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Efficacy of Acoramidis in Wild-Type and Variant Transthyretin Amyloid Cardiomyopathy

Results From ATTRibute-CM and Its Open-Label Extension

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IMPORTANCE Transthyretin amyloid cardiomyopathy (ATTR-CM), a progressive disease caused by misfolded transthyretin (TTR), occurs as wild-type (ATTRwt-CM) or variant (ATTRv-CM) forms. p.Val142Ile is the most common variant in the US, linked to rapid progression and increased mortality. Acoramidis achieves near-complete (≥90%) TTR stabilization and showed clinical benefit in the 30-month ATTRibute-CM trial and through month 42 in the ongoing open-label extension (OLE).

OBJECTIVE To evaluate the efficacy of acoramidis in ATTRwt-CM, ATTRv-CM, and variant subgroups (p.Val142Ile and non-p.Val142Ile).

DESIGN, SETTING, AND PARTICIPANTS This international, multicenter, phase 3, randomized placebo-controlled study took place from April 2019 to May 2023 with ongoing OLE (month 42). ATTRibute-CM enrolled 632 participants with ATTR-CM; 611 of 632 were included in the modified intention-to-treat (mITT) population. There were 380 participants who continued into the OLE. These data were analyzed from January 2025 to July 2025.

INTERVENTIONS Oral acoramidis, 712 mg, or placebo twice daily for 30 months, followed by 12 months of open-label treatment.

MAIN OUTCOMES AND MEASURES All-cause mortality (ACM), cardiovascular-related hospitalizations (CVH), serum TTR, 6-minute walk distance, Kansas City Cardiomyopathy Questionnaire Overall Summary score, and N-terminal pro B-type natriuretic peptide in participants with ATTRwt-CM and ATTRv-CM. Post-hoc analyses were conducted in variant subgroups, including p.Val142Ile.

RESULTS Overall, 552 participants with wild-type ATTR-CM (mean [SD] age, 78 [6.3] years; 92.0% male and 8.0% female) and 59 participants with variant ATTR-CM (mean [SD] age, 73 [7.7] years; 77.3% male and 22.7% female) were randomized (mITT population), including 35 with p.Val142Ile. Consistent efficacy was observed in wild-type and variant subgroups for ACM/CVH through month 30 and ACM through month 42. At month 30, acoramidis reduced the risk of ACM/first CVH vs placebo by 31% in ATTRwt-CM (hazard ratio [HR], 0.69; 95% CI, 0.52-0.90; $P = .007$) and by 59% in ATTRv-CM (HR, 0.41; 95% CI, 0.21-0.81; $P = .01$). ACM was reduced through month 42 with HRs of 0.70 (95% CI, 0.50-0.98; $P = .04$) and 0.41 (95% CI, 0.19-0.93; $P = .03$) in the ATTRwt-CM and ATTRv-CM groups, respectively. Consistent treatment benefit was observed in participants with ATTRwt-CM and ATTRv-CM for secondary end points. Within variant subgroups (p.Val142Ile vs non-p.Val142Ile), consistent treatment benefits were observed for ACM/CVH through month 30 and ACM through month 42.

CONCLUSIONS AND RELEVANCE The beneficial effect of acoramidis was observed consistently in ATTRwt-CM and ATTRv-CM groups. These hypothesis-generating results indicate that further studies are warranted to better characterize the therapeutic benefit of acoramidis in variant subgroups.

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Multimedia

Supplemental content

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and underdiagnosed cause of heart failure, resulting from deposition of misfolded transthyretin (TTR) protein in the myocardium[1-4] due to a pathogenic mutation in the *TTR* gene (hereditary or variant disease [ATTRv-CM]) or without a *TTR* mutation, in older adults (wild-type disease [ATTRwt-CM]). Although the precise prevalence of ATTR-CM is unknown, it is estimated that ATTRv-CM comprises about 20% of patients with ATTR-CM.[5]

To date, over 130 pathogenic destabilizing *TTR* variants have been identified, resulting in amyloid fibril formation and tissue deposition, primarily in the heart and peripheral nerves.[6] TTR destabilization in ATTRv-CM leads to lower serum TTR ([sTTR] also known as prealbumin) concentration, which has been associated with an earlier onset and a more aggressive disease phenotype than ATTRwt-CM.[2,7,8] Lower sTTR levels are also associated with increased risk of mortality and adverse outcomes in patients with ATTRwt-CM or ATTRv-CM, and in the general population.[8-12]

The p.Val142Ile variant (updated nomenclature, previously known as V122I) is the most prevalent cause of ATTRv-CM worldwide,[13,14] affecting predominantly individuals of Western African ancestry, with a carrier frequency of 3% to 4% in the Black US population. The p.Val142Ile mutation exhibits variable penetrance, with homozygous individuals often experiencing earlier disease onset.[15,16] However, once clinical manifestations appear, the disease tends to progress rapidly, with 2-year to 3-year mortality exceeding 50% in untreated affected individuals.[7,14,16-18]

Acoramidis is a novel, orally administered TTR stabilizer that achieves near-complete (≥90%) TTR stabilization.[19-21] The phase 3 ATTRibute-CM trial (NCT03860935), performed in a contemporary ATTR-CM population, demonstrated that acoramidis significantly improved all-cause mortality (ACM) and cardiovascular-related hospitalizations (CVH), with benefits observed as early as 3 months into treatment.[22,23] Acoramidis has received regulatory approval in the US, European Union, United Kingdom, and Japan for the treatment of adults with ATTR-CM.[24-27]

In this study, we evaluated the clinical efficacy of acoramidis observed in ATTRibute-CM in participants with ATTRwt-CM and ATTRv-CM, including the p.Val142Ile participant subgroup.

Key Points

Question Is the efficacy of acoramidis similar between those with transthyretin amyloid cardiomyopathy with wild-type (ATTRwt-CM) and with a pathogenic/likely pathogenic variant (ATTRv-CM)?

Finding Among 611 participants, in this study, 9.6% had ATTRv-CM with similar reduction in all-cause mortality and first cardiovascular hospitalization compared with ATTRwt-CM at 30-month trial completion. Of 380 participants who continued in the open-label extension, 7.1% had ATTRv-CM with a similar reduction in all-cause mortality at 42-month follow-up.

Meaning In patients randomized to acoramidis and followed up in the open-label extension, reduction in all-cause mortality and cardiovascular hospitalization was similar in those with ATTRv-CM and ATTRwt-CM.

Methods

Study Design and Participant Population

The ATTRibute-CM and open-label extension (OLE) study designs have been published previously.[22,28] Briefly, ATTRibute-CM study was a phase 3, randomized, double-blind, 30-month study. Participants were randomly assigned 2:1 to receive either acoramidis, 712 mg (equivalent to 800 mg acoramidis hydrochloride), or matching placebo tablets administered orally twice daily for 30 months. Stratification was based on TTR genotype, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and estimated glomerular filtration rate (eGFR) levels, according to the National Amyloidosis Centre staging criteria.[29] During the double-blind study, participants were permitted to initiate tafamidis, if available, and at the discretion of the investigator, as a concomitant medication after they had completed 12 months of the blinded study treatment. All randomized participants received at least 1 dose of blinded study treatment. After completing treatment in the ATTRibute-CM study, participants were invited to participate in the OLE study.[22,28] In the OLE, all participants received open-label acoramidis: those who had previously received acoramidis during the ATTRibute-CM study continued to receive it (continuous acoramidis) and those who had received placebo were switched to acoramidis-only treatment (placebo to acoramidis). Participants who had received concomitant tafamidis at some point during the ATTRibute-CM study were required to discontinue it prior to entering the OLE. Efficacy analyses were conducted in the prespecified modified intention-to-treat (mITT) population (n = 611), which consisted of all randomized participants with a baseline eGFR level of 30 or more mL/min/1.73 m^2. Safety and tolerability were assessed in the safety population, which consisted of all randomized participants (n = 632).

The completed ATTRibute-CM study was conducted and the ongoing OLE study is being conducted, in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The studies were approved by the independent review board or ethics committee at each participating site. All participants provided written informed consent. The Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines were followed.

Prespecified efficacy analyses were performed within the ATTRwt-CM and ATTRv-CM subgroups, based on the genotype stratification factor (ATTRwt-CM or ATTRv-CM) recorded at randomization. At month 30, efficacy analyses compared acoramidis and placebo. For the month 42 analyses, a data cut was conducted after all OLE participants had completed at least 12 months in the OLE (or had discontinued early) and observations were analyzed comparing the continuous acoramidis and placebo with acoramidis

cohorts.[28] The composite of time to ACM or first CVH is reported at month 30 and month 42, the annual frequency of CVH is reported at month 30, and ACM is reported at month 42. Additional details of evaluation of ACM and CVH are provided in the eMethods in Supplement 1.

Other efficacy end points are reported through month 30, including the primary end point using a 4-component hierarchical Finkelstein and Schoenfeld analysis, previously described[22,23] and change from baseline in sTTR, NT-proBNP, 6-minute walk distance (6MWD), and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score.

The following additional post hoc efficacy analyses were performed within the ATTRv-CM population, according to the actual variant reported (p.Val142Ile or non-p.Val142Ile subgroups): composite of time to ACM or first CVH and annual frequency of CVH at month 30, ACM at month 42, and change from baseline in sTTR at day 28 and month 30.

The Interactive Voice and Web Response System was used for the prespecified genotype stratum (ATTRwt-CM vs ATTRv-CM); however, it did not capture variant-specific data. Therefore, post hoc analyses within the variant subgroup—stratified by individual variants—were conducted using the Electronic Data Capture system, which captured detailed variant-level information.

Statistical Analysis

The primary end point was analyzed using the stratified Finkelstein and Schoenfeld method, supplemented by win-ratio estimates, which have been described previously.[22,30] Time-to-first-event analyses (composite of ACM or first CVH) were performed using a stratified Cox proportional hazards model. The annualized frequency of CVH was analyzed using a negative binomial regression model.

The change from baseline in 6MWD, KCCQ-OS score, NT-proBNP (in log-scale), and sTTR level were analyzed using a mixed model for repeated measures. In general, statistical analyses were conducted using consistent methodology as the prespecified analyses in ATTRibute-CM, with appropriate considerations for the reduced sample size in the variant, p.Val142Ile and non-p.Val142Ile subgroups.[22] Additional details of statistical analyses are provided in the eMethods in Supplement 1.

This article includes several prespecified and post hoc analyses that are outside the scope of our alpha-controlled testing scheme covering the primary and key secondary end points in the overall mITT population. Two-sided *P* values less than .05 are taken to indicate nominal statistical significance. Interaction *P* values were calculated to compare the heterogeneity of treatment effect in key clinical end points between genotypic classifications at randomization (ATTRwt-CM vs ATTRv-CM) and within the variant subgroup by mutation status, as recorded in the clinical database (p.Val142Ile vs non-p.Va142Ile variant). In addition, interaction *P* values were calculated between p.Val142Ile vs non-pVal142Ile in the mITT population. Statistical analysis was performed using SAS software version 9.4 (SAS Institute).

Results

Study Population and Baseline Characteristics

Among the 611 participants in the mITT population enrolled in ATTRibute-CM (**Table**; eFigure 1 in Supplement 1), 59 (9.7%) were categorized as having ATTRv-CM at randomization. Of these, 39 were randomized to acoramidis and 20 to placebo. The 3 most common ATTRv-CM variants recorded in the clinical database were p.Val142Ile (n = 35; including 4 homozygotes), p.Ile88Leu (n = 7), and p.Thr80Ala (n = 5) (eTable 1 in Supplement 1). Compared with ATTRwt-CM, participants with ATTRv-CM were younger (mean age, 74 vs 78 years for acoramidis; mean age, 71 vs 78 years for placebo), had lower baseline sTTR levels (17.8 vs 23.5 mg/dL for acoramidis; 17.2 vs 24.3 mg/dL for placebo), and had lower KCCQ-OS scores (68.5 vs 72.1 for acoramidis; 63.2 vs 71.3 for placebo). Other baseline parameters, including NT-proBNP, 6MWD, New York Heart Association class distribution, and duration of ATTR-CM, were comparable between ATTRv-CM and ATTRwt-CM populations. In both the ATTRwt-CM and ATTRv-CM subgroups, concomitant tafamidis use was about 8% to 10% lower in acoramidis-treated participants vs placebo-treated participants.

Primary Efficacy and Clinical Outcome End Points

A consistent treatment effect of acoramidis was observed in the ATTRwt-CM and ATTRv-CM subgroups for each end point assessed: primary 4-component hierarchical end points (**Figure 1**A), composite of ACM or first CVH (Figure 1B), and frequency of CVH, all at month 30 (Figure 1C), and ACM at month 42 (Figure 1D). There was no significant evidence of heterogeneity of treatment effect for any of the clinical outcome end points analyzed according to parametric models (interaction *P* values > .05; Figure 1B-D).

For the primary 4-component hierarchical end point at month 30 in the overall population, the win ratio for acoramidis vs placebo was 1.8 (95% CI, 1.40-2.24; *P* < .001). Win ratios were 1.8 (95% CI, 1.40-2.21; *P* < .001) in the ATTRwt-CM subgroup and 2.5 (95% CI, 1.30-4.91; *P* = .006) in the ATTRv-CM subgroup (Figure 1A).

The hazard ratio (HR) for the composite end point of ACM or first CVH (ACM/first CVH) at month 30 in acoramidis recipients was 0.69 (95% CI, 0.52-0.90; *P* = .007) in the ATTRwt-CM subgroup and 0.41 (95% CI, 0.21-0.81; *P* = .01) in the ATTRv-CM subgroup; interaction *P* = .17 (Figure 1B). This corresponds to a 31% and 59% risk reduction vs placebo. The Kaplan-Meier curves for this end point are shown in **Figures 2**A and B. Of note, in the ATTRv-CM placebo group, the event rate for ACM/first CVH was 75.0% (15 of 20) through month 30, compared with 46.2% (18 of 39) in the ATTRv-CM acoramidis group (Figure 2B). The rate in the ATTRv-CM acoramidis group is comparable with that of the ATTRwt-CM population (eFigure 2 in Supplement 1).

Risk reduction for the annual frequency of CVH with acoramidis was 49% in the ATTRwt-CM subgroup (relative risk ratio, 0.51; 95% CI, 0.36-0.73; *P* < .001) and 62% in the ATTRv-CM subgroup (relative risk ratio, 0.38; 95% CI, 0.14-1.03; *P* = .06; interaction for *P* = .57) (Figure 1C).

Table. Demographics and Baseline Characteristics in Participants of ATTRibute-CM by Genotype[a]

Characteristic	No. (%)			
	ATTRv-CM (n = 59)[b]		ATTRwt-CM (n = 552)[b]	
	Acoramidis (n = 39)	Placebo (n = 20)	Acoramidis (n = 370)	Placebo (n = 182)
Age, mean (SD), y	74 (7.6)	71 (7.8)	78 (6.2)	78 (6.3)
Sex				
Male	33 (84.6)	14 (70.0)	341 (92.2)	167 (91.8)
Female	6 (15.4)	6 (30.0)	29 (7.8)	15 (8.2)
Self-reported race or ethnicity				
Asian	2 (5.1)	0	8 (2.2)	3 (1.6)
Black	14 (35.9)	7 (35.0)	5 (1.4)	3 (1.6)
White	18 (46.2)	11 (55.0)	340 (91.9)	168 (92.3)
Other[c]	5 (12.8)	1 (5.0)	2 (0.5)	2 (1.1)
Not reported	0	1 (5.0)	15 (4.1)	6 (3.3)
NT-proBNP, median (IQR), pg/mL	2326 (1312-4567)	2341 (1521.5-3534)	2265 (1315-3729)	2274 (1105-3590)
eGFR, mean (SD), mL/min/1.73 m^2	65.0 (21.0)	64.0 (14.5)	62.0 (16.9)	62.4 (17.9)
NAC stage				
I	28 (71.8)	14 (70.0)	213 (57.6)	182 (58.2)
II	8 (20.5)	5 (25.0)	122 (33.0)	61 (33.5)
III	3 (7.7)	1 (5.0)	35 (9.5)	15 (8.2)
Duration of ATTR-CM, mean (SD), y	1.3 (1.06)	1.5 (1.07)	1.2 (1.22)	1.1 (1.21)
NYHA class				
I	2 (5.1)	1 (5.0)	49 (13.2)	16 (8.8)
II	35 (89.7)	16 (80.0)	253 (68.4)	140 (76.9)
III	2 (5.1)	3 (15.0)	68 (18.4)	26 (14.3)
sTTR level, mean (SD), mg/dL	17.8 (5.1)	17.2 (5.2)	23.5 (5.3)	24.3 (5.8)
6MWD, mean (SD), m	364.6 (94.93)	354.7 (97.07)	362.6 (104.49)	351.2 (93.74)
KCCQ-OS, mean (SD)	68.5 (17.2)	63.2 (24.7)	72.1 (19.6)	71.3 (20.1)
Atrial fibrillation diagnosis[d]	26 (66.7)	8 (40.0)	229 (61.9)	121 (66.5)
Tafamidis drop-in[e]	4 (10.3)	4 (20.0)	57 (15.4)	42 (23.1)

Abbreviations: 6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sTTR, serum transthyretin.

[a] Modified intention-to-treat population.

[b] Values vary slightly for various characteristics based on available data.

[c] Includes America Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other, and multiple races.

[d] Diagnosis at baseline is defined as medical history of atrial fibrillation and/or presence of atrial fibrillation or atrial flutter on baseline electrocardiogram.

[e] Tafamidis drop-in was allowed after month 12.

The HR for ACM at month 42 in participants receiving acoramidis was 0.70 (95% CI, 0.50-0.98; $P = .04$) in the ATTRwt-CM subgroup and 0.41 (95% CI, 0.19-0.93; $P = .03$) in the ATTRv-CM subgroup, corresponding to 30% and 59% observed risk reductions, respectively; the interaction P value was .24 (Figure 1D).

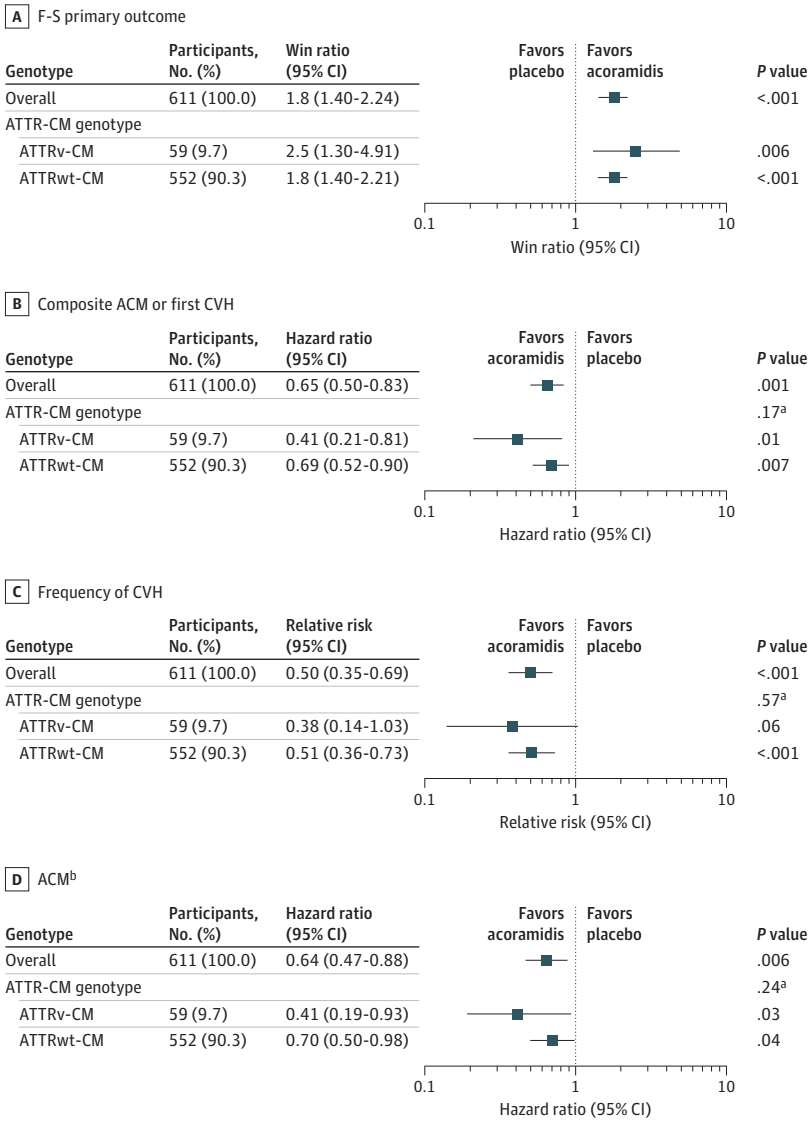
The Kaplan-Meier curves for this end point are shown in Figure 2C and D. Of note, in the ATTRv-CM group the event rate for ACM was 60.0% (12 of 20) through month 42 with placebo vs 30.8% (12 of 39) with acoramidis (Figure 2C and D). This latter rate is comparable with the ACM event rates observed in the ATTRwt-CM population (eFigure 3 in Supplement 1). The corresponding HR values for the composite end point of ACM or first CVH through month 42 were 0.60 (95% CI, 0.47-0.77; $P < .001$) for participants with ATTRwt-CM and 0.35 (95% CI, 0.18-0.67; $P = .002$) for the ATTRv-CM population (eFigure 4 in Supplement 1).

Biomarkers, Functional Assessment, and Quality of Life

In participants with ATTRv-CM receiving acoramidis, sTTR increased at day 28 (first assessment postrandomization) to levels comparable with those achieved in participants with ATTRwt-CM receiving acoramidis (**Figure 3**A). This occurred despite approximately 25% lower sTTR levels in the ATTRv-CM population at baseline. At day 28, acoramidis treatment resulted in an observed mean (SD) sTTR increase from baseline of 8.9 (4.4) mg/dL in ATTRwt-CM participants and 12.4 (6.7) mg/dL in participants with ATTRv-CM. These observed changes were sustained through month 30 (Figure 3A). The least-squares mean difference in sTTR increase at month 30 among those receiving acoramidis vs placebo was 6.6 mg/dL ($P < .001$) and 12.0 mg/dL ($P < .001$) in ATTRwt-CM and ATTRv-CM, respectively.

An increase in NT-proBNP was observed over 30 months in participants receiving placebo. The increase was numerically greater in the placebo ATTRv-CM population than the placebo ATTRwt-CM population (Figure 3B). The ratio (acoramidis to placebo) for NT-proBNP adjusted geometric mean fold-change at month 30 was 0.55 (95% CI, 0.48-0.64; $P < .001$) in the ATTRwt-CM population and 0.35 (95% CI, 0.23-0.54; $P < .001$) in ATTRv-CM. The greater relative effect of acoramidis in attenuating the increase in NT-proBNP in the AT-

Figure 1. Forest Plots for Efficacy Outcomes by Transthyretin Amyloid Cardiomyopathy (ATTR-CM) Genotype



Forest plots of the modified intention-to-treat population by ATTR-CM genotype for the primary 4-component hierarchical end point at month 30 (A), time to all-cause mortality (ACM) or first cardiovascular hospitalization (CVH) from baseline through month 30 (B), frequency of CVH from baseline through month 30 (C), and time to ACM from baseline through month 42 (D). ACM included 1 participant with wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) in the placebo arm who received an implanted cardiac mechanical assist device and 1 participant with variant transthyretin amyloid cardiomyopathy (ATTRv-CM) in the placebo arm who received a heart transplant. F-S indicates Finkelstein and Schoenfeld.

[a]*P* value from testing the interaction of subgroup × treatment and other *P* values are for testing the treatment difference at a given value of subgroup variable.

TRv-CM population mitigated the 30-month rise in NT-proBNP, yielding levels comparable with those observed in acoramidis-treated participants with ATTRwt-CM.

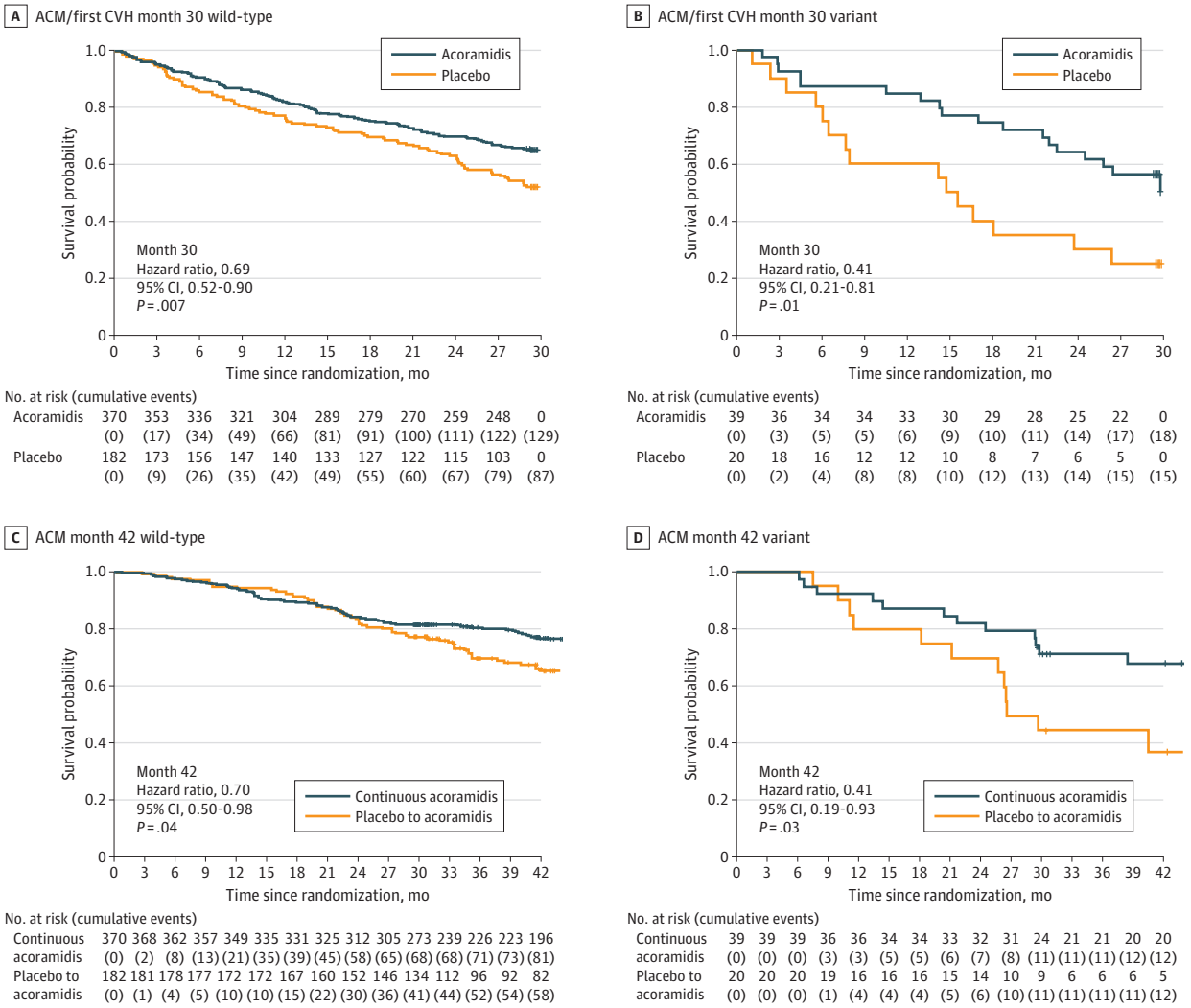
A decline in 6MWD over 30 months was observed in participants receiving placebo, with a numerically greater reduction in the placebo ATTRv-CM group than the placebo ATTRwt-CM group (Figure 3C). Relative to placebo, acoramidis treatment resulted in a least-squares mean difference in 6MWD at month 30 of 34.4 m (*P* = .001) in the ATTRwt-CM group and 86.7 m (*P* = .005) in the ATTRv-CM group. The 6MWD change from baseline at month 30 in the ATTRv-CM acoramidis group was comparable with that observed in the ATTRwt-CM acoramidis group (Figure 3C).

Health-related quality of life, as measured by KCCQ-OS, declined over 30 months, with numerically greater worsening in the placebo ATTRv-CM group than the placebo ATTRwt-CM group (Figure 3D). Relative to placebo, acoramidis treatment resulted in a least-squares mean difference through month 30 of 8.8 points (*P* < .001) in participants with ATTRwt-CM and 20.3 points (*P* = .002) in those with ATTRv-CM (Figure 3D). The mean change from baseline at month 30 in the ATTRv-CM acoramidis group was comparable with that observed in ATTRwt-CM acoramidis group.

Misclassification of ATTRv-CM Population

Fifty-nine participants were categorized as having ATTRv-CM based on stratification at randomization, whereas a variant was subsequently identified and reported in the clinical database in 56 participants (additional details are provided in the eAppendix in Supplement 1). A sensitivity analysis conducted in those 56 participants across all efficacy end points demonstrated treatment effects with acoramidis that were consistent with those observed with the prespecified analyses on the 59 participants (eTable 2 in Supplement 1).

Figure 2. Kaplan-Meier Curves for Time to All-Cause Mortality (ACM) or First Cardiovascular Hospitalization (CVH) in the Wild-Type Transthyretin Amyloid Cardiomyopathy (ATTRwt-CM) and Variant Transthyretin Amyloid Cardiomyopathy (ATTRv-CM) Subgroups



Kaplan-Meier curves of the modified intention-to-treat population for time to ACM or first CVH from baseline through month 30 in the ATTRwt-CM subgroup (A) and the ATTRv-CM subgroup (B), and time to ACM from baseline through month 42 in the ATTRwt-CM subgroup (C) and the ATTRv-CM subgroup (D).

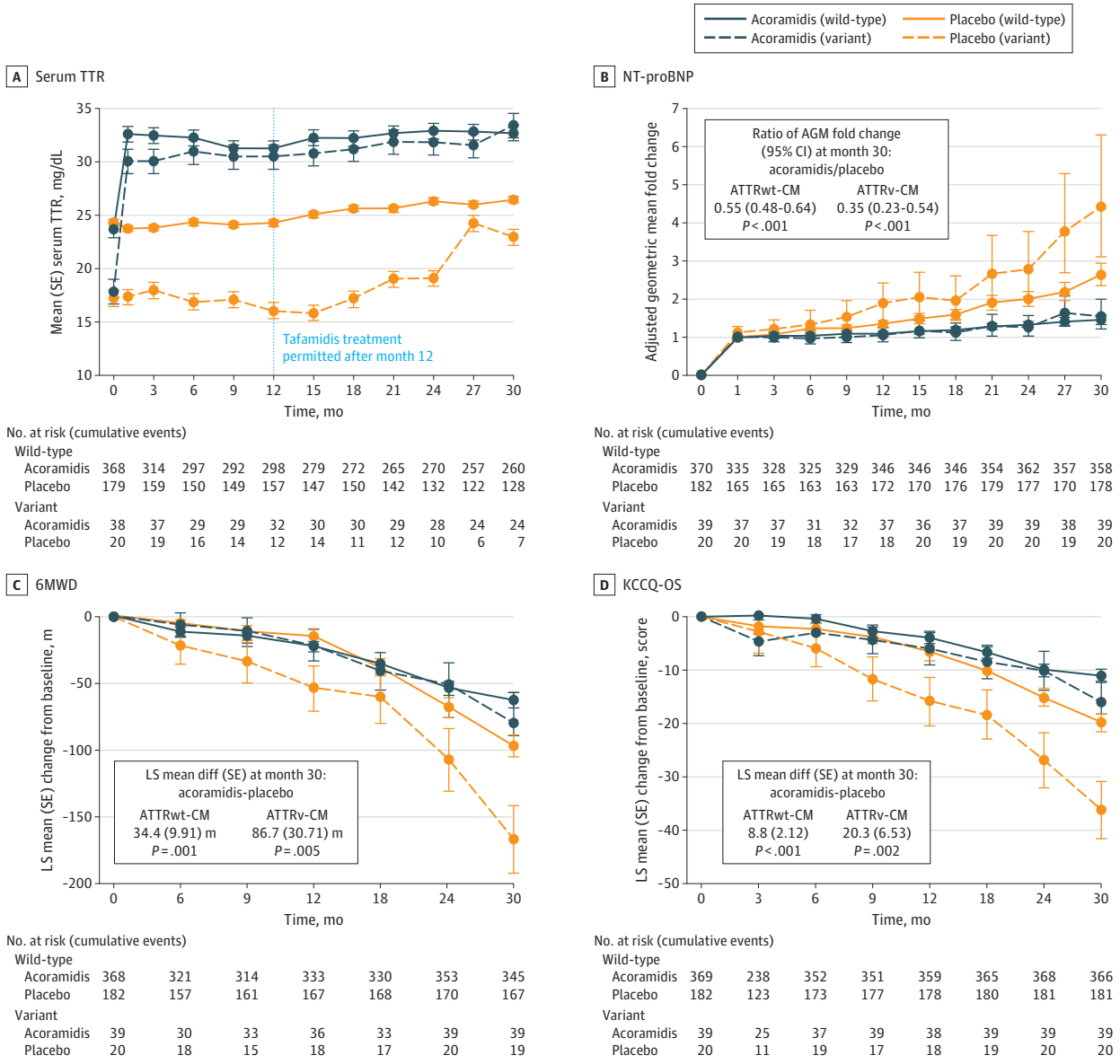
Efficacy in the p.Val142Ile Variant Subpopulation

Baseline characteristics within the ATTRv-CM population (p.Val142Ile variant [n = 35] and non-p.Val142Ile subgroups [n = 21]) are shown in eTable 3 in Supplement 1. Homozygosity for p.Val142Ile was reported in 1 participant in the acoramidis group and 3 participants in the placebo group. The non-p.Val142Ile subgroup is a small, heterogeneous subgroup encompassing 9 different *TTR* variants (eTable 1 in Supplement 1).

Subgroup analysis comparing participants with p.Val142Ile variant to non-p.Val142Ile variants showed no significant heterogeneity of treatment effect. Interaction *P* values were .75 for the composite ACM/first CVH end point through month 30 and .64 for ACM through month 42, indicating consistent treatment effects between p.Val142Ile and non-p.Val142Ile variants (eTable 4 in Supplement 1). In addition, there was no significant heterogeneity of treatment effect in ACM/first CVH through month 30 (interaction *P* = .05) and for ACM through month 42 (interaction *P* = .17) between the p.Val142Ile (n = 35) and the rest of the mITT ATTRibute-CM participant population (n = 576).

At month 30, 43.5% (10 of 23) of acoramidis recipients with p.Val142Ile variant experienced the composite of ACM or first CVH, compared with 83.3% (10 of 12) of those in the placebo group, corresponding to an observed 69% risk reduction (HR, 0.31; 95% CI, 0.12-0.81). At month 42, 26.1% of acoramidis recipients (6 of 23) with p.Val142Ile variant experienced ACM compared with 66.7% of those in the placebo group (8 of 12), corresponding to an observed 69% risk reduction (HR, 0.31; 95% CI, 0.10-0.97) (**Figure 4**; eTable 4 in Supplement 1). A 71% risk reduction in the annual frequency of CVH at month 30 was observed with acoramidis

Figure 3. Change From Baseline to Month 30 in Biomarkers, Functional Assessments, and Quality of Life in Modified Intention-to-Treat Population



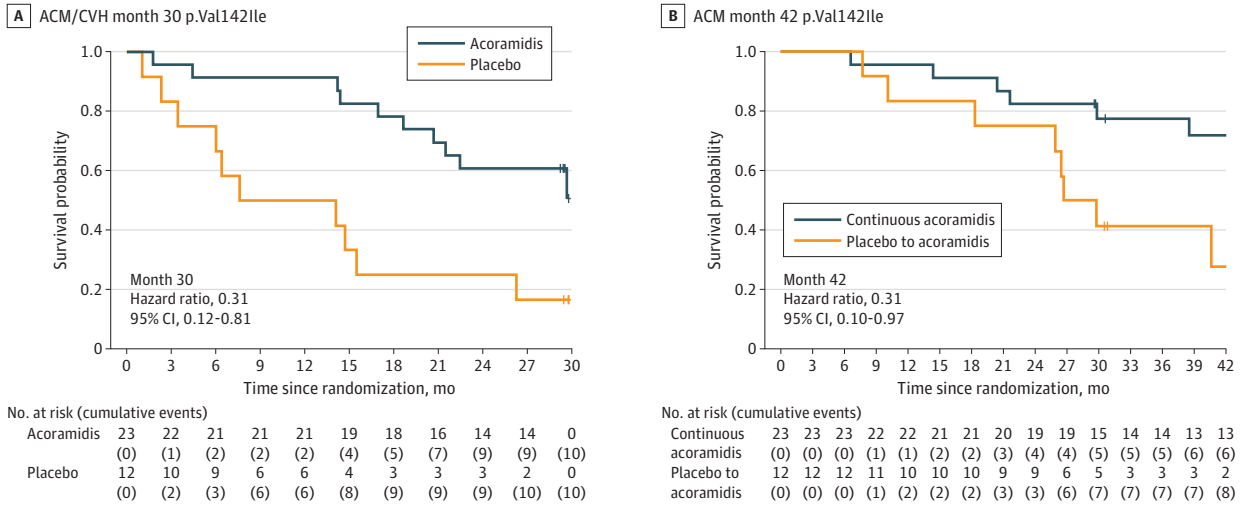
Mean serum transthyretin (TTR) levels change from baseline to month 30 (A) in geometric mean fold change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (from mixed model for repeated measures) (B), 6-minute walk distance (6MWD) (C), and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score in the wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) and variant transthyretin amyloid cardiomyopathy (ATTRv-CM) subgroups (D). Observed values are displayed. Among the 7 participants with ATTRv-CM who received placebo and completed the month 30 visit, 2 received concomitant tafamidis treatment after month 12. In the 5 participants who received placebo without concomitant tafamidis and who completed the month 30 visit, mean (SD) serum TTR was 18.4 (3.32) mg/dL at baseline and 19.0 (4.20) mg/dL at month 30. LS indicates least squares.

(eTable 4 in Supplement 1). The effects on sTTR at day 28 and month 30 in p.Val142Ile and non-p.Val142Ile subgroups are shown in eTable 4 in Supplement 1.

Safety

The safety profile of acoramidis in participants with ATTRv-CM in ATTRibute-CM was consistent with that observed in the safety population (n = 632). Treatment-emergent adverse events occurred in 100.0% of participants with ATTRv-CM treated with acoramidis compared with 95.0% of the placebo group (eTable 5 in Supplement 1). In the ATTRv-CM subgroup, serious adverse events were reported in 56.1% of participants receiving acoramidis vs 80.0% receiving placebo (eTable 5 in Supplement 1). Treatment-emergent adverse events related to study drug were infrequent (n = 4 [9.8%] acoramidis vs n = 0 [0%] placebo), and none of these events were categorized as serious (eTable 5 in Supplement 1). The safety profile in the ATTRwt-CM population was consistent with the

Figure 4. Kaplan-Meier Curves of Modified Intention-to-Treat Population for Time to All-Cause Mortality (ACM) or First Cardiovascular Hospitalization (CVH) in Participants With p.Val142Ile Variant Transthyretin Amyloid Cardiomyopathy (ATTRv-CM)



Kaplan-Meier curves for time to ACM or first CVH from baseline through month 30 (A) and time to ACM from baseline through month 42 in participants with p.Val142Ile ATTRv-CM (B).

previously reported safety profile in the overall population (eTable 5 in Supplement 1).[22]

Discussion

Several key insights emerge from the results presented in this article. First, consistent efficacy of acoramidis was observed in both ATTRwt-CM and ATTRv-CM populations in prespecified analyses. In addition, a post hoc analysis revealed similar treatment effects within the ATTRv-CM subgroup, in p.Val142Ile and non-p.Val142Ile variants. While the point estimates were suggestive of potentially greater treatment benefit within the variant participants, we observed no statistically significant heterogeneity of effects, and the number of variant participants was small. These findings have biological plausibility. Acoramidis was rationally designed to mimic the protective p.Thr139Met variant and stabilized wild-type and variant TTR equally.[31] It achieves this through enthalpically driven binding involving hydrogen bonds, ionic interactions, and engagement with multiple TTR subunits.[19,31] This distinct mechanism has been shown to result in near-complete (≥90%) TTR stabilization in experimental studies involving multiple TTR variants, including p.Val142Ile.[20]

Second, the efficacy observed in ATTRv-CM is of clinical relevance given the high unmet medical need. Findings from ATTRibute-CM confirm the particularly adverse natural history previously described in these populations, with approximately 75% of participants with ATTRv-CM treated with placebo experiencing death or CVH within 30 months and a similar proportion in the p.Val142Ile subgroup dying by 42 months.[7,16,17]

Third, our findings underscore the importance of genetic testing when making a diagnosis of ATTR-CM, particularly to identify individuals carrying the p.Val142Ile variant, who remain frequently underdiagnosed despite substantial disease burden and the availability of an effective treatment option.[13] A recent epidemiological study highlighted the high prevalence and public health implications of the p.Val142Ile variant in the Black population in the US. This study estimated that over 400 000 Black individuals in the US aged 50 to 95 years carry the p.Val142Ile variant, with a projected cumulative loss of nearly 1 million life-years due to heart failure.[32] If the treatment effects observed in this subgroup within ATTRibute-CM are confirmed in larger, adequately powered clinical trials or real-world settings, the implications could be meaningful at both the individual and public health levels. Such findings would support efforts to improve the identification of at-risk individuals and expand access to disease-modifying therapies like acoramidis in this underserved high-risk population. In addition, our observations of consistent efficacy across both wild-type and variant ATTR-CM emphasize the importance of broad disease awareness and maintaining clinical suspicion irrespective of genotype, followed by appropriate diagnostic testing to enable timely diagnosis and initiation of treatment.

Lastly, these findings in a limited number of patients with ATTRv-CM provide support for further clinical investigations. Acoramidis may have the potential for ATTR disease primary prevention in carriers of pathogenic TTR variants. This concept is currently being evaluated in the ACT-EARLY clinical trial (NCT06563895). In addition, further studies are warranted to evaluate the efficacy of acoramidis in transthyretin-mediated polyneuropathy, based on the assumption that near-complete TTR stabilization may confer therapeutic benefits similar to those observed in ATTR-CM.

Limitations

Our results have important limitations. Several of the analyses presented here are post-hoc, such as those involving participants with the p.Val142Ile variant. The sample sizes were also small for the various subgroups. While we conducted heterogeneity tests to identify meaningful treatment effect differences between subgroups, such tests are known to have low power and the lack of significant findings that do not necessarily support a conclusion of complete absence of heterogeneous effects. Accordingly, our observations in the p.Val142Ile and non-p.Val142Ile subgroups are hypothesis generating and should encourage further investigation in larger variant-specific studies with acoramidis. Our study has also not addressed previously described barriers affecting efficacy in participants with p.Val142Ile ATTR-CM, such as comorbidities that may influence the heart failure syndrome or social determinants of health.[33] In our study, variant misclassification occurred due to discrepancies between the recorded variant status reported at randomization and the variants subsequently recorded in the clinical database. However, sensitivity analyses showed consistent efficacy across clinical end points in both populations. In addition, concomitant tafamidis was initiated in a subset of participants at variable times during the study with an imbalance toward greater use in the placebo group than the acoramidis group, which may have led to an underestimation of the effect of acoramidis. Our study did not include a standalone tafamidis subgroup, as this would have introduced bias (concomitant tafamidis could only be initiated if a participant had survived for 12 months). Lastly, baseline imbalances between participants who received acoramidis during the 30-month ATTRibute-CM trial and those entering the OLE—driven by prior treatment benefit in the acoramidis group and greater disease progression in the placebo group—may have influenced the observed treatment effect.

Conclusions

Prespecified analyses from the ATTRibute-CM study provide evidence that acoramidis confers consistent clinical benefit across multiple end points, including ACM, CVH, key biomarkers (NT-proBNP, serum TTR), functional status, and quality of life in both the ATTRwt-CM and ATTRv-CM groups. Taken together, these results reinforce the therapeutic benefit of near-complete TTR stabilization by acoramidis in both ATTRwt-CM and ATTRv-CM.

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REFERENCES

1. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072

2. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140(1):16-26. doi:10.1161/CIRCULATIONAHA.118.038169

3. Kittleson MM, Ruberg FL, Ambardekar AV, et al; Writing Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(11):1076-1126. doi:10.1016/j.jacc.2022.11.022

4. Ruberg FL, Maurer MS. Cardiac amyloidosis due to transthyretin protein: a review. *JAMA*. 2024;331(9):778-791. doi:10.1001/jama.2024.0442

5. Porcari A, Razvi Y, Masi A, et al. Prevalence, characteristics and outcomes of older patients with hereditary versus wild-type transthyretin amyloid cardiomyopathy. *Eur J Heart Fail*. 2023;25(4):515-524. doi:10.1002/ejhf.2776

6. Rowczenio D, Wechalekar A. Mutations in hereditary amyloidosis. Accessed October 21, 2025. http://www.amyloidosismutations.com

7. Rapezzi C, Elliott P, Damy T, et al. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. *JACC Heart Fail*. 2021;9(2):115-123. doi:10.1016/j.jchf.2020.09.011

8. Shetty NS, Gaonkar M, Patel N, et al. Determinants of transthyretin levels and their association with adverse clinical outcomes among UK Biobank participants. *Nat Commun*. 2024;15(1):6221. doi:10.1038/s41467-024-50231-1

9. Greve AM, Christoffersen M, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Association of low plasma transthyretin concentration with risk of heart failure in the general population. *JAMA Cardiol*. 2021;6(3):258-266. doi:10.1001/jamacardio.2020.5969

10. Christoffersen M, Greve AM, Hornstrup LS, Frikke-Schmidt R, Nordestgaard BG, Tybjærg-Hansen A. Transthyretin tetramer destabilization and increased mortality in the general population. *JAMA Cardiol*. 2025;10(2):155-163. doi:10.1001/jamacardio.2024.4102

11. Hanson JLS, Arvanitis M, Koch CM, et al. Use of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin. *Circ Heart*

Fail. 2018;11(2):e004000. doi:10.1161/CIRCHEARTFAILURE.117.004000

12. Maurer MS, Judge DP, Gillmore JD, et al. Early increase in serum transthyretin by acoramidis independently predicts improved survival in TTR amyloid cardiomyopathy. *J Am Coll Cardiol*. 2025;85(20):1911-1923. doi:10.1016/j.jacc.2025.03.542

13. Chandrashekar P, Alhuneafat L, Mannello M, et al. Prevalence and outcomes of p.Val142Ile TTR amyloidosis cardiomyopathy: a systematic review. *Circ Genom Precis Med*. 2021;14(5):e003356. doi:10.1161/CIRCGEN.121.003356

14. Mazzarotto F, Argirò A, Zampieri M, et al. Investigation on the high recurrence of the ATTRv-causing transthyretin variant Val142Ile in central Italy. *Eur J Hum Genet*. 2023;31(5):541-547. doi:10.1038/s41431-022-01235-2

15. Reddi HV, Jenkins S, Theis J, et al. Homozygosity for the V122I mutation in transthyretin is associated with earlier onset of cardiac amyloidosis in the African American population in the seventh decade of life. *J Mol Diagn*. 2014;16(1):68-74. doi:10.1016/j.jmoldx.2013.08.001

16. Razvi Y, Ioannou A, Patel RK, et al. Deep phenotyping of p.(V142I)-associated variant transthyretin amyloid cardiomyopathy: Distinct from wild-type transthyretin amyloidosis? *Eur J Heart Fail*. 2024;26(2):383-393. doi:10.1002/ejhf.3088

17. Swiecicki PL, Zhen DB, Mauermann ML, et al. Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid*. 2015;22(2):123-131. doi:10.3109/13506129.2015.1019610

18. Razvi Y, Ioannou A, Chacko L, et al. A multi-modality, multi-parametric phenotyping study of transthyretin amyloid cardiomyopathy associated with the p.V142I TTR variant. *Eur Heart J*. 2022;43(suppl 2). doi:10.1093/eurheartj/ehac544.1793

19. Miller M, Pal A, Albusairi W, et al. Enthalpy-driven stabilization of transthyretin by AG10 mimics a naturally occurring genetic variant that protects from transthyretin amyloidosis. *J Med Chem*. 2018;61(17):7862-7876. doi:10.1021/acs.jmedchem.8b00817

20. Ji A, Wong P, Judge DP, Graef IA, Fox J, Sinha U. Acoramidis produces near-complete TTR stabilization in blood samples from patients with variant transthyretin amyloidosis that is greater than that achieved with tafamidis. *Euro Heart J*. 2023;44(Supp2). doi:10.1093/eurheartj/ehad655.989

21. Ji AX, Betz A, Sinha U. Differential binding affinities and kinetics of transthyretin stabilizers. *J Cardiovasc Pharmacol*. 2025;86(2):204-209. doi:10.1097/FJC.0000000000001726

22. Gillmore JD, Judge DP, Cappelli F, et al; ATTRibute-CM Investigators. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2024;390(2):132-142. doi:10.1056/NEJMoa2305434

23. Judge DP, Alexander KM, Cappelli F, et al. Efficacy of acoramidis on all-cause mortality and cardiovascular hospitalization in transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2025;85(10):1003-1014. doi:10.1016/j.jacc.2024.11.042

24. European Medicines Agency. Beyonttra (acoramidis) [SmPC]. Accessed October 21, 2025. https://www.ema.europa.eu/en/medicines/human/EPAR/beyonttra

25. BridgeBio Pharma Inc. ATTRUBY (acoramidis) [package insert]. Accessed October 21, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf

26. GlobeNewswire. Beyonttr (acoramidis), the first near-complete TTR stabilizer (≥90%), approved in Japan to treat ATTR-CM. Accessed October 21, 2025. https://www.globenewswire.com/news-release/2025/03/27/3050413/0/en/Beyonttra-acoramidis-the-First-Near-complete-TTR-Stabilizer-90-Approved-in-Japan-to-Treat-ATTR-CM.html

27. Gov.uk. Press release: Acoramidis approved to treat wild-type or variant transthyretin amyloidosis in adults with cardiomyopathy. Accessed October 21, 2025. https://www.gov.uk/government/news/acoramidis-approved-to-treat-wild-type-or-variant-transthyretin-amyloidosis-in-adults-with-cardiomyopathy

28. Judge DP, Gillmore JD, Alexander KM, et al. Long-term efficacy and safety of acoramidis in ATTR-CM: initial report from the open-label extension of the ATTRibute-CM trial. *Circulation*. 2025;151(9):601-611. doi:10.1161/CIRCULATIONAHA.124.072771

29. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2018;39(30):2799-2806. doi:10.1093/eurheartj/ehx589

30. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med*. 1999;18(11):1341-1354. doi:10.1002/(SICI)1097-0258(19990615)18:11<1341::AID-SIM129>3.0.CO;2-7

31. Penchala SC, Connelly S, Wang Y, et al. AG10 inhibits amyloidogenesis and cellular toxicity of the familial amyloid cardiomyopathy-associated V122I transthyretin. *Proc Natl Acad Sci U S A*. 2013;110(24):9992-9997. doi:10.1073/pnas.1300761110

32. Selvaraj S, Claggett B, Shah SH, et al. Cardiovascular burden of the V142I transthyretin variant. *JAMA*. 2024;331(21):1824-1833. doi:10.1001/jama.2024.4467

33. Fahed G, Collins BN, Cai N, et al. Race, genetics, and social determinants of health in transthyretin cardiac amyloidosis: a literature review and call to action. *Curr Cardiol Rep*. 2025;27(1):66. doi:10.1007/s11886-025-02220-z