A Trial Emulation Study Comparing Tafamidis and Acoramidis in Transthyretin Amyloid Cardiomyopathy: The ReplicATTR Study

Evaluating the comparative effectiveness of acoramidis versus tafamidis for all-cause mortality using trial emulation, calibration, and indirect treatment comparison techniques

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Background

As the ATTR-CM therapy landscape continues to evolve, there is a **growing need for comparative data** between approved treatments to guide optimal clinical decision making.

However, there are **no head-to-head trials**, and directly **comparing results of the Phase III ATTR-CM studies is not possible** because of differences in study design and population.[1]

Comparative **real-world evidence studies have not been published** to date.

The Harvard Medical School–FDA initiative, **RCT-DUPLICATE**, has shown that when RCT designs are closely emulated, and key confounders and endpoints are measured reliably, **real-world data-based estimates can closely replicate RCT results**.[2–5]

ATTR-CM, transthyretin amyloid cardiomyopathy; FDA, U.S. Food and Drug Administration; RCT, randomised controlled trial; RCT-DUPLICATE, Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims.

1. Dimza M, et al. *US Cardiol.* 2025;19:e21. **2.** RCT-DUPLICATE. https://www.rct-duplicate.org/. Accessed 15 January 2026. **3.** Franklin JM, et al. *Circulation.* 2021;143:1002–1013. **4.** Wang SV, et al. *JAMA.* 2023;329:1376–1385. **5.** Wang SV, et al. *Clin Pharmacol Ther.* 2025;117:1820–1828.

Methods

- Guided by the RCT-DUPLICATE framework,[1] we conducted a comparative effectiveness study using a hybrid design to compare acoramidis versus tafamidis with respect to **42-month all-cause mortality**.
- A real-world cohort of patients who initiated tafamidis was identified from electronic medical records† (2019–2024) using observational analogues to emulate ATTRibute-CM trial (NCT03860935)[2] eligibility criteria and baseline characteristics.

Benchmarking and calibration

1 REPLICATE (ATTR-ACT)

A real-world **tafamidis** cohort was replicated from the phase III **tafamidis** ATTR-ACT trial

Phase III ATTR-ACT **tafamidis** cohort → *Matched inclusion criteria and characteristics* → Real-world ATTR-ACT-aligned **tafamidis** cohort

2 CALCULATE

The outcomes between the matched cohorts were compared to calculate the calibration factor summarising the real-world to randomised trial differences

Phase III ATTR-ACT **tafamidis** cohort vs Real-world ATTR-ACT-aligned **tafamidis** cohort: *42-month all-cause mortality comparison*

Calibration factor

Calibrated indirect comparison

3 REPLICATE (ATTRibute-CM)

Another real-world **tafamidis** cohort was replicated, this time matched to the phase III **acoramidis** ATTRibute-CM trial

Phase III ATTRibute-CM **acoramidis** cohort → *Matched inclusion criteria and characteristics* → Real-world ATTRibute-CM-aligned **tafamidis** cohort

4 CALIBRATE

The outcomes of the ATTRibute-CM-aligned real-world **tafamidis** cohort were then adjusted using the calibration factor, to allow for comparison with the **acoramidis** randomised trial outcomes

Real-world ATTRibute-CM-aligned **tafamidis** cohort

Observed 42-month all-cause mortality = 35.4%

Calibrated 42-month all-cause mortality = 31.2%

†Data obtained from the TriNetX US Real-World Data Network, which aggregates de-identified electronic health record data for ~117 million US patients from academic medical centres, integrated delivery networks, specialty hospitals, and large outpatient practices.

RCT-DUPLICATE, Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims.

1. RCT-DUPLICATE. https://www.rct-duplicate.org/. Accessed 15 January 2026. **2.** Gillmore JD, et al. *N Engl J Med.* 2024;390:132–142.

Results

Baseline characteristics

Characteristics	ATTRibute-CM acoramidis cohort (n=409)[1–3]	ReplicATTR RW tafamidis cohort (n=617)[1]
Age, years, mean±SD	77.3±6.5	77.3±6.5
Male sex, %	91.4	91.4
Hypertension, %	56.8	56.8
Atrial fibrillation, %	57.7	57.7
CAD, %	18.3	18.3
NT-proBNP, ng/L, mean±SD	2865±2150	2865±2150

Reweighting of the RW tafamidis cohort **achieved baseline characteristics similar to those in the ATTRibute-CM acoramidis arm.**[†1]

Outcomes

Outcomes	ATTRibute-CM acoramidis cohort (n=409)[1–3]	ReplicATTR RW tafamidis cohort (n=617)[1]
42-month all-cause mortality, % (95% CI)	24.0 (20.0–28.7)	31.2 (25.3–39.0)
Relative risk (95% CI)[‡]	0.78 (0.60–0.99)	
Relative risk reduction, %[‡]	22.0	
Absolute risk reduction, %[‡]	7.0	
NNT[‡]	15	

Acoramidis was associated with a **significant relative risk reduction in 42-month all-cause mortality** versus tafamidis.[1]

ATTRibute-CM acoramidis cohort baseline data reported here are for the mITT population and slightly differ to those published for the intention-to-treat population by Gillmore, et al. 2024.[3]
†After reweighting using the method of moments, all baseline characteristics used in the reweighting achieved standardised mean differences of <0.10, which indicates adequate balance;
‡Based on Monte Carlo Simulation.
CAD, coronary artery disease; CI, confidence interval; NNT, number needed to treat; NT-proBNP, N-terminal pro B-type natriuretic peptide;
RW, real-world; SD, standard deviation.
1. Data on file. **2.** Judge DP, et al. *Circulation.* 2025;151:601–611. **3.** Gillmore JD, et al. *N Engl J Med.* 2024;390:132–142.

Key limitations

- Despite including several prognostic variables, **residual confounding cannot be excluded**.
- While the calibration factor in theory accounts for the remaining systematic differences between the trial and real-world data, **application of the calibration factor requires the strong assumption that the net effect of these systematic differences is similar across the populations and treatment comparisons.**

- ~70% of initially identified patients were excluded because of missing NT-proBNP data.
- This introduces **potential selection bias** and **limits the representativeness** of the analysed cohort.

Despite the limitations, ReplicATTR uses **state-of-the-art, established methodology** during a time in which **other comparative evidence generation approaches are not yet feasible.**

NT-proBNP, N-terminal pro B-type natriuretic peptide.

Conclusions

- The finding that acoramidis was associated with a 22% RRR in 42-month all-cause mortality compared with tafamidis suggests that **acoramidis may offer a more favourable profile** in patients with ATTR-CM.
- The estimated NNT was 15, which is **meaningful** in the context of contemporary HF RCTs that compare active therapies.[1]

- These results may have **implications for clinical practice**, particularly as clinicians now have multiple therapeutic options available, without direct comparative guidance to inform treatment selection.

- These findings should be considered **hypothesis-generating and require confirmation** in head-to-head studies.

ATTR-CM, transthyretin amyloid cardiomyopathy; HF, heart failure; NNT, number needed to treat; RCT, randomised controlled trial; RRR, relative risk reduction.

1. Srivastava PK, et al. *JAMA Cardiol.* 2018;3:1226–1231.