11th ANNUAL HEART FAILURE UPDATE 2024

Friday May 24 - Saturday May 25

Marriott Chateau Champlain, Montreal, Quebec

CHFS SCIC

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

𝕏 @CanHFSociety #HFupdate

Amyloidosis Update

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Disclosures

- **Grants/Research Support:** Pfizer, Ionis, Servier, Takeda, Novartis, BridgeBio-Eidos

- **Speaking/Consulting Honoraria:** Pfizer, Ionis, Sobi, Alnylam, Sanofi-Genzyme, Astra-Zeneca, Takeda, Novo Nordisk

Learning Objectives

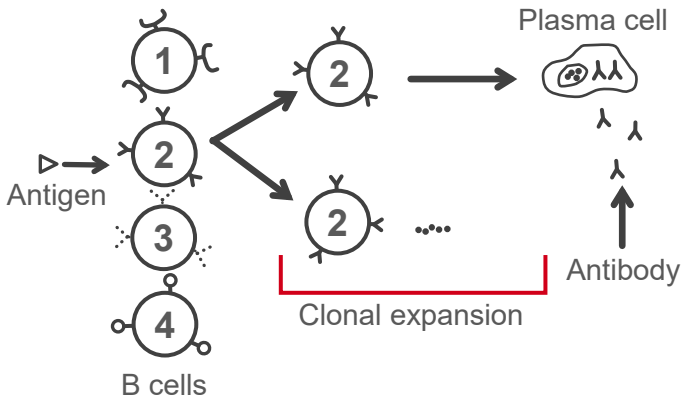
- Provide a brief overview of how to diagnose and manage ATTR cardiac amyloidosis

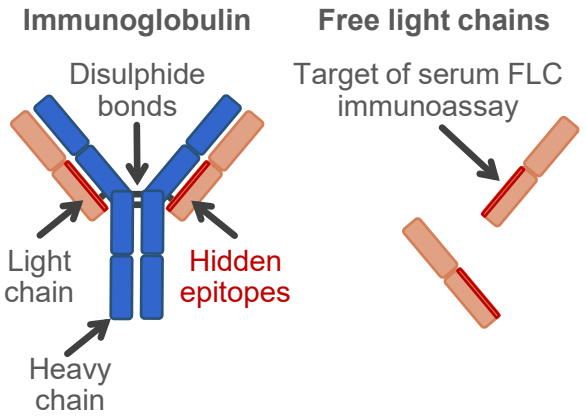
- Highlight the latest groundbreaking trials on potential new therapies for the treatment of ATTR cardiac amyloidosis

What is Amyloidosis?

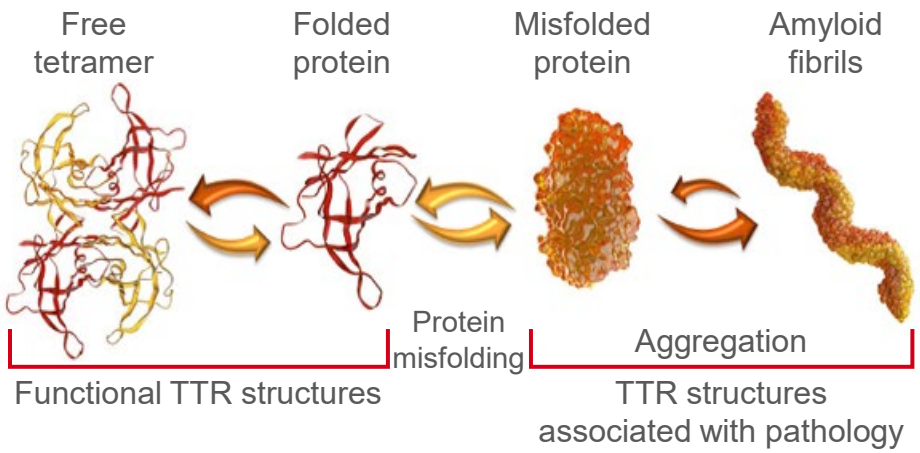
- Group of disorders caused by extracellular deposition of insoluble abnormal fibrils composed of **misfolded proteins** of different types
- Usually systemic disease with 1–2 organ types predominantly affected
- Two main types cause **cardiac infiltration**, resulting in increased wall thickness and heart failure

Light chain (AL)





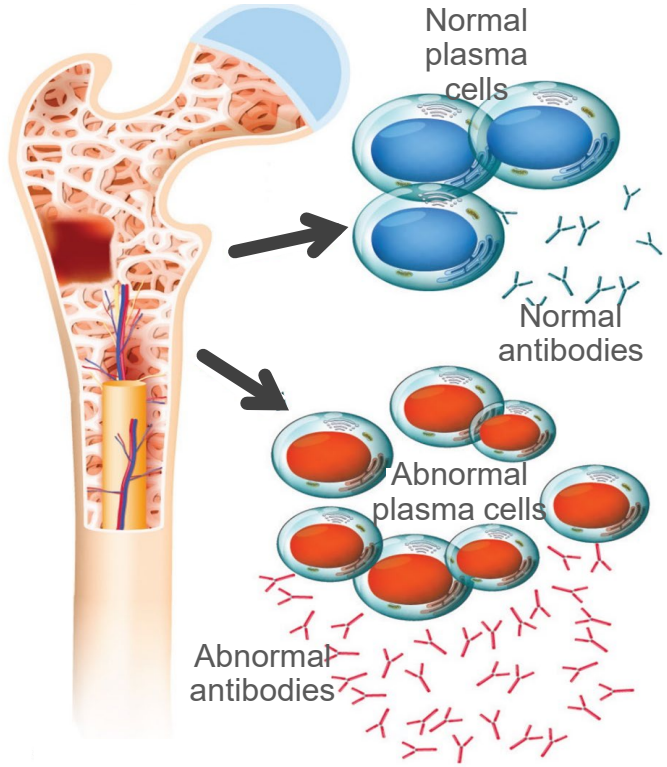
Transthyretin (ATTR)



AL: amyloid light chain; ATTR: transthyretin amyloid cardiomyopathy; FLC: free light chain.
Merlini G, Bellotti V. *New England J Med. 2003*;349(6)583-596.
THAOS Registry

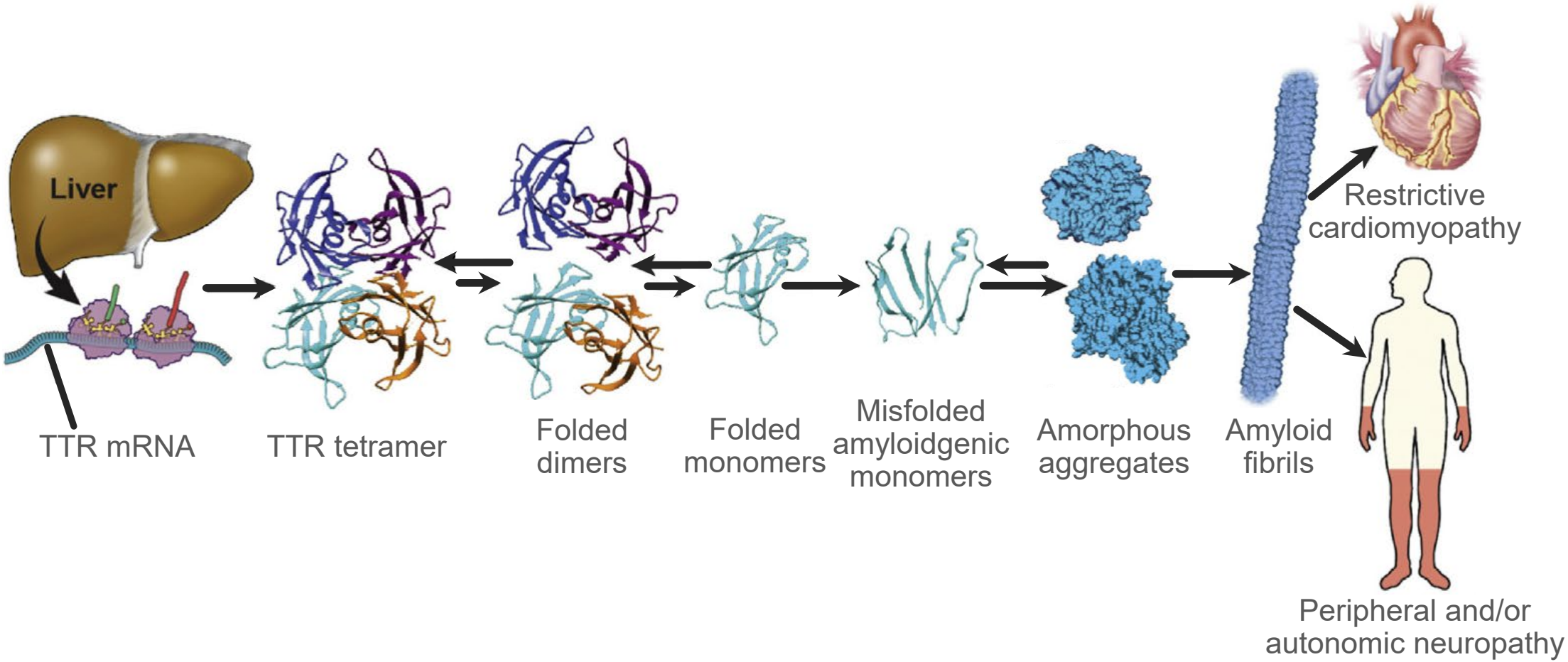
Light Chain (AL) Amyloidosis

- Malignant hematologic disorder – plasma cell dyscrasia
  - Light chain producing clonal plasma cell disorder
  - Related to but distinct from multiple myeloma, although the two may coexist
  - Amyloid light chain fibrils have a **direct toxic myocardial effect**
- Cardiac > renal > 50% involvement



Schentrup D. *Clin Rev*. 2018;28:16-21.

Transthyretin Amyloidosis



TTR: transthyretin.

Ruberg. *JACC.* 2019;73:2872.

Transthyretin Amyloidosis

Two subtypes

Hereditary

- Transthyretin gene mutation
- Relatively rare in Canada (more prevalent in certain racial/ethnic populations)
- **Cardiomyopathy and/or neuropathy phenotype**

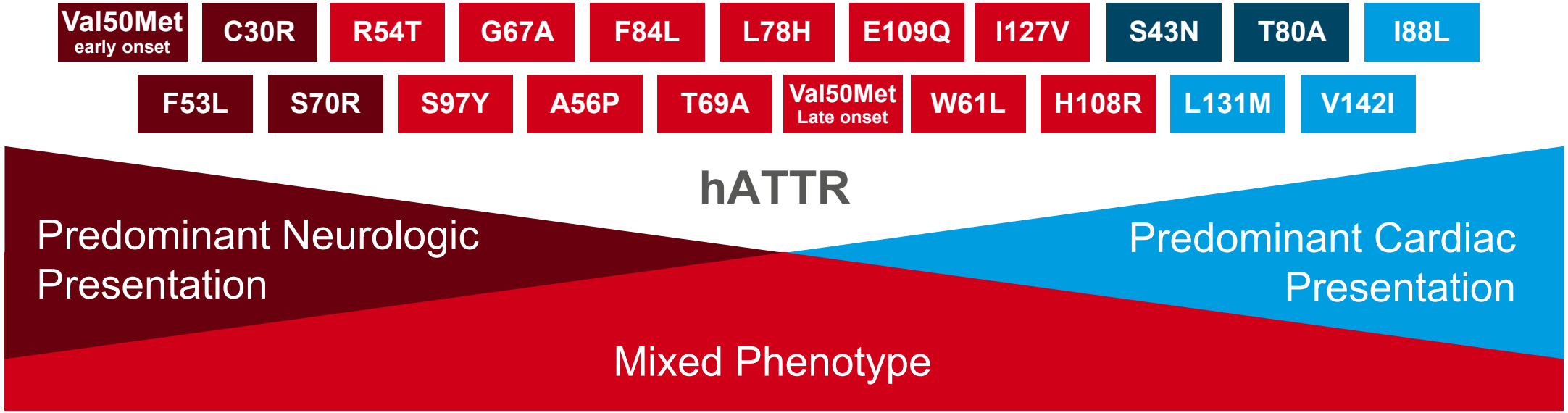
Wild-type

- **Age-related**, no gene mutation, male predominance
- Previously known as senile systemic amyloidosis
- Most common type of ATTR cardiomyopathy

ATTR: transthyretin amyloid.

Rapezzi. *Eur Heart J.* 2013;34(7):520-528.

hATTR Phenotype–Genotype Associations



- More than 130 TTR mutations have been identified
- Transmitted in an autosomal dominant manner with variable penetrance
- Although some genotypes are associated predominantly with polyneuropathy or cardiomyopathy, most patients with hATTR have mixed clinical phenotypes

hATTR: hereditary transthyretin amyloid.

Rowczenio. *Hum Mutat.* 2014;35:E2403; Ando. *Orphanet J Rare Dis.* 2013;8; Coelho. *Curr Med Res Opin.* 2013;29:63; Adams. *Nat Rev Neurol.* 2019;15:387. Figure source: Rapezzi. *Eur Heart J.* 2013;34:520.

hATTR Phenotype–Genotype Associations

Val50Met
early onset

Incidence >1:500 in Portugal, South America
Neuropathy

Irish, Appalachian
Mixed phenotype

T80A

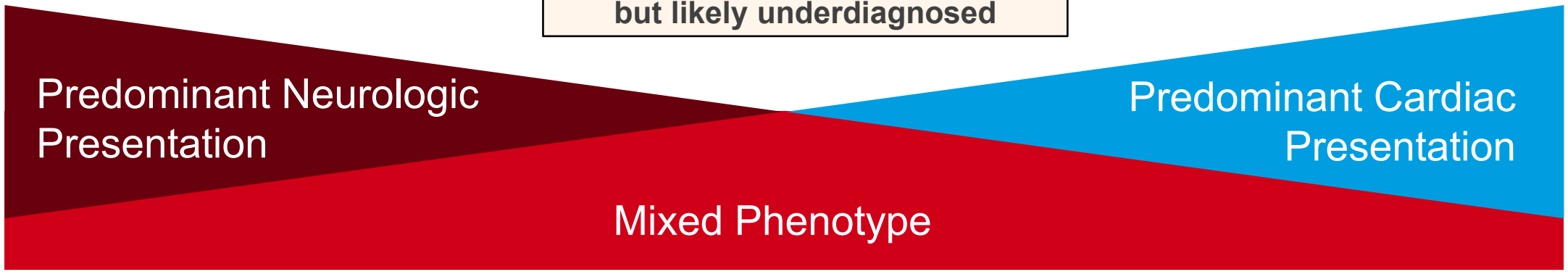
Val50Met
Late onset

Scandinavia, Southeast Asia,
Mixed phenotype

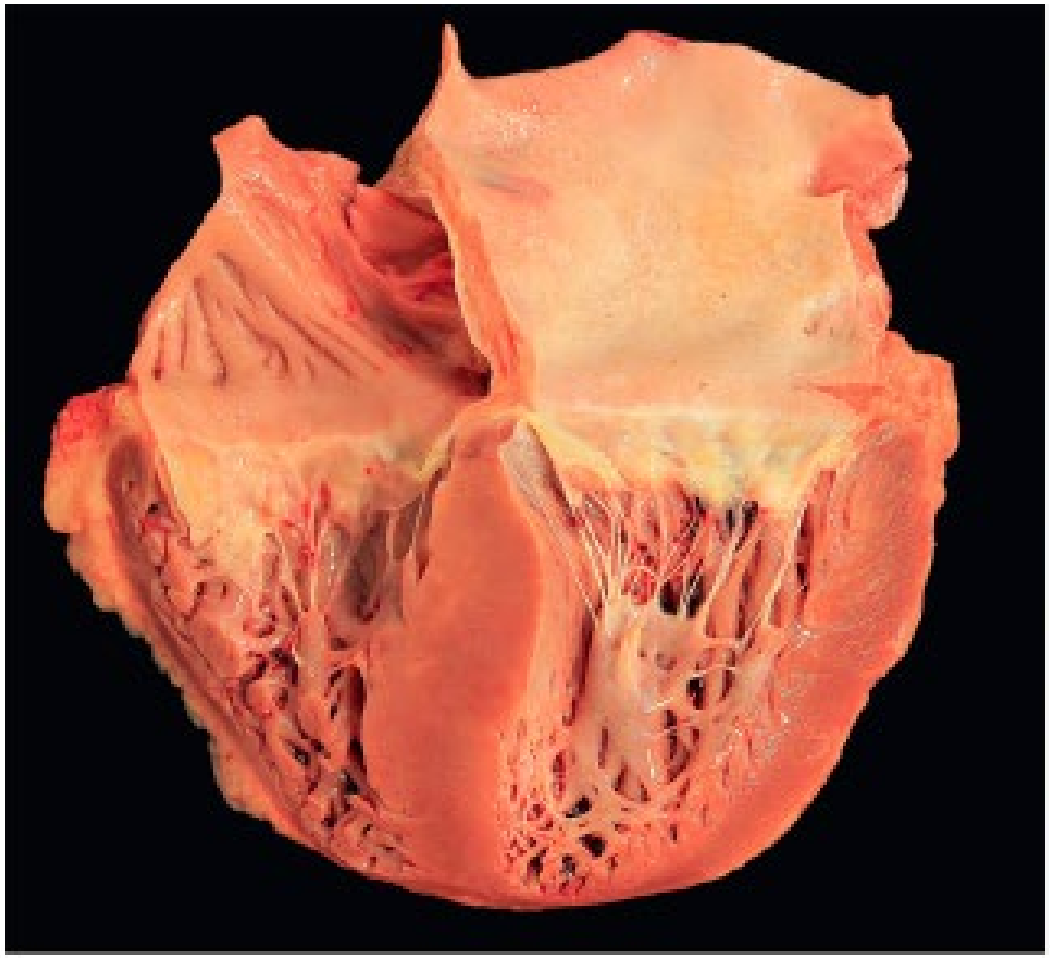
V142I

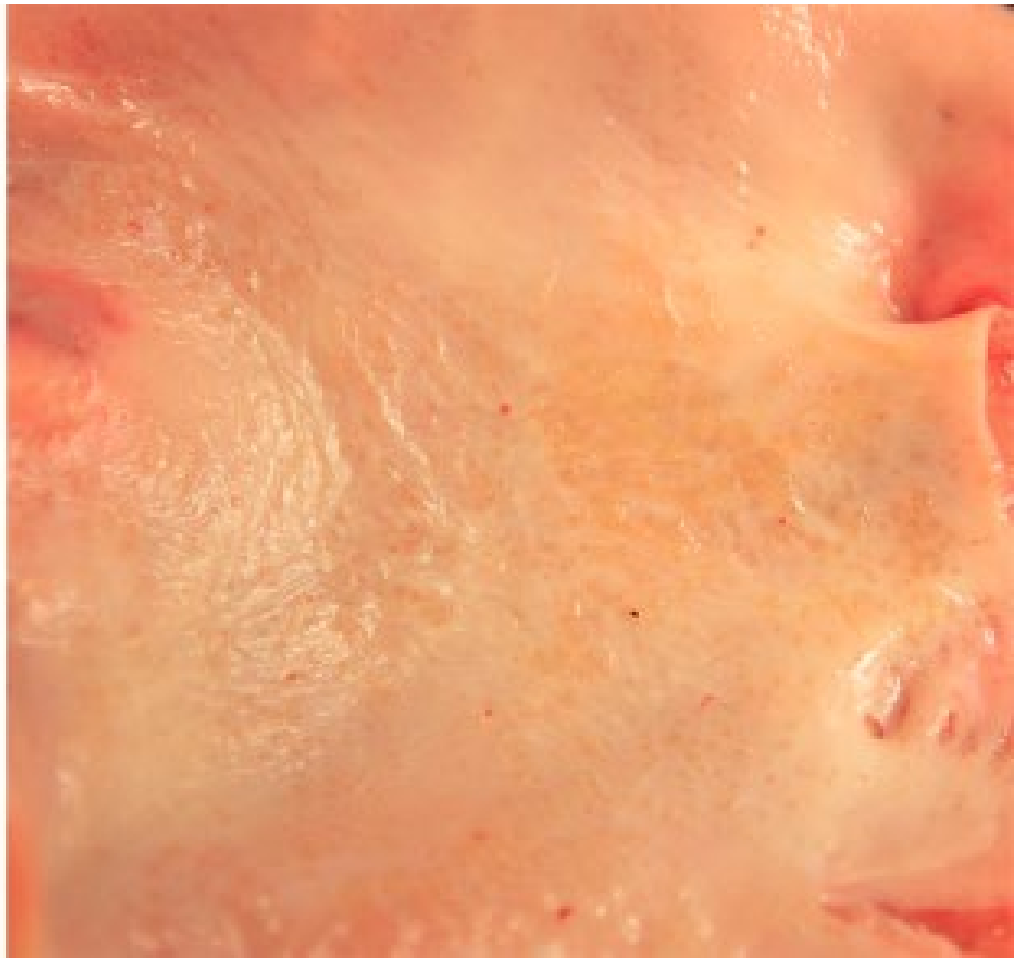
Mutation prevalence 3–4% of African-Caribbeans
Cardiomyopathy

Prevalence of **wild-type** unknown but likely underdiagnosed



Cardiac Amyloidosis



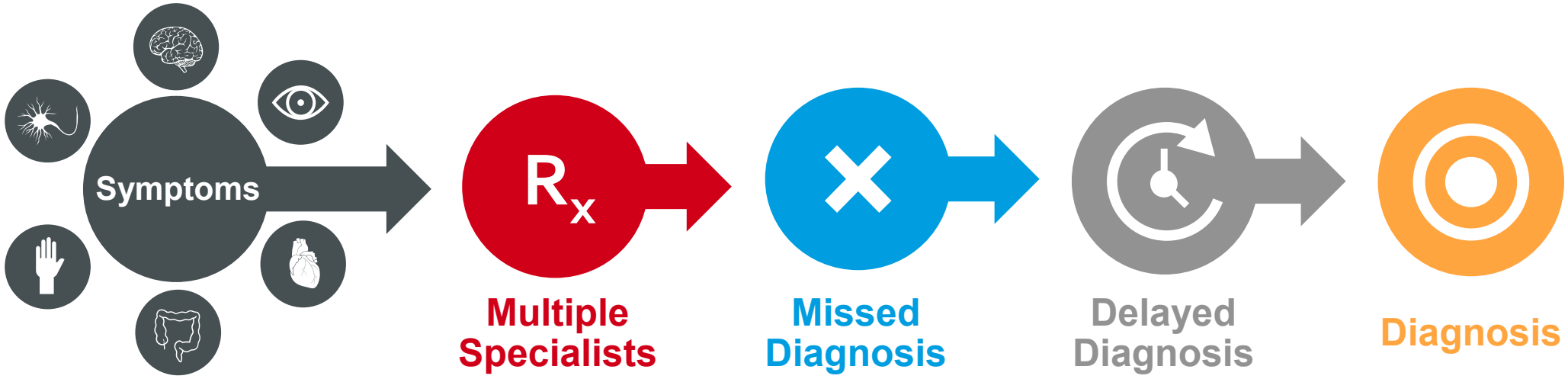


Falk. *JACC* 2016;68:1323.

Difficult Diagnosis→Delayed Diagnosis

- Phenotypic heterogeneity
- Nonspecific signs and symptoms
- Multiple diagnostic tests available
- Many nonspecific findings on testing
- Variable mutation penetrance
  - **Family history often unhelpful**

- Managed by multiple medical subspecialties
- Delay from symptom onset to diagnosis ATTR may be ≥2–10 yrs!
  - Multiple specialist appointments and medical testing
- Requires **high index of suspicion**



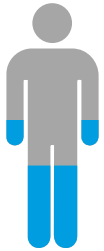
Cardiac Manifestations

- Heart failure – frequently biventricular, variable LVEF
- Atrial fibrillation
- Conduction system disease
- Ventricular arrhythmia – may be asymptomatic
- Aortic stenosis – low-flow low-gradient

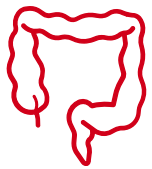
LVEF: left ventricular ejection fraction.
Fine. *Can J Cardiol.* 2020;36(3):322.

ATTR Clinical Manifestations

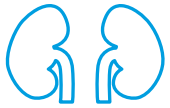
- Look for progressive multisystem involvement, which may include



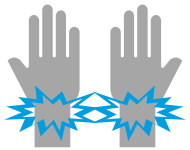
Progressive, symmetric sensorimotor neuropathy



GI complaints
(e.g., chronic diarrhea, constipation or diarrhea, nausea)



Renal abnormalities
(e.g., albuminuria or mild azotemia)



Bilateral carpal tunnel syndrome

Unexplained weight loss

Vitreous opacities

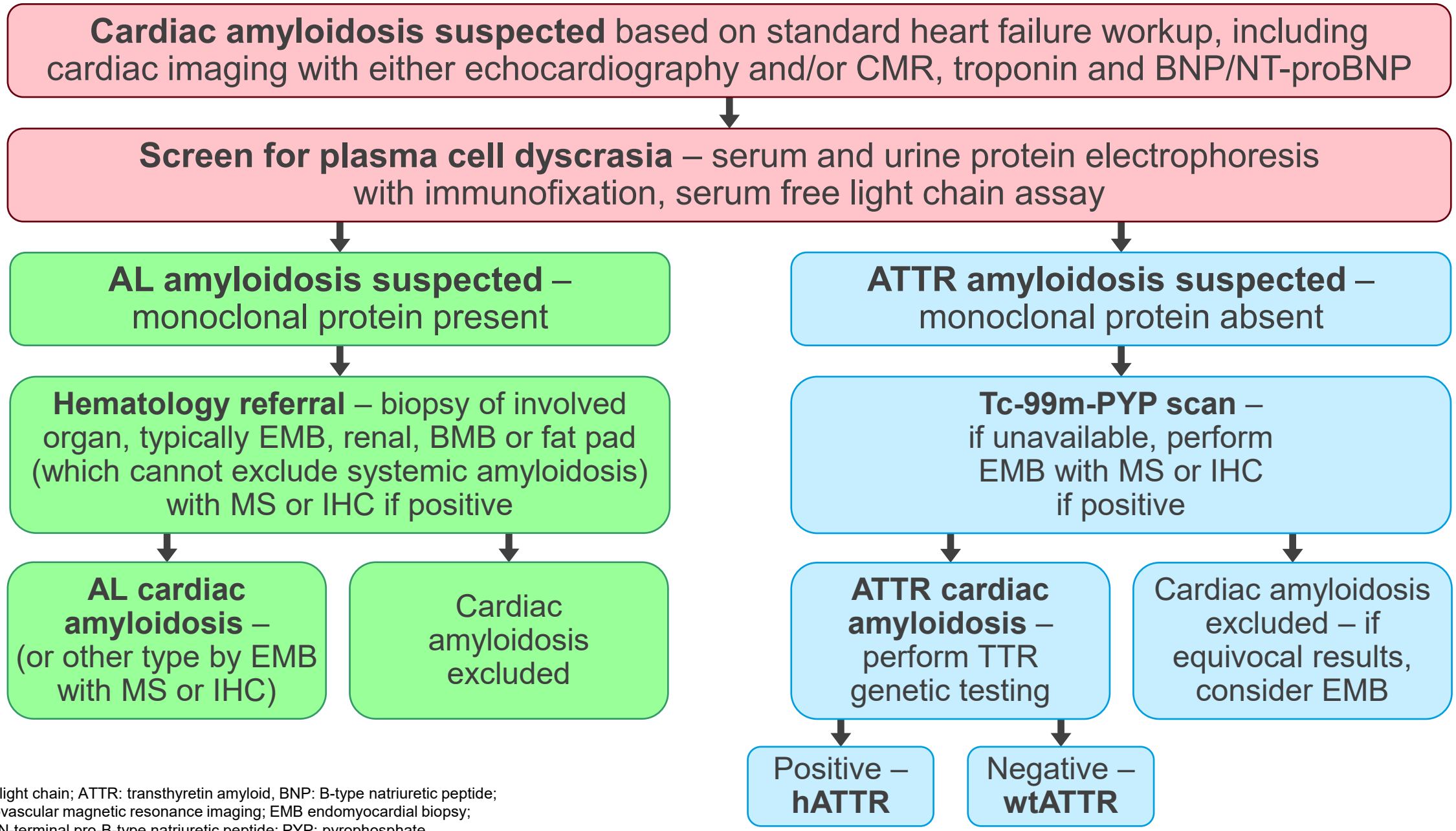
Early autonomic dysfunction
(e.g., erectile dysfunction or postural hypotension)

Cardiac signs & symptoms
(e.g., cardiac hypertrophy, arrhythmias, ventricular blocks, or cardiomyopathy)

Additional alert signs:

- \+ Rapid disease progression
- \+ **Failure of response to therapies**
- \+ Positive family history

ATTR: transthyretin amyloid.



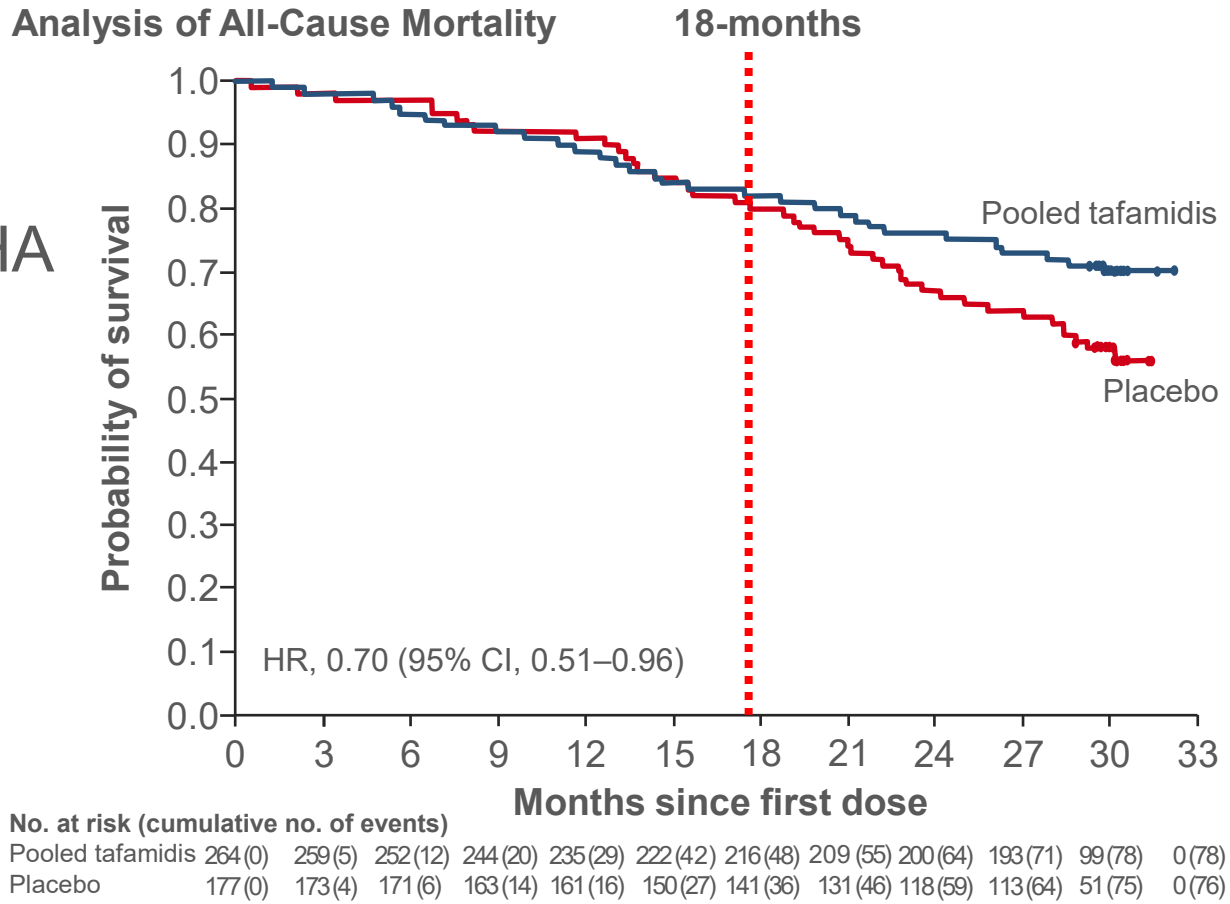
AL: amyloid light chain; ATTR: transthyretin amyloid, BNP: B-type natriuretic peptide; CMR: cardiovascular magnetic resonance imaging; EMB endomyocardial biopsy; NTproBNP: N-terminal pro-B-type natriuretic peptide; PYP: pyrophosphate.

Fine. *Can J Cardiol.* 2020;36(3):322.

Tafamidis

- NYHA class I-III symptoms
- Hereditary and wild-type
- Subgroup analysis suggests benefit greatest for patients with NYHA class I-II
- Once daily oral dosing, well-tolerated

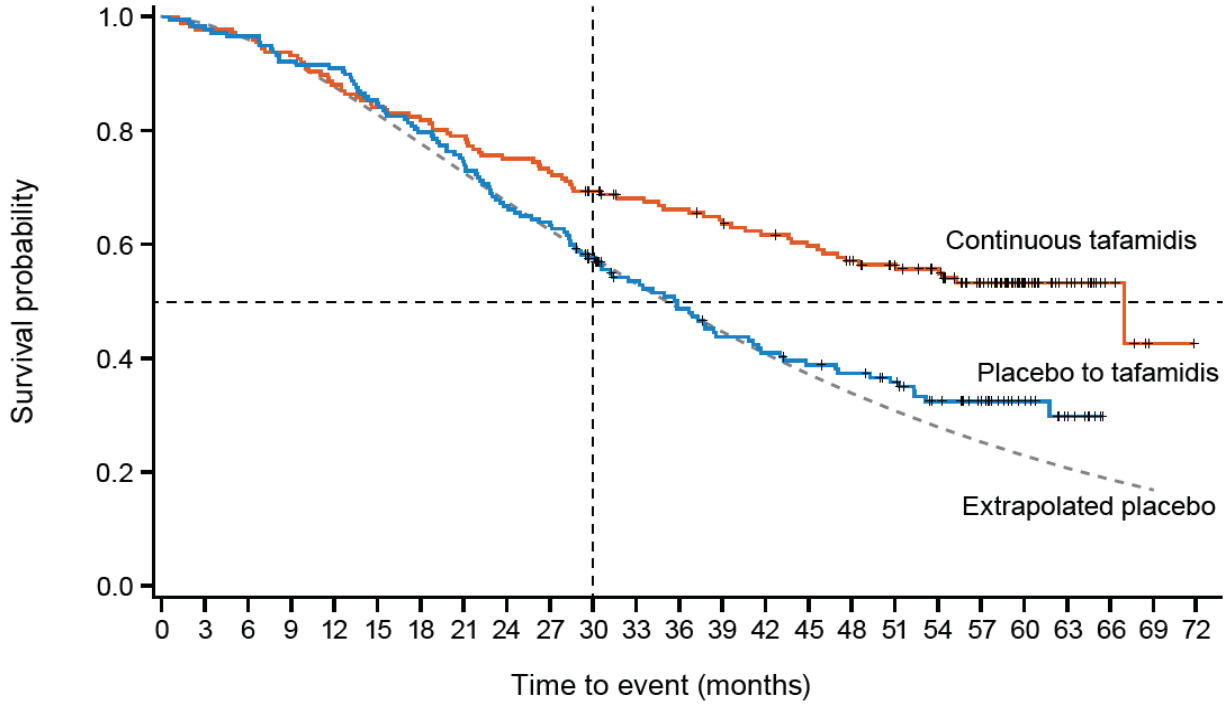
ATTR-ACT Study



NYHA: New York Heart Association.

Maurer. *N Engl J Med.* 2018;379(11):1007.

ATTR-ACT Extension Study



Patients remaining at risk (cumulative events)

Continuous tafamidis	176 (0)	172 (4)	170 (6)	164 (12)	155 (21)	148 (28)	144 (32)	139 (37)	132 (44)	128 (48)	117 (54)	107 (56)	104 (59)	99 (63)	95 (66)	91 (69)	85 (73)	78 (74)	72 (75)	56 (78)	30 (78)	17 (78)	6 (78)	1 (79)	0 (79)
Placebo to tafamidis	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	93 (75)	77 (81)	70 (88)	62 (95)	58 (99)	54 (102)	51 (104)	45 (106)	36 (110)	29 (110)	15 (110)	8 (111)	0 (111)	0 (111)	0 (111)

Median survival:

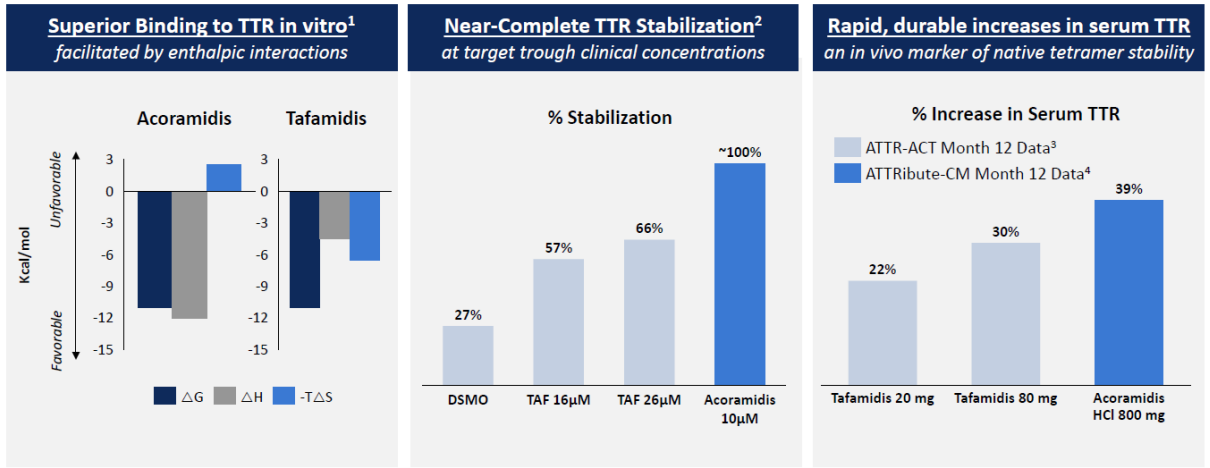
- 'Placebo to tafamidis': 35.8 months
- 'Continuous tafamidis': 67.0 months*
- Extrapolated placebo: 35.2 months

Results

- Survival curves for 'continuous tafamidis' diverged from 'placebo to tafamidis' after ~17 months
- Survival curves for 'placebo to tafamidis' diverged from extrapolated placebo after ~44 months (~14 months after the start of the LTE) in favor of patients treated with 'placebo to tafamidis'

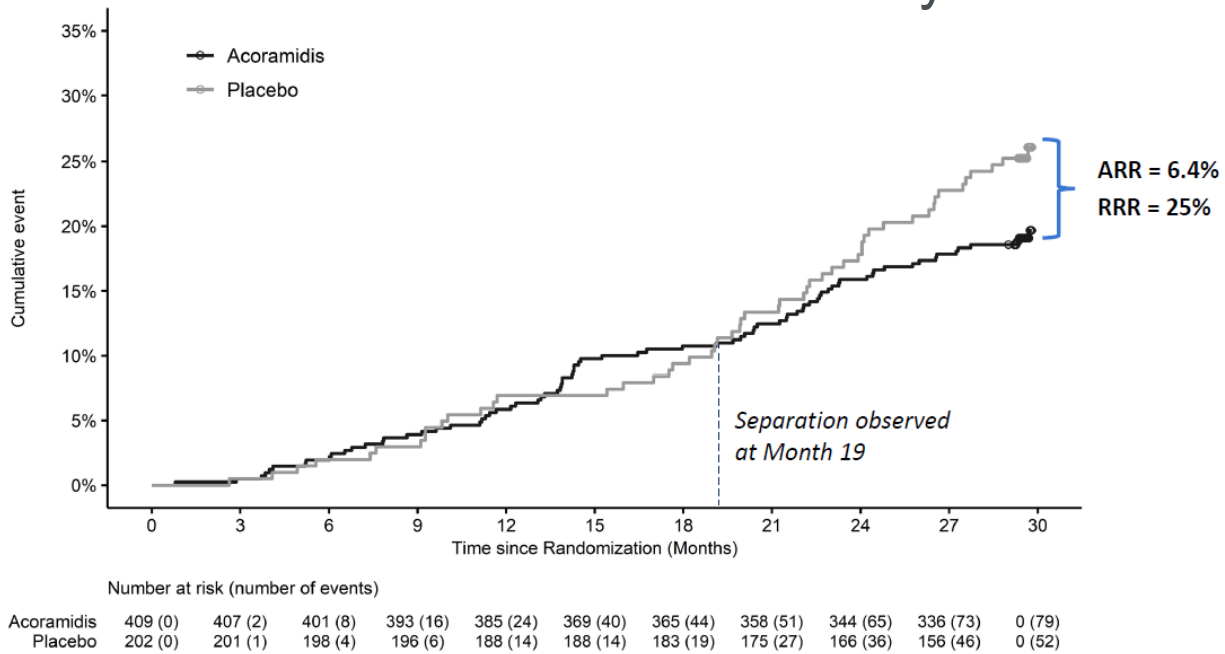
Elliott, et al. *Circ Heart Fail.* 2021.

Acoramidis



[1]Miller, M. et al. J Med Chem. 2018;61:7862-7876. [2]Ji, A.X., et al. American Heart Association Scientific Sessions, 2019. [3]Estimated from Damy, T., et al., Eur J Heart Fail. 2021;23(2):277-285. [4]BridgeBio Part A press release, December 27, 2021.

ATTRibute-CM Study
All-cause mortality



Number at risk (number of events)

Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

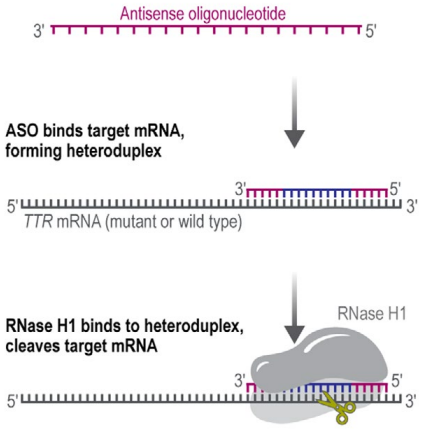
Gillmore et al. *ESC* 2023.

Transthyretin Gene Silencers – hATTR-PN

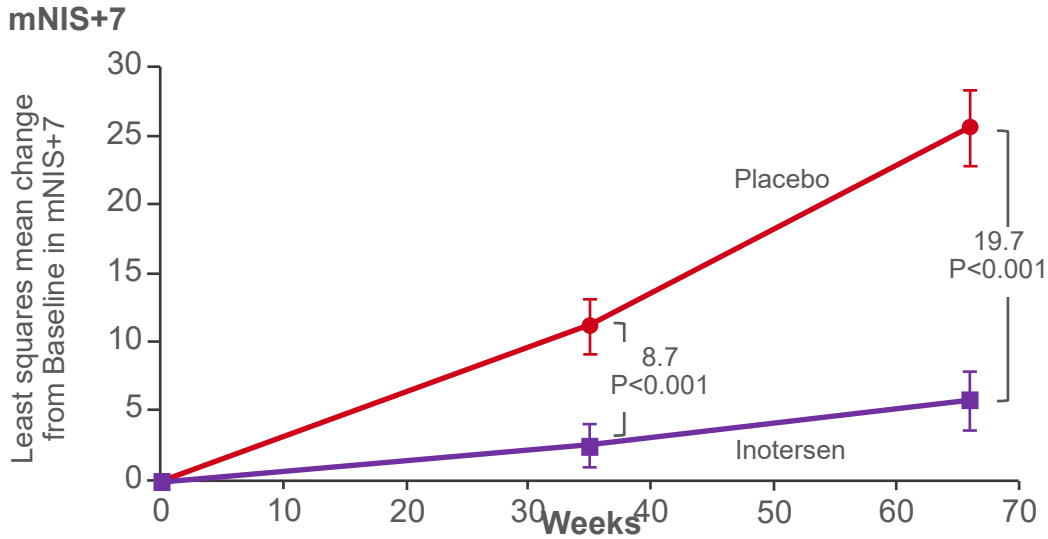
Hepatocyte → ↓ TTR production

Inotersen

- SC Q 1 wk
- Antisense oligonucleotide
- Need to monitor platelets

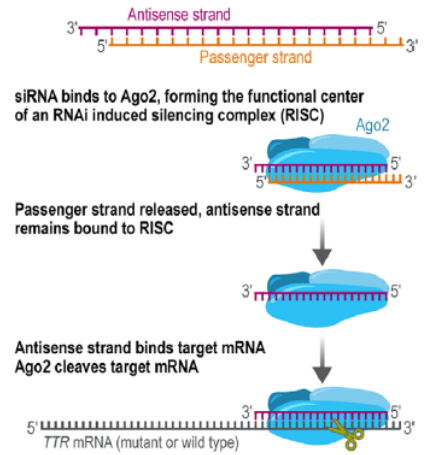


NEURO-TTR

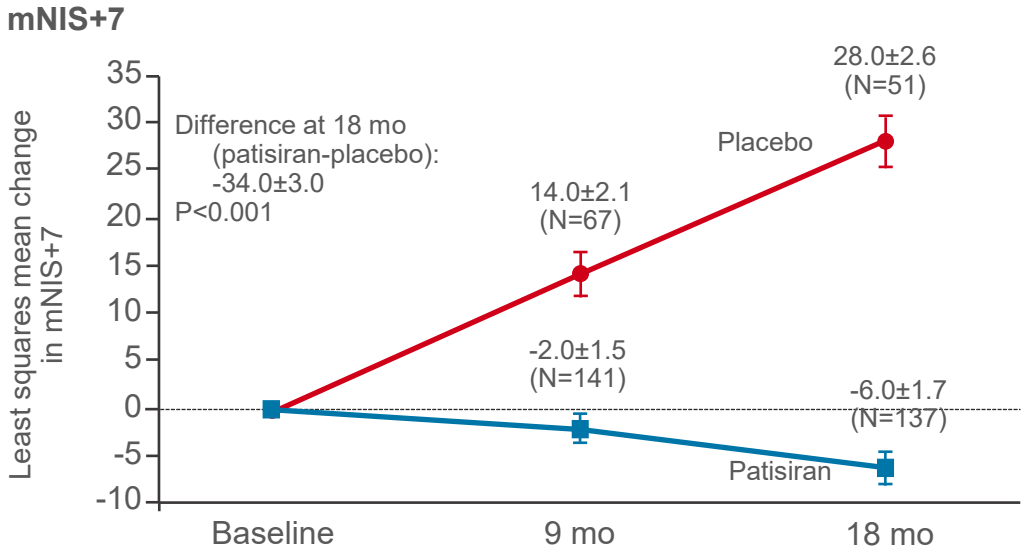


Patisiran

- IV Q 3 wks
- Micro-interfering RNA



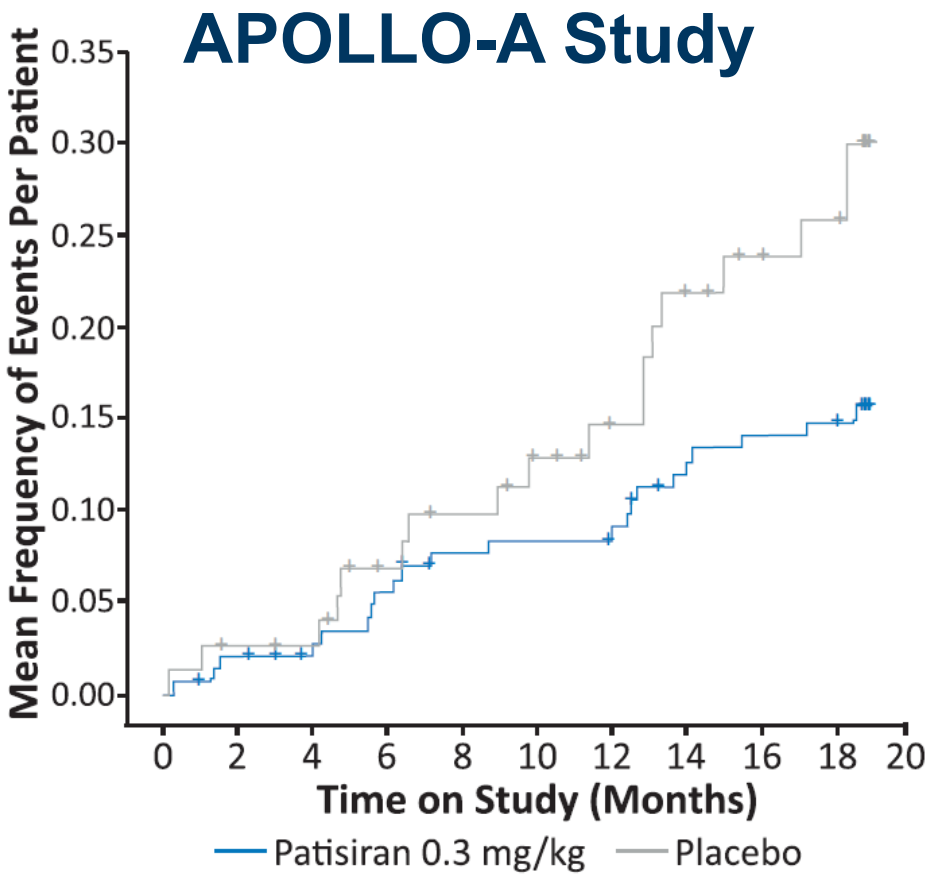
APOLLO-A



hATTR-PN: hereditary transthyretin amyloid-polyneuropathy.

Benson. *N Engl J Med* 2018;379(1):22; Adams. *N Engl J Med* 2018;379(1):11; Branagan. J Peripher *Nerv Syst* 2022;27:228.

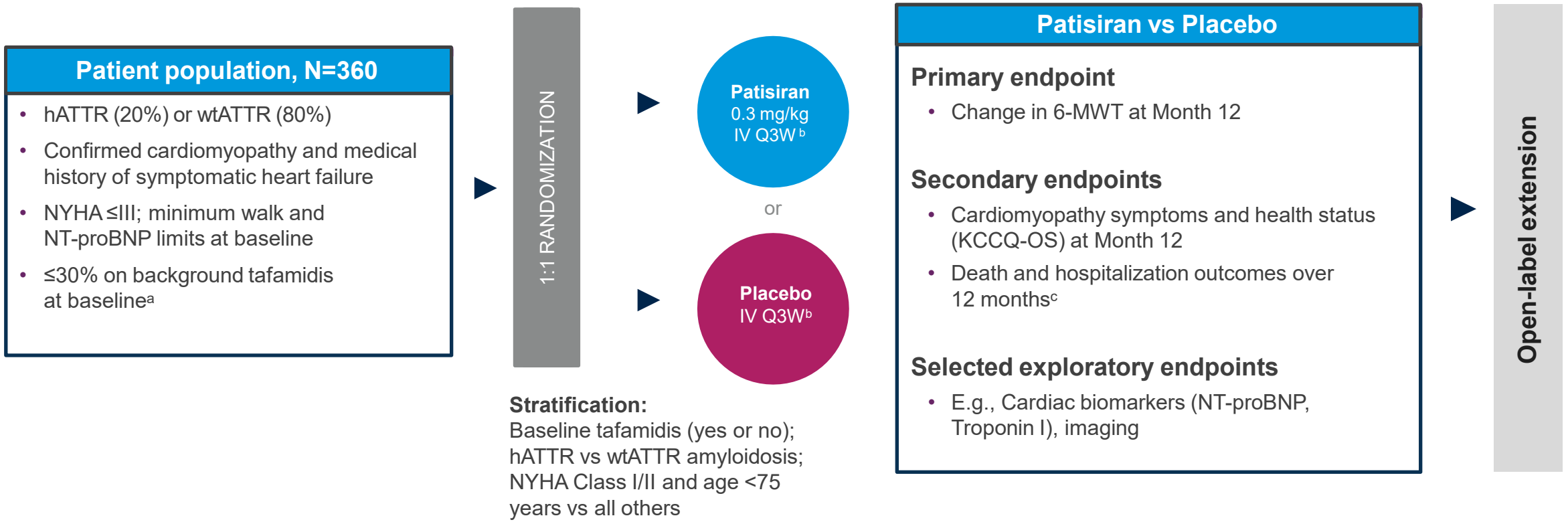
Patisiran CV Outcomes – hATTR-PN



Lower all cause mortality and CV hospitalizations

CV: cardiovascular; hATTR-PN: hereditary transthyretin amyloid-polyneuropathy.
Solomon. *Circulation.* 2019;139:431.

APOLLO-B – RCT Patisiran ATTR-CM

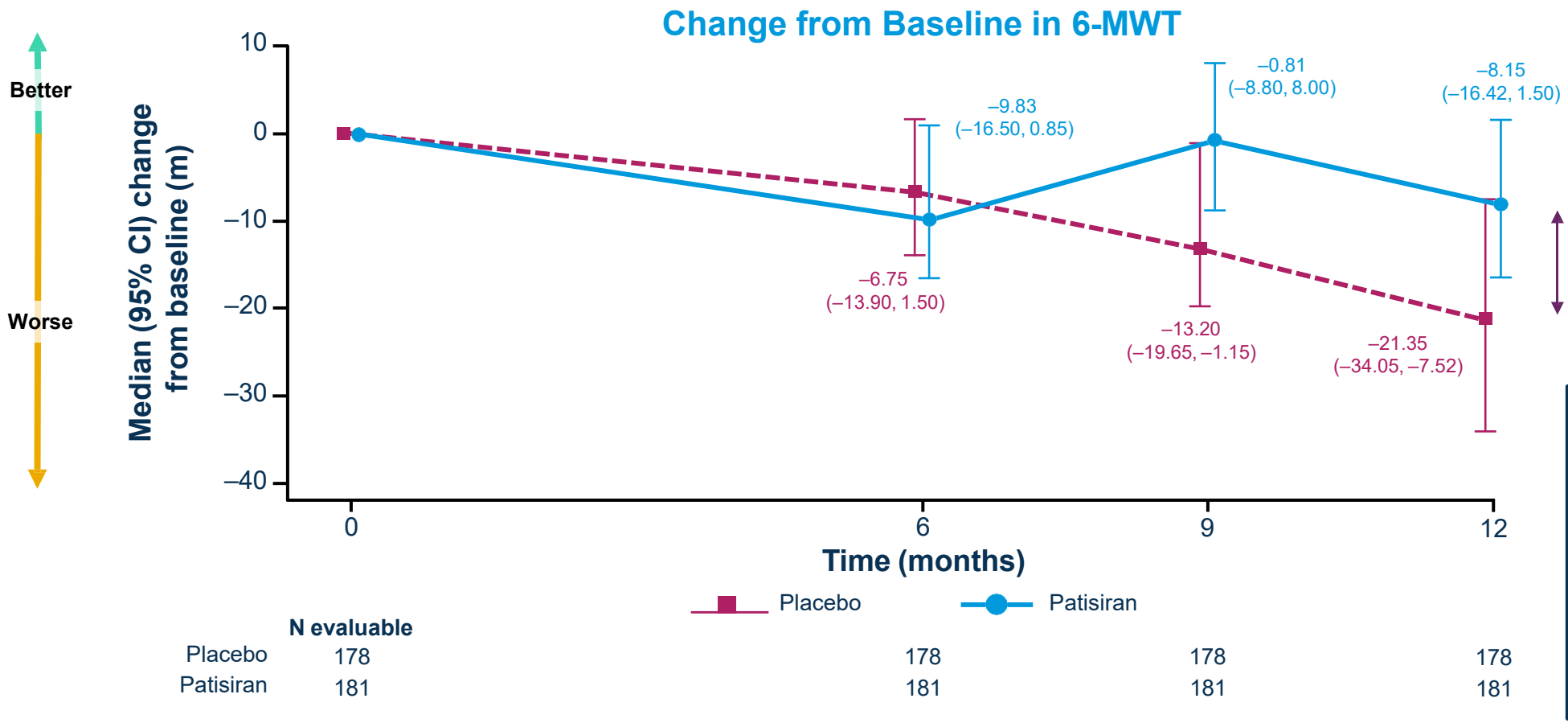


[a]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [b]To reduce likelihood of infusion-related reactions, patients receive following premedications or equivalent at least 60 min. before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. [c]Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population. ATTR-CM: transthyretin amyloid cardiomyopathy; h; hereditary; KKCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score. wt: wild-type; 6-MWT: 6-minute walk test.

Courtesy of Alnylam-ISA 2022

Patisiran for ATTR-CM

APOLLO-B Study



HL estimate of median difference (95% CI): **14.693** (0.693, 28.692) **p=0.0162**

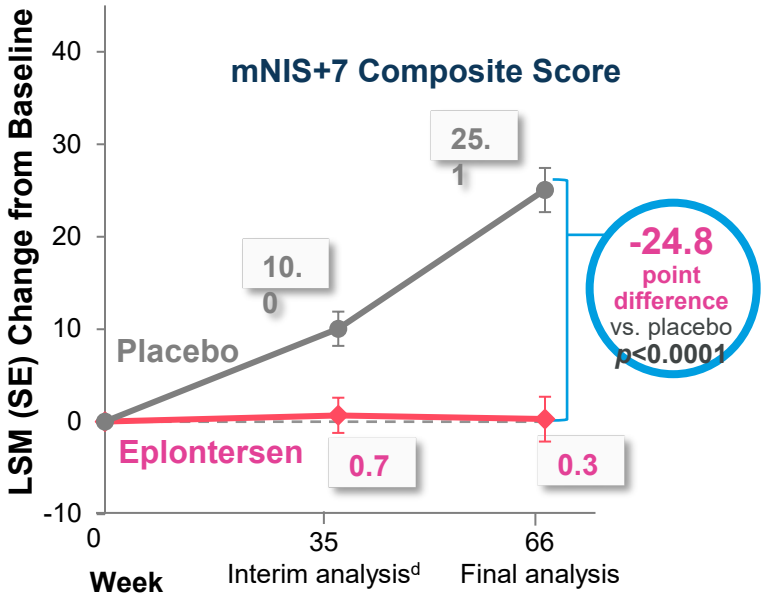
Patient pop, N=360

- hATTR (20%) or wtATTR (80%)
- Symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline
- ≤30% on background tafamidis at baseline

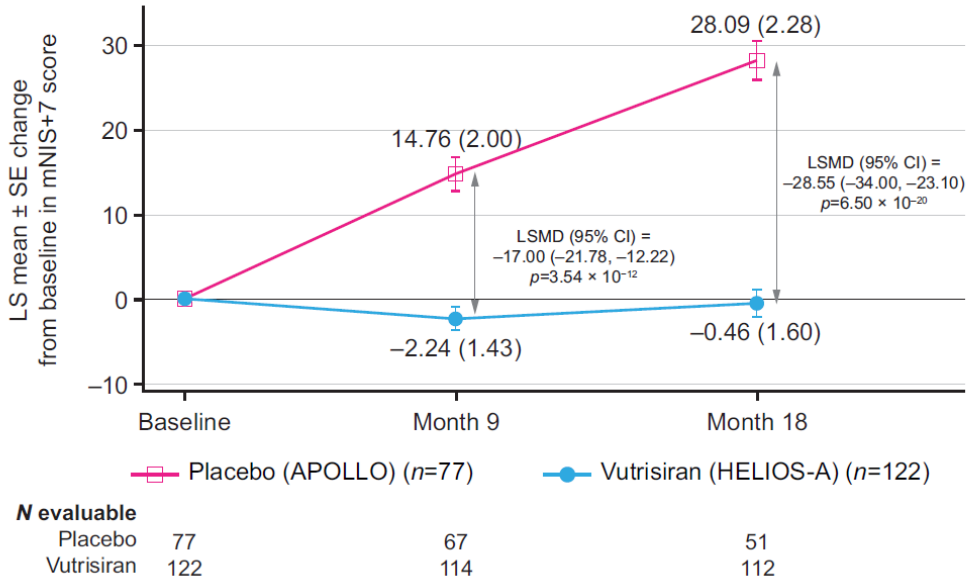
6-MWT: 6-minute walk test.
Courtesy of Alnylam-ISA 2022

Next Generation TTR Gene Silencers

Eplontersen



Vutrisiran



NeuroTTRansform Study

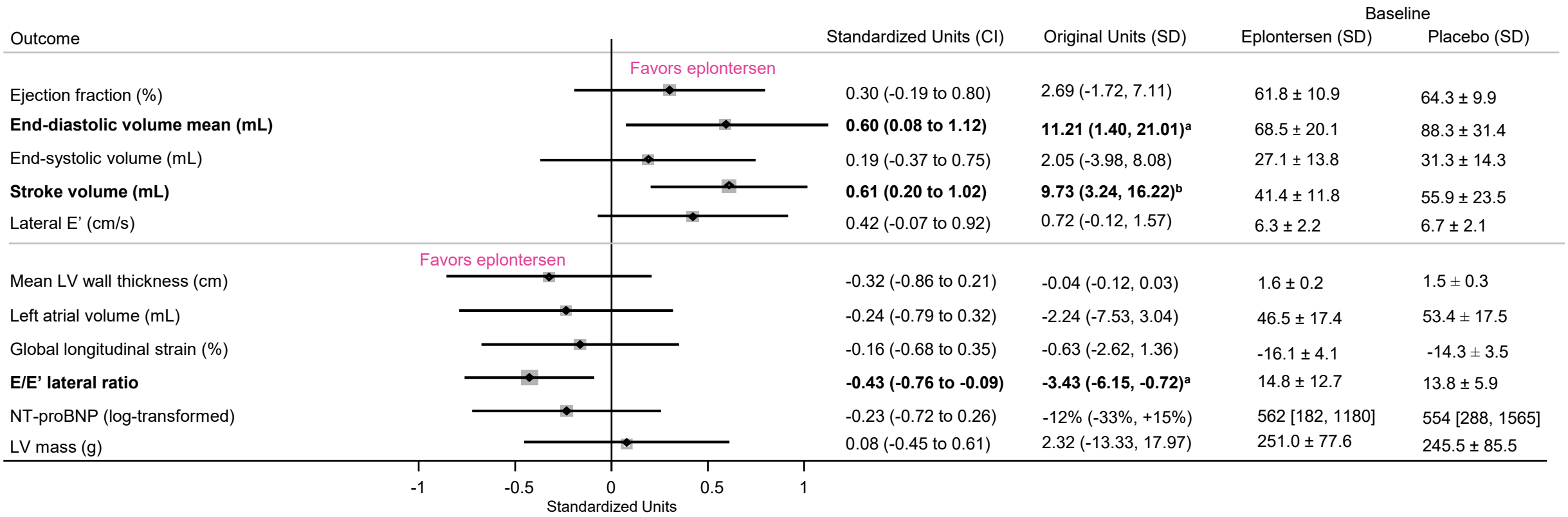
- SC Q monthly dosing, no safety concerns
- **CardioTTRansform Study ATTR-CM - ongoing**

Helios-A Study

- IV Q 3 monthly dosing, no safety concerns
- **Helios-B Study ATTR-CM - ongoing**

ATTR-CM: transthyretin amyloid cardiomyopathy; SC: subcutaneous; TTR: transthyretin.
Courtesy of AstraZeneca 2023; Adams. Amyloid Mar 2022;1:1.

Eplontersen - Cardiac Outcomes



Outcome	Standardized Units (CI)	Original Units (SD)	Baseline Eplontersen (SD)	Baseline Placebo (SD)
Ejection fraction (%)	0.30 (-0.19 to 0.80)	2.69 (-1.72, 7.11)	61.8 ± 10.9	64.3 ± 9.9
End-diastolic volume mean (mL)	**0.60 (0.08 to 1.12)**	**11.21 (1.40, 21.01)[a]**	68.5 ± 20.1	88.3 ± 31.4
End-systolic volume (mL)	0.19 (-0.37 to 0.75)	2.05 (-3.98, 8.08)	27.1 ± 13.8	31.3 ± 14.3
Stroke volume (mL)	**0.61 (0.20 to 1.02)**	**9.73 (3.24, 16.22)[b]**	41.4 ± 11.8	55.9 ± 23.5
Lateral E' (cm/s)	0.42 (-0.07 to 0.92)	0.72 (-0.12, 1.57)	6.3 ± 2.2	6.7 ± 2.1
Mean LV wall thickness (cm)	-0.32 (-0.86 to 0.21)	-0.04 (-0.12, 0.03)	1.6 ± 0.2	1.5 ± 0.3
Left atrial volume (mL)	-0.24 (-0.79 to 0.32)	-2.24 (-7.53, 3.04)	46.5 ± 17.4	53.4 ± 17.5
Global longitudinal strain (%)	-0.16 (-0.68 to 0.35)	-0.63 (-2.62, 1.36)	-16.1 ± 4.1	-14.3 ± 3.5
E/E' lateral ratio	**-0.43 (-0.76 to -0.09)**	**-3.43 (-6.15, -0.72)[a]**	14.8 ± 12.7	13.8 ± 5.9
NT-proBNP (log-transformed)	-0.23 (-0.72 to 0.26)	-12% (-33%, +15%)	562 [182, 1180]	554 [288, 1565]
LV mass (g)	0.08 (-0.45 to 0.61)	2.32 (-13.33, 17.97)	251.0 ± 77.6	245.5 ± 85.5

Placebo-adjusted effect of eplontersen on cardiac structure and function in the cardiomyopathy group

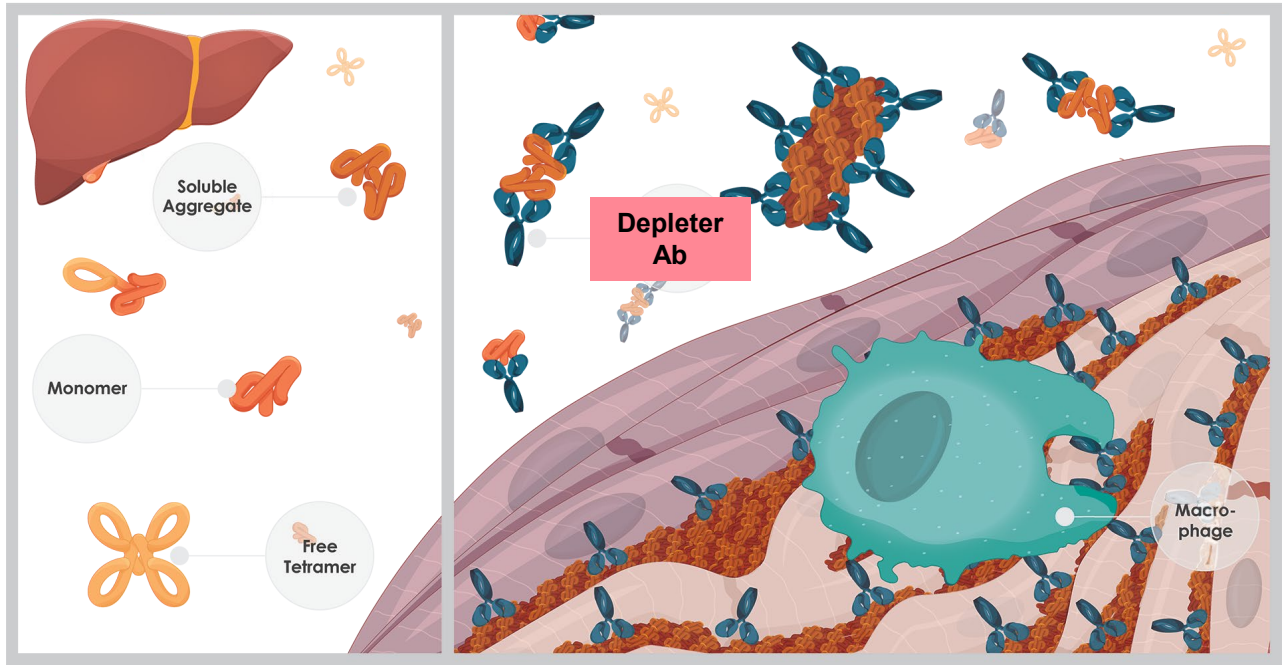
Note: For each outcome, the changes from baseline were standardized using a mean of 0 and a standard deviation of 1. Cardiomyopathy group includes patients with 1) a clinical diagnosis of ATTRv-CM on their CRF (ie, the CM baseline diagnosis-only subgroup), or 2) interventricular septum thickness ≥13 mm on baseline ECHO plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of ≥150 mm Hg at any time during the trial (including screening and baseline visits).

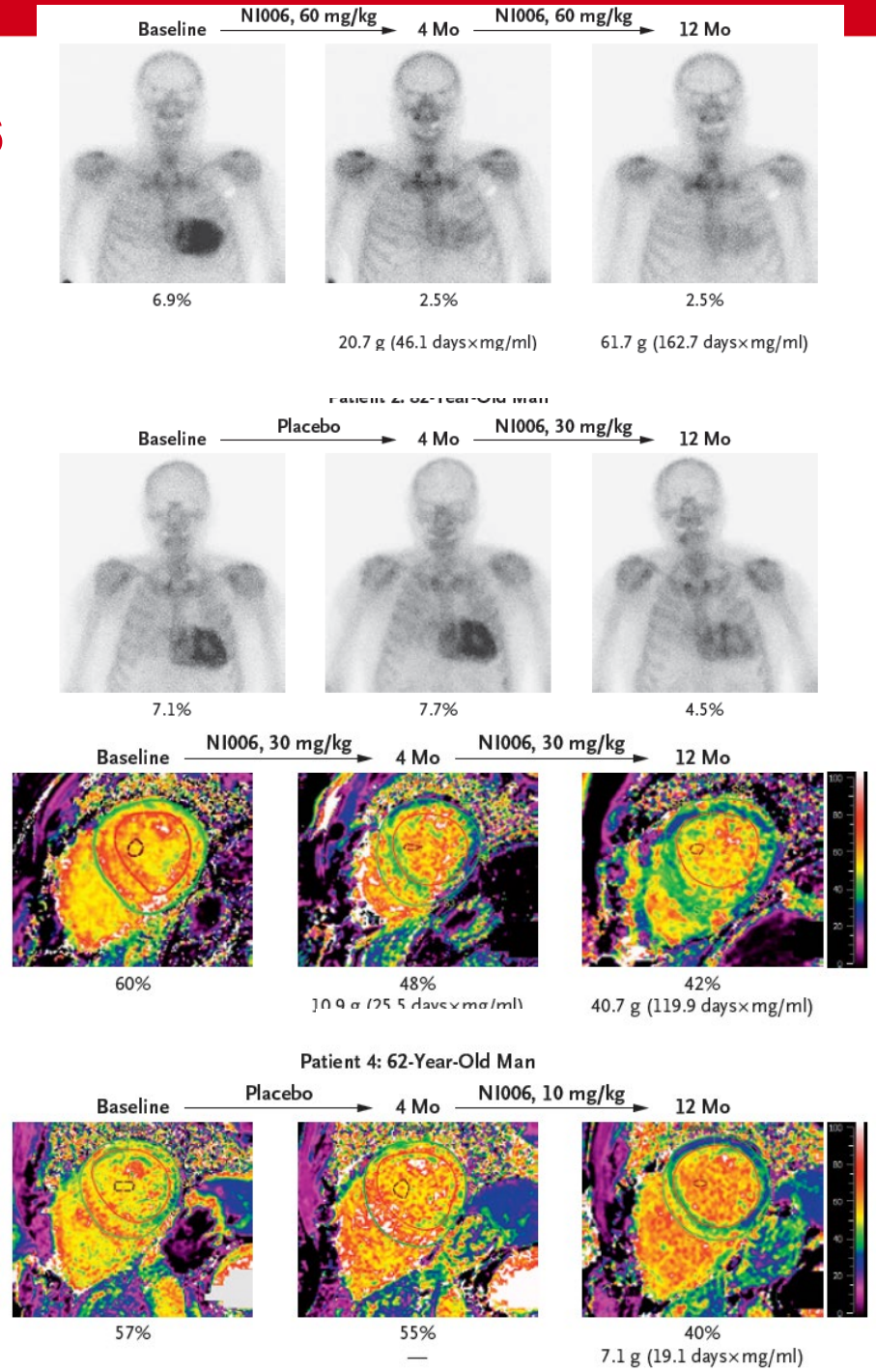
[a]nominal p=0.05; [b]nominal p=0.01.

Masri A et al. Presented at: HFSA Annual Scientific Meeting 2023; October 6-9, 2023; Cleveland, Ohio.

Depleters

NI006





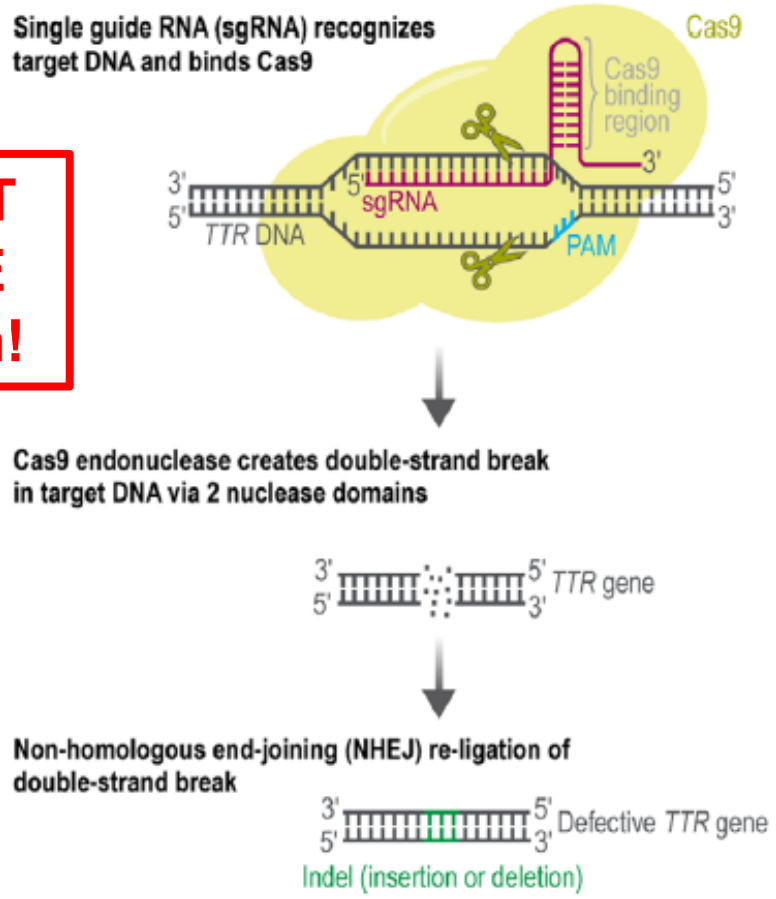
- Binds to amyloid but not normal TTR, induces Ab-mediated phagocytosis
- **Two agents in development, phase III RCTs in the works**

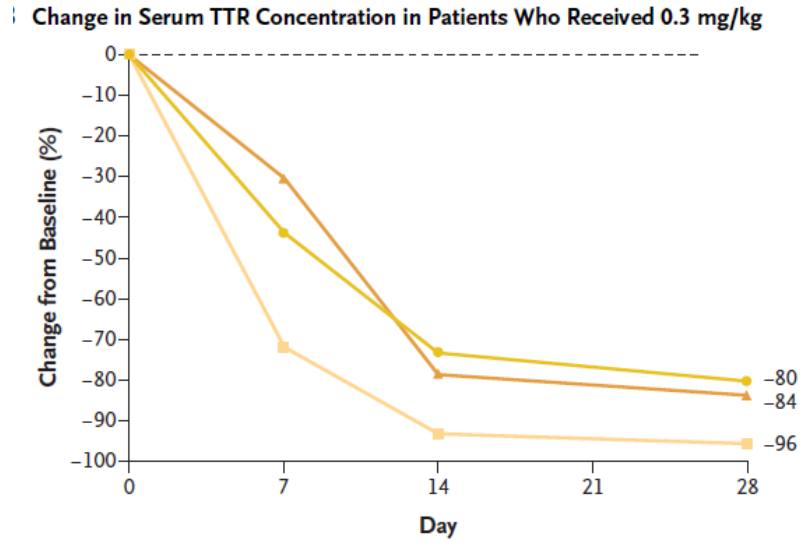
RCT: randomized controlled trial; TTR: transthyretin.
www.prothenca.com; Garcia-Pavia. *NEJM* 2023.

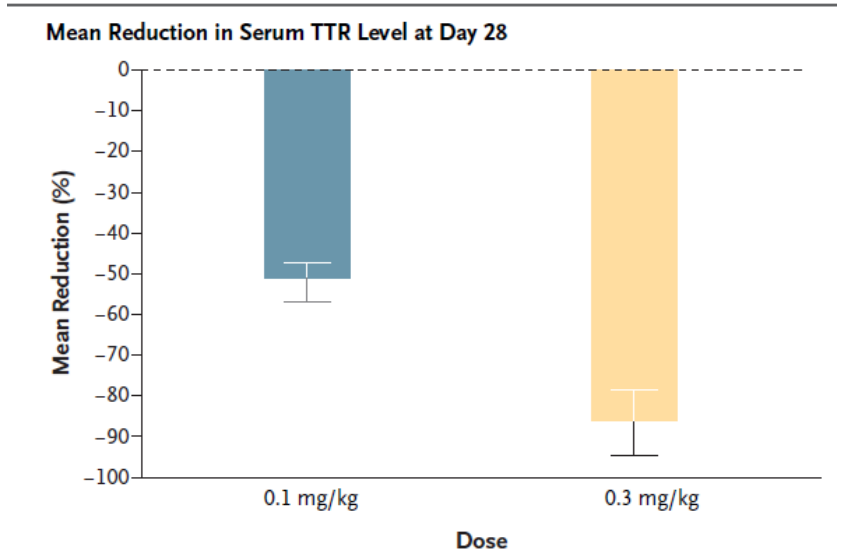
CRISPR-Cas9 – TTR Gene Editing

NTLA-2001 – one time infusion!

Phase III RCT MAGNITUDE starting soon!





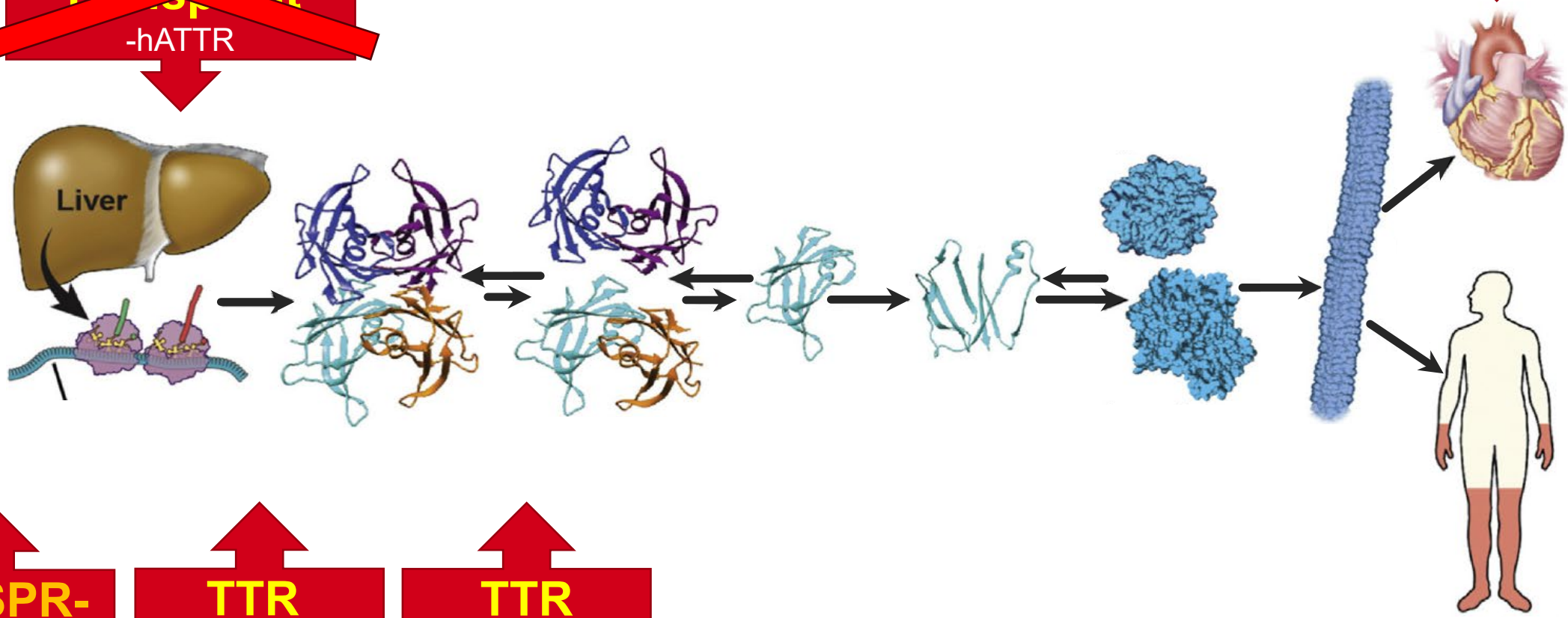


Clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease

Branagan. *J Peripher Nerv Syst.* 2022;27:228.
Gillmore. *NEJM.* 2021;385(6):493.

Liver Transplant
-hATTR

Depleters
-ATTR-CM



CRISPR-Cas9
-ATTR-CM

TTR Silencers
-hATTR-PN
-ATTR-CM

TTR Stabilizers
-Multiple
-ATTR-CM

Control symptoms

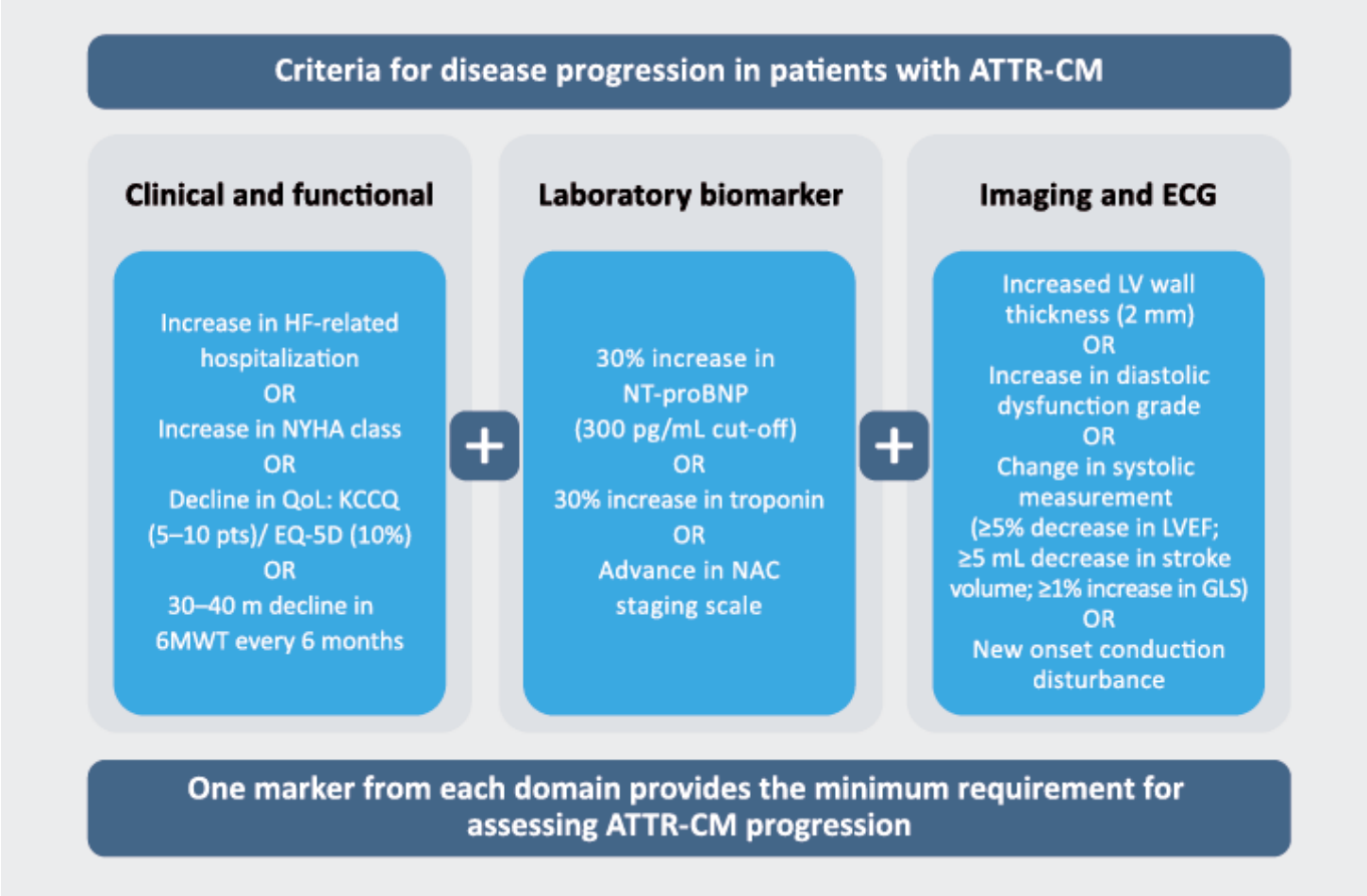
Disease Monitoring and Progression

Every 6 months

- ECG
- Blood tests including NT-proBNP and troponin
- Neurological evaluation (if ATTRv)
- 6MWD (optional)
- KCCQ (optional)

Every 12 months

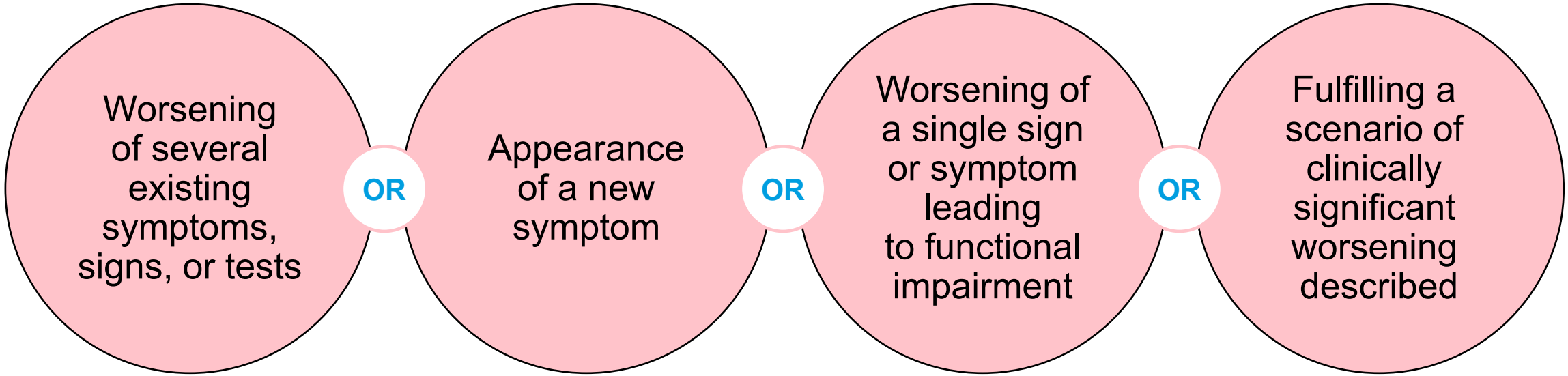
- Echocardiography/CMR
- 24-h Holter ECG
- Ophthalmological evaluation (if ATTRv)



CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; KKCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NTproBNP: N-terminal pro-B-type natriuretic peptide; 6-MWT: 6-minute walk test.
Garcia-Pavia et al. *Eur Hrt J*. 2021. Garcia-Pavia et al. *Eur J Hrt Fail*. 2021.

ATTR Disease Progression

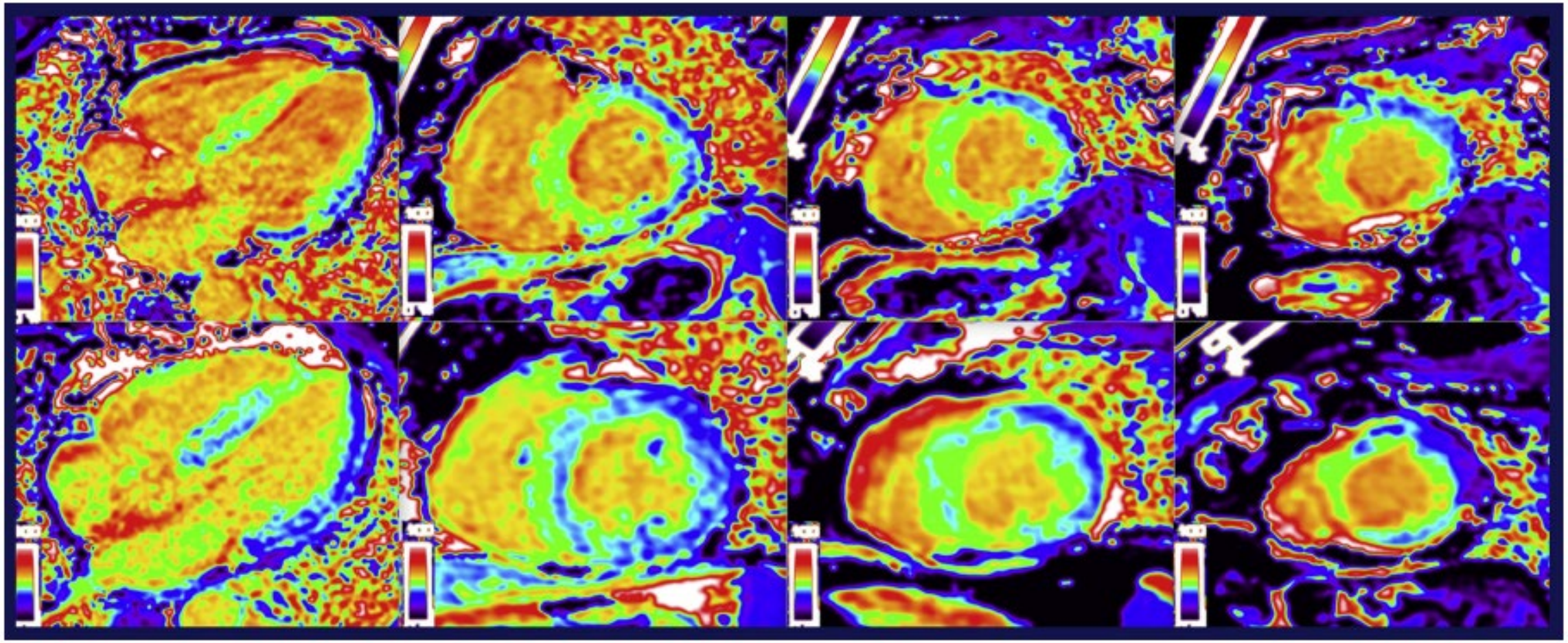
Progression in ATTR amyloidosis may be indicated by



Adams. Orphanet *J Rare Dis.* 2021;16:411.

Cardiac MRI – Extracellular Volume

Improvement on Patisiran at 12-months

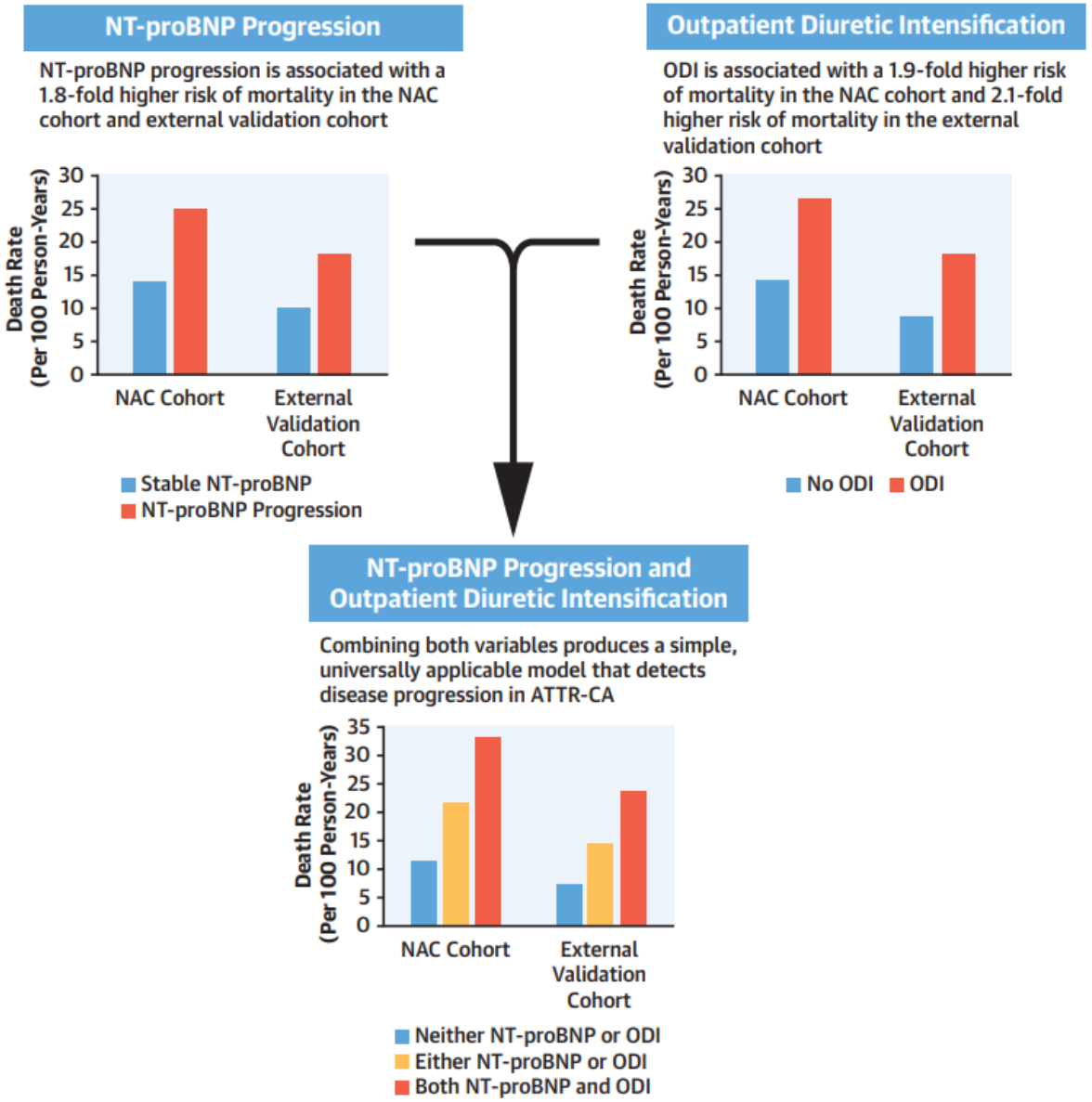


Fontana. *JACC Img.* 2021;14:189.

Disease Progression

NTproBNP

- ↑>700, AND
- ↑>30%



Loop diuretic

- Any dose↑, OR
- Initiation

Ioannou. JACC 2024;83(14):1276

Summary

- Cardiac amyloidosis diagnostic approach (algorithm) has remained similar over the last few years
- Tafamidis remains the only medication approved for ATTR-CM
  - 1st generation silencers inotersen and patisiran for ATTRh-PN
  - 2nd generation silencers eplontersen and vutrisiran for ATTRh-PN, with ATTR-CM studies ongoing
- New treatment classes in development – depleters, CRISP-Cas9
- NTproBNP and diuretic intensification novel approach to defining disease progression

Amyloidosis Update

- Thank you!
- Question / comments?
- nmfine@ucalgary.ca

Q&A Period

THANK YOU!

Please remember to complete the session evaluation

Next Up! Please make your way down to the *Exhibit Hall (Samuel ABC) for a Health Break* and then proceed to the *Champlain Ballroom for Plenary 2 Clinical Pearls and Conundrums in HF Clinical Care* beginning at 3:00 pm.