >II

NT-proBNP

hs-TnI



Greater improvements in KCCQ-CCS scores, pVO_2 and NYHA class

Olivotto,I et al. Lancet 2020;396:759-69

VALOR-HCM: Phase III RCT to study the delay of SRT in symptomatic oHCM

STUDY DESIGN

- **N=112**, randomized 1:1, placebo-controlled, oral mavacamten (5 mg with a 2-step dose titration) 16 weeks
- Severe symptoms despite maximally tolerated medical therapy
  - NYHA class III/IV, or class II with exertional syncope or near syncope
  - Maximal medical HCM therapy could include disopyramide and/or combination BB and CCB
- Dynamic LVOT gradient ≥ 50 mm Hg
- **Actively considering SRT**

STUDY ENDPOINTS

Primary endpoint

- **Decision to proceed with SRT by week 16 or guideline eligible at week 16**

Secondary endpoints (from baseline to Week 16)

- Postexercise LVOT gradient
- NYHA class status
- KCCQ-23 CSS
- Cardiac biomarkers (NT-proBNP & Troponin I)

KEY RESULTS

Efficacy

- **Proceeding or Eligibility for invasive SRT at Week 16** (Difference -58.93%, p<0.0001)
- Resting LVOT gradient (Difference -33.4 mmHg, p<0.001
- Valsalva LVOT gradient (Difference -47.6 mmHg, p<0.001)
- ≥ 1 NYHA class improvement
- KCCQ-23 CSS (Difference 9.4, p<0.001)
- Cardiac biomarkers (NT-proBNP & Troponin I)

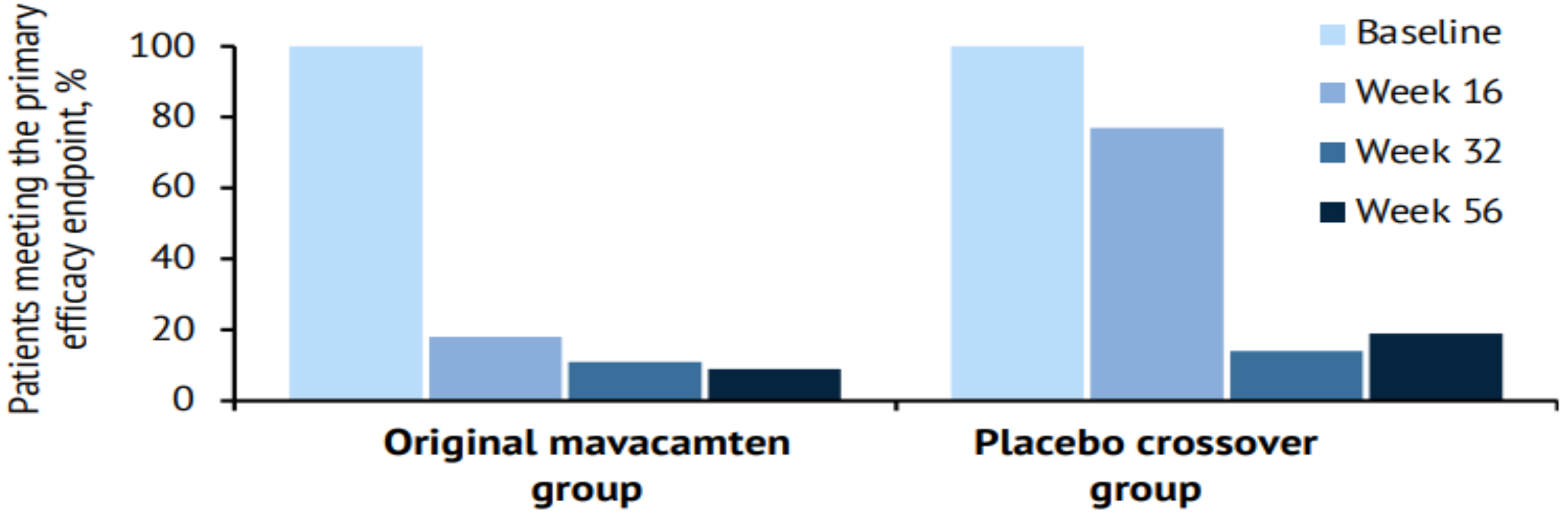
Safety

- **No new safety signal**
- Modest reductions in LVEF (Difference -4.0%, p=ns)
- No permanent discontinuations due to LVEF ≤30%
- No subjects experienced SAEs of CHF, syncope, or SCD
- First evidence of concomitant use with disopyramide (20%)

Desai MY. Oral presentation at the American College of Cardiology's 71st Annual Scientific Session & Expo (ACC.22); April 2–4, 2022; Presentation 402-09.

Efficacy of Cardiac Myosin Inhibitor Mavacamten: VALOR-HCM

Phase 3, double-blind RCT: SRT composite endpoint (N = 108 at week 56)



Cross over from placebo to Mavacamten at 16-56 weeks (40 weeks exposure)

Desai MY et al. JAMA Cardiol. 2023;8:968-977.

Practical application re Treatment of oHCM

- Obstructive HCM is prevalent among HCM.
- Disease-targeted therapy in the form of myosin-actin cross bridging modulation which can reduce symptoms, LVOT gradient and can delay septal reduction therapy is now available for clinical use
- Longer term (beyond 56 weeks) effects and hard outcome benefit, however, are still unknown.

New Standards in the Management of Heart Failure and Cardiomyopathy

Conclusions

- Guideline-directed outcome-modifying therapy is now available in HF with **all** categories of LVEF
- Additional benefit will accrue with **early** initiation of therapy, including hospitalized patients before discharge

- Targeted therapies that improve clinical outcome and symptoms are now available in ATTR-CM; promising additional therapies are under investigations
- Myosin-actin modulation is first targeted-therapy in oHCM; Mavacamten is highly effective but long term effects and impact on hard clinical outcomes remain unclear