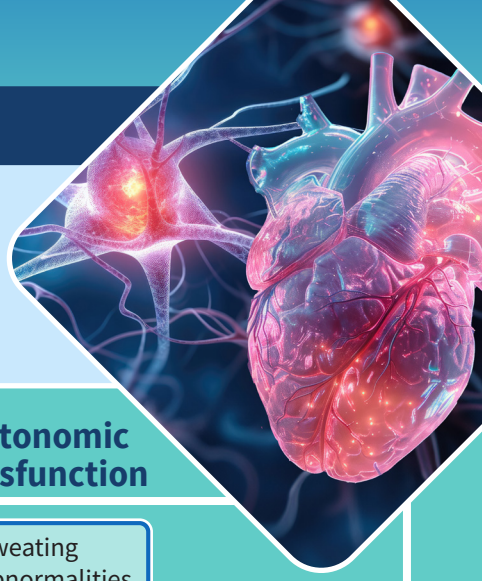
CORNERSTONE CLINICAL TOOL

Case-Based Catalysts in ATTR Management:

Dynamic Discussions on the Latest Data and Current Clinical Challenges



Red Flags for Transthyretin Amyloidosis (ATTR)

Cardiac

- Symptoms of Heart Failure (often HFpEF)
- Atrial Fibrillation
- LV Thickening
- Bradyarrhythmias/ Conduction Abnorm./ Pacemakers
- Elevated BNP/NT-proBNP, Persistently Elevated Cardiac Troponins

Musculoskeletal

- Carpel Tunnel Syndrome
- Back Pain/Lumbar Spinal Stenosis
- Ruptured Distal Biceps Tendon/Popeye Sign
- Shoulder, Knee, and Hip Pain or Surgery
- Trigger Finger

Polyneuro.

- Painful Neuropathy in Hands and Feet
- Muscle Weakness, Difficulty Walking, and Falls

Autonomic Dysfunction

- Sweating Abnormalities
- Chronic Diarrhea/ Constipation/Weight Loss
- Orthostatic Hypotension/ Intolerance to Blood Pressure Medications
- Urinary Retention or Incontinence
- Erectile Dysfunction

Suspicion of ATTR-Cardiomyopathy (CM)

Negative (Exclusion of AL Amyloidosis)

- G 0 → ATTR Amyloidosis Unlikely
- G 1 → **Histological Confirmation for Diagnosis**
- G 2-3 → **Histological Confirmation for Diagnosis**

ATTR-CM Confirmed

→ Genetic Testing ATTRwt-CM or ATTRv-CM

Positive

- G 1-3 → **Histological Confirmation for Diagnosis** → AL Amyloidosis

Monoclonal Proteins?
Serum free light chains (SFLC)
Serum/Urine Protein Electrophoresis With Immunofixation (SIFE/UIFE)

Scintigraphy
Myocardial uptake of 99mTc-labeled tracers in single photon emission computed tomography (SPECT)

Grade (G) 0: No Cardiac/Bone Uptake
G 1: Cardiac < Bone Uptake
G 2: Cardiac = Bone Uptake
G 3: Cardiac > Bone Uptake

Suspicion of ATTR-Polyneuropathy (PN)

Negative (Exclusion of Monoclonal Gammopathy)

→ TTR Genetic Testing

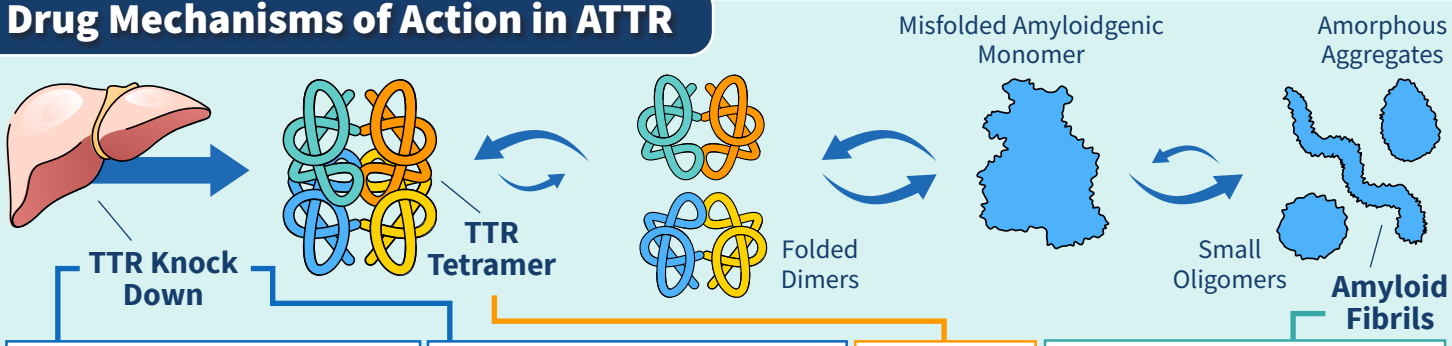
- **Positive**
  - Family Hx → G 2-3 → CMR Consistent With Cardiac Amyloidosis → **ATTR-PN Confirmed**
  - No Family Hx → **Histological Confirmation for Diagnosis** → **ATTR-PN Confirmed**
- **Negative** → **Histological Confirmation for Diagnosis** → **ATTR-PN Confirmed**



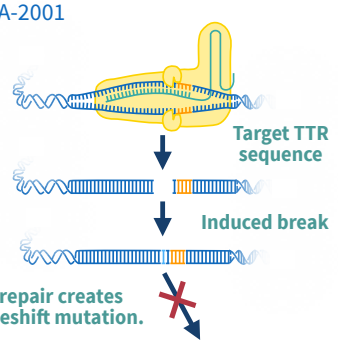
Cornerstone Medical Education

This activity is supported through an independent educational grant from AstraZeneca and Ionis Pharmaceuticals.

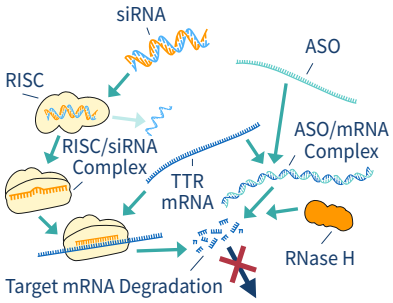
Drug Mechanisms of Action in ATTR



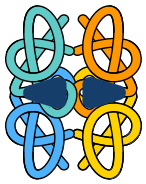
Gene Editing
NTLA-2001



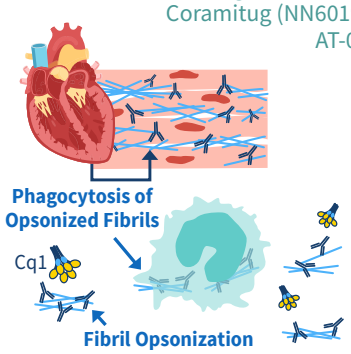
Block Protein Synthesis
Vutrisiran, Patisiran, Eplontersen



Stabilize Tetramer
Acoramidis
Tafamidis



Remove Amyloid Fibrils
Clíramitug (ALXN 2220)
Coramitug (NN6019)
AT-02



Current Status of Treatments Approved for ATTR

	ATTR-CM		ATTR-PN	
	FDA-Approval	**Phase III RCT**	**FDA-Approval**	**Phase III RCT**
Acoramidis	• **Approved** (2024). • Tx of ATTR-CM (wild-type or hereditary) in adults to reduce CV death and CV-related hospitalization.	• **ATTRibute-CM** completed. • Ongoing OLE.	• **No**.	• None.
Eplontersen	• **No**. • FDA Fast Track Designation (2024).	• **CARDIO-TTRansform** completed.	• **Approved** (2023). • Tx of ATTR-PN (hereditary) in adults.	• **NEURO-TTRansform** completed.
Patisiran	• **No**. • In 2023, FDA denied expansion of indication to include CM despite positive APOLLO-B outcomes.	• **APOLLO-B** completed. • No active trials.	• **Approved** (2018). • Tx of ATTR-PN (hereditary) in adults.	• **APOLLO** completed.
Tafamidis	• **Approved** (2019). • Tx of ATTR-CM (wild-type or hereditary) in adults to reduce CV death and CV-related hospitalization.	• **ATTR-ACT** completed.	• **No**.	• None.
Vutrisiran	• **Approved** (2025). • Tx of ATTR-CM (wild-type or hereditary) in adults to reduce CV death, CV-related hospitalization, and urgent HF visits.	• **HELIOS-B** completed.	• **Approved** (2022). • Tx of hereditary ATTR-PN in adults.	• **HELIOS-A** completed.

Information current as of October 11, 2026.

Next: **CARDIO-TTRansform Trial Results Examined in Greater Detail**

Cornerstone Medical Education

This activity is supported through an independent educational grant from AstraZeneca and Ionis Pharmaceuticals.

CARDIO-TTRansform: Phase 3 Trial of Eplontersen vs Placebo in ATTR-CM

Study Design

Concomitant TTR Stablizers Allowed ***(57% of Patients at Baseline)***

1432 Patients With ATTR-CM Treated With SOC

- **Eplontersen** 45 mg SC Q4W (N=715)
- **Placebo** SC Q4W (N=717)

→ **Post-Treatment Evaluation** (20 Weeks) *or* **Open-Label Extension**

Week: -10 | 0 | 13 | 25 | 37 | 49 | 61 | 73 | 85 | 97 | 109 | 121 | 133 | 150 | **140** | **160**

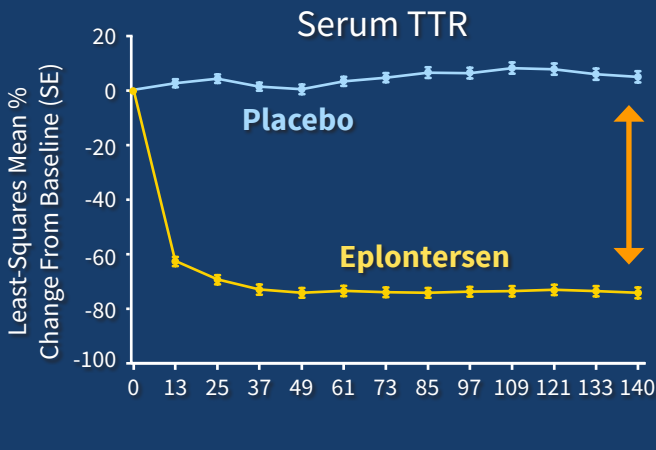
Screening Period | **Mandatory In-Clinic Visits**

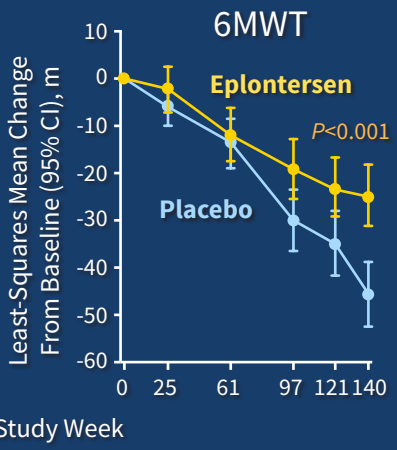
Primary Endpoint Composite of CV Mortality and Recurrent CV Clinical Events Up to Week 140.

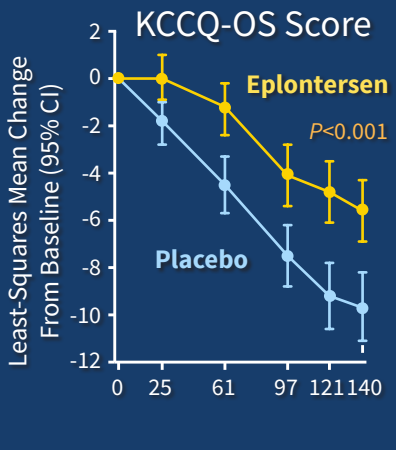
Secondary Endpoints

- Change in 6MWT Distance at Week 140
- Change in KCCQ-OS Score at Week 140
- Total Recurrent CV Clinical Events Up to Week 140
- Primary Endpoint in Patients Receiving Stabilizer at Baseline Up to Week 140
- All-Cause Mortality Up to Weeks 160 and 140
- CV Mortality Up to Weeks 160 and 140

Eplontersen Led to **Rapid, Deep, and Sustained Decrease** in **Serum TTR** and **Substantial Improvements** in **Functional Capacity and Quality of Life**

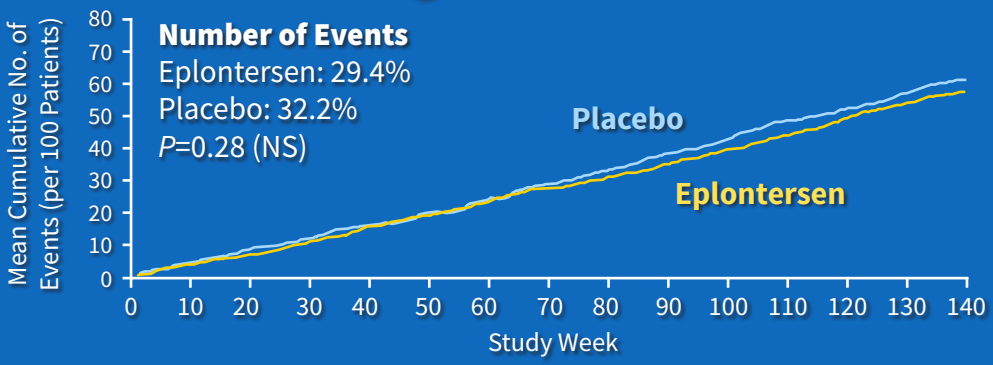






Study Week

But **No Significant Difference** in the **Primary Endpoint**



Composite CV Mortality and Recurrent CV Clinical Events Up to Week 140.

Next Page:
Impact of Baseline Stabilizer Use on Trial Outcomes

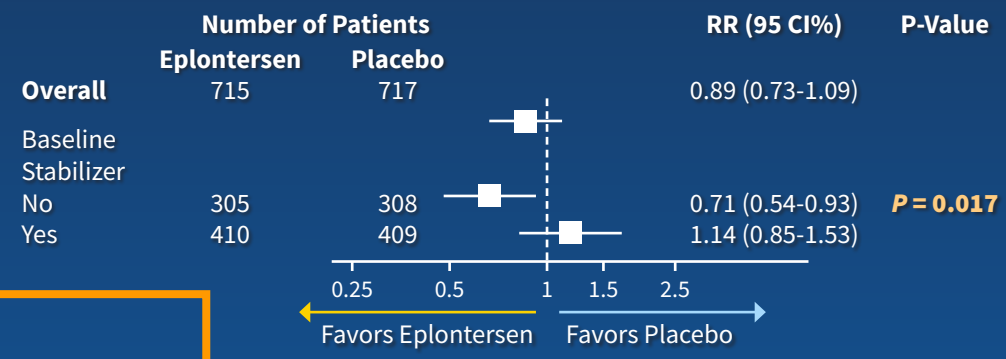
Cornerstone Medical Education

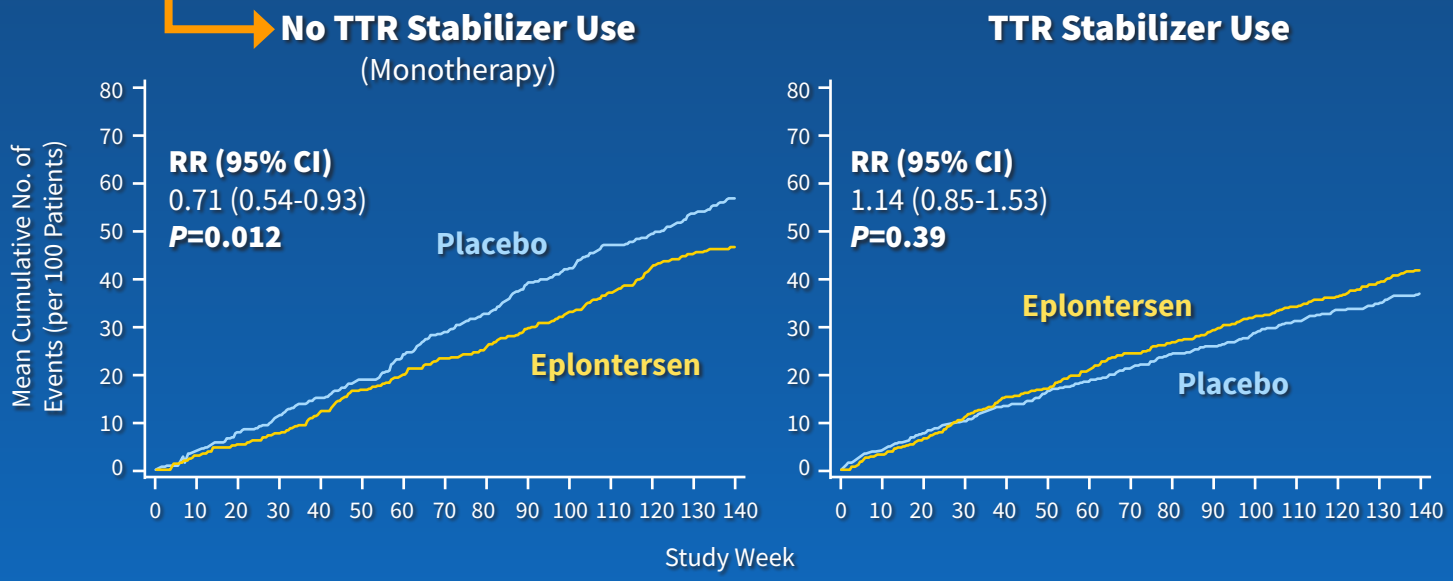
This activity is supported through an independent educational grant from AstraZeneca and Ionis Pharmaceuticals.

Results by Baseline Stabilizer Use in the CARDIO-TTRansform Trial

Eplontersen reduced the event rate among patients not receiving a stabilizer at baseline, whereas no benefit was observed among those receiving a stabilizer.

Eplontersen **Reduced the Risk of Primary Endpoint Events** in the **Monotherapy Subgroup**





Prespecified Endpoints	No TTR Stabilizer Use (Monotherapy) (N=613) Efficacy vs Placebo (95% CI)	P-Value	TTR Stabilizer Use (N=819) Efficacy vs Placebo (95% CI)	P-Value
Primary Endpoint	RR: 0.71 (0.54-0.93)	**0.012**	RR: 1.14 (0.85-1.53)	0.39
Δ 6MWT (m)	LSMD: 29.90 (14.3-45.5)	**<0.001**	LSMD: 12.00 (-1.0 to 25.0)	0.07
Δ KCCQ-OS (Points)	LSMD: 7.6 (4.2-11.0)	**<0.001**	LSMD: 1.1 (-1.3 to 3.6)	0.37
Recurrent CV events	RR: 0.67 (0.50-0.90)	**0.008**	RR: 1.16 (0.85-1.58)	0.35
All-Cause Death	HR: 0.85 (0.62-1.16)	0.30	HR: 0.70 (0.49-1.01)	0.06
CV Death	HR: 0.90 (0.61-1.32)	0.59	HR: 0.83 (0.55-1.25)	0.37

Sources: Fontana M, Masri A, Solomon SD, et al. N Engl J Med. Published online August 28, 2026; Masri A, et al. Presented at: ESC Congress 2026; August 28-31, 2026; Munich, Germany; García-Pavía P, Cappelli F, Davis MK, et al. Nat Med. Published online August 30, 2026; Nativi-Nicolau JN, et al. Heart Fail Rev. 2021 Feb 20;27(3):785–793; Gertz M, et al. BMC Fam Pract. 2020;21(1):198; Margolin E, et al. Cardiol Ther. 2025 Jul 19;14(3):385–401; Griffin JM, et al. JACC Heart Fail. 2025 May;13(5):685-694; Package Inserts at https://www.accessdata.fda.gov for acoramidis, eplontersen, patisiran, tafamidis, and vutrisiran; Hellenbart EL, et al. Pharmacotherapy. 2025 Feb;45(2):124-144.

Cornerstone Medical Education

This activity is supported through an independent educational grant from AstraZeneca and Ionis Pharmaceuticals.