# Amiloidosi cardiaca da transtiretina: terapia ottimale e prospettive future

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# INTRODUZIONE

- ✓ Le amiloidosi sono un gruppo di malattie rare, caratterizzate dall'accumulo extracellulare di sostanza amiloide all'interno di diversi organi e tessuti.

- ✓ Questo materiale insolubile si presenta sotto forma di piccole fibrille (circa 10 nm di diametro) ed è composto da proteine mal ripiegate che si aggregano in maniera anomala e si accumulano in tessuti e organi.

- ✓ Esistono diverse forme di amiloidosi, ognuna delle quali è dovuta ad una specifica proteina difettosa.

- ✓ La **transtiretina** (TTR) è una proteina di 55 kDa prodotta principalmente dagli epatociti nel fegato e dal plesso coroideo e dall'epitelio retinico. La principale funzione fisiologica della TTR è il trasporto di tiroxina (T4) e retinolo legati alla proteina legante il retinolo (RBP). La TTR ha una struttura tetramerica composta da quattro subunità identiche ricche di foglietti β con due siti di legame per T4 e quattro siti di legame per RBP.

- ✓ Nell' aATTR i tetrameri della TTR sono destabilizzati, sia a causa di cambiamenti strutturali derivanti da mutazioni genetiche (nell'ATTRv) sia a causa di fattori legati all'età ancora sconosciuti (nell'amiloidosi ATTRwt). I monomeri di TTR risultanti tendono a ripiegarsi in modo anomalo e ad aggregarsi in fibrille amiloide insolubili. Questi depositi di fibrille si accumulano nello spazio extracellulare di vari tessuti e organi, più comunemente cuore, sistema nervoso periferico, reni, sistema GE e occhi.



G Ital Cardiol 2023;24(2):127-135
J. Clin. Med. 2025, 14, 4785

# La terapia ottimale dell'amiloidosi cardiaca TTR si basa su tre cardini:

1. Diagnosi precoce

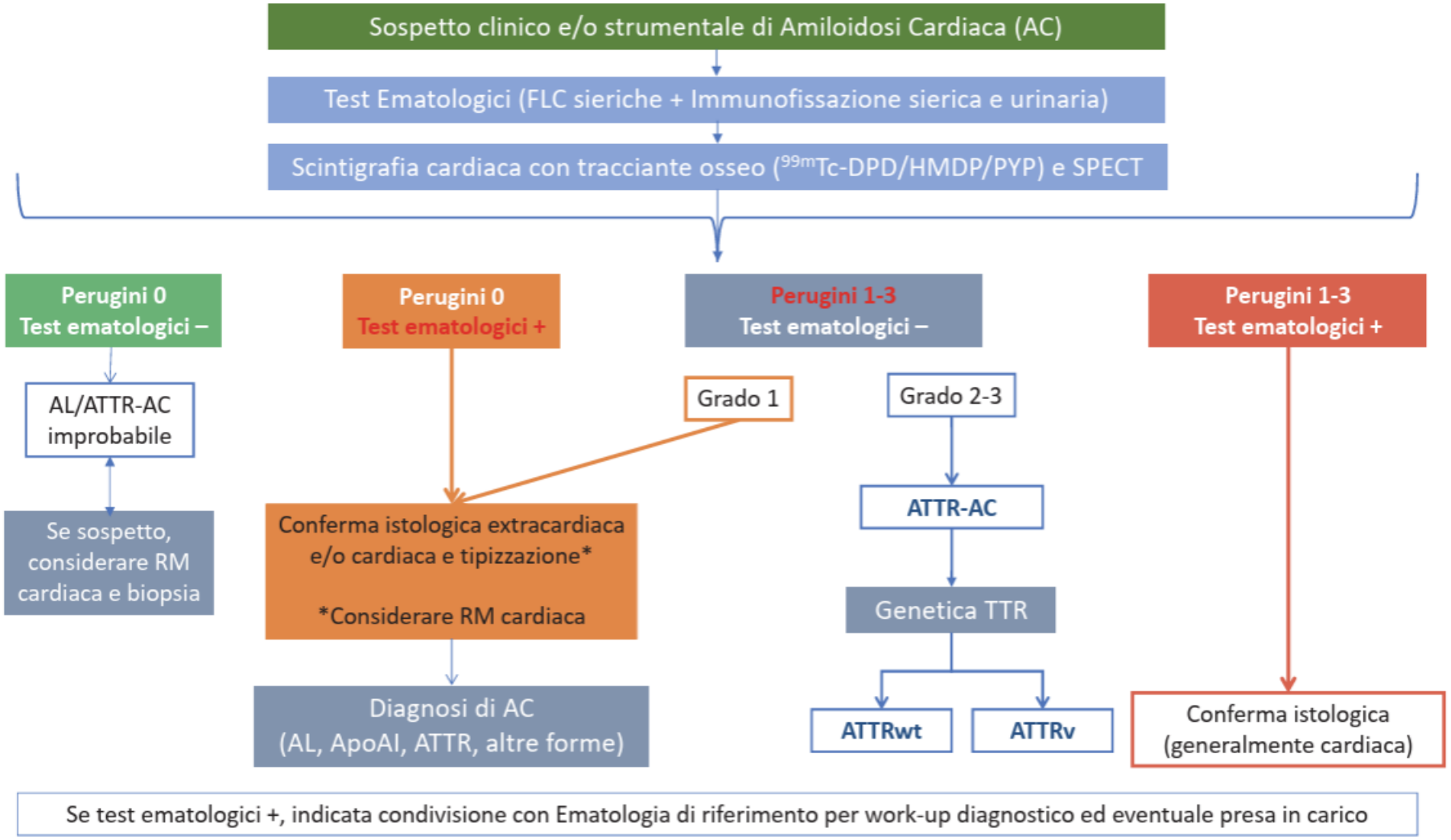
2. Il trattamento e la prevenzione delle comorbilità e delle complicanze

3. TERAPIE ‘’DISEASE-MODIFYNG‘’



G Ital Cardiol 2023;24(2):127-135
J. Clin. Med. 2025, 14, 4785

# 1. Diagnosi precoce

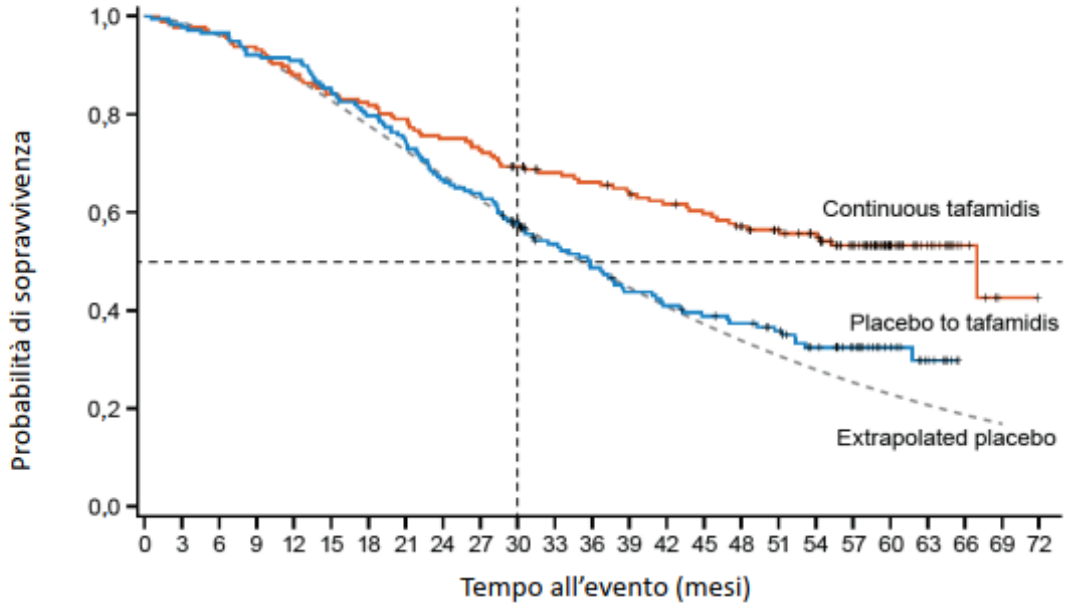





G Ital Cardiol 2024;25(12):900-920

# Diagnosi precoce >> trattamento precoce >> trattamento efficace

## Curva di sopravvivenza Kaplan-Meier per mortalità da tutte le cause negli studi ATTR-ACT e LTE rispetto a un'estrapolazione basata su un modello di sopravvivenza con placebo[15]




Pazienti a rischio
(eventi cumulativi)

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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) |

Modificato da Fig. 2 Rif. 15

Continuous tafamidis: pazienti in trattamento con tafamidis nello studio ATTR-ACT e nello studio di estensione[15]

Placebo to tafamidis: pazienti nel gruppo controllo che hanno assunto placebo nello studio ATTR-ACT e sono stati sottoposti allo *switch* a tafamidis nello studio di estensione[15]

Extrapolated placebo: estrapolazione basata su un modello di sopravvivenza in pazienti trattati con placebo nello studio ATTR-ACT nel caso in cui avessero continuato il trattamento con placebo oltre i 30 mesi[15]

**Risultati**

- Le curve di sopravvivenza delle due *coorti* divergono dopo ~17 mesi[15]
- La curva di sopravvivenza del gruppo 'placebo to tafamidis' diverge dalla curva estrapolata dopo ~44 mesi a favore dei pazienti trattati con tafamidis nello studio LTE[#15]

**Sopravvivenza mediana**

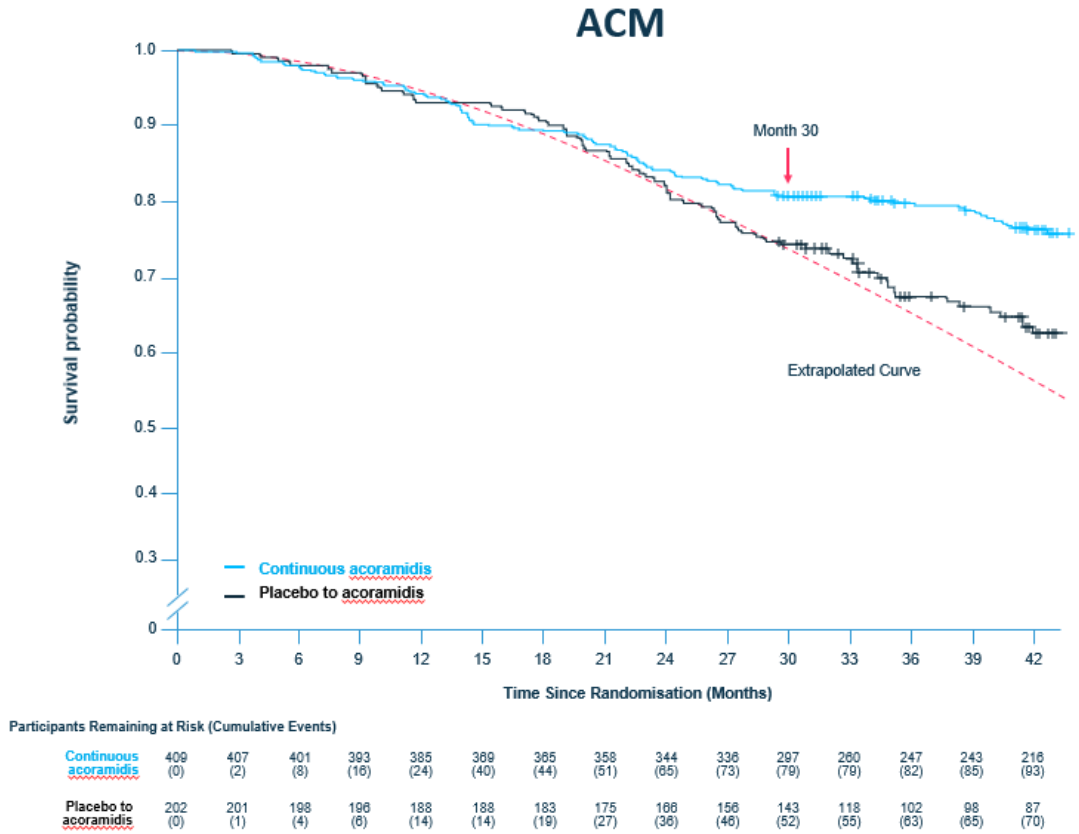
- 'Placebo to tafamidis': 35,8 mesi[15]
- 'Continuous tafamidis': 67,0 mesi**[15]
- 'Extrapolated placebo': 35,2 mesi[15]



Circ Heart Fail. 2022;15:e008193

# Diagnosi precoce >> trattamento precoce >> trattamento efficace

## The treatment effect of acoramidis on ACM continued and was statistically significant at 42 months




**33.7% RRR**

HR (95% CI): 0.64 (0.47, 0.88)
p=0,006

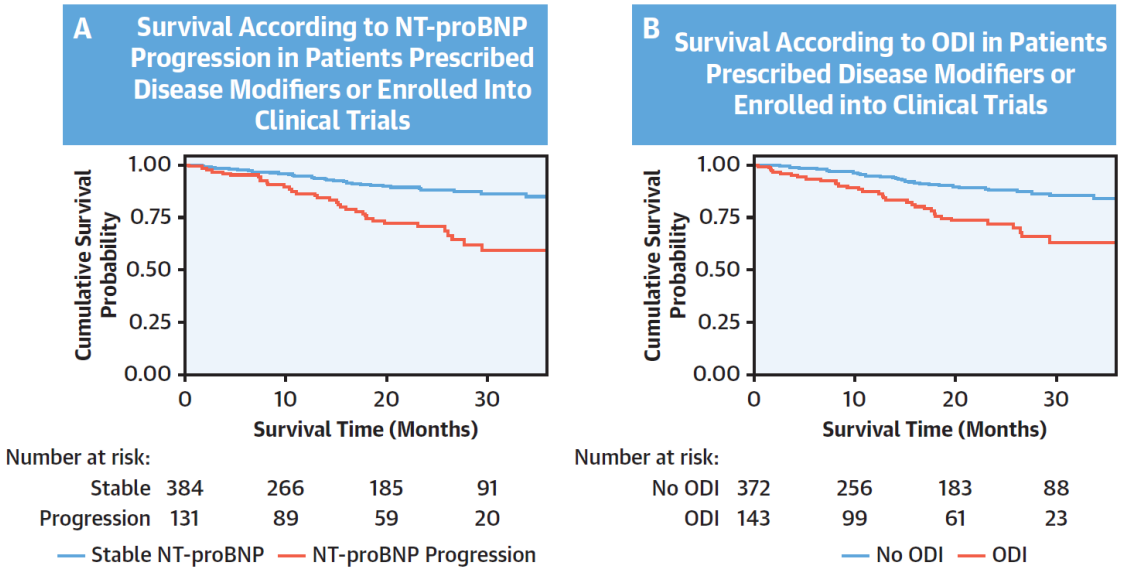


Circulation. 2025;151:601–611. DOI: 10.1161/CIRCULATIONAHA.124.072771

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 14, 2024


# Stratifying Disease Progression in Patients With Cardiac ATTR Amyloidosis

**FIGURE 2** Disease Progression in Clinical Trials and Disease-Modifying Therapy




Landmark Kaplan-Meier curves demonstrating the association between (A) N-terminal pro-B-type natriuretic peptide (NT-proBNP) progression and (B) outpatient diuretic intensification (ODI) at 1 year, and subsequent survival in patients enrolled into clinical trials or prescribed disease-modifying therapy.



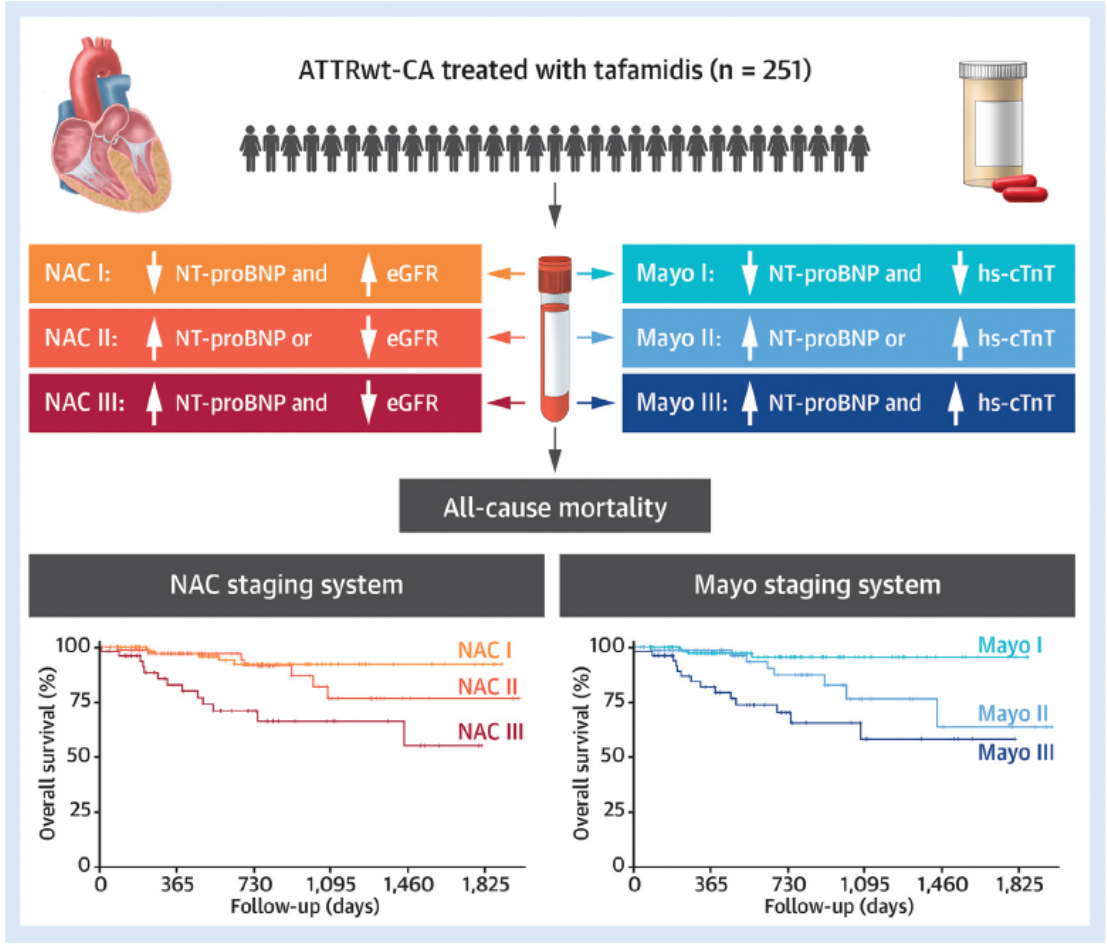
JACC: ADVANCES


ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

# Accuracy of Established Prognostic Staging Systems for Cardiac Transthyretin Amyloidosis in the Tafamidis Era

**CENTRAL ILLUSTRATION** Accuracy of Established Prognostic Staging Systems for Cardiac Transthyretin Amyloidosis in the Tafamidis Era




Müller ML, et al. JACC Adv. 2025;4(2):101568.

# 2. Il trattamento e la prevenzione delle comorbilità e delle complicanze cardiovascolari

## Aortic Stenosis

- Severe AS confers worse prognosis.
- Concomitant ATTRwt risk factor for periprocedural AV block.
- TAVR improves outcome in amyloid-AS.

## Thromboembolism

- High risk, common.
- Anticoagulate if AF, consider in selected cases in SR.
- Anticoagulate independent of CHADS-VASC score.

## Conduction disorders

- PPM according to standard indications.
- Consider CRT if high paced burden expected.

## Heart failure

- Control fluid.
- Diuretics.
- Deprescribe B-Blockers.
- Avoid ACEI/ARB.
- LVAD not suitable for most patients.
- Heart transplant for selected cases.

## Atrial Fibrillation

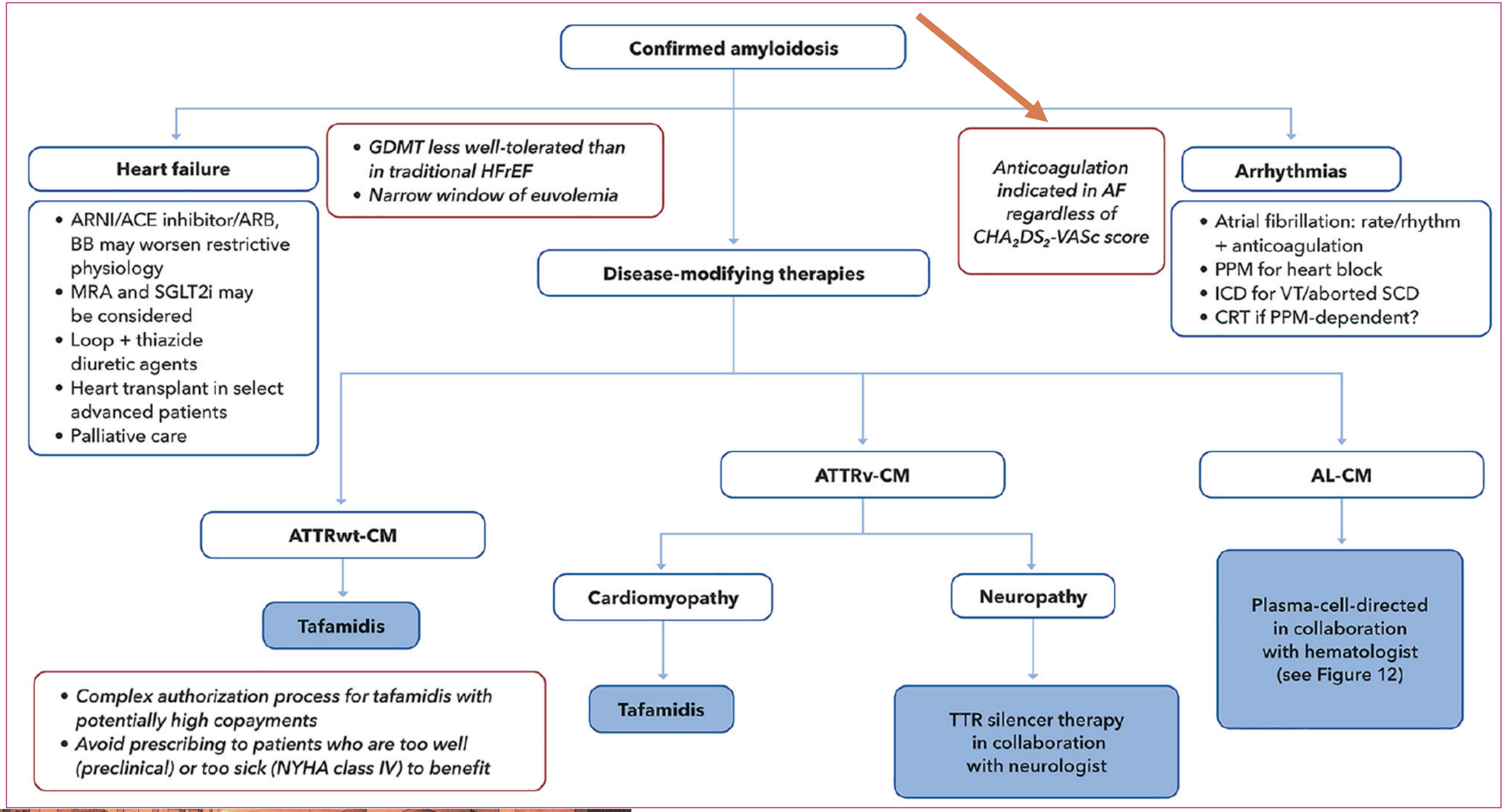
- Amiodarone, preferred AA.
- Use digoxin cautiously.
- Electrical CV has significant risk of complications and AF recurrence is frequent.
- Exclude thrombi before electrical CV.
- AF ablation data scarce and controversial.

## Ventricular arrhythmias

- ICD for secondary prevention.
- ICD in primary prevention usually not recommended.
- Transvenous ICD preferred over subcutaneous ICD.



Garcia-Pavia P. et al., Diagnosis and treatment of cardiac amyloidosis. EJHF 2021

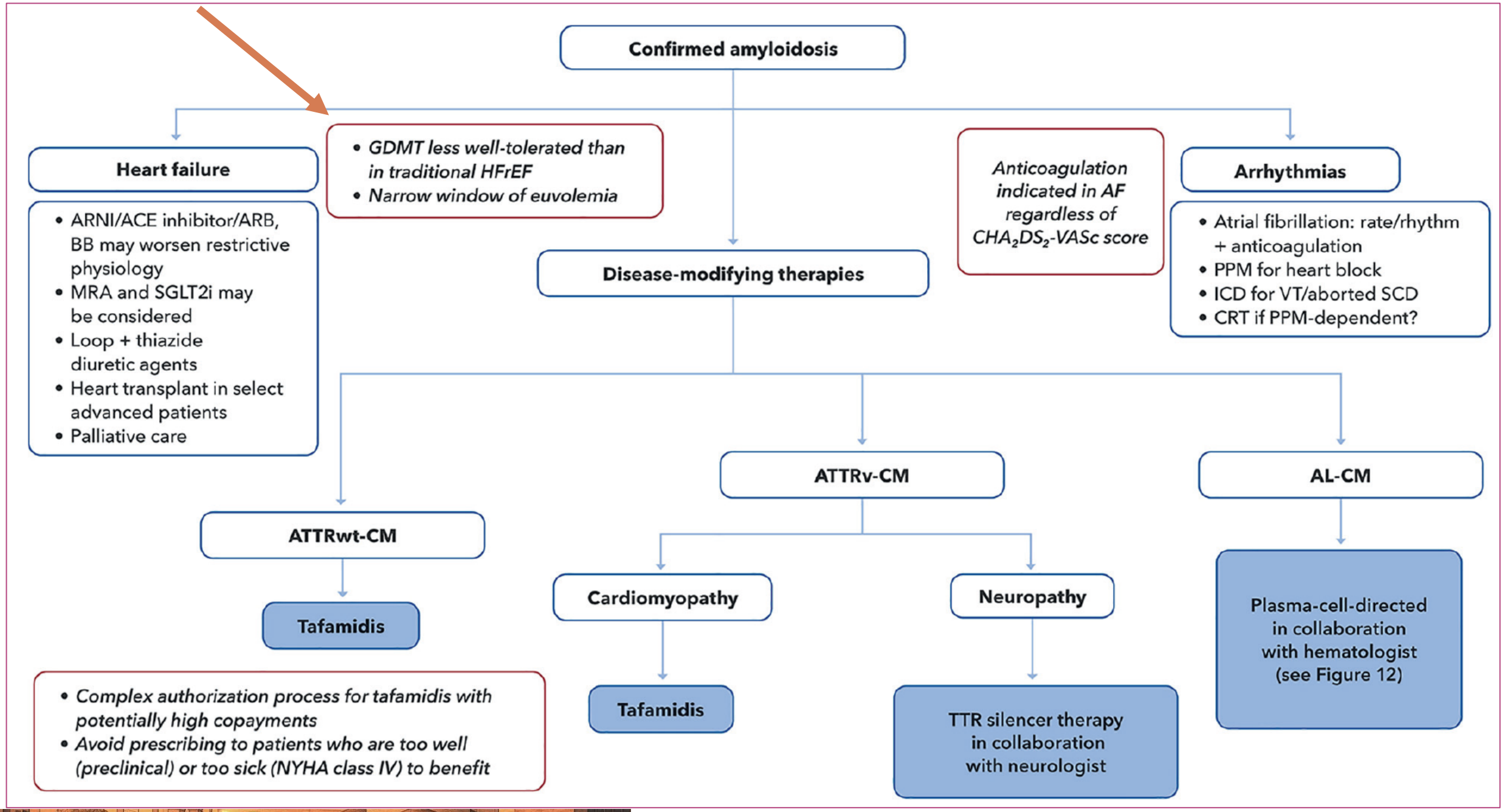





Garcia-Pavia P. et al., Diagnosis and treatment of cardiac amyloidosis. EJHF 2021

# Fibrillazione atriale

- Prevalenza 70% in ATTR
- **Rischio tromboembolico:**
  - Rischio alto di trombosi, anche in pazienti anticoagulati
  - Anticoagulazione a prescindere dal $CHA_2DS_2VASc$
  - Sempre ecografia TE prima della cardioversione
  - Non evidenze specifiche per i DOAC, ma attualmente utilizzati in prima scelta
- **Controllo della FC:**
  - Generalmente FC non elevata
  - BB bassa dose (se tollerati come pressione)
  - Digitale: evidenza di legame in vitro alle fibrille di amiloide; dati recenti suggeriscono utilizzo sicuro se buon monitoraggio
  - Considerare ablate & pace
- **Controllo del ritmo**: amiodarone come prima scelta; CVE sempre da considerare; considerare isolamento VVPP





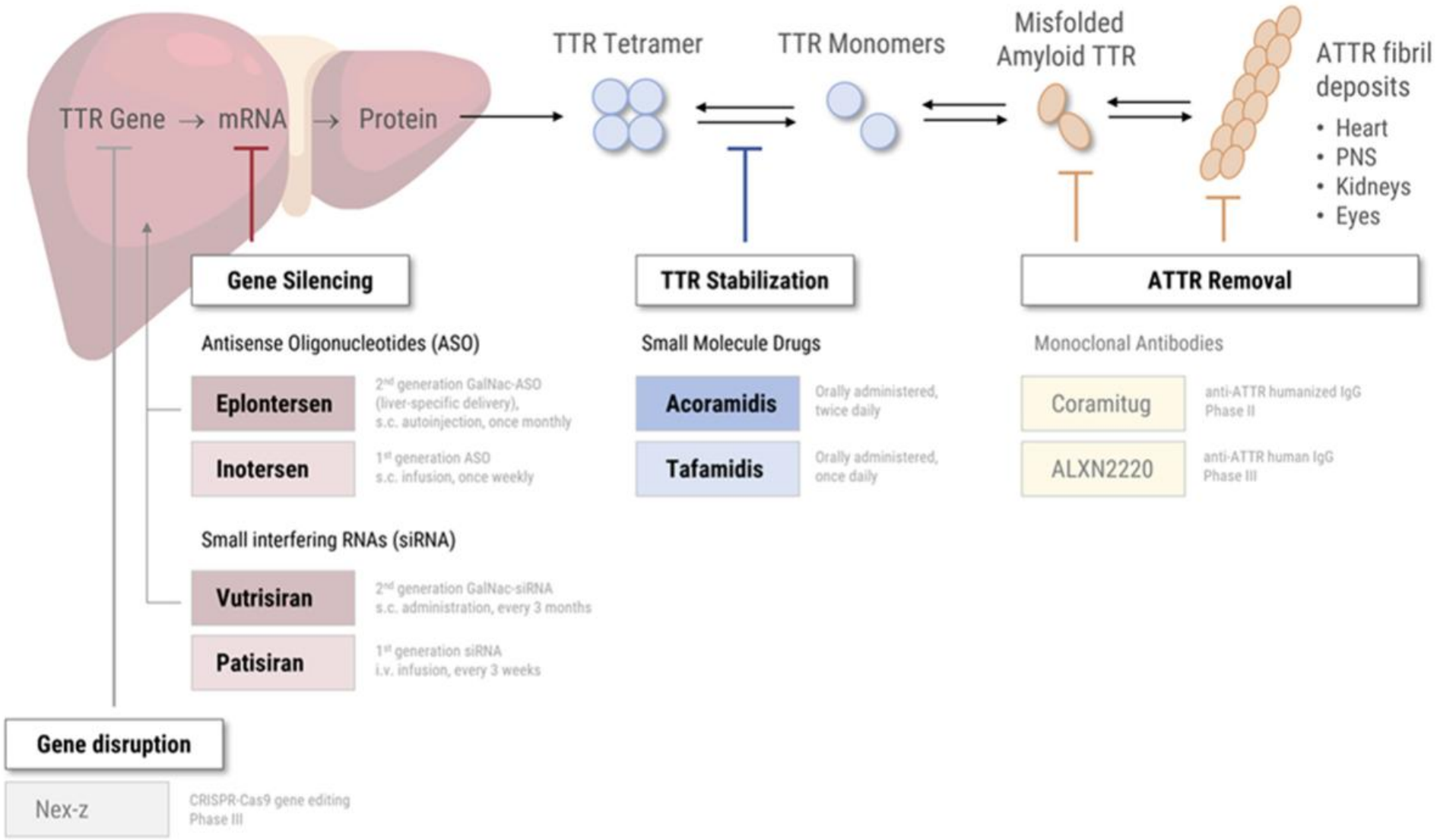

Garcia-Pavia P. et al., Diagnosis and treatment of cardiac amyloidosis. EJHF 2021

**Tabella 6.** Possibile ruolo delle terapie standard per il trattamento dello scompenso cardiaco nell'amiloidosi cardiaca da transtiretina.

| Studi in ATTR-AC | Follow up (mesi) | Tasso di interruzione | Benefici del trattamento | Potenziali raccomandazioni in ATTR-AC* | Cautele in ATTR-AC |
|---|---|---|---|---|---|
| **Beta-bloccanti** | | | | | |
| Aimo et al.[104] | 16 | 22% | Non valutato | Considerare beta-bloccante a bassa dose nella FE ≤40% | Ipotensione sintomatica<br>Peggioramento dei sintomi posturali<br>Sindrome da bassa portata negli stadi avanzati<br>Peggioramento dell'incompetenza cronotropa<br>Bradicardia sintomatica |
| Tini et al.[105] | 14 | 19% | Non valutato | | |
| Cheng et al.[106] | 72 | 50% | Interruzione del trattamento associata a riduzione della mortalità globale | | |
| Barge-Caballero et al.[107] | 17 | 34% | Riduzione della mortalità globale | | |
| Ioannou et al.[101] | 27.8 | 22% | Riduzione della mortalità globale nella FE ≤40% (indipendentemente dalla presenza di cardiopatia ischemica) | | |
| **ACEi/ARB** | | | | | |
| Cheng et al.[106] | 72 | 59% | Nessuna associazione con la mortalità globale | Non attuali indicazioni | Ipotensione sintomatica, specialmente se concomitante neuropatia disautonomica<br>Rischio di cadute<br>Iperpotassiemia<br>Deterioramento della funzione renale |
| Ioannou et al.[101] | 27.8 | 33% | Nessuna associazione con la mortalità globale | | |
| **MRA** | | | | | |
| Cheng et al.[106] | 72 | 25% | Nessuna associazione con la mortalità globale | Considerare MRA in tutto lo spettro di FE | Iperpotassiemia<br>Deterioramento della funzione renale |
| Ioannou et al.[101] | 27.8 | 8% | Riduzione della mortalità globale (tutto lo spettro di FE) | | |
| Sperry et al.[108] (sottostudio TOPCAT) | 31 | Non valutato | Riduzione del composito di morte CV e ospedalizzazioni per SC (simile ai benefici osservati nella popolazione generale del TOPCAT) | | |
| **ARNI** | | | | | |
| – | – | – | Nessun dato in ATTR-AC | Non attuali indicazioni | Ipotensione sintomatica, specialmente se concomitante neuropatia disautonomica<br>Rischio di cadute<br>Iperpotassiemia<br>Deterioramento della funzione renale |
| **SGLT2i** | | | | | |
| Zampieri et al.[109] | 8 | 6.6% | Dati descrittivi di minor necessità di terapia diuretica e miglioramento della classe NYHA | Considerare gli SGLT2i in tutto lo spettro di FE | Infezioni urinarie ricorrenti<br>Pollachiuria<br>Riduzione transitoria di eGFR |
| Dobner et al.[110] | 3 | Non valutato | Riduzione di NT-proBNP | | |
| Lang et al.[111] | 5.6 (gruppo SGLT2i) | 11.5% | Minor dose di diuretico dell'ansa<br>Riduzione del peso corporeo<br>Riduzione dell'acido urico | | |
| Porcari et al.[103] | 28 | 4.5% | Riduzione della mortalità globale e CV e delle ospedalizzazioni per SC<br>Minor tasso di declino di eGFR<br>Minor incremento di NT-proBNP<br>Minor necessità di diuretico dell'ansa<br>Stabilità della classe NYHA | | |

G Ital Cardiol 2024;25(12):900-920

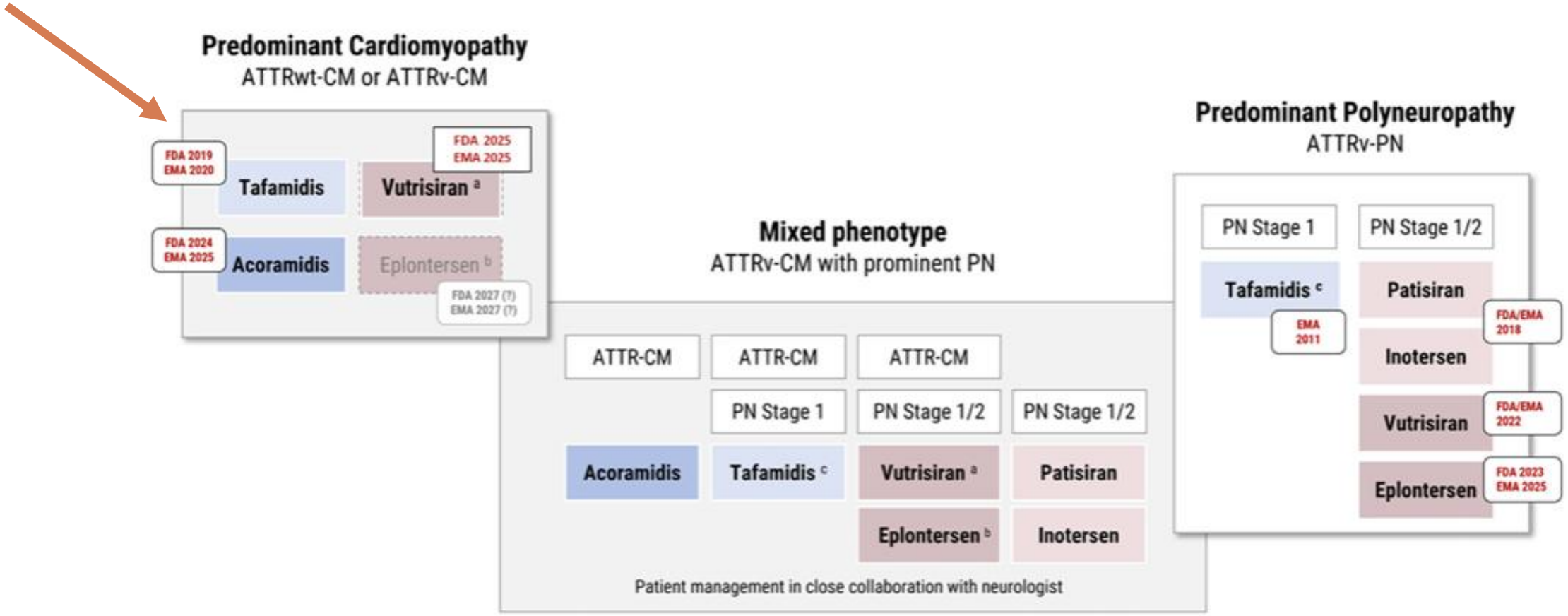
# 3. TERAPIE "DISEASE-MODIFYNG"






J. Clin. Med. 2025, 14, 4785

# 3. TERAPIE "DISEASE-MODIFYNG"

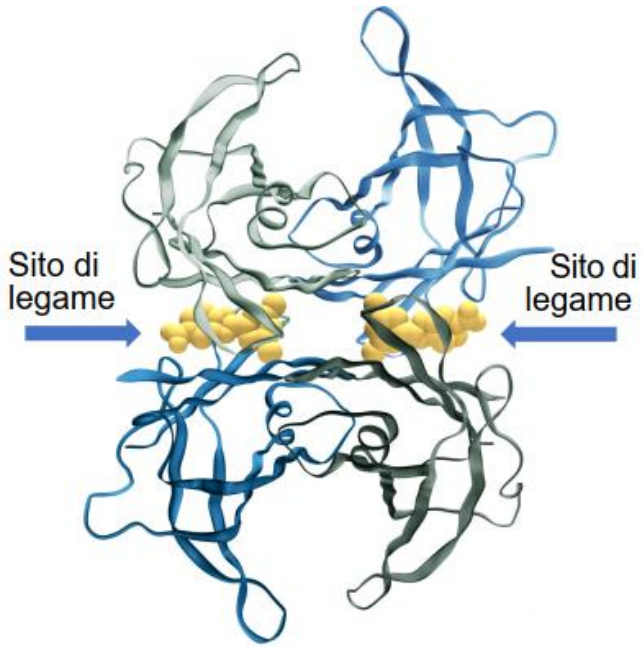





J. Clin. Med. 2025, 14, 4785

**TAFAMIDIS:**

Agisce bloccando la scissione dei tetrameri di transtiretina in monomeri instabili ed in grado di formare fibrille di amiloide




The NEW ENGLAND JOURNAL of MEDICINE

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

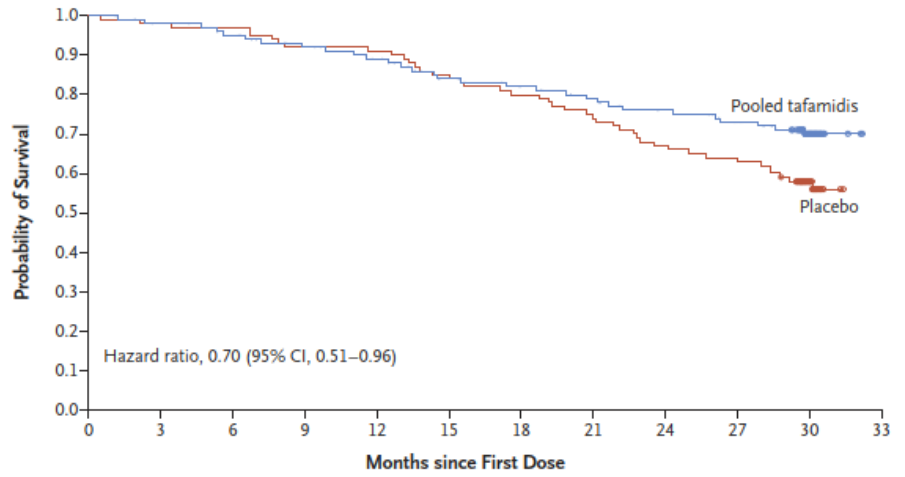
## Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

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*

**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 | |

**Figure 2. Primary Analysis and Components.**

Panel A shows the results of the primary analysis as determined with the use of the Finkelstein–Schoenfeld method. Panel B shows an analysis of all-cause mortality for pooled tafamidis and for placebo, a secondary end point. Panel C shows the frequency of cardiovascular-related hospitalizations, also a secondary end point.

Nel trial ATTR-ACT tafamidis si è dimostrato in grado di ridurre del 30% la mortalità per tutte le cause a 33 mesi e del 53% a 5 anni, oltre a migliorare la classe funzionale e la qualità della vita.

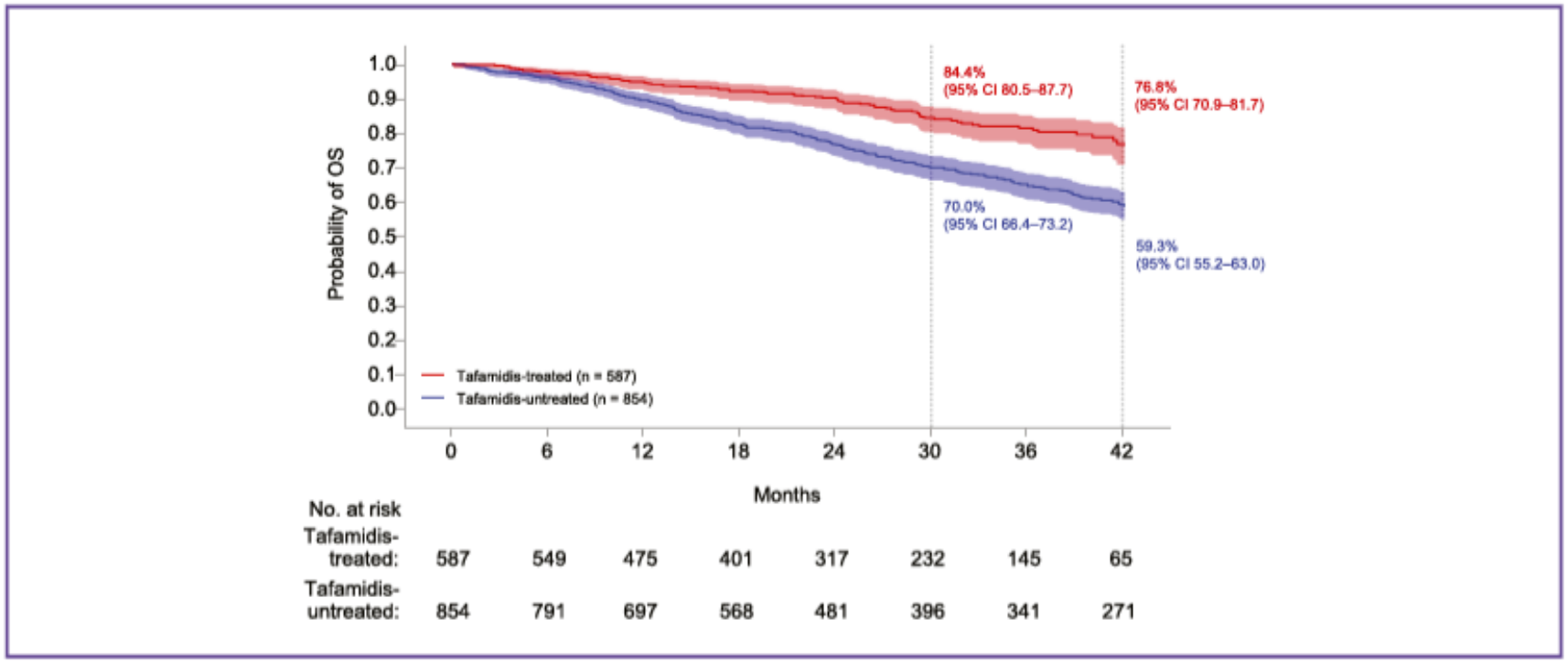

G Ital Cardiol 2023;24(2):127-135
JACC Heart Fail 2021;9:115-23
N Engl J Med. 2018 Sep 13;379(11):1007-1016
Eur Heart J 2021;42:3599-726
Circ Heart Fail. 2022;15:e008193

Journal of Cardiac Failure 31 (2025) 525–533

JCF
Journal of Cardiac Failure

# Survival in a Real-World Cohort of Patients With Transthyretin Amyloid Cardiomyopathy Treated With Tafamidis: An Analysis From the Transthyretin Amyloidosis Outcomes Survey (THAOS)

PABLO GARCIA-PAVIA, MD, PhD[1,2,3] ARNT V. KRISTEN, MD[4] BRIAN DRACHMAN, MD[5] MARTIN CARLSSON, MS[6] LESLIE AMASS, PhD[6] FRANCA STEDILE ANGELI, MD, PhD[6] and MATHEW S. MAURER, MD[7], on behalf of the THAOS investigators[a]




**Visual take home graphic.** Kaplan-Meier plot of overall survival in tafamidis-treated and tafamidis-untreated patients. CI, confidence interval; OS, overall survival.

# ACORAMIDIS:

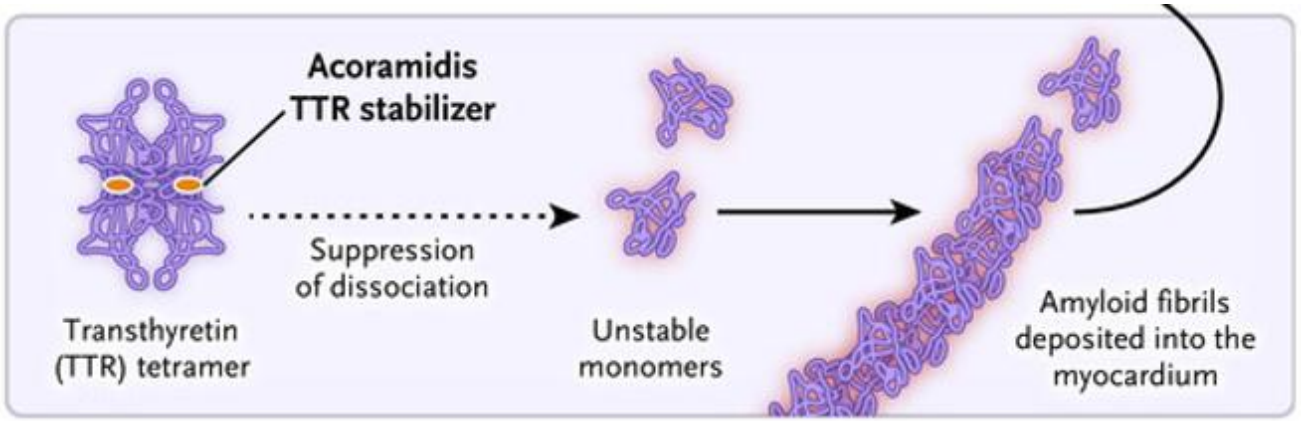
E’ uno stabilizzatore ad alta affinità che agisce inibendo la dissociazione dei tetrameri di TTR in fibrille insolubili

The NEW ENGLAND JOURNAL of MEDICINE

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*






N Engl J Med 2024;390:132-142

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Gillmore JD et al. DOI: 10.1056/NEJMoa2305434

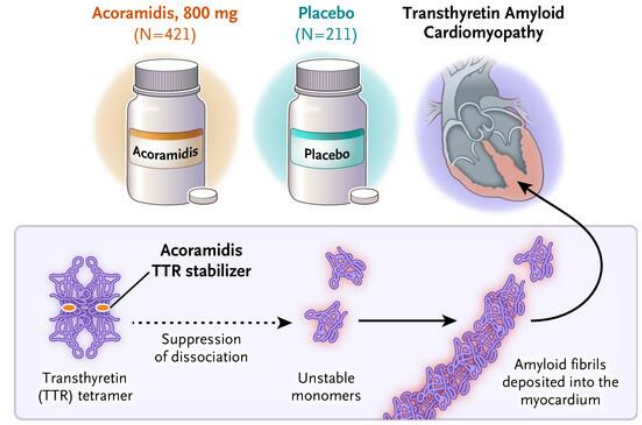
## CLINICAL PROBLEM

Transthyretin amyloid cardiomyopathy is characterized by the destabilization of transthyretin (TTR) tetramers, dissociation into unstable monomers, and their subsequent deposition as amyloid fibrils in the myocardium. This condition is a restrictive cardiomyopathy that causes heart failure, usually with preserved ejection fraction. Delayed diagnosis and impaired quality of life are common. Whether acoramidis, a TTR stabilizer, can improve clinical outcomes is unclear.

## CLINICAL TRIAL

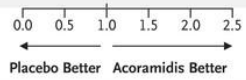
**Design:** A phase 3, double-blind, randomized, placebo-controlled trial evaluated the efficacy and safety of acoramidis in patients with transthyretin amyloid cardiomyopathy.

**Intervention:** 632 patients with transthyretin amyloid cardiomyopathy were randomly assigned in a 2:1 ratio to receive 800 mg of acoramidis or placebo twice daily for 30 months. The primary analysis compared four outcomes in a hierarchical manner: death from any cause, cardiovascular-related hospitalization, the change from baseline in the N-terminal pro–B-type natriuretic peptide (NT-proBNP), and the change from baseline in the 6-minute walk distance.




**Primary Efficacy Analysis and Prespecified Secondary Analyses**

| Hierarchical Components | Win Ratio (95% CI) | P Value |
|---|---|---|
| Death from any cause, cardiovascular-related hospitalization, NT-proBNP, 6-min walk distance | 1.8 (1.4–2.2) | <0.001 |
| Death from any cause, cardiovascular-related hospitalization, 6-min walk distance | 1.4 (1.1–1.8) | |
| Death from any cause, cardiovascular-related hospitalization | 1.5 (1.1–2.0) | |




## RESULTS

**Efficacy:** The use of acoramidis resulted in a significantly better four-step primary hierarchical outcome than placebo.

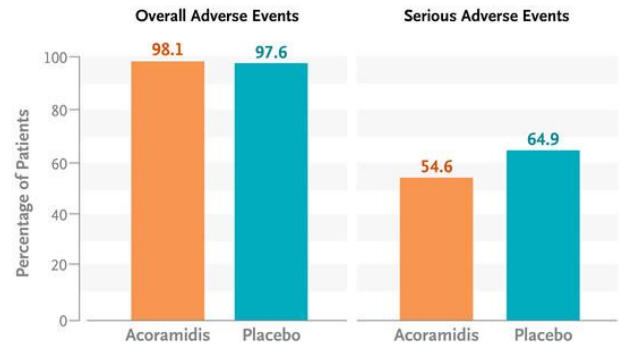
**Safety:** The overall incidence of adverse events during treatment was similar in the two groups. Serious adverse events were less frequent in the acoramidis group than in the placebo group.

## LIMITATIONS AND REMAINING QUESTIONS

- Most patients had wild-type transthyretin amyloid cardiomyopathy, and results may not be generalizable to other variants.
- Most of the patients were White and male, which further limits the generalizability of the data.

**Links: Full Article | NEJM Quick Take**

**Safety**



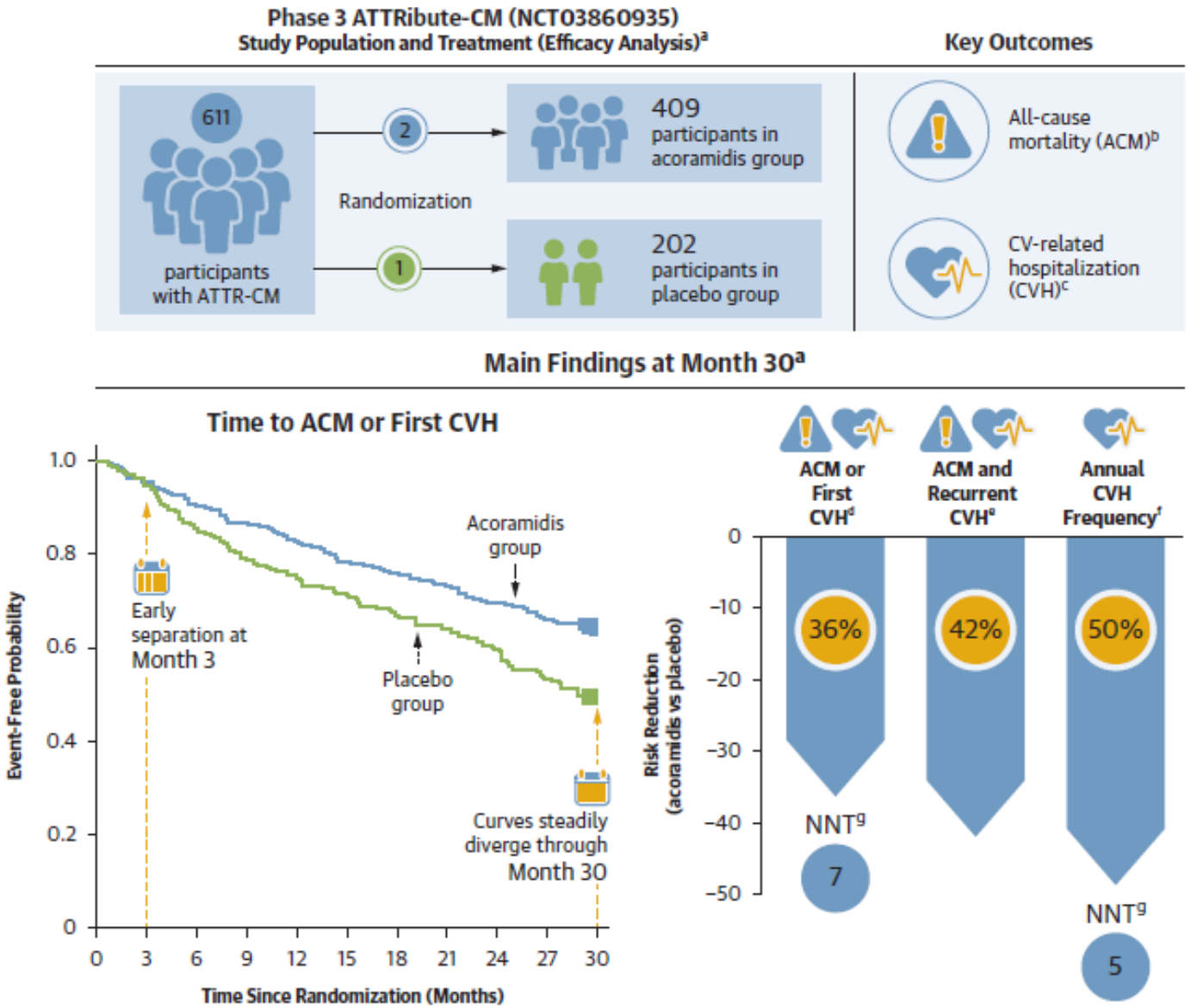

## CONCLUSIONS

In patients with transthyretin amyloid cardiomyopathy, the TTR stabilizer acoramidis had benefits over placebo on a primary end point with components of mortality, morbidity, and function.

JACC
VOL. 85, NO. 10, 2025


# Efficacy of Acoramidis on All-Cause Mortality and Cardiovascular Hospitalization in Transthyretin Amyloid Cardiomyopathy

**CENTRAL ILLUSTRATION** Early Benefits of Acoramidis on All-Cause Mortality and Cardiovascular-Related Hospitalization in Transthyretin Amyloid Cardiomyopathy




Judge DP, et al. JACC. 2025;85(10):1003-1014.



FARMACO/INDICAZIONE NON ANCORA AUTORIZZATI IN ITALIA

# **VUTRISIRAN:**
è un silenziatore genetico della famiglia dei siRNA

AMYLOID
https://doi.org/10.1080/13506129.2022.2091985

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RESEARCH ARTICLE

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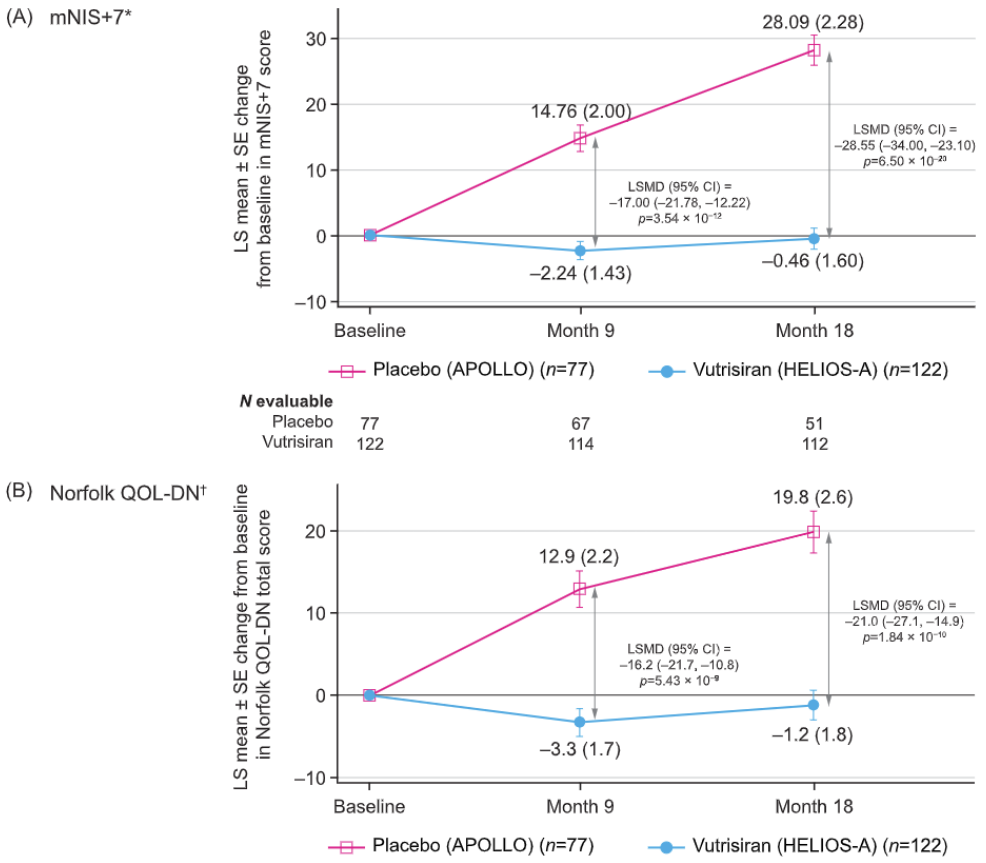
## Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial






AMYLOID
https://doi.org/10.1080/13506129.2022.2091985

ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 397–410
doi:10.1002/ejhf.3138

**RESEARCH ARTICLE**

# Impact of vutrisiran on exploratory cardiac parameters in hereditary transthyretin-mediated amyloidosis with polyneuropathy

**Pablo Garcia-Pavia[1,2,3]*, Martha Grogan[4], Parag Kale[5], John L. Berk[6], Mathew S. Maurer[7], Isabel Conceição[8], Marcelo Di Carli[9], Scott D. Solomon[10], Chongshu Chen[11], Elena Yureneva[11], John Vest[11], and Julian D. Gillmore[12]**



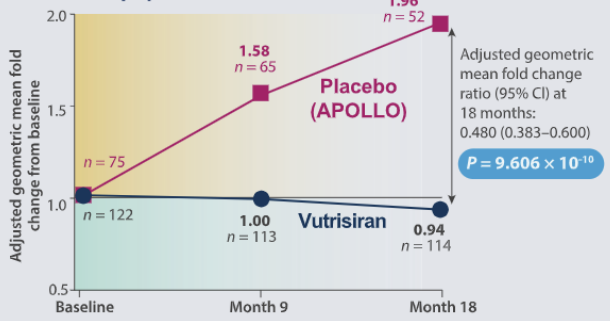
**Exploratory analyses from the HELIOS-A study demonstrated evidence of the potential benefit of vutrisiran on cardiac manifestations in patients with ATTRv amyloidosis with polyneuropathy**

**Study populations**

**HELIOS-A study (vutrisiran 25 mg SC Q3M)**
mITT population ($n = 122$) ····· Cardiac subpopulation ($n = 40$)

**APOLLO study (external placebo)**
mITT population ($n = 77$) ····· Cardiac subpopulation ($n = 36$)

**Change from baseline to Month 18 in NT-proBNP in the mITT population**




mITT population consisted of randomized patients who received any study drug

**Echocardiography**
**HELIOS-A vutrisiran vs APOLLO placebo (mITT)**

- ↑ Cardiac output (nominal $P = 1.144 \times 10^{-5}$)
- ↑ LV end-diastolic volume (nominal $P = 4.021 \times 10^{-5}$)
- ↑ LV stroke volume (nominal $P = 5.754 \times 10^{-6}$)

Similar results in the cardiac subpopulation were nominally significant for cardiac output and LV stroke volume

**$^{99m}$Tc scintigraphy[a]**
**HELIOS-A vutrisiran vs baseline**

The following were reduced or stabilised in vutrisiran-treated patients:

- Normalised LV total uptake: ↓68.1%
- Heart-to-contralateral lung ratio: ↓64.6%
- Perugini grade: ↓28.1% or ↝68.4%

**Vutrisiran had an acceptable safety profile, including no cardiac safety concerns**

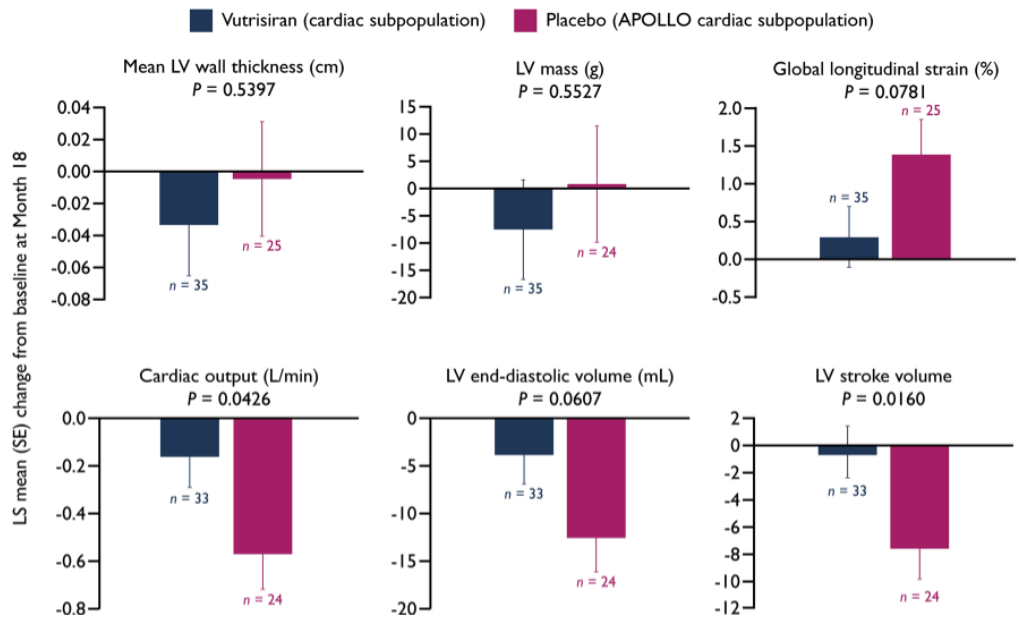



**Figure 3** Least squares (LS) mean change from baseline at Month 18 for prespecified echocardiographic parameters and left ventricular (LV) stroke volume in the cardiac subpopulation. SE, standard error.

# VUTRISIRAN >> HELIOS B

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ORIGINAL ARTICLE

## Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy


**BACKGROUND**

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, fatal disease. Vutrisiran, a subcutaneously administered RNA interference therapeutic agent, inhibits the production of hepatic transthyretin.

**METHODS**

In this double-blind, randomized trial, we assigned patients with ATTR-CM in a 1:1 ratio to receive vutrisiran (25 mg) or placebo every 12 weeks for up to 36 months. The primary end point was a composite of death from any cause and recurrent cardiovascular events. Secondary end points included death from any cause, the change from baseline in the distance covered on the 6-minute walk test, and the change from baseline in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score. The efficacy end points were assessed in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline) and were tested hierarchically.

**RESULTS**

A total of 655 patients underwent randomization; 326 were assigned to receive vutrisiran and 329 to receive placebo. Vutrisiran treatment led to a lower risk of death from any cause and recurrent cardiovascular events than placebo (hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; P=0.01; hazard ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; P=0.02) and a lower risk of death from any cause through 42 months (hazard ratio, 0.65; 95% CI, 0.46 to 0.90; P=0.01). A primary end-point event occurred in 163 patients in the vutrisiran group and in 202 in the placebo group. In the overall population, treatment with vutrisiran resulted in less of a decline in the distance covered on the 6-minute walk test than placebo (least-squares mean difference, 26.5 m; 95% CI, 13.4 to 39.6; P<0.001) and less of a decline in the KCCQ-OS score (least-squares mean difference, 5.8 points; 95% CI, 2.4 to 9.2; P<0.001). Similar benefits were observed in the monotherapy population. The incidence of adverse events was similar in the two groups (99% in the vutrisiran group and 98% in the placebo group); serious adverse events occurred in 62% of the patients in the vutrisiran group and in 67% of those in the placebo group.

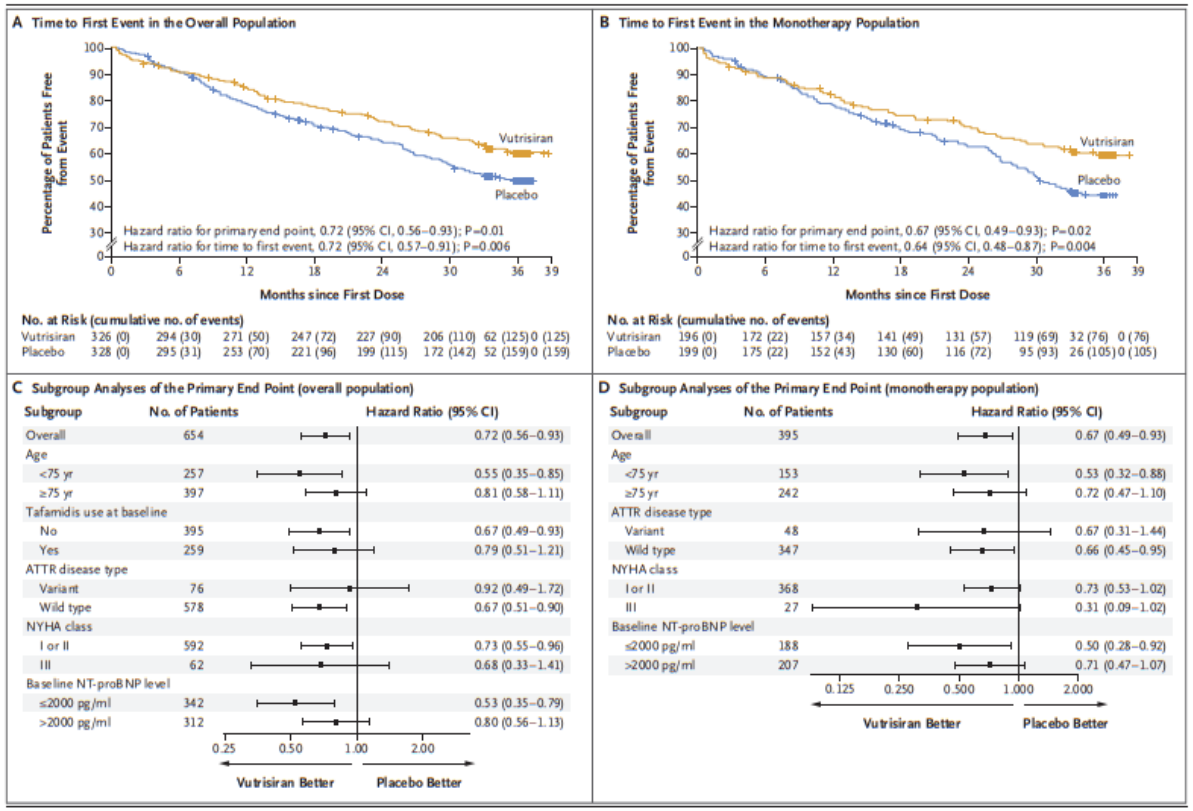
**CONCLUSIONS**

Among patients with ATTR-CM, treatment with vutrisiran led to a lower risk of death from any cause and cardiovascular events than placebo and preserved functional capacity and quality of life. (Funded by Alnylam Pharmaceuticals; HELIOS-B ClinicalTrials.gov number, NCT04153149.)


**Table 2. Primary and Secondary End Points.***

| End Point | Overall Population | | | Monotherapy Population | | |
|---|---|---|---|---|---|---|
| | Vutrisiran (N=326) | Placebo (N=328) | Measure of Effect | Vutrisiran (N=196) | Placebo (N=199) | Measure of Effect |
| **Primary end point** | | | | | | |
| Death from any cause and recurrent cardiovascular events | | | Hazard ratio, 0.72 (95% CI, 0.56 to 0.93) P=0.01 | | | Hazard ratio, 0.67 (95% CI, 0.49 to 0.93) P=0.02 |
| Death from any cause | | | Hazard ratio, 0.69 (95% CI, 0.49 to 0.98) P=0.04 | | | Hazard ratio, 0.71 (95% CI, 0.47 to 1.06) P=0.12 |
| Recurrent cardiovascular events | | | Relative rate ratio, 0.73 (95% CI, 0.61 to 0.88) P=0.001 | | | Relative rate ratio, 0.68 (95% CI, 0.53 to 0.86) P=0.001 |
| Patients with at least one event — no. (%) | 125 (38) | 159 (48) | | 76 (39) | 105 (53) | |
| Death from any cause† | 51 (16) | 69 (21) | | 36 (18) | 46 (23) | |
| Recurrent cardiovascular events | 112 (34) | 133 (41) | | 66 (34) | 87 (44) | |
| **Secondary end points** | | | | | | |
| Death from any cause through 42 mo | | | Hazard ratio, 0.65 (95% CI, 0.46 to 0.90) P=0.01 | | | Hazard ratio, 0.66 (95% CI, 0.44 to 0.97) P=0.045 |
| Patients who died — no. (%) | 60 (18) | 85 (26) | | 43 (22) | 58 (29) | |
| Least-squares mean change from baseline at 30 mo in distance covered on the 6-min walk test — m‡ | −45.4 (95% CI, −54.5 to −36.3) | −71.9 (95% CI, −81.3 to −62.4) | Difference, 26.5 (95% CI, 13.4 to 39.6) P<0.001§ | −59.7 (95% CI, −72.7 to −46.7) | −91.8 (95% CI, −104.4 to −79.2) | Difference, 32.1 (95% CI, 14.0 to 50.2) P<0.001§ |
| Least-squares mean change from baseline in KCCQ-OS score at 30 mo — points¶ | −9.7 (95% CI, −12.0 to −7.4) | −15.5 (95% CI, −18.0 to −13.0) | Difference, 5.8 (95% CI, 2.4 to 9.2) P<0.001§ | −10.8 (95% CI, −14.1 to −7.5) | −19.5 (95% CI, −22.9 to −16.1) | Difference, 8.7 (95% CI, 4.0 to 13.4) P<0.001§ |
| Improved or stable NYHA class at 30 mo — % | 68 | 61 | Difference, 8.7 (95% CI, 1.3 to 16.1) P=0.02‖ | 66 | 56 | Difference, 12.5 (95% CI, 2.7 to 22.2) P=0.01‖ |

# VUTRISIRAN >> HELIOS B



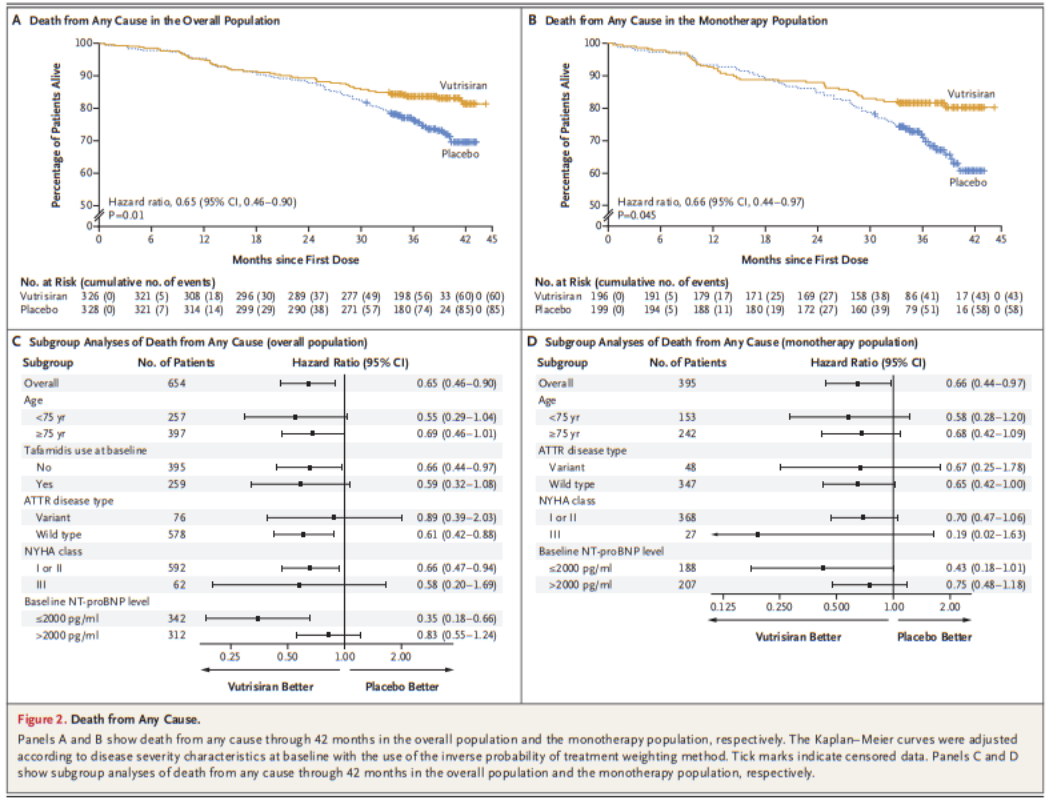




**Figure 2. Death from Any Cause.**

Panels A and B show death from any cause through 42 months in the overall population and the monotherapy population, respectively. The Kaplan–Meier curves were adjusted according to disease severity characteristics at baseline with the use of the inverse probability of treatment weighting method. Tick marks indicate censored data. Panels C and D show subgroup analyses of death from any cause through 42 months in the overall population and the monotherapy population, respectively.

# EPLONTERSEN

è un silenziatore genico della famiglia degli oligonucleutidi antisenso

Original Investigation

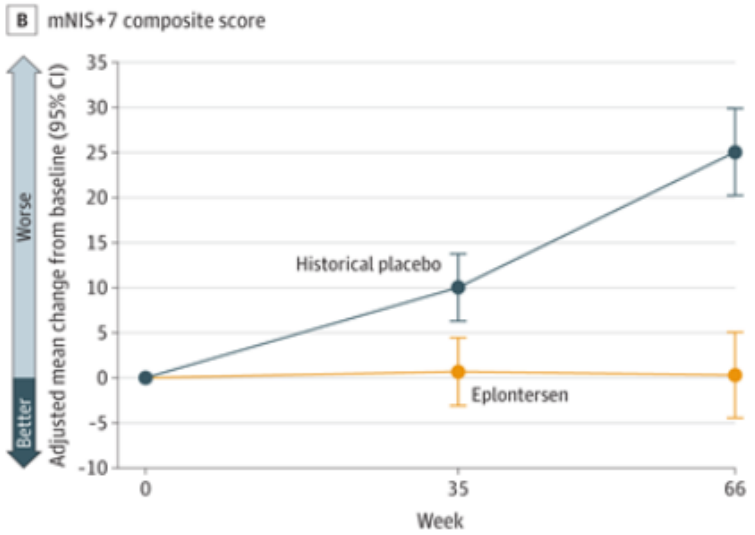
September 28, 2023

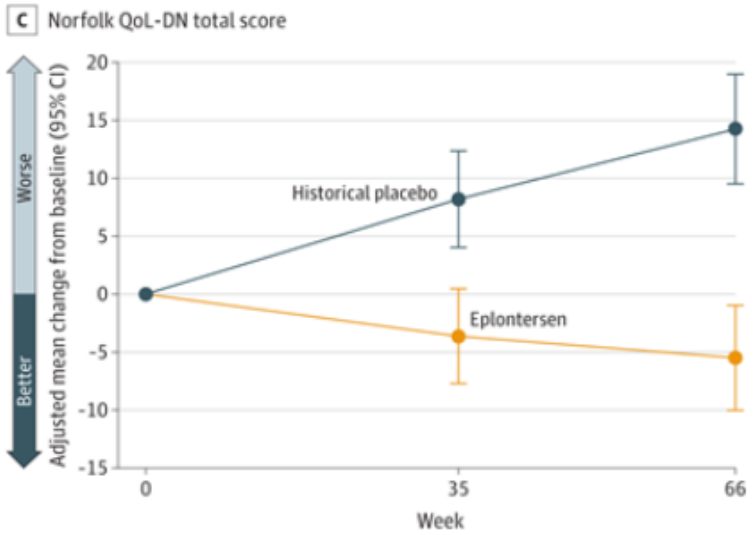
## Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy

Teresa Coelho, MD, PhD[1]; Wilson Marques Jr, MD, PhD[2]; Noel R. Dasgupta, MD[3]; et al

» Author Affiliations | Article Information

*JAMA*. 2023;330(15):1448-1458. doi:10.1001/jama.2023.18688



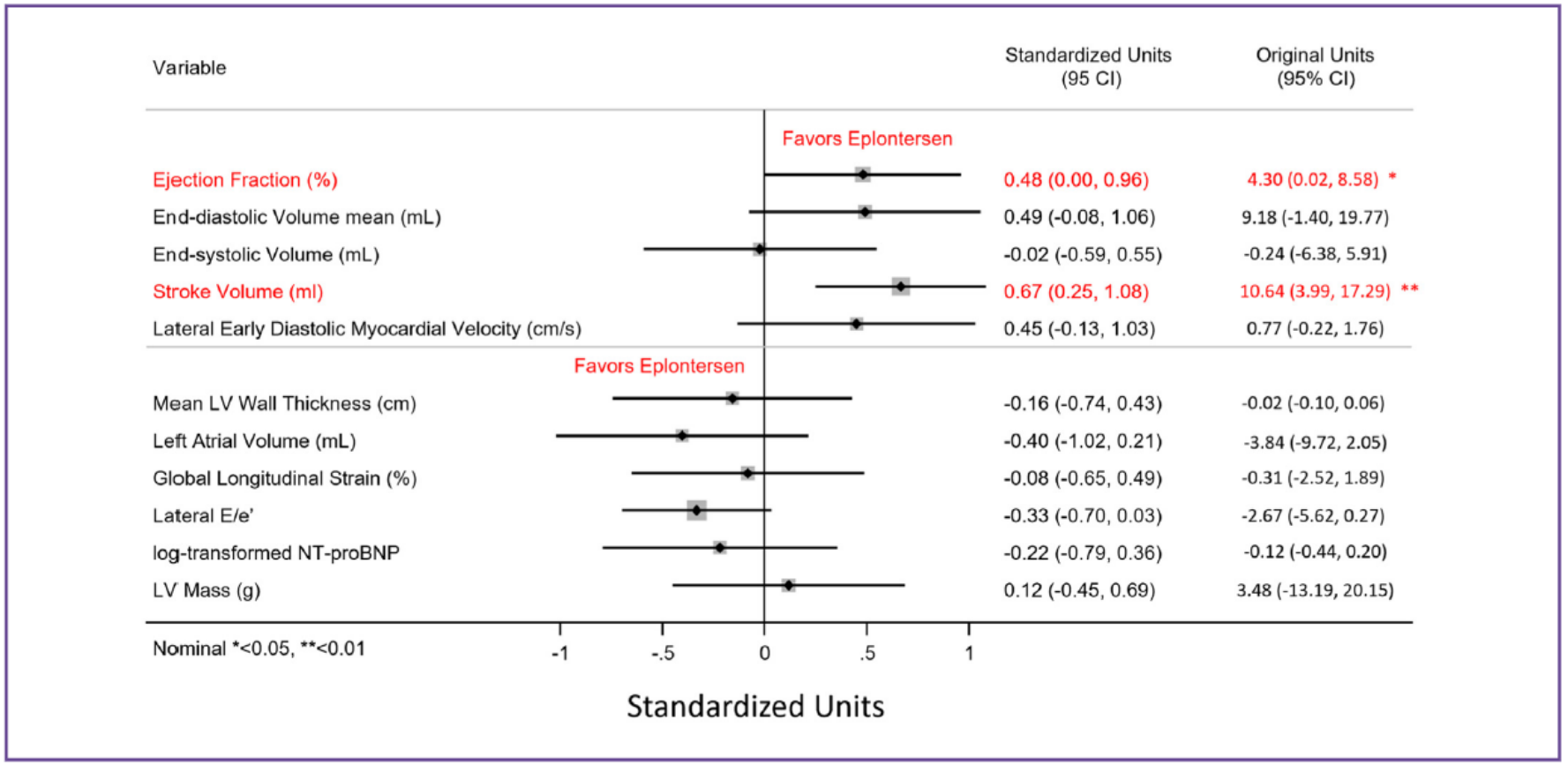

JAMA. 2023;330(15):1448-1458

Journal of Cardiac Failure 30 (2024) 973–980

JCF
Journal of Cardiac Failure

# Effect of Eplontersen on Cardiac Structure and Function in Patients With Hereditary Transthyretin Amyloidosis

Ahmad Masri[1] Mathew S. Maurer[2] Brian L. Claggett[3] Ian Kulac[3] Marcia Waddington Cruz[4] Isabel Conceição[5] Markus Weiler[6] John L. Berk[7] Morie Gertz[8] Julian D. Gillmore[9] Stephen Rush[10] Jersey Chen[11] Wunan Zhou[11] Jesse Kwoh[12] Jason M. Duran[12] Sotirios Tsimikas[12,13] and Scott D. Solomon[3]



# EPLONTERSEN



## CARDIO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-LRx and AKCEA-TTR-LRx) in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM)

### Study Description

Go to ▾

Brief Summary:

To evaluate the efficacy of eplontersen compared to placebo in participants with ATTR-CM receiving available standard of care (SoC). For more information, please visit https://www.cardio-ttransform.com.

| Condition or disease | Intervention/treatment | Phase |
|---|---|---|
| Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM) | Drug: Eplontersen<br>Drug: Placebo | Phase 3 |

Detailed Description:

This is a multicenter, double-blind study in approximately 1400 participants, who will be randomized to receive subcutaneous (SC) injections of either eplontersen or placebo once every 4 weeks. Participants will also receive daily supplemental doses of the recommended daily allowance of vitamin A.

### Study Design

Go to ▾

| | |
|---|---|
| Study Type : | Interventional (Clinical Trial) |
| Actual Enrollment : | 1438 participants |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignment |
| Masking: | Double (Participant, Investigator) |
| Primary Purpose: | Treatment |
| Official Title: | A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients With Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR CM) |
| Actual Study Start Date : | March 13, 2020 |
| Estimated Primary Completion Date : | June 2025 |
| Estimated Study Completion Date : | November 2025 |

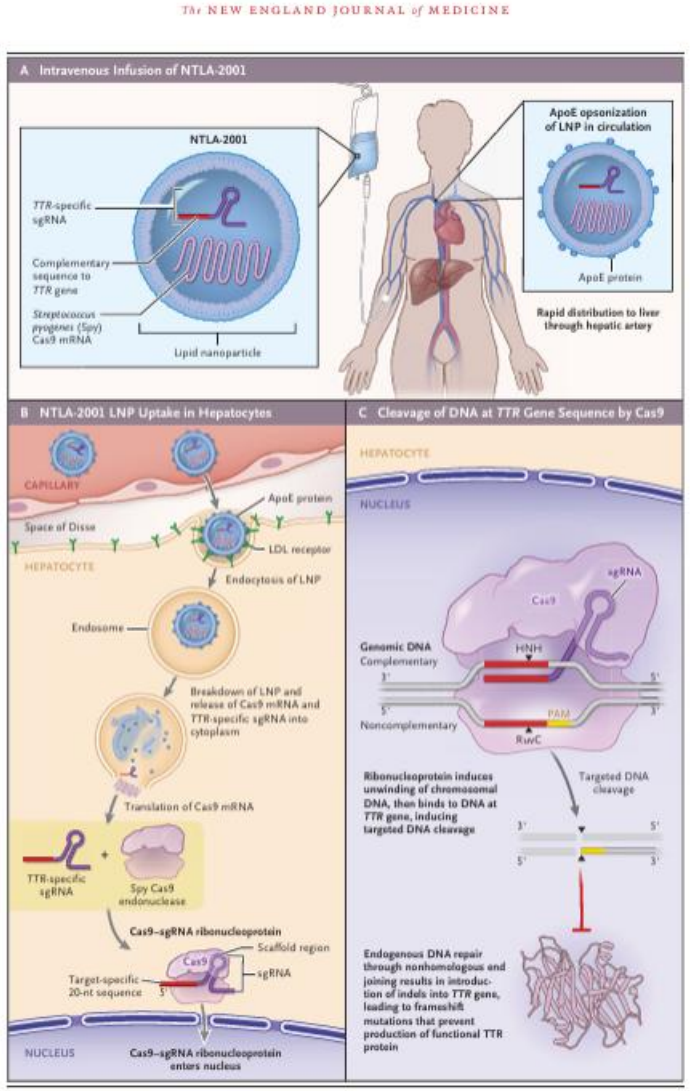
# IL FUTURO……. TTR Gene Editing based on CRISPR-Cas9

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

## CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.






J. Clin. Med. 2025, 14, 4785

ORIGINAL ARTICLE

# CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

**Authors**: Marianna Fontana, M.D., Ph.D. , Scott D. Solomon, M.D. , Jessica Kachadourian, Pharm.D., Liron Walsh, M.D., Ricardo Rocha, M.D., David Lebwohl, M.D. , Derek Smith, M.S., +12 , and Julian D. Gillmore, M.D., Ph.D. Author Info & Affiliations

**Published November 16, 2024 | N Engl J Med 2024;391:2231-2241 | DOI: 10.1056/NEJMoa2412309**
VOL. 391 NO. 23 | Copyright © 2024

## Abstract

**BACKGROUND**

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, often fatal disease. Nexiguran ziclumeran (nex-z) is an investigational therapy based on CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease) targeting the gene encoding transthyretin (TTR).

**METHODS**

In this phase 1, open-label trial, we administered a single intravenous infusion of nex-z to patients with ATTR-CM. Primary objectives included assessment of the effect of nex-z on safety and pharmacodynamics, including the serum TTR level. Secondary end points included changes in N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, high-sensitivity cardiac troponin T levels, the 6-minute walk distance, and the New York Heart Association (NYHA) class.

**RESULTS**

A total of 36 patients received nex-z and completed at least 12 months of follow-up. Of these patients, 50% were in NYHA class III and 31% had variant ATTR-CM. The mean percent change from baseline in the serum TTR level was −89% (95% confidence interval [CI], −92 to −87) at 28 days and −90% (95% CI, −93 to −87) at 12 months. Adverse events were reported in 34 patients. Five had transient infusion-related reactions, and two had transient liver-enzyme elevations that were assessed as treatment-related. Serious adverse events, most of which were consistent with ATTR-CM, were reported in 14 patients. The geometric mean factor change from baseline to month 12 was 1.02 (95% CI, 0.88 to 1.17) in the NT-proBNP level and 0.95 (95% CI, 0.89 to 1.01) in the high-sensitivity cardiac troponin T level. The median change from baseline to month 12 in the 6-minute walk distance was 5 m (interquartile range, −33 to 49). A total of 92% of the patients had either improvement or no change in their NYHA class.

**CONCLUSIONS**

In this phase 1 study involving patients with ATTR-CM, treatment with a single dose of nex-z was associated with transient infusion-related reactions and consistent, rapid, and durable reductions in serum TTR levels. (Funded by Intellia Therapeutics and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT04601051.)

MAGNITUDE CLINICAL TRIAL

MAGNITUDE Study | Study Medication | ATTR-CM | About Clinical Research | Study Clinic Locations

## What is the MAGNITUDE study?

The MAGNITUDE study is a clinical research study for people with ATTR and cardiomyopathy (ATTR-CM). Researchers want to know if the research medicine called nexiguran ziclumeran (nex-z, also known as NTLA-2001) is safe and what effect it has on ATTR-CM.

You may be compensated for your time and inconvenience related to study participation for the visits you complete. Certain costs related to study participation, such as travel and meals, will also be available for study participants for reimbursement. Please ask your study team for more information about it.

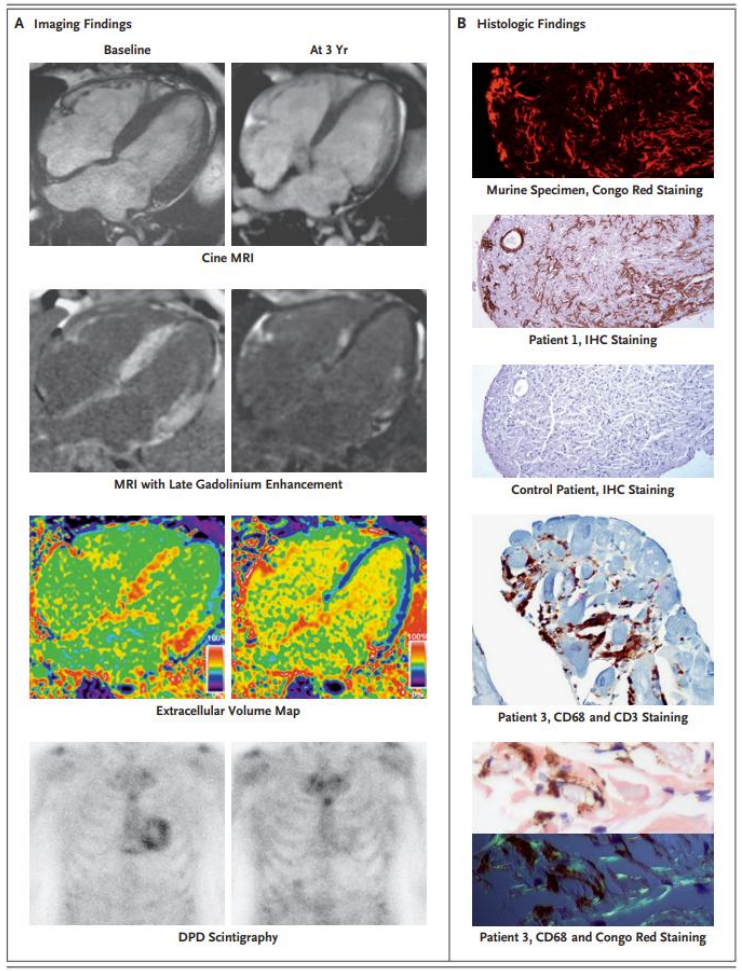
# IL FUTURO ….. ANTICORPI MONOCLONALI

The main goal of these “TTR depleters” is to reverse the course of the disease and prevent re-accumulation, especially in patients with advanced disease.
One notable approach is the development of monoclonal antibodies (mAbs) designed to specifically bind to misfolded TTR and mark the amyloid fibrils for clearance by phagocytes.
As a result, the amyloid fibrils in the heart and the peripheral nervous system are effectively removed

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

**Antibody-Associated Reversal of ATTR Amyloidosis–Related Cardiomyopathy**




J. Clin. Med. 2025, 14, 4785

# IL FUTURO ….. ANTICORPI MONOCLONALI

AMYLOID
2025, VOL. 32, NO. 1, 14–21
https://doi.org/10.1080/13506129.2024.2420809

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RESEARCH ARTICLE

OPEN ACCESS Check for updates

## PRX004 in variant amyloid transthyretin (ATTRv) amyloidosis: results of a phase 1, open-label, dose-escalation study

Ole B. Suhr[a], Martha Grogan[b], Ana Martins da Silva[c#], Chafic Karam[d], Pablo Garcia-Pavia[e], Brian Drachman[d], Wagner Zago[f], Radhika Tripuraneni[f#] and Gene G. Kinney[f]

[a]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [b]Mayo Clinic, Rochester, MN, USA; [c]Unidade Corino de Andrade, Centro Hospitalar Universitário do Porto, Porto, Portugal; [d]University of Pennsylvania, Philadelphia, PA, USA; [e]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain; [f]Prothena Biosciences Inc, Brisbane, CA, USA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.

# CONCLUSIONI

1. Diagnosi precoce >> trattamento precoce >> trattamento efficace

2. Il trattamento e la prevenzione delle comorbilità e delle complicanze >> un setting particolare

3. TERAPIE ‘’DISEASE-MODIFYNG‘’ >> in futuro molte possibilità terapeutiche >> precision medicine



G Ital Cardiol 2023;24(2):127-135
J. Clin. Med. 2025, 14, 4785

**GRAZIE**

**Dott.ssa Margherita Cannillo**
**SC Cardiologia Ospedale Civile di Ivrea ASL TO4**