XI Reunión. Estado del Arte en
INSUFICIENCIA CARDIACA
PRÁCTICA CLÍNICA Y MODELOS ORGANIZATIVOS
Sede: Hotel Meliá MaríaPita, A Coruña
A CORUÑA 27-28 SEPTIEMBRE 2024

XI Meeting. State of the Art in
HEART FAILURE
CLINICAL PRACTICE AND ORGANIZATIONAL MODELS
Venue: Hotel Meliá MaríaPita, A Coruña
# ACoruñaHF2024
A CORUÑA 27-28 SEPTEMBER 2024

# New therapies for ATTR-CM

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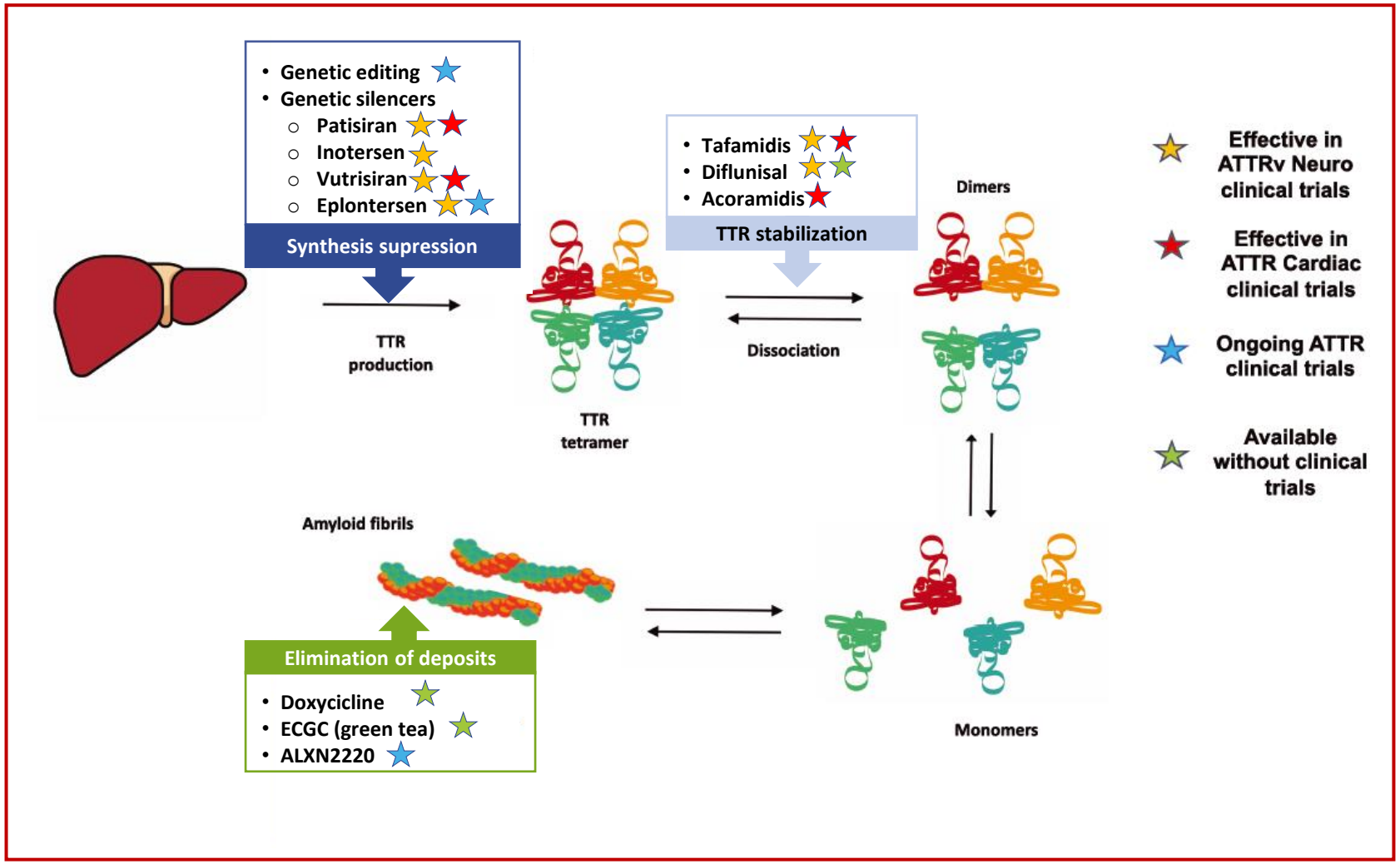
*Basurto University Hospital- Bilbao*

# The ATTR treatment is based on three categories: TTR stabilizers, TTR silencers, and anti-TTR antibodies





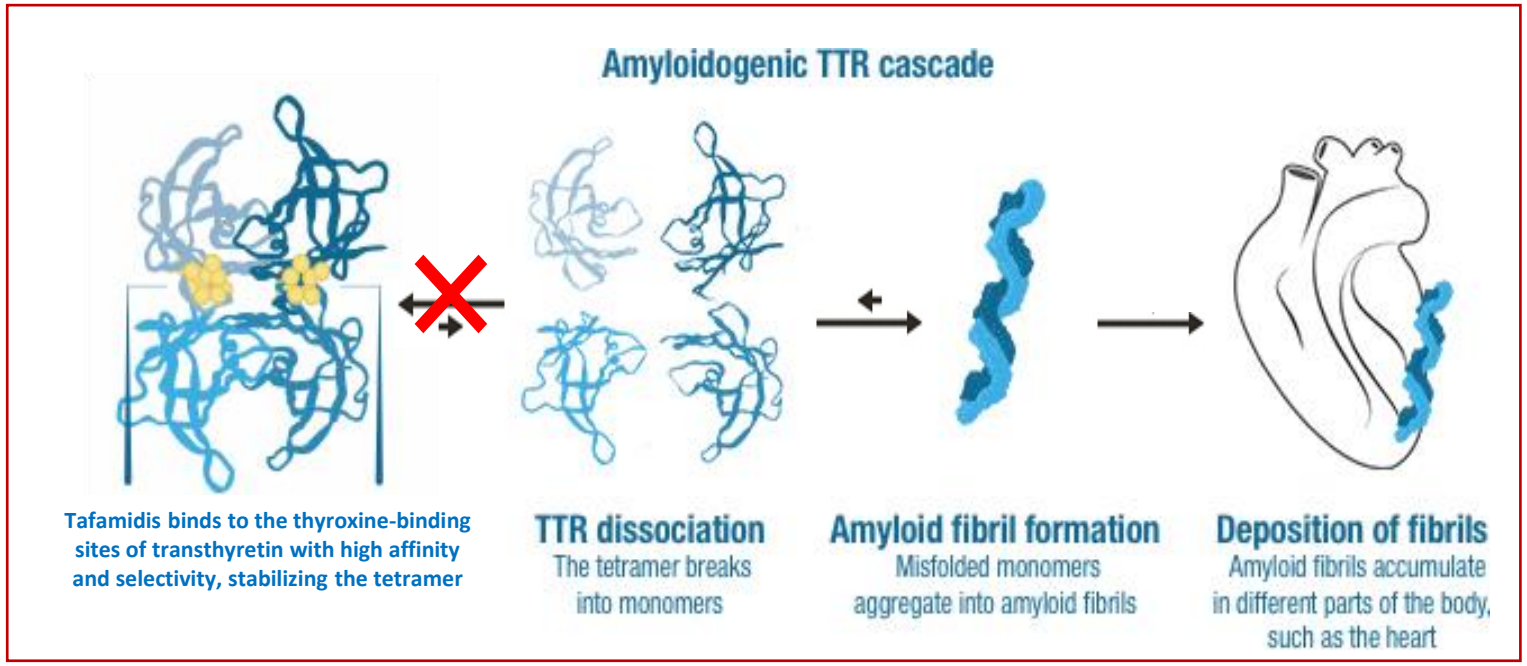

Garcia-Pavia P et al. Eur J Heart Fail. 2021;23(4):512-526.

# ATTR-ACT was the first study in patients with ATTR-CM

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 Coruña Heart Failure Academy

Maurer MS et al. N Engl J Med. 2018;379(11):1007-1016

# The ATTR-ACT study included adult patients with ATTRwt-CM or ATTRv-CM and heart failure

## Inclusion criteria

- ✓ **Patients between 18 and 90 years old**
- ✓ **TTR amyloid cardiomyopathy (wild type or variant)** defined by:
  - ✓ Presence of amyloid deposits in **biopsy tissue**, such as fat aspirate, salivary gland, median nerve connnective tissue sheath, or cardiac
  - ✓ Evidence of cardiac involvement by echocardiography with an **end-diastolic interventricular septal wall thickness >12 mm**
- ✓ **A medical history of Heart Failure (HF)** with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures that required/requires treatment with a diuretic for improvement
- ✓ **6-minute walk test >100 m**
- ✓ **NT-proBNP≥ 600 pg/ml**

**Patients included form December 2013 to August 2024**

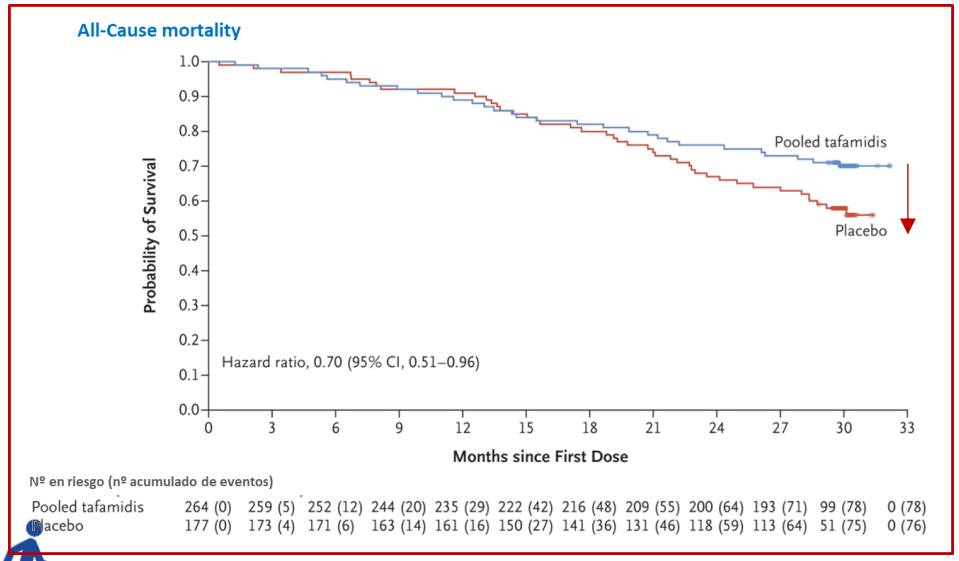
**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Tafamidis (N=264) | Placebo (N=177) |
|---|---|---|
| Age — yr | | |
| Mean | 74.5±7.2 | 74.1±6.7 |
| Median (range) | 75 (46–88) | 74 (51–89) |
| Sex — no. (%) | | |
| Male | 241 (91.3) | 157 (88.7) |
| Female | 23 (8.7) | 20 (11.3) |
| NYHA Class — no. (%) | | |
| Class I | 24 (9.1) | 13 (7.3) |
| Class II | 162 (61.4) | 101 (57.1) |
| Class III | 78 (29.5) | 63 (35.6) |
| Modified BMI† | 1058.8±173.8 | 1066.4±194.4 |
| NT-proBNP level — pg/ml | | |
| Median | 2995.9 | 3161.0 |
| Interquartile range | 1751.5–4861.5 | 1864.4–4825.0 |



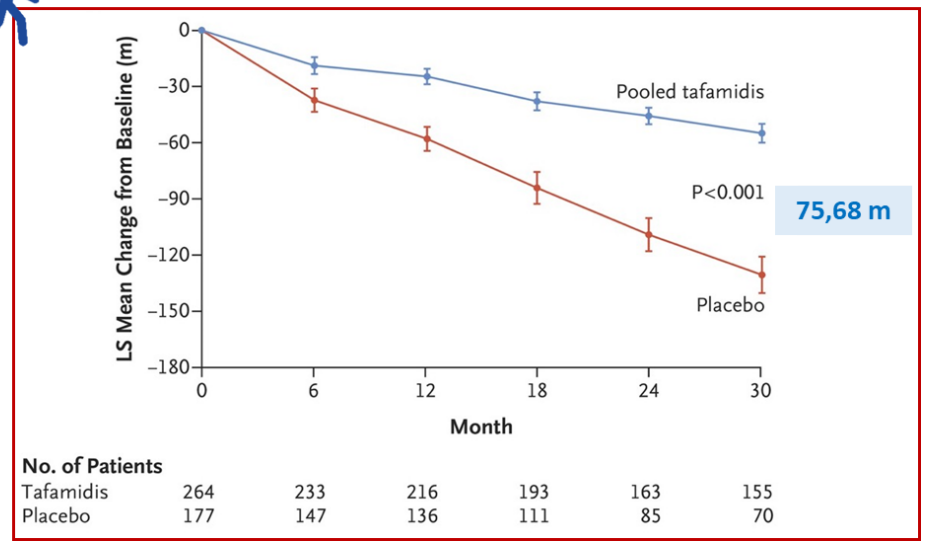
Maurer MS et al. N Engl J Med. 2018;379(11):1007-1016

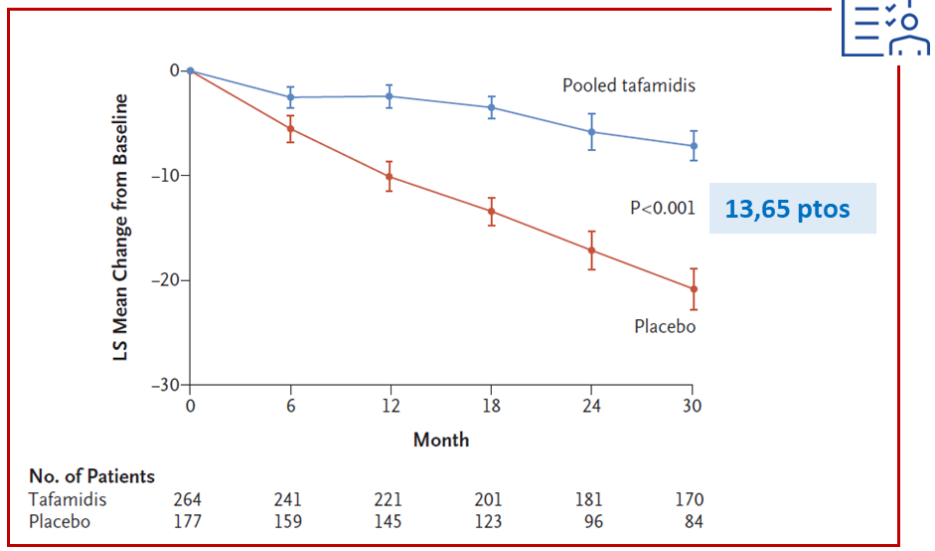
# Tafamidis reduced the risk of all-cause mortality and CV hospitalization, and slowed the deterioration in functional capacity and quality of life




**30% reduction in all-cause mortality**

**Reduces the frequency of hospital admissions for CV causes (32%), with the exception of the subgroup of patients in NYHA III functional class.**

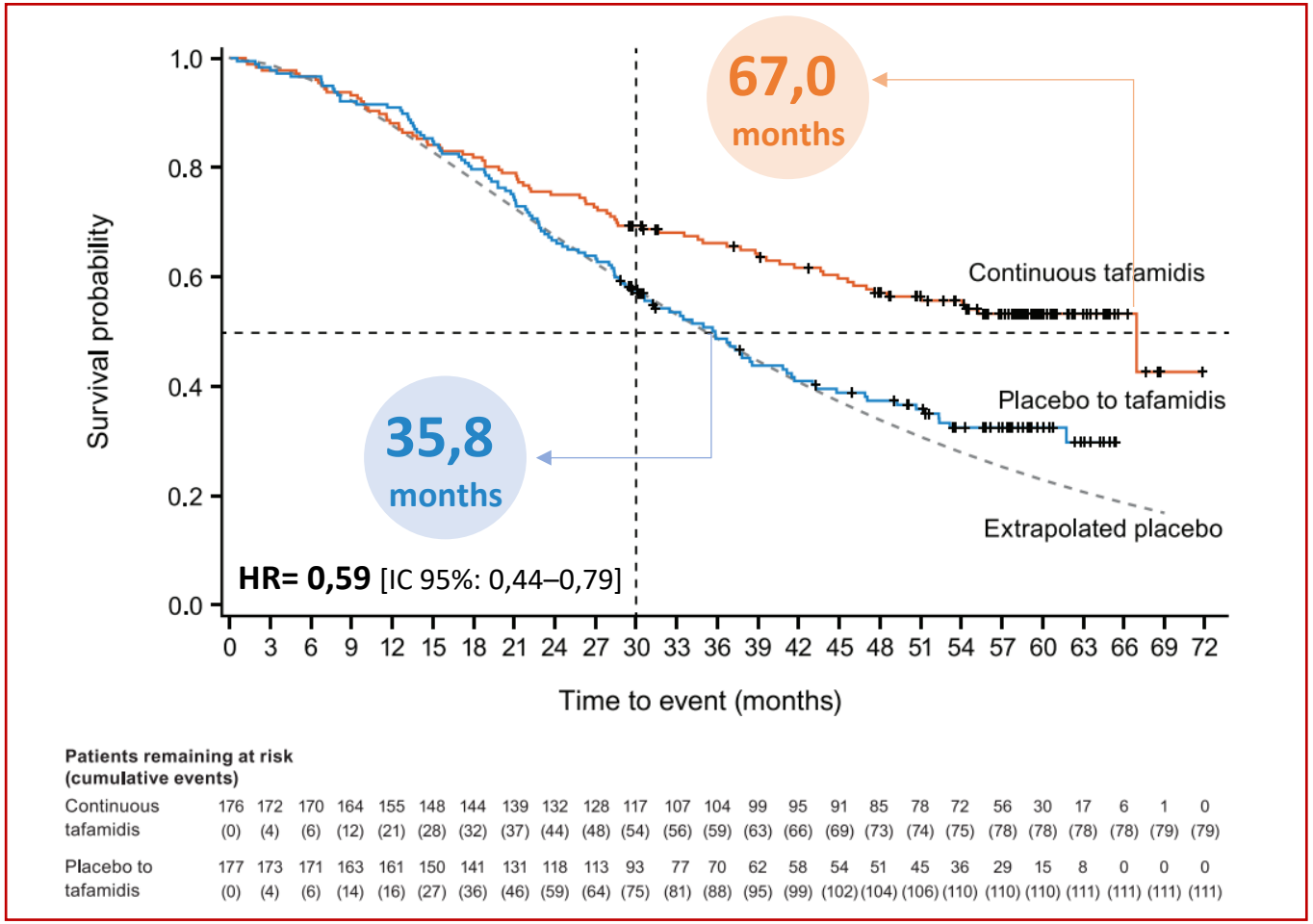





Maurer MS et al. N Engl J Med. 2018;379(11):1007-1016

# Tafamidis treatment improves long-term survival in patients with ATTR-CM




**41% reduction in the risk of all-cause mortality in patients with continuous tafamidis treatment compared with those first receiving placebo**

**Continuous tafamidis** (n=176)

Follow-up median: 58,5 months

All-cause mortality: **44,9%**
5 year survival rate: **53,2%.**

**Placebo/Tafamidis** (n=177)

Follow-up median: 57,1 months

All-cause mortality: **62,7%**
5 year survival rate: **32,4%.**



A Coruña Heart Failure Academy

Elliott P et al. Circ Heart Fail. 2022;15:e008193

# Osakidetza therapeutic positioning report

El paciente debe cumplir todos los siguientes criterios para inicio de tratamiento:

- Edad ≥ 45 en las formas ATTRv (amiloidosis por transtiretina variante) y edad ≥ 60 años en las formas ATTRwt (amiloidosis por transtiretina nativa). En los pacientes mayores de 85 años se valorará individualmente la indicación del tratamiento teniendo en cuenta su funcionalidad mediante escala Barthel; tratamiento indicado para pacientes independientes o con dependencia ligera, Barthel >90).
  Se debe tener en cuenta que en los ensayos clínicos no se han incluido pacientes de 90 años o mayores.
- Antecedentes de insuficiencia cardiaca, con al menos una hospitalización previa o evidencia clínica de insuficiencia cardiaca (sin hospitalización) que requiriesen tratamiento diurético.
- Clase funcional I a III de la New York Heart Association (NYHA).
- Espesor pared ventricular > 12 mm.
- Test de la marcha de 6 minutos de > 100 m.
- Transaminasas < 2 LSN.
- FG >25 ml/min.
- Valor de NT-proBNP (péptido natriurético pro-B de tipo N-terminal) ≥ 600 pg/mL.
- No estar recibiendo otros tratamientos modificadores de la enfermedad para la ATTR.
- Ausencia de comorbilidad clínicamente relevante que condicione una reducción de la expectativa o calidad de vida del paciente.
- Fracción de eyección preservada. **In ATTR-ACT LVEF 48,5%**

**Criterios de discontinuación del tratamiento**

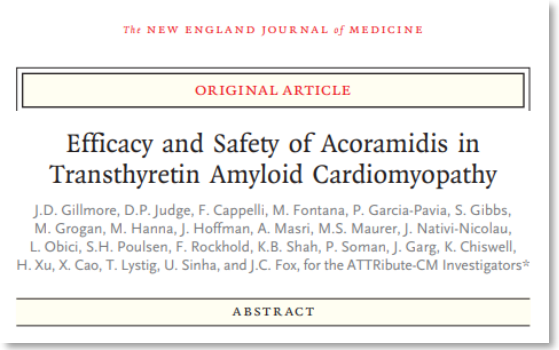
Se discontinuará el tratamiento cuando el paciente presente alguno de los siguientes criterios:

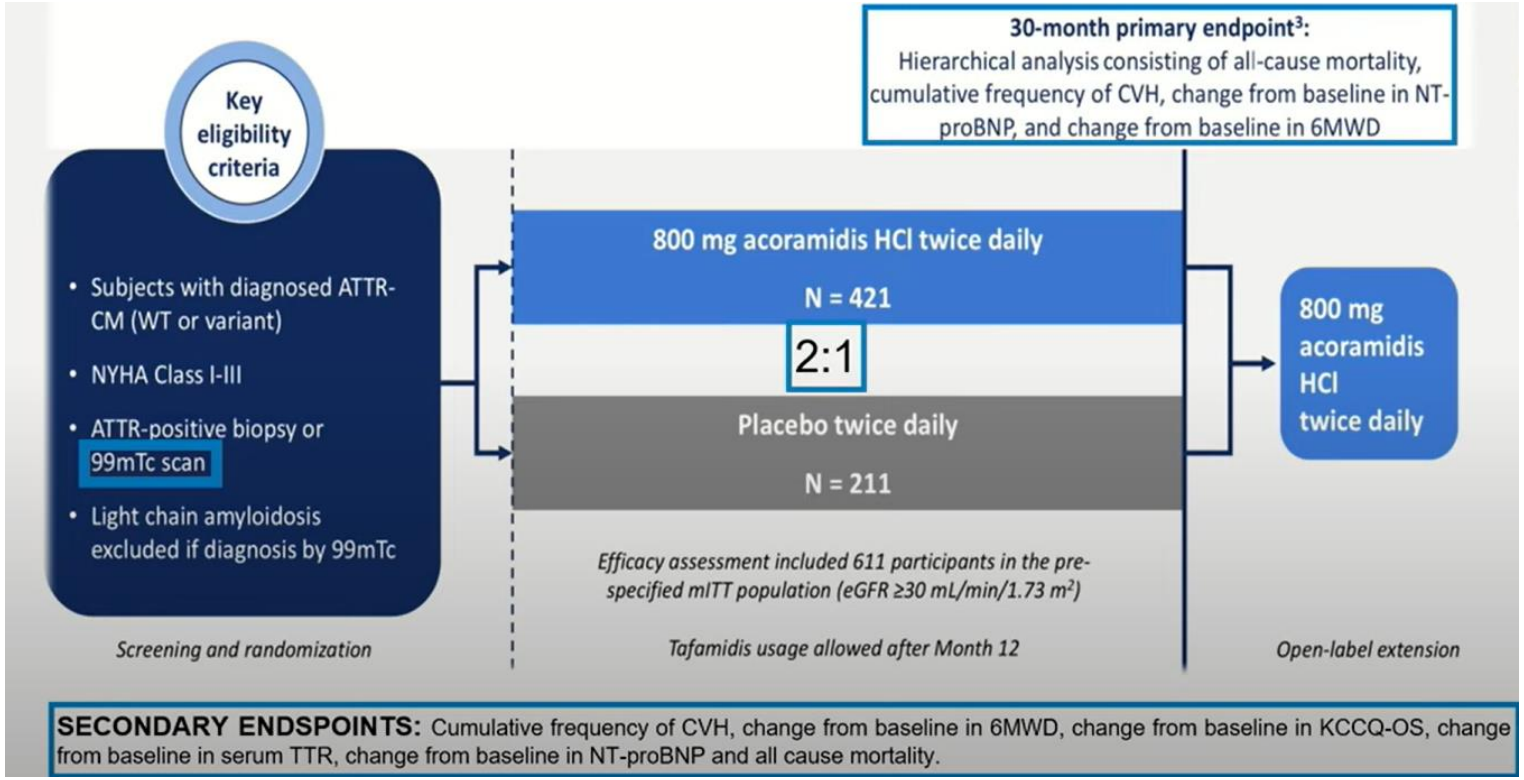
- Progresión de la enfermedad definida como a la clase IV de la NYHA u hospitalizaciones repetidas por insuficiencia cardiaca descompensada.
- Haber recibido un trasplante de corazón o de hígado.
- Implante un dispositivo de asistencia ventricular.
- Desarrollo de comorbilidad clínicamente relevante que condicione una reducción de la expectativa o calidad de vida del paciente.
- Tratamiento considerado fútil por su cardiólogo responsable.
- Falta de adherencia al tratamiento.

**Tafamidis is the first and only authorized disease-modifying drug treatment in ATTR-CM**

# Acoramidis, ATTRibute-CM trial

- ✓ As compared with other well-characterized TTR stabilizers (tafamidis, diflunisal, and tolcapone), **acoramidis has shown improved potency, binding affinity,** binding-site occupancy, binding thermodynamics, and TTR stabilization when assayed by a number of quantitative techniques.




*Treatment with tafamidis was not permitted during the initial 12 months of the trial, although such treatment was permitted thereafter. 17.5% of the patients received tafamidis and the median time until the initiation was 17.2 months*



A Coruña Heart Failure Academy

Gillmore J D, et al. N Engl J Med 2024;390:132-142

# ATTRibute-CM trial, inclusion and exclusion criteria

**Inclusion Criteria**

To be eligible to participate in the study, subjects must meet all the following criteria:

1. Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.
2. Be male or female ≥18 to ≤90 years of age.
3. Have an established diagnosis of ATTR-CM with either wild-type TTR or a variant TTR genotype (confirmed by genotyping) based on either (1) endomyocardial biopsy, or (2) positive $^{99m}$Tc-pyrophosphate or -bisphosphonate scan, combined with accepted laboratory criteria excluding a diagnosis of AL amyloidosis (based on both immunofixation electrophoresis (IFE) of serum and/or urine, and serum free light chain (sFLC) analysis); subjects with concurrent monoclonal gammopathy of undetermined significance (MGUS) may require confirmation of the diagnosis of ATTR-CM by endomyocardial biopsy with mass spectrometric analysis. Diagnosis of ATTR-CM will be confirmed by central review of the clinical data that were used to establish the diagnosis.
4. Have
   - **a.** a history of heart failure evidenced by at least one prior hospitalization for heart failure **or**
   - **b.** clinical evidence of heart failure without prior heart failure hospitalization manifested by signs or symptoms of volume overload or elevated intracardiac pressures (e.g., elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, or peripheral edema) **or**
   - **c.** heart failure symptoms that required or require ongoing treatment with a diuretic.
5. Have NYHA Class I-III symptoms due to ATTR cardiomyopathy.
6. Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use acceptable method(s) of contraception beginning with randomization and continuing for 30 days after the last dose of AG10.
7. For subjects taking cardiovascular medical therapy, with the exception of diuretic dosing, must be on stable doses (defined as no greater than 50% dose adjustment and no categorical changes of medications) for at least 2 weeks prior to Screening.
8. Have completed ≥150 m on the 6MWT on 2 consecutive tests prior to randomization.
9. Must have NT-proBNP levels ≥300 pg/mL at Screening.
10. Must have LV wall (interventricular septum or LV posterior wall) thickness ≥13 mm as measured by transthoracic echocardiogram or cardiac magnetic resonance (CMR) documented in medical history within 10 years of Screening or at Screening echocardiogram.

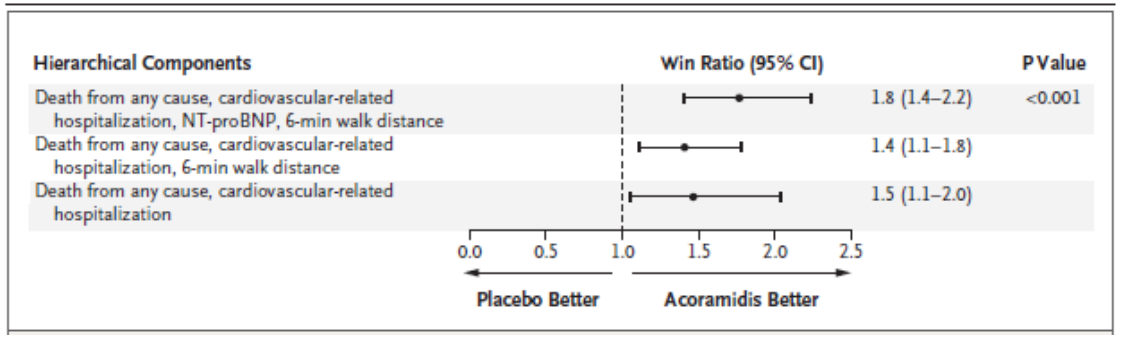
**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

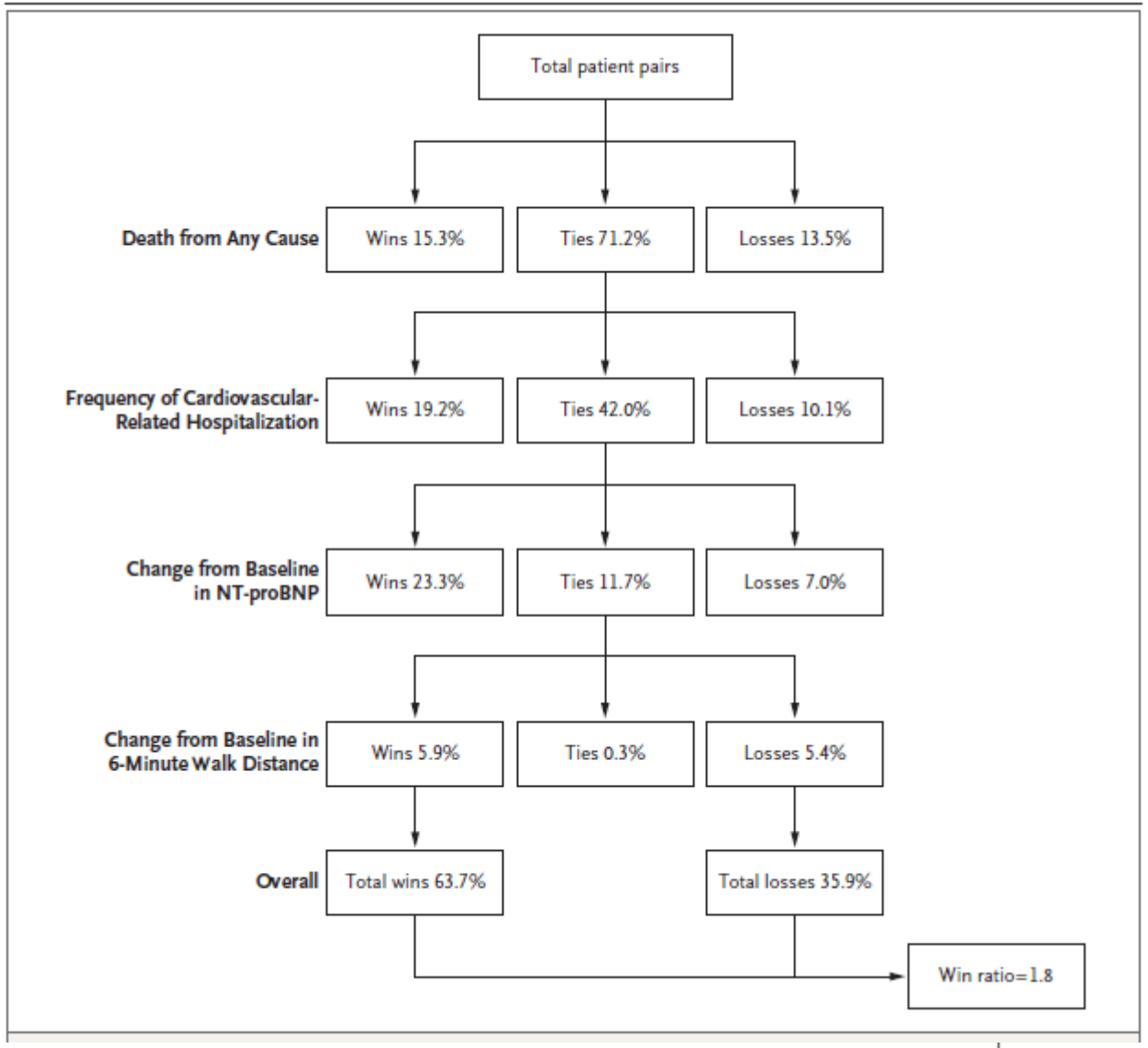
| Characteristic | Acoramidis (N=421) | Placebo (N=211) | All Patients (N=632) |
|---|---|---|---|
| Age — yr | 77.4±6.5 | 77.1±6.8 | 77.3±6.6 |
| Sex — no. (%) | | | |
| Male | 384 (91.2) | 186 (88.2) | 570 (90.2) |
| Female | 37 (8.8) | 25 (11.8) | 62 (9.8) |
| NT-proBNP — ng/liter | | | |
| Mean | 2946±2226 | 2725±1971 | 2872±2145 |
| Median (IQR) | 2326 (1332–4019) | 2306 (1128–3754) | 2326 (1278–3910) |
| Mean eGFR — ml/min/1.73 m$^2$ | 61±18 | 61±19 | 61±18 |
| NAC stage — no. (%)‡ | | | |
| I | 241 (57.2) | 120 (56.9) | 361 (57.1) |
| II | 134 (31.8) | 69 (32.7) | 203 (32.1) |
| III | 46 (10.9) | 22 (10.4) | 68 (10.8) |
| NYHA functional class — no. (%) | | | |
| I | 51 (12.1) | 17 (8.1) | 68 (10.8) |
| II | 293 (69.6) | 162 (76.8) | 455 (72.0) |
| III | 77 (18.3) | 32 (15.2) | 109 (17.2) |



Gillmore J D, et al. N Engl J Med 2024;390:132-142

# Acoramidis, in the ATTRibute-CM trial, demonstrated benefit at the primary endpoint

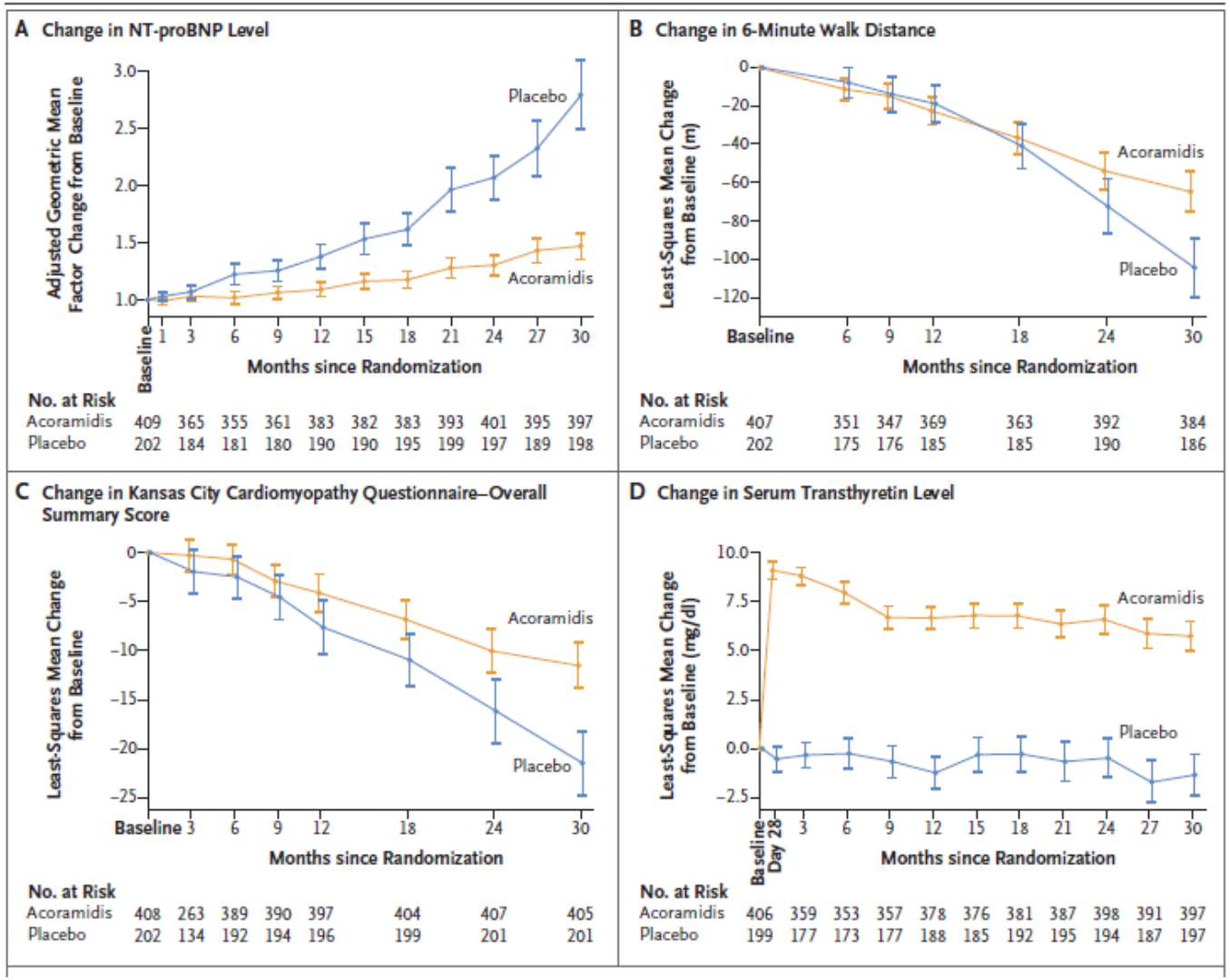


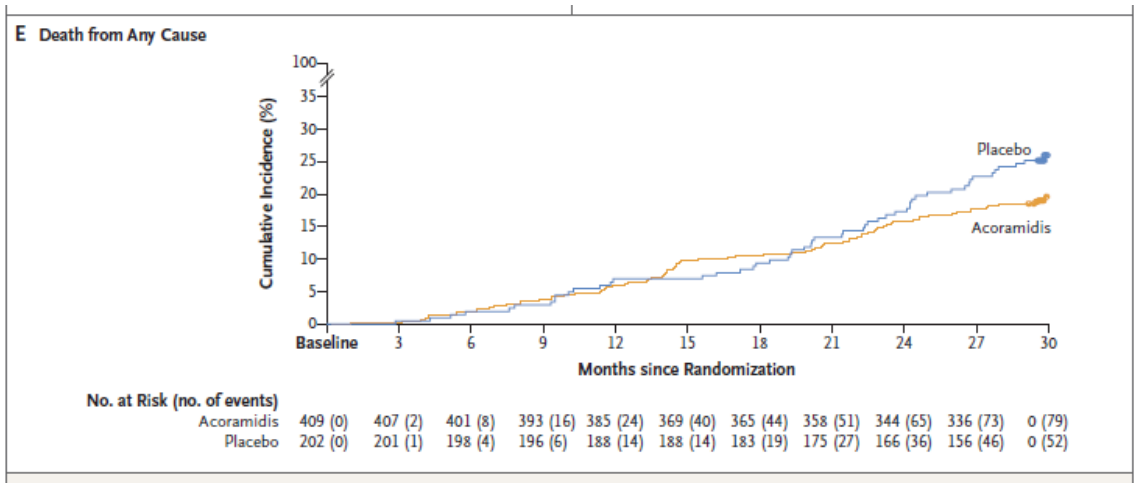






Gillmore J D, et al. N Engl J Med 2024;390:132-142

# Acoramidis, ATTRibute-CM trial, secondary endspoints




The reduction in all-cause mortality was not statistically significant

The observed 30-month survival of 74.3% in the placebo group in ATTRibute-CM was greater than the corresponding percentage of 70.5% in the combined tafamidis treatment groups in ATTR-ACT

**The FDA has approved acoramidis to treat patients with ATTR-CM**



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Gillmore J D, et al. N Engl J Med 2024;390:132-142

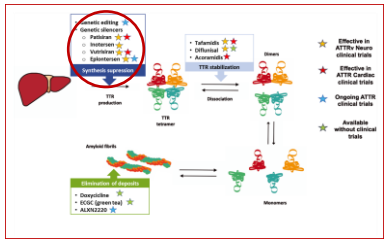
# APOLLO-B Trial, Patisiran Treatment in patients with ATTR-CM

- ✓ Patisiran, an **RNA interference therapeutic agent** with a lipid nanoparticle delivery system, targets the common 3′ untranslated region of TTR messenger RNA in the liver to **reduce circulating transthyretin** protein levels in both variant and wild-type ATTR amyloidosis
- ✓ Patisiran has been **approved for the treatment of variant ATTR amyloidosis in patients with polyneuropathy** on the basis of the results of the phase 3 APOLLO trial, which showed that patisiran halted or reversed the progression of neuropathy and improved quality of life.


**In APOLLO-B trial 360 patients randomly assigned to receive patisiran (0,3 mg per kg every 3 weeks) or placebo for 12 months**

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Patisiran (N=181) | Placebo (N=178) |
|---|---|---|
| Median age at screening (range) — yr | 76 (47–85) | 76 (41–85) |
| Male sex — no. (%) | 161 (89) | 160 (90) |
| Wild-type ATTR amyloidosis — no. (%) | 144 (80) | 144 (81) |
| Median time since diagnosis of ATTR amyloidosis (range) — yr | 0.8 (0.0–6.0) | 0.4 (0.0–10.0) |
| Treatment with tafamidis — no. (%) | | |
| At baseline | 46 (25) | 45 (25) |
| Started during 12-month double-blind period | 5 (3) | 3 (2) |
| ATTR amyloidosis stage — no. (%)‡ | | |
| Stage 1 | 124 (69) | 120 (67) |
| Stage 2 | 46 (25) | 45 (25) |
| Stage 3 | 11 (6) | 13 (7) |
| NYHA class — no. (%) | | |
| Class I | 10 (6) | 15 (8) |
| Class II | 156 (86) | 150 (84) |
| Class III | 15 (8) | 13 (7) |
| Median 6-minute walk distance (IQR) — m | 358.0 (295.0–420.0) | 367.7 (300.0–444.3) |
| Score on the KCCQ-OS§ | 69.8±21.2 | 70.3±20.7 |
| Laboratory values | | |
| Median NT-proBNP level (IQR) — pg/ml | 2008.0 (1135.0–2921.0) | 1813.0 (952.0–3079.0) |





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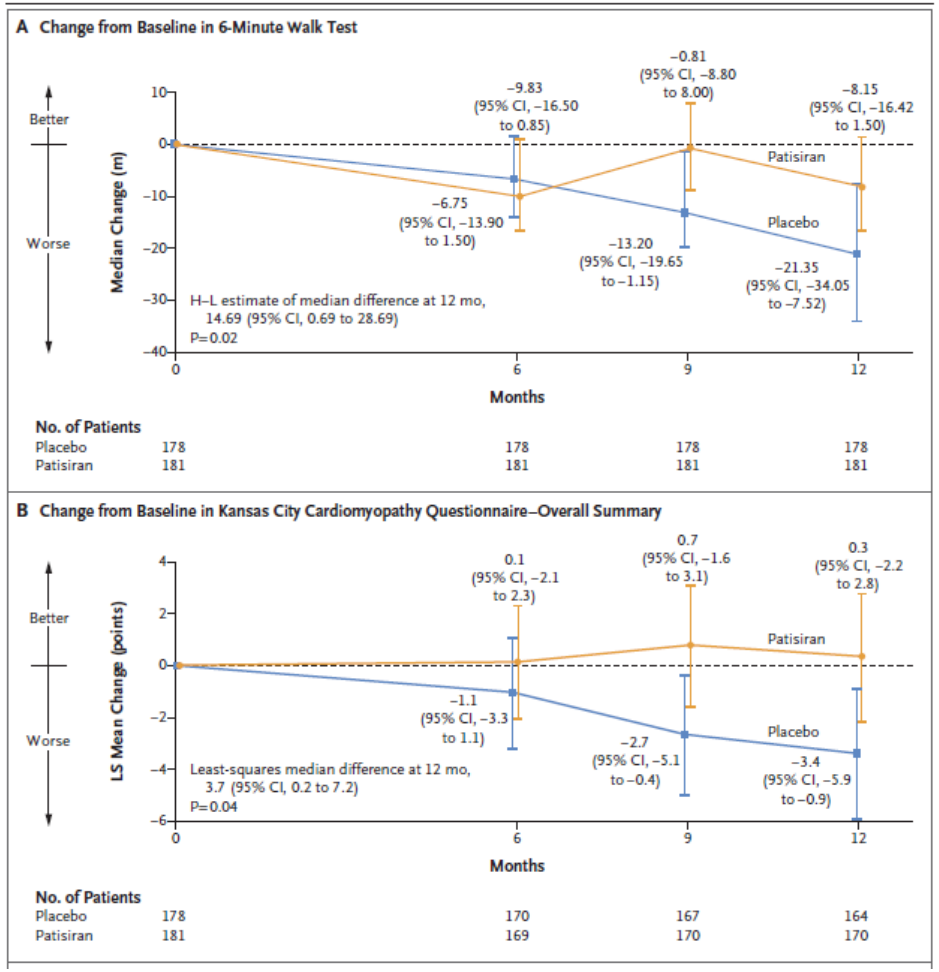
Maurer M.S. et al. N Engl J Med. 2023;389;1553-1565

# APOLLO-B Trial, Patisiran Treatment in patients with ATTR-CM




- ✓ At month 12, **the decline in the 6-minute walk distance was lower** in the patisiran group than in the placebo group. **The KCCQ-OS score increased** in the patisiran group and declined in the placebo group.
- ✓ Significant benefits were not observed for the second secondary end point (**composite of death from any cause, cardiovascular events, and change from baseline in the 6MWT distance**) over 12 months.
- ✓ **Infusion-related reactions**, arthralgia, and muscle spasms occurred more often among patients in the patisiran group than among those in the placebo group.

**The magnitude of its effect was not considered clinically sufficient to condition its approval in heart disease by the FDA.**

**As previously announced**, the FDA's Cardiovascular and Renal Drugs Advisory Committee met on September 13, 2023 to discuss the sNDA for patisiran and voted 9:3 that the benefits of patisiran outweigh its risks for the treatment of the cardiomyopathy of ATTR amyloidosis.



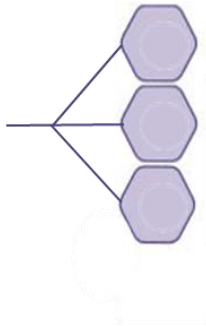
Maurer M.S. et al. N Engl J Med. 389;17

# Vurisiran, a RNAi therapeutic that reduces the production of the TTR protein

- ✓ Vutrisiran is a subcutaneously administered **RNA interference therapeutic agent** that inhibits hepatic synthesis of both wild-type and variant TTR messenger RNA at their source, resulting in rapid knockdown of the pathogenic protein before amyloid-causing monomers can form.
- ✓ **Enhance potency** as compared with earlier RNA interference therapeutic agents and allow for administration once every 3 months.
- ✓ Vutrisiran is **currently approved for the treatment of hereditary ATTR amyloidosis with polyneuropathy**

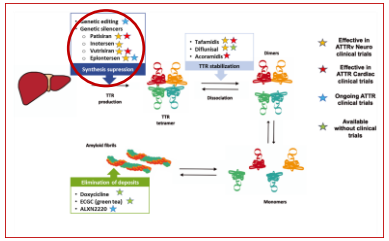
**ARNi de doble cadena**

Un ARNi de doble cadena modificado químicamente que se dirige a una secuencia específica del ARNm de la TTR.

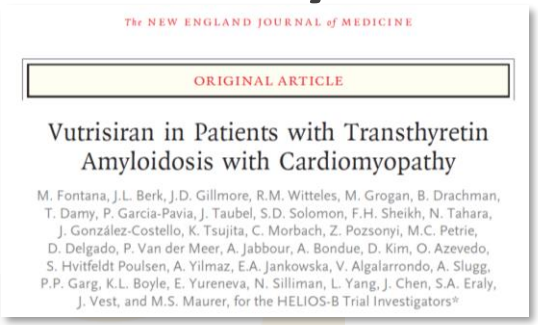


**Conjugado GalNAc**

Ligando que contiene 3 residuos de GalNAc (monosacárido derivado de la galactosa) para permitir el transporte a los hepatocitos



# HELIOS-B Study Desing: A Randomised, double-blind outcomes study in ATTR-CM




All the patients were instructed to take the recommended daily allowance of vitamin A.

**Patient Population**

**(N=655)**

- NTproBNP >300 and < 8,500
- ATTR: wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150 m; NT-proBNP limits[a] at baseline
- Approximately 40% of patients on tafamidis at baseline

**Select Exclusion Criteria:**

- NYHA Class IV HF
- PND Score ≥III at the screening visit
- Received prior TTR lowering treatment
- eGFR <30 ml/min
- NYHA III and ATTR stage 3 (NTproBNP >3,000 and eGFR <45 ml/min)

**1:1 RANDOMISATION[b]**

**Vutrisiran** SC q3M 25 mg

or

**Placebo** SC q3M

**Primary Endpoints**

- Composite outcome of all-cause mortality and recurrent CV events during double-blind (DB) period (**Month 33-36**) in:
  - Overall population
  - Monotherapy population (patients not on tafamidis at baseline)

**Secondary Endpoints[c]**

- Change from BL to **Month 30** in 6-MWT distance
- Change from BL to **Month 30** in KCCQ-OS
- All-cause mortality through **42 Months**
- Change from BL to **Month 30** in NYHA class

**Vutrisiran** SC q3M 25 mg

Vital status was ascertained for 99.8% of patients

Day -45 — **Screening period** — Day 1 (Baseline) — **Variable DB period** — M33 — M36 — M42 — OLE — M60

At the end of the double-blind period (a variable follow-up of 33 to 36 months), patients were eligible to be enrolled in the ongoing open-label extension period for up to 24 months



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Marianna Fontana M. D, et all. N Engl J Med 2024

# Contemporary Population

| Parameter | | Overall Population | |
|---|---|---|---|
| | | Placebo (N=328) | Vutrisiran (N=326) |
| Age (years), median (range) | | 76 (46, 85) | 77 (45, 85) |
| Male sex, n (%) | | 306 (93.3) | 299 (91.7) |
| hATTR amyloidosis, n (%) | | 39 (11.9) | 37 (11.3) |
| NYHA class, n (%) | I | 35 (10.7) | 49 (15.0) |
| | II | 258 (78.7) | 250 (76.7) |
| | III | 35 (10.7) | 27 (8.3) |
| ATTR disease stage, n (%) | 1 | 229 (69.8) | 208 (63.8) |
| | 2 | 87 (26.5) | 100 (30.7) |
| | 3 | 12 (3.7) | 18 (5.5) |
| Baseline 6-MWT, meters, mean (SD) | | 377 (96) | 372 (104) |
| Baseline KCCQ-OS, points, mean (SD) | | 72.26 (19.92) | 72.96 (19.44) |
| Baseline NT-proBNP, ng/L, median (IQR) | | 1801 (1042, 3082) | 2021 (1138, 3312) |
| Baseline Troponin I, ng/L, median (IQR) | | 65.2 (41.1, 105.5) | 71.9 (44.9, 115.9) |

No differences in age and gender

35.6% in ATTR-ACT and 17.2% in ATTRibute

10% in ATTRibute

350 m in ATTR-ACT

67 in ATTR-ACT

3,100 in ATTR-ACT and 2,300 in ATTRibute

**This differences could reflect an evolution in disease awareness and earlier diagnosis, and thus better prognosis within the recently diagnosed target patient population**





Marianna Fontana M. D, et all. N Engl J Med 2024

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| NYHA class, n (%) | I | 35 (10.7) | 49 (15.0) |
| | II | 258 (78.7) | 250 (76.7) |
| | III | 35 (10.7) | 27 (8.3) |
| ATTR disease stage, n (%) | 1 | 229 (69.8) | 208 (63.8) |
| | 2 | 87 (26.5) | 100 (30.7) |
| | 3 | 12 (3.7) | 18 (5.5) |
| Baseline 6-MWT, meters, mean (SD) | | 377 (96) | 372 (104) |
| Baseline KCCQ-OS, points, mean (SD) | | 72.26 (19.92) | 72.96 (19.44) |
| Baseline NT-proBNP, ng/L, median (IQR) | | 1801 (1042, 3082) | 2021 (1138, 3312) |
| Baseline Troponin I, ng/L, median (IQR) | | 65.2 (41.1, 105.5) | 71.9 (44.9, 115.9) |

**Substantial use of effective background medications**

- **Tafamidis** Time from study start to initial drop-in dose (median): 17 months
  - Baseline ~40% in both treatment arms
  - Drop-in on monotherapy population during DB period ~21% and ~22% for placebo and vutrisiran, respectively
- **SGLT2 inhibitors**
  - Baseline ~3% in both treatment arms
  - Drop-in during DB period ~35% and ~31% for placebo and vutrisiran, respectively

**Substantial use of diuretics**

- Baseline ~80% in both treatment arms
- Outpatient initiation or intensification of diuretics after first dose was ~56% and ~48% for placebo and vutrisiran, respectively

**Patients were not randomised to baseline tafamidis;** patients on baseline tafamidis were generally healthier based on NYHA class, NT-proBNP, 6-MWT, and KCCQ-OS score

**Evolution toward earlier diagnosis and improved HF management; contemporary patients have less advanced disease, and are managed with tafamidis, SGLT2 inhibitors, and diuretics**



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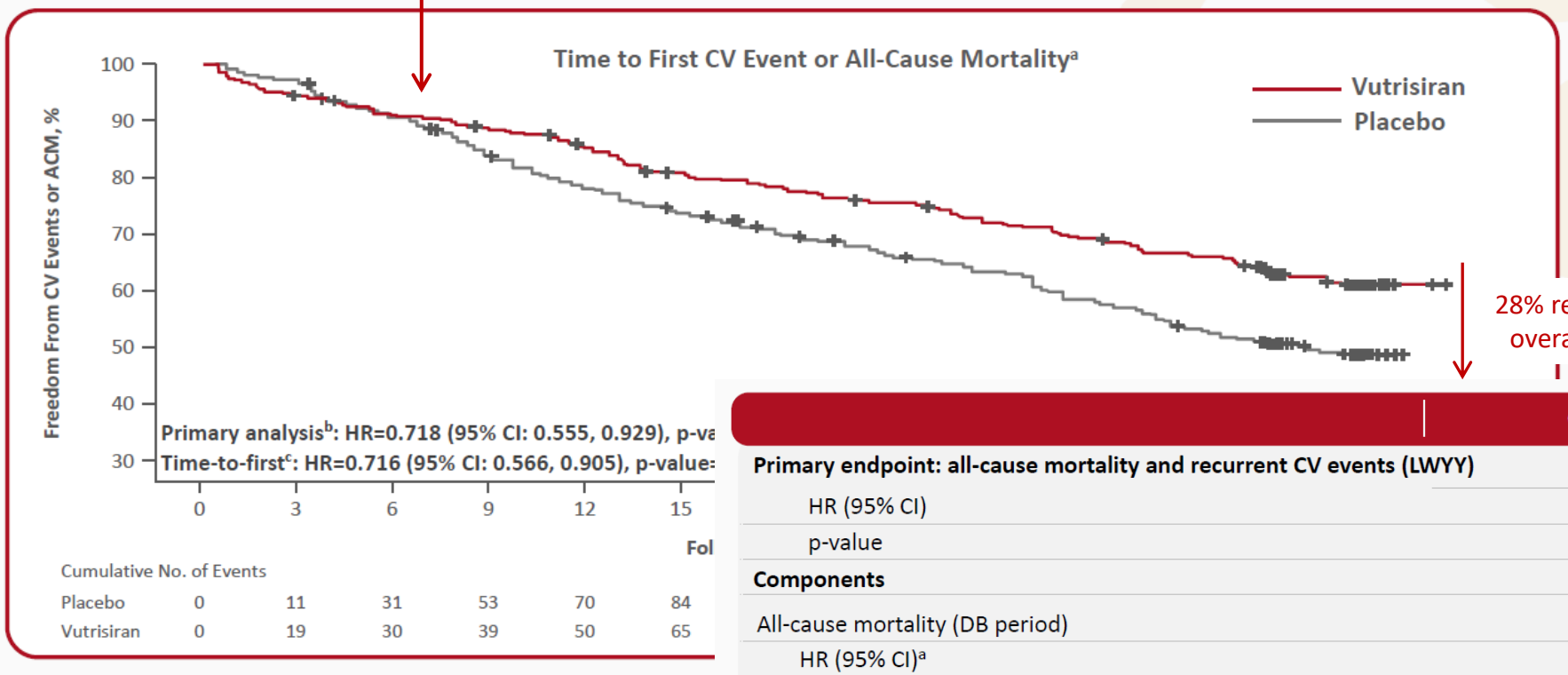
# Primary Endpoint: Statistically Significant Reduction in the Composite of All-Cause Mortality and Recurrent CV Events

Curves diverge 6 months after randomization




28% reduction in the overall population

| | Overall population (N = 654) |
|---|---|
| **Primary endpoint: all-cause mortality and recurrent CV events (LWYY)** | |
| HR (95% CI) | **0.718** (0.555, 0.929) |
| p-value | **0.0118** |
| **Components** | |
| All-cause mortality (DB period) | |
| HR (95% CI)[a] | **0.694** (0.490, 0.982) |
| Log-rank p-value | **0.0389** |
| Recurrent CV events (Poisson regression) | |
| Relative rate ratio (95% CI) | **0.733** (0.610, 0.882) |
| p-value | **0.0010** |



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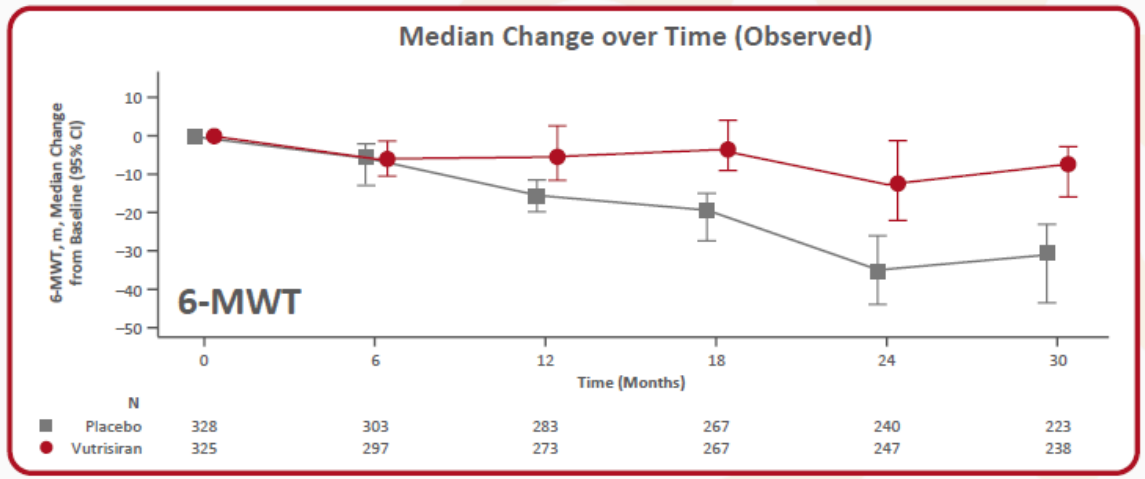
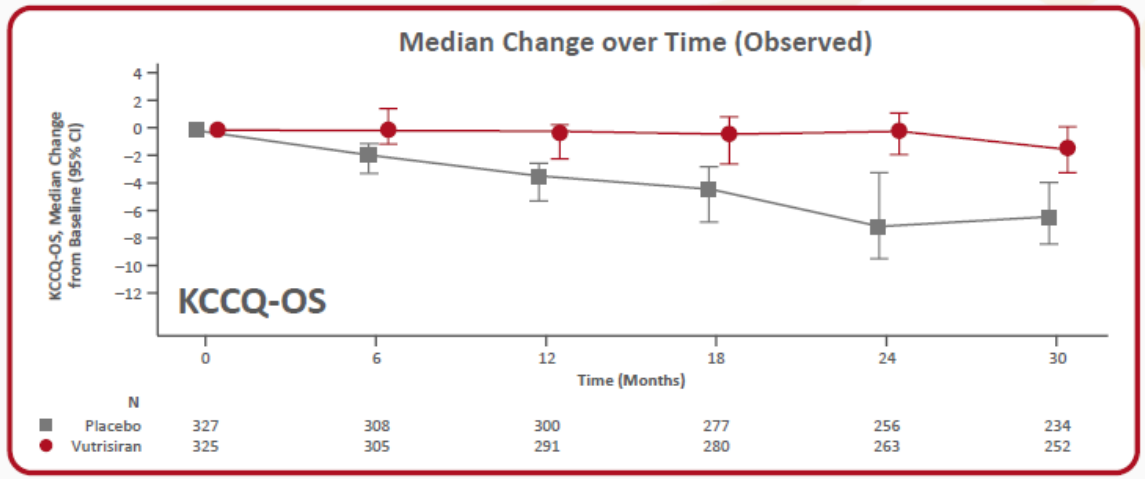
# Vutrisiran maintains functional capacity, health status, and quality of life




| Change from Baseline at Month 30 | Overall Population | |
|---|---|---|
| | Placebo (N=328) | Vutrisiran (N=326) |
| **6-MWT, n** | 285 | 294 |
| Median | -30.65 | -7.50 |
| LS mean (SEM) | -71.88 (4.79) | -45.42 (4.62) |
| LS mean difference (95% CI) | — | 26.46 (13.38, 39.55) |
| p-value | — | 0.00008 |
| **KCCQ-OS, n** | 298 | 306 |
| Median | -6.25 | -1.30 |
| LS mean (SEM) | -15.49 (1.26) | -9.68 (1.19) |
| LS mean difference (95% CI) | — | 5.80 (2.40, 9.20) |
| p-value | — | 0.0008 |
| **NYHA Class, n** | 328 | 326 |
| Stable or improved % | 61 | 68 |
| Difference in % patients stable or improved (95% CI) | — | 8.7 (1.3, 16.1) |
| p-value | — | 0.0217 |





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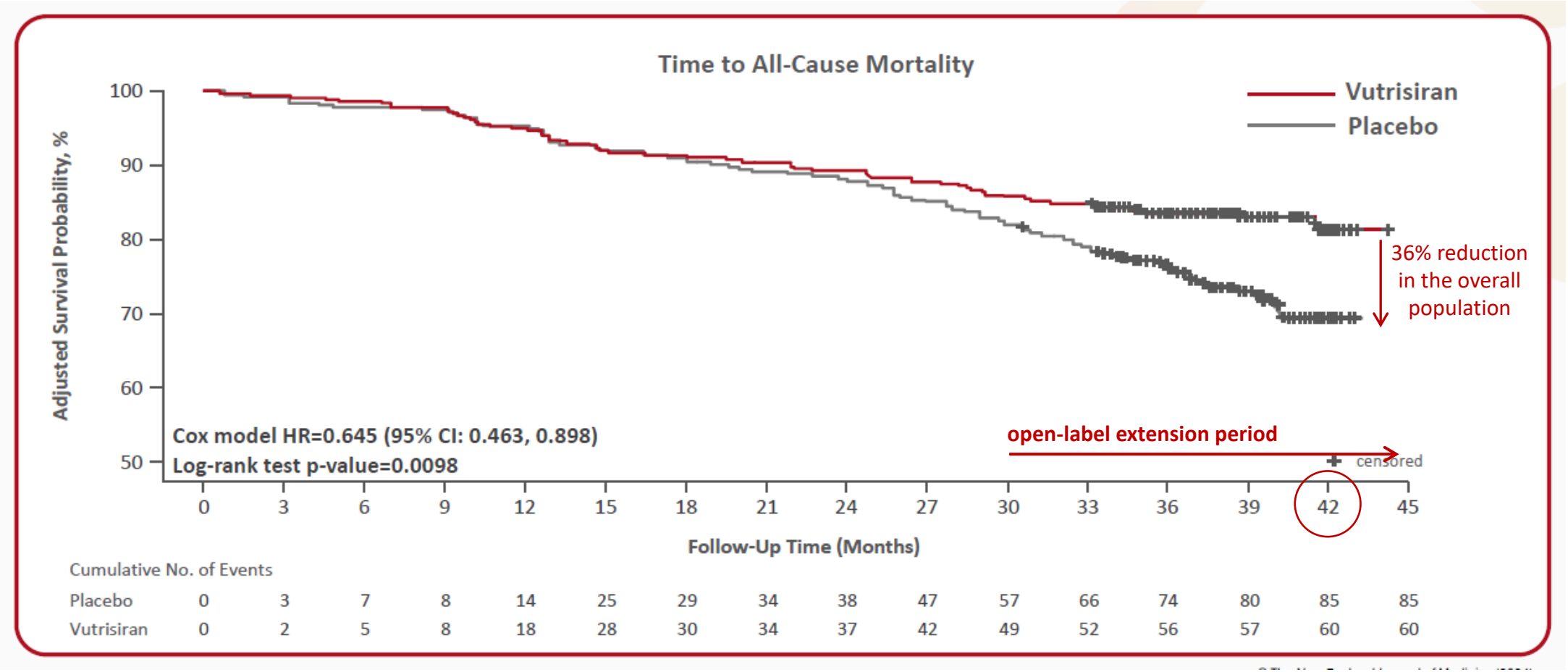
# Secondary Endpoint: Statistically Significant Reduction in All-Cause Mortality Througt 42 Months



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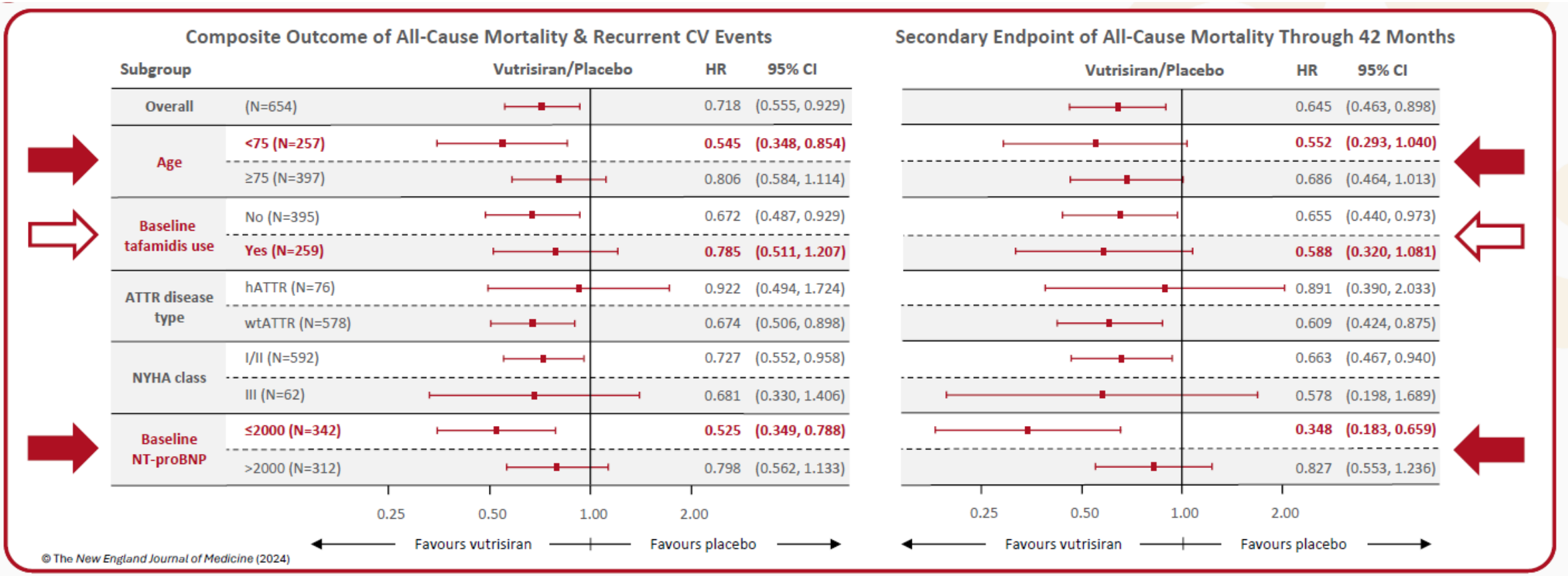
# Consistent Benefits across All Prespecified Subgroups




- ✓ **Greater benefits seen in patients with earlier disease** (age <75 years and NTproBNP ≤2000 ng/l), with 46% and 48% reduction, respectively, in primary composite endpoint, and 45% and 65% reduction, respectively, in all-cause mortality.
- ✓ **Consistente benefit in patients with or without baseline tafamidis**



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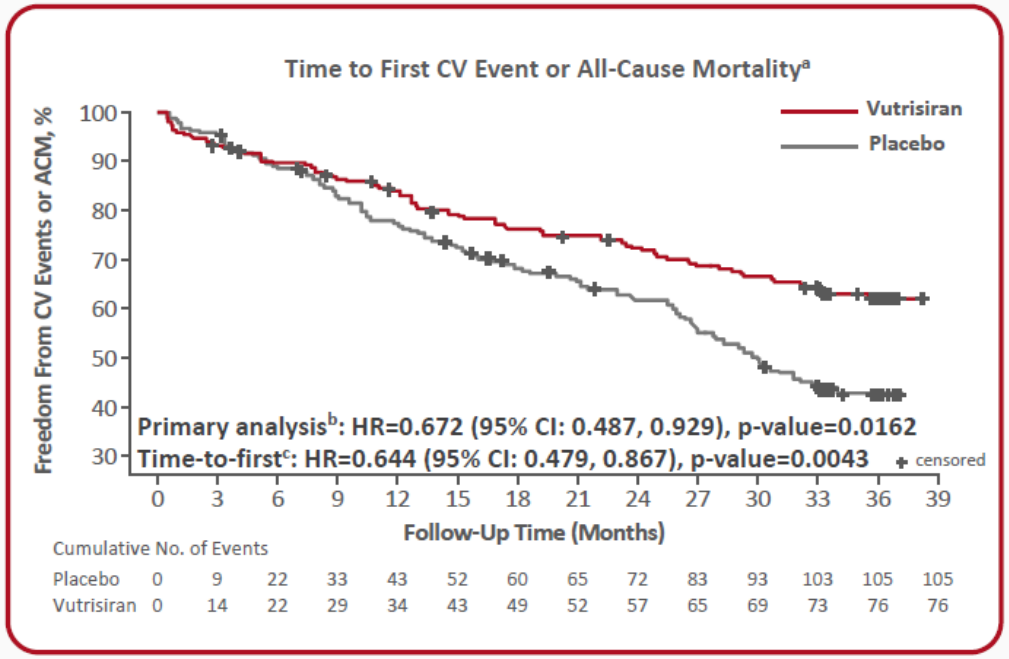
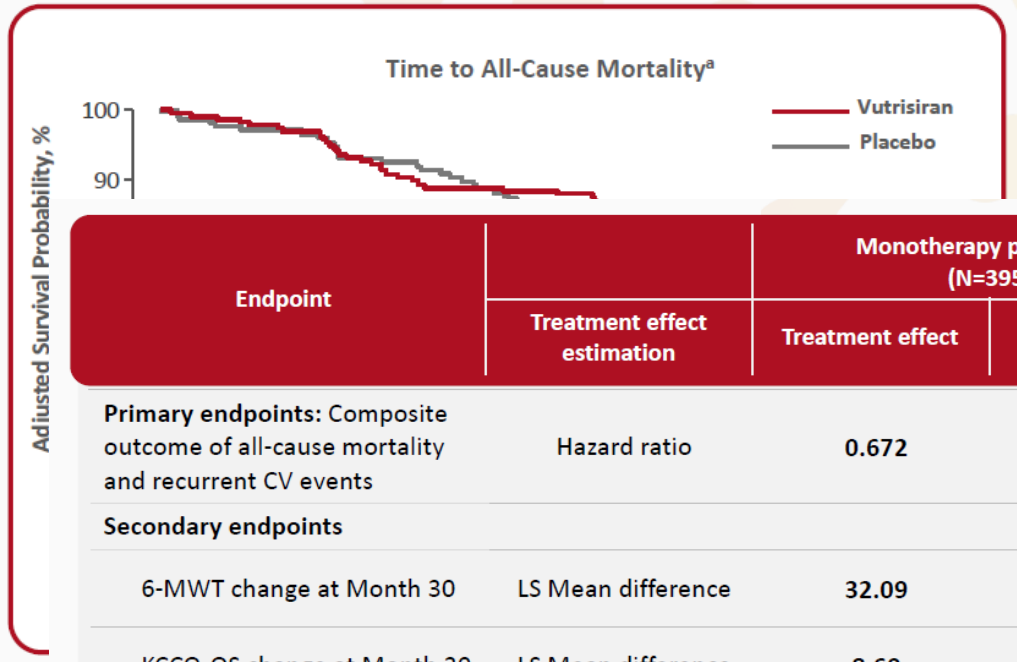
# Statistically Significant Outcomes Benefit with Vutrisiran Monotheraphy




**33% reduction in the primary composite endpoint**

| Endpoint | Treatment effect estimation | Monotherapy population (N=395) Treatment effect | p-value |
|---|---|---|---|
| **Primary endpoints:** Composite outcome of all-cause mortality and recurrent CV events | Hazard ratio | **0.672** | **0.0162** |
| **Secondary endpoints** | | | |
| 6-MWT change at Month 30 | LS Mean difference | **32.09** | **0.0005** |
| KCCQ-OS change at Month 30 | LS Mean difference | **8.69** | **0.0003** |
| All-cause mortality through Month 42 | Hazard ratio | **0.655** | **0.0454** |
| NYHA class: % stable or improved at Month 30 | Adjusted % difference | **12.5%** | **0.0121** |



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# Safety Profile

| AE Category, n (%) | Overall Population | |
|---|---|---|
| | Placebo (N=328) | Vutrisiran (N=326) |
| AEs | 323 (98.5) | 322 (98.8) |
| SAEs | 220 (67.1) | 201 (61.7) |
| Severe AEs | 194 (59.1) | 158 (48.5) |
| AE leading to treatment discontinuation | 13 (4.0) | 10 (3.1) |
| Deaths[a] | 63 (19.2) | 49 (15.0) |



- ✓ **The mayority of AEs were mild or moderate**
- ✓ No AEs seen ≥3% more frequently with vutrisiran compared with placebo
- ✓ Cardiac AEs were similar or lower with vutrisiran compared with placebo



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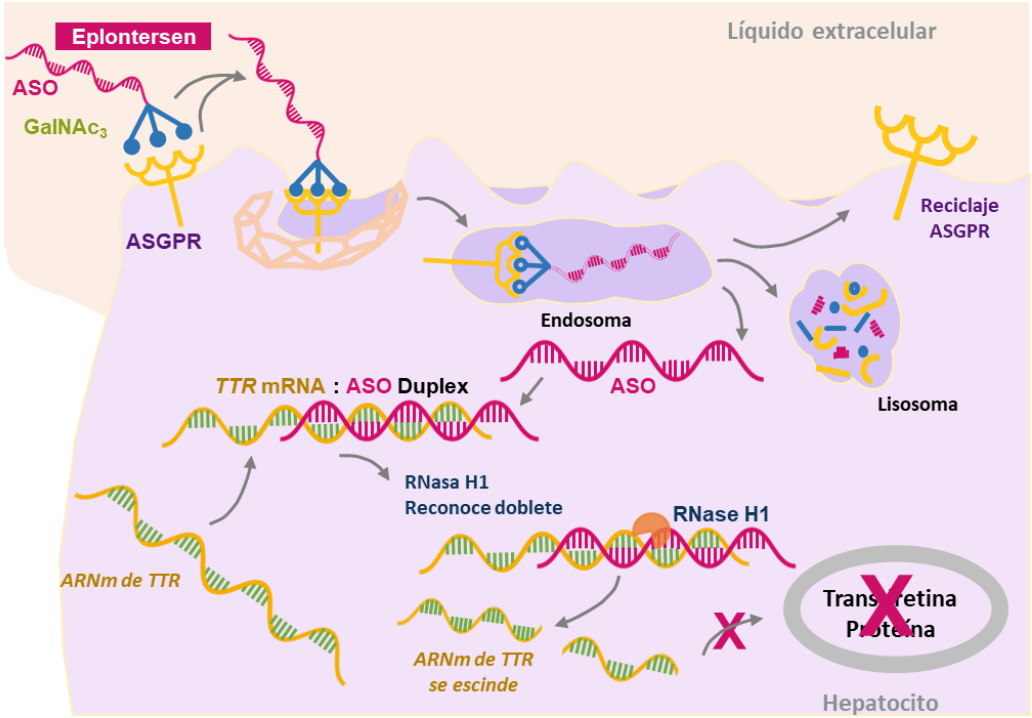
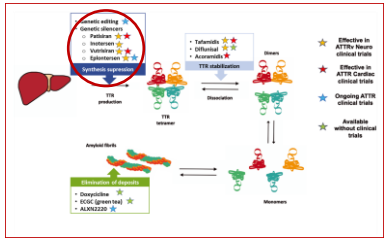
# Eplontersen

- ✓ Eplontersen is an investigational ASO that is being developed for the treatment of ATTR amyloidosis. It is designed to bind to wild-type (acquired) TR mRNA, as well as all TTR variants tested, to prevent protein translation, thus resulting in degradation of the TTR mRNA and lower TTR protein production.
- ✓ Eplontersen uses the advanced LICA technology platform in which **the ASO is conjugated to the ligand GalNAc3**. The conjugation of the ASO is thought to **enhance drug delivery to the hepatocyte**, the primary producer of TTR.
- ✓ Compared to unconjugated ASOs such as inotersen, this hepatocyte-targeted delivery with GalNAc3-conjugation **increases drug potency** 20-30-fold, reduces systemic drug exposure, **supports lower, less frequent dosing**, and could potentially increase the safety margin.

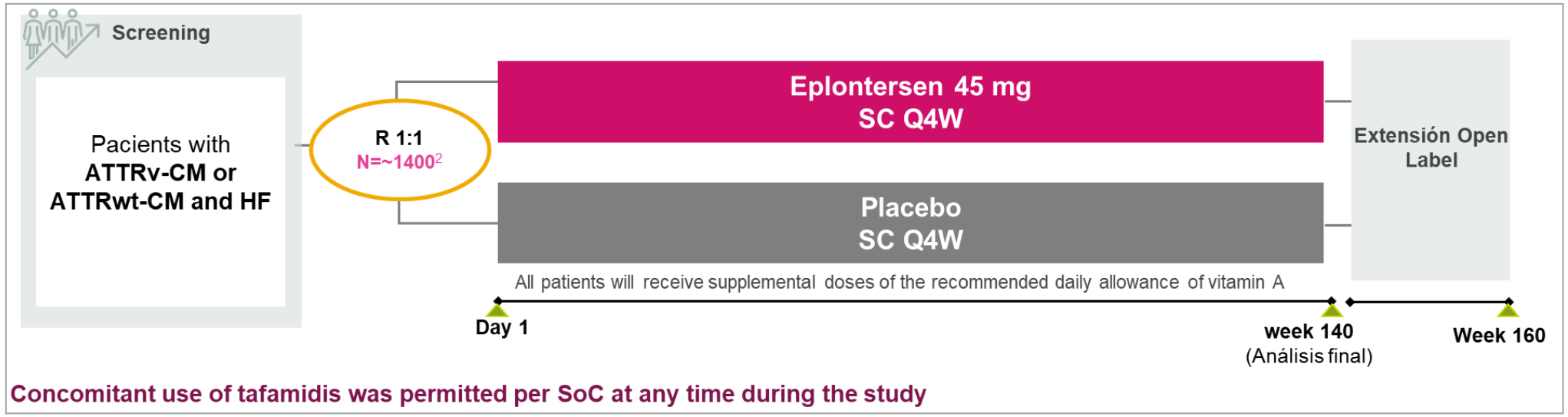


# Eplontersen in patients with ATTR-CM, ongoing trial

cardio TTRansform

**Global, Randomized, Multicenter, Double-Blind, Placebo-Controlled Trial in Patients With ATTRv-CM and ATTRwt-CM**




**Concomitant use of tafamidis was permitted per SoC at any time during the study**

**Results 2025/2026**

# Genetic editing in patients with ATTR-CM

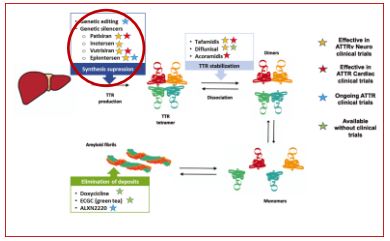
The NEW ENGLAND JOURNAL of MEDICINE

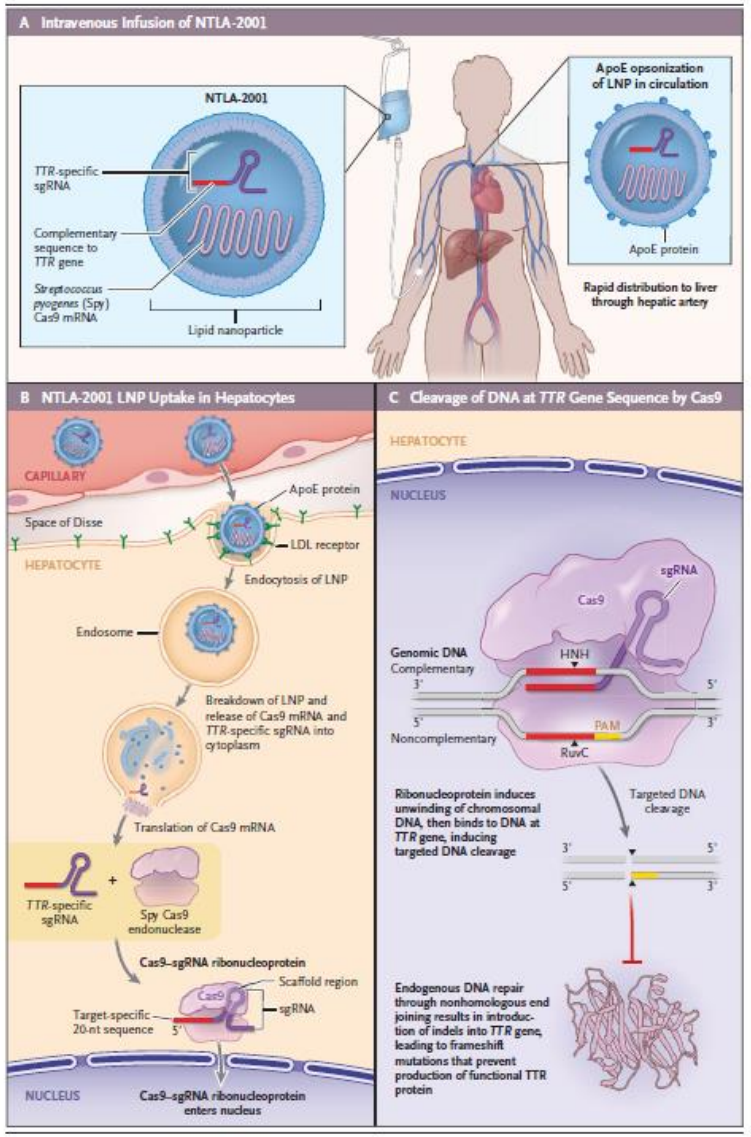
ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

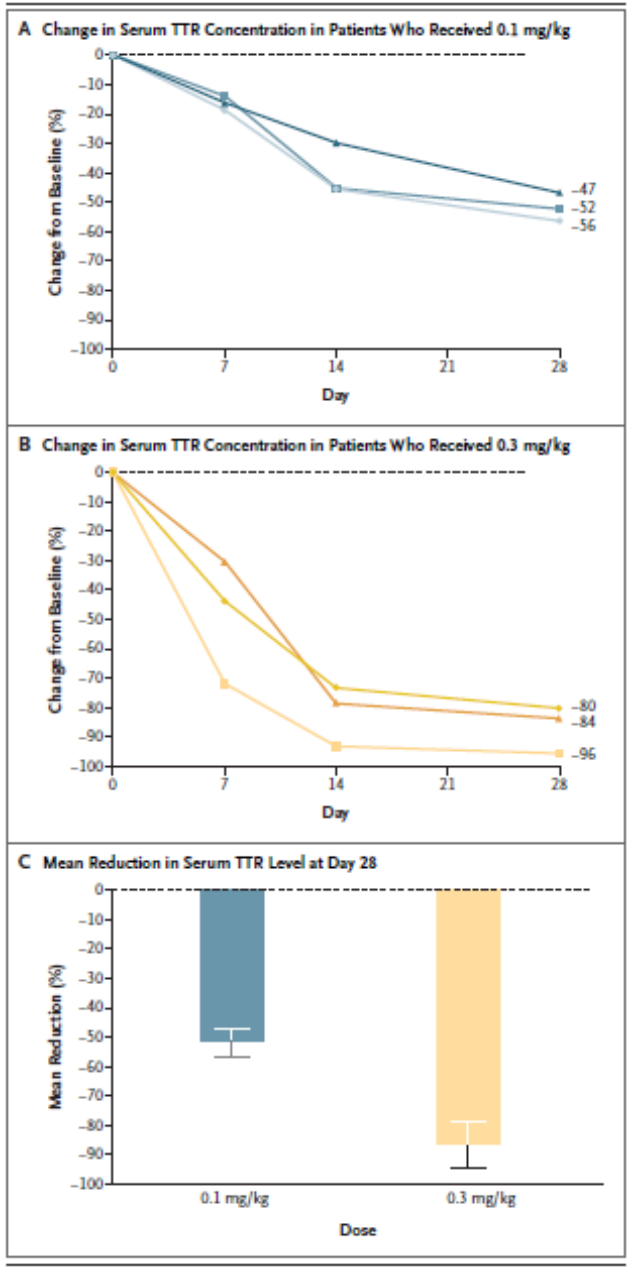
CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

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.

- ✓ NTLA-2001 is **an in vivo gene-editing therapeutic agent** that is designed to treat ATTR amyloidosis by reducing the concentration of TTR in serum. It is based on the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (**CRISPR-Cas9**) system and comprises a lipid nanoparticle encapsulating messenger RNA for Cas9 protein and a single guide RNA targeting *TTR*.





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# MAGNITUDE: A Phase 3 Study of NTLA-2001 in Participants With ATTR-CM

RECRUITING

**MAGNITUDE: A Phase 3 Study of NTLA-2001 in Participants With Transthyretin Amyloidosis With Cardiomyopathy (ATTR-CM)**

ClinicalTrials.gov ID NCT06128629

**CRISPR gene editing**

Sponsor Intellia Therapeutics

Information provided by Intellia Therapeutics (Responsible Party)

Last Update Posted 2024-09-20

- ✓ **765 patients**
- ✓ Primary endpoint: Composite outcome of **CV mortality and CV events**

## Spain

Madrid, Spain, 28222

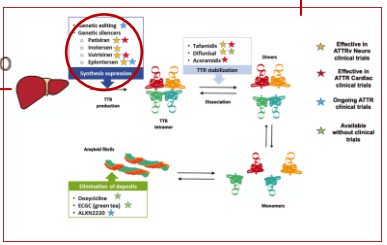
Hospital Universitario Puerta de Hierro Majadahonda

Inclusion Criteria:

- Documented diagnosis of ATTR amyloidosis with cardiomyopathy
- Medical history of heart failure (HF)
- Symptoms of HF are optimally managed and clinically stable within 28 days prior to administration of study intervention
- Screening NT-proBNP, a blood marker of HF severity, greater than or equal to 1000 pg/mL (or greater than or equal to 2000 pg/mL if participant has known atrial fibrillation)

Exclusion Criteria:

- New York Heart Association (NYHA) Class IV HF
- Polyneuropathy Disability score of IV (confined to wheelchair or bed)
- Has hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection
- History of active malignancy within 3 years prior to screening
- RNA silencer therapy (patisiran, inotersen and/or eplontersen) within 12 months prior to dosing. Any prior vutrisiran use is not allowed
- Initiation of tafamidis within 6 months prior to study dosing
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
- Liver failure
- Uncontrolled blood pressure
- Unable or unwilling to take vitamin A supplementation for the duratio



# Study of ALXN2220 Versus Placebo in Adults with ATTR-CM (DepleTTR-CM)

Inclusion Criteria:

- Centrally confirmed diagnosis of ATTR-CM with either wild-type or variant TTR genotype
- End-diastolic interventricular septal wall thickness ≥ 11 mm for women or ≥ 12 mm for men on echocardiography measured at Screening
- NT-proBNP > 2000 pg/mL at Screening
- Treatment with a loop diuretic for at least 30 days prior to Screening
- History of heart failure NYHA Class II-IV at Screening
- Life expectancy of ≥ 6 months as per the Investigator's judgment
- Males and females of childbearing ability must use contraception

Exclusion Criteria:

- Known leptomeningeal amyloidosis
- Known light chain (AL) or secondary amyloidosis (AA), or any other form of systemic amyloidosis
- Acute coronary syndrome, unstable angina, stroke, transient ischemic attack, coronary revascularization, cardiac device implantation, cardiac valve repair, or major surgery within 3 months of Screening
- Uncontrolled clinically significant cardiac arrhythmia, per Investigator's assessment
- LVEF < 30% on echocardiography
- Renal failure requiring dialysis or an eGFR < 20 mL/min/1.73 m2 at Screening
- Polyneuropathy with PND score IV

**The trials with withdrawers are the first that will allow patients to be included in NYHA IV.**

RECRUITING

**Study of ALXN2220 Versus Placebo in Adults With ATTR-CM (DepleTTR-CM)**

ClinicalTrials.gov ID NCT06183931

Sponsor Alexion Pharmaceuticals, Inc.

Information provided by Alexion Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-09-05

- ✓ **1,000 patients**
- ✓ Primary endpoint: Composite outcome of **all-cause mortality and CV events**

# The future of ATTR-CM treatment

ACTIVE, NOT RECRUITING

coramitug

Phase 2

**A Research Study to Look at How a New Medicine Called NNC6019-0001 Works and How Safe it is for People Who Have Heart Disease Due to Transthyretin (TTR) Amyloidosis**

ClinicalTrials.gov ID NCT05442047

Sponsor Novo Nordisk A/S

Information provided by Novo Nordisk A/S (Responsible Party)

Last Update Posted 2024-09-19

RECRUITING

Phase 2

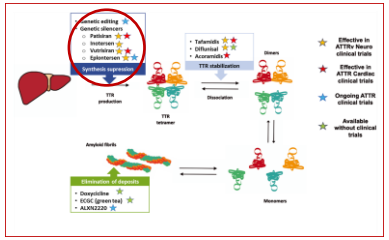
**A Phase I/IIa, Open-label, Single Ascending Dose and Dose-expansion Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of YOLT-201 in Patients With Transthyretin Amyloidosis Polyneuropathy (ATTR-PN) or Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM)**

ClinicalTrials.gov ID NCT06539208

Sponsor YolTech Therapeutics Co., Ltd

Information provided by YolTech Therapeutics Co., Ltd (Responsible Party)

Last Update Posted 2024-08-06



# Conclusions

- ✓ **Tafamidis is the only drug available for the treatment of patients with ATTR-CM, but acoramidis and vutrisiran have already demonstrated their benefit in clinical trials. Patisiran, despite showing benefit in the primary objective of APOLLO-B, has not been approved by the FDA because it is not considered clinically significant.**

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- ✓ The studies are not comparable to each other. Although they have similar inclusion criteria, patients included in most recent studies are in more recent stages of the disease, with a probable better prognosis.

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- ✓ It will be necessary to establish criteria for starting treatment (until now only patients with clinical HF), the starting drug (monotherapy or combined treatment), criteria for disease progression, response to treatment and switching between treatments (biomarkers, echo, etc.).

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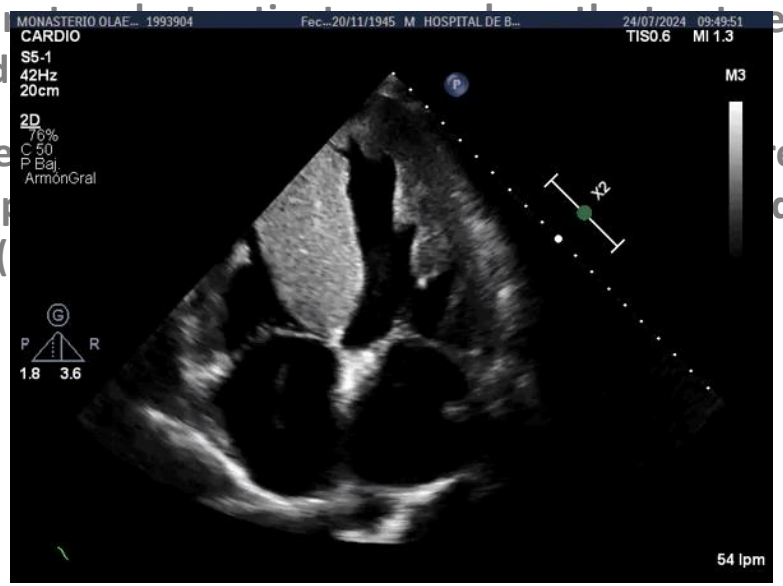


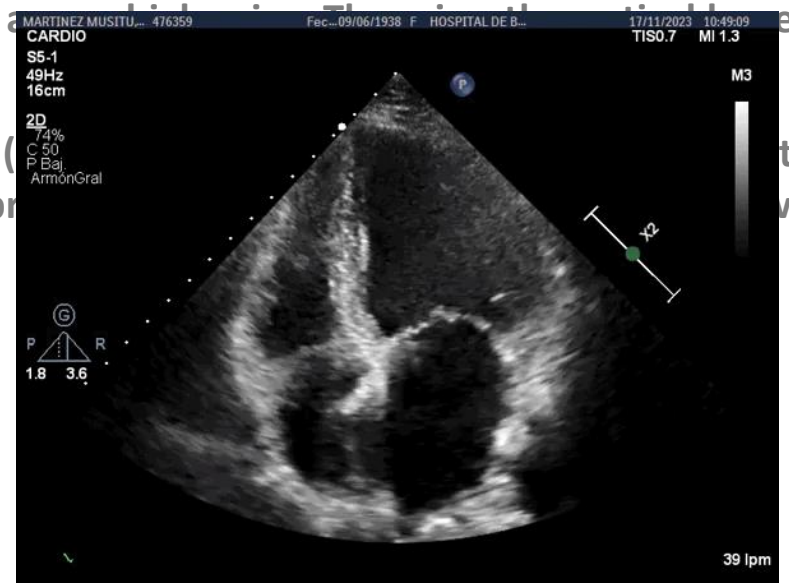

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- ✓ It will be necessary to establish criteria for starting treatment (until now only patients with clinical HF), the starting drug (monotherapy or combined treatment), criteria for disease progression, response to treatment and switching between treatments (biomarkers, echo, etc.).
- ✓ Every patient with ATTR-CM should be considered for inclusion in a clinical trial.

# Thank you