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Effect of Acoramidis on Heart Failure–Related Health Status
A Secondary Analysis of the ATTRibute-CM Randomized Clinical Trial

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IMPORTANCE In patients with transthyretin amyloid cardiomyopathy (ATTR-CM), acoramidis achieves near-complete (≥90%) transthyretin stabilization and reduces mortality and cardiovascular-related hospitalizations; however, its effect on patient-reported health status has not been comprehensively described.

OBJECTIVE To evaluate the effect of acoramidis on heart failure (HF)–related health status as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS) in patients with ATTR-CM.

DESIGN, SETTING, AND PARTICIPANTS ATTRibute-CM was a phase 3, multicenter, international, placebo-controlled randomized clinical trial conducted from April 2019 through May 2023. Adults with ATTR-CM were eligible for inclusion. Data were analyzed from July 2023 through November 2023.

INTERVENTIONS Acoramidis hydrochloride (800 mg) or placebo twice daily for 30 months.

MAIN OUTCOMES AND MEASURES The prespecified secondary outcome was least-squares mean (LSM) difference in KCCQ-OS over 30 months, analyzed using a mixed-effects model for repeated measures. Post hoc analysis at month 30 included being "alive and not worse" (KCCQ-OS <5-point decrease from baseline), "alive and well" (KCCQ-OS >60 and <10-point decrease from baseline), and "alive and better" (KCCQ-OS >5-point increase from baseline).

RESULTS Among 632 adults with ATTR-CM enrolled, 611 were included in the modified intention-to-treat population. Overall mean (SD) age was 77.2 (6.6) years, and 56 participants (9.2%) were female. Baseline mean (SD) KCCQ-OSs were 71.7 (19.4) and 70.5 (20.7) in the acoramidis (n = 409) and placebo (n = 202) groups, respectively. At month 30, a statistically significant, clinically meaningful treatment benefit was observed for acoramidis vs placebo (LSM difference, 9.9; 95% CI, 6.0-13.9; $P < .001$). At month 30 (acoramidis: 367; placebo: 188), 171 acoramidis recipients (47%) were "alive and not worse" vs 56 placebo recipients (30%) (odds ratio, 2.1; 95% CI, 1.4-3.1; $P < .001$; number needed to treat [NNT] = 6). More acoramidis recipients (168 [46%]) were "alive and well" vs placebo (59 [31%]) (odds ratio, 1.9; 95% CI, 1.3-2.8; $P < .001$; NNT = 7). Similarly, 93 acoramidis recipients (25%) were "alive and better" vs 26 placebo recipients (14%) (odds ratio, 2.1; 95% CI, 1.3-3.4; $P = .002$; NNT = 9).

CONCLUSIONS AND RELEVANCE In this secondary analysis of the ATTRibute-CM randomized clinical trial, in patients with ATTR-CM, acoramidis significantly attenuated the decline in HF-related health status compared with placebo. These results suggest meaningful patient-centered benefits and clinically relevant modification of disease trajectory with acoramidis.

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Supplemental content

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Transthyretin (TTR) amyloid cardiomyopathy (ATTR-CM) is a progressive and frequently fatal condition caused by the destabilization of TTR tetramers that dissociate into misfolded monomers, which deposit as insoluble amyloid fibrils in the myocardium, leading to impairment of diastolic, systolic, valvular, and conductive function.[1-3] Patients with ATTR-CM frequently experience declines in their health status, characterized by progressive symptoms, functional impairment, and poor quality of life (QoL).[4,5]

The primary goals in the management of ATTR-CM are to halt or slow disease progression and to preserve or improve patients' health status, including their symptoms, function, and QoL.[6] Patient-reported outcomes are, therefore, essential for evaluating the impact of new therapies. Health status in patients with heart failure (HF) is commonly assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), which captures the impact of HF on patients' lives from their own perspectives.[7,8] Patients with ATTR-CM have lower KCCQ scores and experience more rapid decline over time than patients with other HF phenotypes,[5] reflecting the progressive nature of the disease and the limited effectiveness of conventional HF therapies.

Recently, therapies have been shown to improve outcomes in ATTR-CM.[9-11] Acoramidis, an approved therapy for ATTR-CM, achieves near-complete (≥90%) TTR stabilization that mimics the stabilizing effects of the protective p.T139M (previously known as T119M) TTR gene variant.[12] In the phase 3, placebo-controlled ATTRibute-CM randomized clinical trial (NCT03860935), acoramidis reduced the key composite end point of mortality and cardiovascular-related hospitalizations (CVH) with an early effect starting from month 3 driven by early reductions in CVH.[9,13] Acoramidis had favorable effects on patient-reported health status and attenuated or slowed the worsening of health status vs placebo in ATTRibute-CM.[9] Given the impact of acoramidis on both mortality and health status and that the KCCQ can only be collected in survivors, a holistic understanding of treatment benefits on both outcomes is needed to better support medical decision-making.

Given the initial results from ATTRibute-CM, which showed favorable effects of acoramidis on patient-reported health status, we expand these analyses here and evaluate the consistency of this benefit across prespecified patient subgroups. Additionally, we describe the efficacy of acoramidis on outcomes in ATTR-CM by integrating survival and health status into a single analysis.

Key Points

Question What is the effect of acoramidis on heart failure–related health status as measured by the Kansas City Cardiomyopathy Questionnaire in patients with transthyretin amyloid cardiomyopathy (ATTR-CM)?

Findings In this secondary analysis of the ATTRibute-CM randomized clinical trial among 611 participants (acoramidis: 409; placebo: 202), acoramidis attenuated the decline in heart failure–related health status vs placebo at month 30. Acoramidis was associated with both significantly greater likelihood of survival without worsening health status and improved or maintained health status vs placebo.

Meaning Beyond the established benefits of acoramidis in improving survival and reducing hospitalizations in ATTR-CM, treatment resulted in better heart failure–related health status relative to placebo.

Methods

Study Design and Participant Population

ATTRibute-CM was a phase 3, double-blind, multicenter randomized clinical trial evaluating the efficacy and safety of acoramidis vs placebo in participants with symptomatic ATTR-CM, and its design has been previously published.[9] The trial protocol is provided in Supplement 1, and the statistical analysis plan is provided in Supplement 2. Briefly, the study enrolled participants from 18 to 90 years of age with either wild-type or variant TTR genotypes and New York Heart Association (NYHA) class I to III symptoms. Participants were randomized 2:1 to receive oral acoramidis hydrochloride, 800 mg, twice daily or matching placebo for 30 months. Randomization was stratified by TTR genotype (wild type or variant), N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (≤3000 or >3000 pg/mL), and kidney function (estimated glomerular filtration rate [eGFR] <45 or ≥45 mL/min/1.73 m^2) at screening. Since tafamidis was approved while the study was ongoing, concomitant treatment with tafamidis was permitted after month 12 at the investigator's discretion.[9]

The study was conducted in accordance with the International Council for Harmonisation, Good Clinical Practice guidelines, and the Declaration of Helsinki[14] and was approved by an institutional review board or independent ethics committee at each participating site. ATTRibute-CM followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.[9] All participants provided written informed consent.

Efficacy analyses were conducted in the prespecified modified intention-to-treat (mITT) population, which included all randomized participants who had a baseline (at randomization) eGFR of 30 mL/min/1.73 m^2 or greater, received at least 1 dose of their assigned treatment following randomization, and at least 1 postbaseline efficacy evaluation. Participants with a baseline eGFR less than 30 mL/min/1.73 m^2 (chronic kidney disease) were excluded from the efficacy analysis but were included for safety monitoring.

KCCQ

The KCCQ is a patient-reported outcome measure that quantifies the impact of HF on patients' symptoms, function, and QoL from their own perspectives.[7] Symptom frequency and burden are quantified by the total symptom (TS) score, whereas physical limitations (PL) and social limitations (SL) and QoL are independently assessed and can be combined into summary scores.[6] The clinical summary (CS) score integrates the TS and PL scores to mirror the NYHA functional class from patients' perspectives. The KCCQ Overall Summary score (KCCQ-OS) combines the CS with the SL and QoL domains to capture a more holistic measure of patients' HF-related health status.

The KCCQ-OS ranges from 0 to 100, with higher scores indicating better health status; 100 represents the best health and 0 represents the worst health. The within-patient minimal clinically important difference (MCID) for the KCCQ-OS is generally considered a change of around 5 points, indicating a meaningful improvement or worsening of health status for patients with HF.[15] Thus, changes of 5 points or less in KCCQ scores are not clinically important for patients, whereas changes of 5, 10, 15, and 20 points represent small, moderate, large, and very large clinical changes in patients' health status, respectively.[6,7,16]

In ATTRibute-CM, the KCCQ assessments were collected at baseline, at months 3, 6, 9, and 12, and then every 6 months until the study conclusion at month 30. Assessments at month 3 were added as a protocol amendment, meaning that not all participants had a month 3 assessment.

Statistical Analysis

A prespecified key secondary end point of ATTRibute-CM was the change in KCCQ-OS from baseline to 30 months with acoramidis vs placebo as calculated by the least-squares mean (LSM) change from a mixed model for repeated measures (MMRM) approach. The MMRM included treatment group, study visit, and stratification factors of TTR genotype (wild type vs variant), NT-proBNP level (≤3000 vs >3000 pg/mL), eGFR level (≥45 vs <45 mL/min/1.73 m^2), and treatment group-by-study visit interaction as factors and used baseline KCCQ-OS as a covariate. Changes in observed scores for KCCQ-OS in both treatment groups were also evaluated. Heterogeneity of treatment effect was assessed across prespecified participant subgroups of baseline characteristics categorized by age, country of enrollment, genotype, NYHA class, NT-proBNP, and eGFR.

A prespecified sensitivity analysis was also conducted, removing participants who received concomitant tafamidis at any time during the study. LSM change from baseline at month 30 was analyzed in participants who received acoramidis only or placebo only using the same MMRM model as described previously.

To support the clinical interpretation of population-level mean effects, the distribution of intraindividual changes in KCCQ-OS at the month 30 assessment was categorized by the proportion of individuals between treatment groups attaining magnitudes of clinically important change. No clinically important change in health status was defined as a score change of more than −5 to less than 5, a small but clinically relevant improvement was 5 or more and less than 10, a moderate improvement was 10 or more and less than 15, a large improvement was 15 or more and less than 20, and a very large improvement was 20 or more points, with similar inverse thresholds used for deteriorations in KCCQ-OS. The odds ratio, 95% confidence interval, and *P* value for the difference in proportions were obtained from the Cochran-Mantel-Haenszel test with stratification factors of genotype, NT-proBNP level, and eGFR level. The numbers needed to treat (NNTs) with 95% confidence intervals were calculated as the inverse of the absolute risk reduction and its 95% confidence interval using the Mantel-Haenszel method.[6,17]

To integrate survival and health status into a single analysis, analyses of participants who were "alive and well"[18-20] and "alive and not worse"[16,21] were performed as described in prior studies in patients with HF symptoms. At month 30, the effect of acoramidis on KCCQ-OS was compared with placebo as participants "alive and not worse" (KCCQ-OS <5-point decrease from baseline), "alive and well" (KCCQ-OS >60 and <10-point decrease from baseline), and "alive and better" (KCCQ-OS >5-point increase from baseline) using a Cochran-Mantel-Haenszel test adjusted for randomization strata as previously described. A threshold of a less than 10-point decrease from baseline was also presented for the "alive and not worse" analysis and a threshold of a more than 10-point increase from baseline was also presented for the "alive and better" analysis (see eTable 1 in Supplement 3 for a breakdown of these definitions).

KCCQ responses were missing for some participants for multiple reasons. Some were missing for known reasons (owing to death or treatment discontinuation) and some for unknown reasons (eg, missed follow-up visit). Therefore, the prespecified imputation strategies for handling missing data differed depending on the type of missing data. For participants who died, the missing KCCQ-OSs due to death were imputed by sampling with replacement from the worst 5% of observed values within each treatment group at a given visit to reflect their poor outcome (n = 131 at month 30). For participants who discontinued treatment, jump to reference multiple imputations were used (n = 51 at month 30). For example, if a participant was assigned to the acoramidis arm and discontinued treatment, their missing values after discontinuation were imputed based on the distribution of the placebo arm (assuming that acoramidis participants would be closer to placebo participants in KCCQ-OS after treatment discontinuation). Participants with missing KCCQ-OS who were alive and had not discontinued treatment were not imputed (1 participant at baseline and 4 participants at month 30), relying on the statistical assumption that they were missing at random. Observed values are also presented in the mean change from baseline analysis. In responder analyses, participants with missing data (drug discontinuation or questionnaire not completed) were not included.

All statistical analyses were performed using SAS software version 9.4 or higher (SAS Institute) and R software version 4.4.1 (R Core Team).

Results

Baseline Characteristics

Consistent with the prespecified efficacy analysis reported for ATTRibute-CM, efficacy analyses in this study were conducted in the mITT population (n = 611), which excluded the 21 participants with chronic kidney disease (stage IV and above) who were included in ATTRibute-CM for analysis of safety outcomes only. Safety outcomes are available in the primary ATTRibute-CM publication.[9] Briefly, the 3 most common treatment-emergent adverse events were cardiac failure (24.0%), COVID-19 (21.1%), and atrial fibrillation (16.6%) for acoramidis and cardiac failure (39.3%), atrial fibrillation (21.8%), and dyspnea (19.0%) for placebo.[9]

Table. Participant Demographics and Characteristics Prior to Initiation of Treatment (Baseline) in the Modified Intention-to-Treat Population (N = 611)

Characteristic	Participants, No. (%)		
	Acoramidis (n = 409)	Placebo (n = 202)	Overall (N = 611)
Age, y			
Mean (SD)	77.3 (6.5)	77.0 (6.7)	77.2 (6.6)
Median (IQR)	78.0 (73.0-82.7)	77.9 (72.9-81.9)	78.0 (73.0-82.0)
Sex			
Female	35 (8.6)	21 (10.4)	56 (9.2)
Male	374 (91.4)	181 (89.6)	555 (90.8)
Race[a]			
Black or African American	19 (4.6)	10 (5.0)	29 (4.7)
White	358 (87.5)	179 (88.6)	537 (87.9)
Other[b]	32 (7.8)	13 (6.4)	45 (7.4)
TTR genotype[c]			
Wild type	370 (90.5)	182 (90.1)	552 (90.3)
Variant	39 (9.5)	20 (9.9)	59 (9.7)
NYHA class			
I	51 (12.5)	17 (8.4)	68 (11.1)
II	288 (70.4)	156 (77.2)	444 (72.7)
III	70 (17.1)	29 (14.4)	99 (16.2)
eGFR, mL/min/1.73 m^2			
Mean (SD)	62.0 (17.4)	62.5 (17.5)	62.2 (17.4)
Median (IQR)	62.0 (49.0-74.0)	61.0 (48.0-74.0)	61.0 (49.0-74.0)
≥45	344 (84.1)	173 (85.6)	517 (84.6)
<45	65 (15.9)	29 (14.4)	94 (15.4)
NT-proBNP, pg/mL			
Median (IQR)	2273 (1315-3872)	2274 (1128-3590)	2273 (1240-3729)
≤3000	268 (65.5)	133 (65.8)	401 (65.6)
>3000	141 (34.5)	69 (34.2)	210 (34.4)
KCCQ scores, mean (SD)			
Physical limitation	73.0 (21.7)	72.2 (20.9)	72.7 (21.4)
Quality of life	67.1 (21.6)	66.4 (24.1)	66.9 (22.5)
Self-efficacy	78.4 (22.5)	80.1 (23.8)	79.0 (22.9)
Social limitation	68.8 (26.0)	67.7 (27.7)	68.4 (26.6)
Symptom burden	78.2 (19.0)	75.9 (21.2)	77.5 (19.8)
Symptom frequency	77.4 (20.4)	75.1 (22.3)	76.6 (21.1)
Symptom stability	52.5 (14.2)	53.1 (17.1)	52.7 (15.2)
Total symptom	77.8 (18.8)	75.3 (21.2)	77.0 (19.6)
Clinical summary	75.4 (18.8)	73.7 (19.3)	74.9 (19.0)
Overall summary	71.7 (19.4)	70.5 (20.7)	71.3 (19.8)

Abbreviations: eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

[a] Self reported.

[b] Not reported: acoramidis, 15 (3.7%); placebo, 7 (3.5%); overall, 22 (3.6%). Asian: acoramidis, 10 (2.4%); placebo, 3 (1.5%); overall, 13 (2.1%). Other (provided as an option for participants to select): acoramidis, 5 (1.2%); placebo, 1 (0.5%); overall, 6 (1.0%). Multiple races: acoramidis, 2 (0.5%); placebo, 0; overall, 2 (0.3%). American Indian or Alaska Native: acoramidis, 0; placebo, 1 (0.5%); overall, 1 (0.2%). Native Hawaiian or Other Pacific Islander: acoramidis, 0; placebo, 1 (0.5%); overall, 1 (0.2%).

[c] TTR genotype as recorded at randomization.

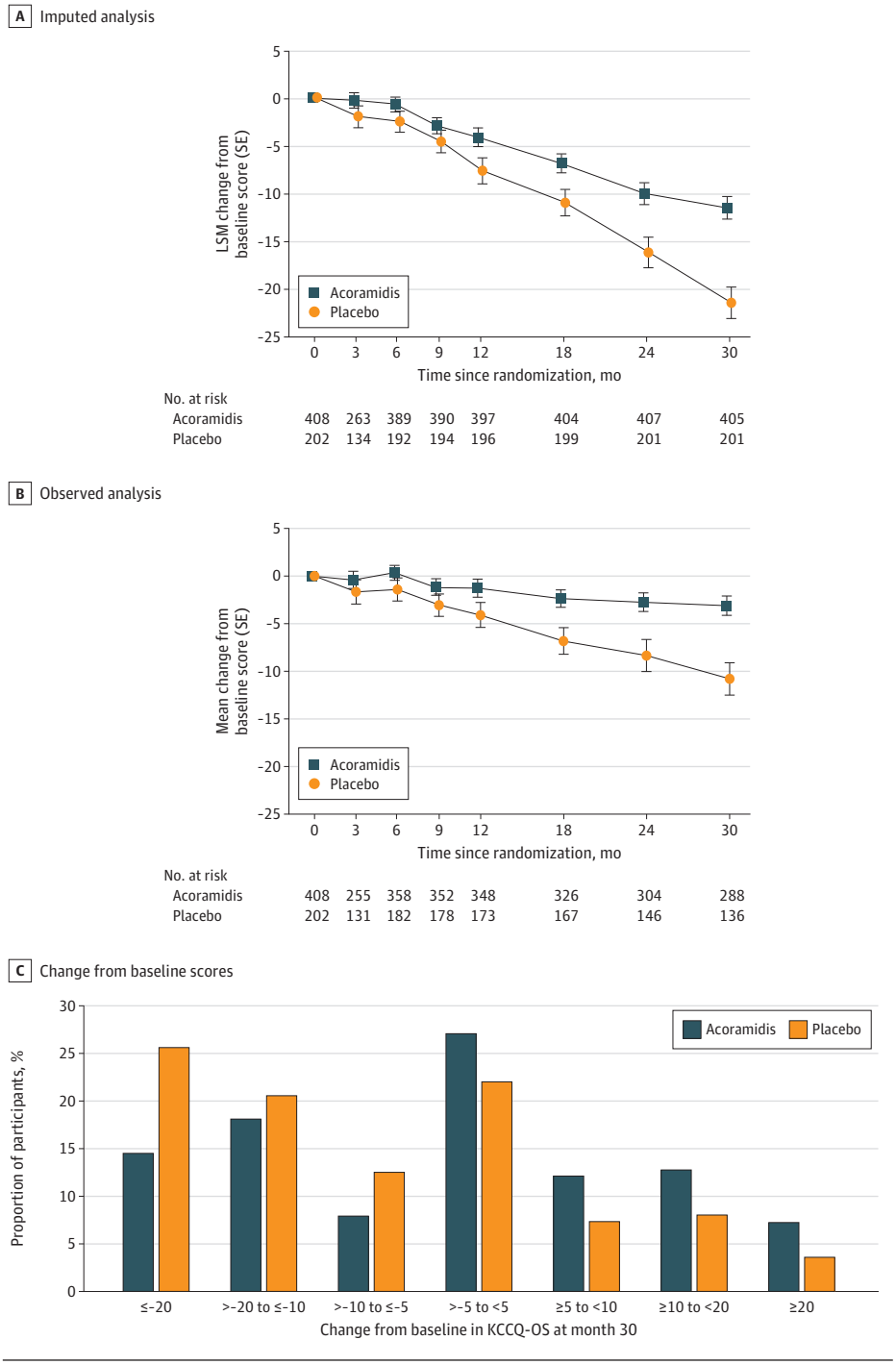
The mITT population included 409 participants in the acoramidis group and 202 participants in the placebo group (eFigure 1 in Supplement 3). The mean (SD) age was 77.2 (6.6) years, 56 participants (9.2%) were female, and 552 (90.3%) had wild-type ATTR-CM. Baseline mean (SD) KCCQ-OSs were relatively high at 71.7 (19.4) and 70.5 (20.7) in the acoramidis and placebo groups, respectively. Comprehensive baseline characteristics were well balanced between groups (**Table**). eTable 2 in Supplement 3 reports KCCQ values as medians with interquartile ranges.

Changes in KCCQ-OS by Assessment Period

In the imputed model, the LSM KCCQ-OS decreased from baseline to month 30 in both treatment groups, with greater deterioration in the placebo group. Mean differences between groups emerged in the first 3 months (**Figure 1**A) and became statistically significant after month 9. By month 30, the LSM (SE) change in KCCQ-OS from baseline was −11.5 (1.2) in the acoramidis group and −21.4 (1.7) in the placebo group, with an LSM difference (acoramidis − placebo) of 9.9 points (95% CI, 6.0-13.9; $P < .001$), corresponding to a moderate clinical benefit with acoramidis compared with placebo. Consistent to the modeling data, a similar benefit was seen based on the analysis for observed data (mean [SD] change from baseline, acoramidis: −3.1 [17.0]; placebo: −10.8 [19.4]) (Figure 1B).

A prespecified sensitivity analysis excluding participants who received concomitant tafamidis at any time during the study demonstrated a clinically moderate and meaningful benefit favoring treatment with acoramidis alone at month 30 vs placebo. The LSM (SE) change in KCCQ-OS was −12.9 (1.3) with acoramidis alone and −22.6 (1.9) with placebo alone (LSM difference between treatment groups, 9.7; 95% CI: 5.3-14.1; $P < .001$) (eTable 3 in Supplement 3). Consistent and favorable effects of acoramidis vs placebo were also observed on all

Figure 1. Line Graphs and Histogram of Change From Baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) Over Time



Line graphs showing mean change from baseline in KCCQ-OS in the modified intention-to-treat (mITT) population over 30 months for the prespecified, imputed analysis (A) and the observed analysis (B). Histogram of the proportions of participants in the mITT population with changes from baseline to month 30 in KCCQ-OS categorized by magnitude (C). Adapted with permission from Gillmore and colleagues.[9] LSM indicates least-squares mean.

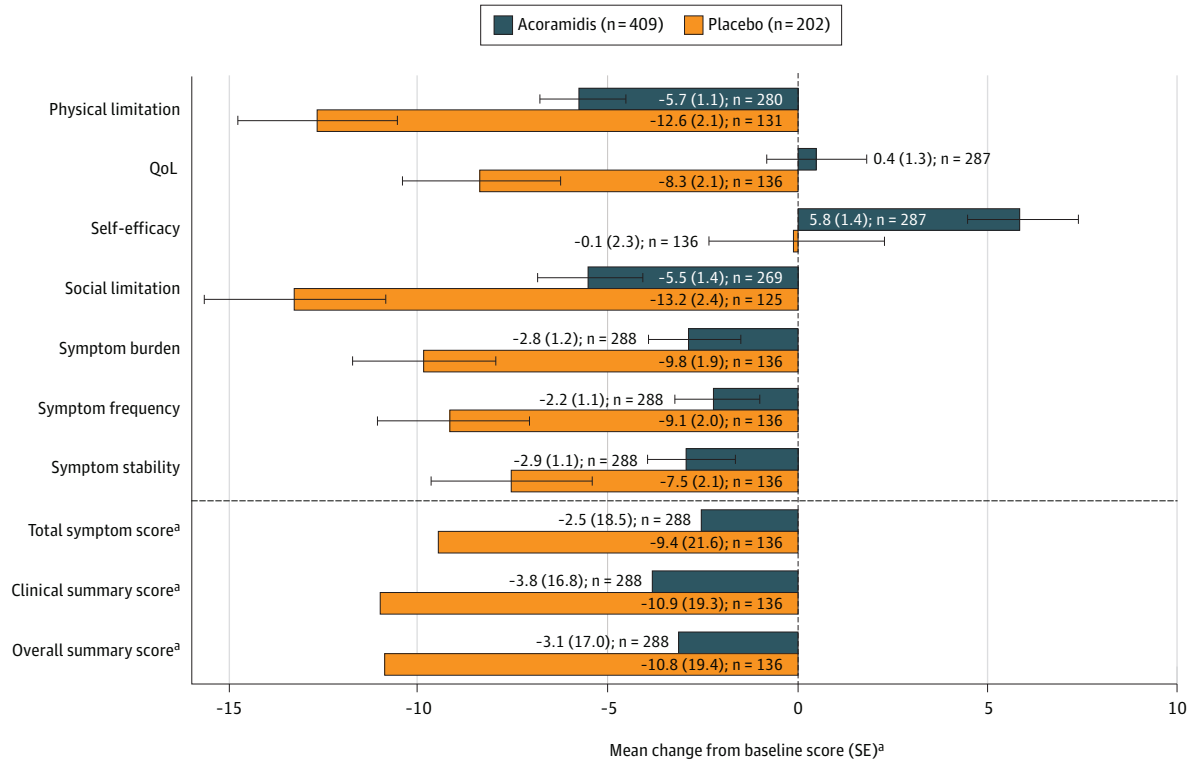
KCCQ domain and summary scores (**Figure 2**). eTable 4 in Supplement 3 reports KCCQ change from baseline values as medians with interquartile ranges.

Change from baseline in KCCQ-OS favored acoramidis at month 30 across prespecified subgroups and randomization stratification factors, which included the variant status, NT-proBNP, eGFR, age, country of enrollment, and NYHA class, with no evidence of heterogeneity in treatment benefit (**Figure 3**).

Proportion of Participants With Clinically Meaningful Change From Baseline in KCCQ-OS at Month 30

At month 30, those assigned to acoramidis were more likely to have an improvement in KCCQ-OS than those assigned to placebo (Figure 1C). Those assigned to acoramidis consistently experienced greater clinical benefit across clinically important magnitudes of change.

Figure 2. Bar Graph Showing Changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) Domain Scores From Baseline to Month 30

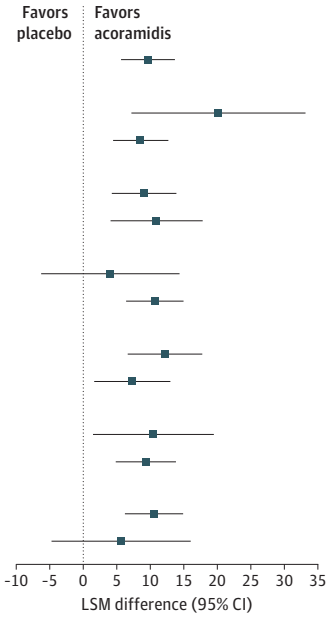


Depicted are observed (no imputation) change from baseline scores for the modified intention-to-treat population, with the number of observations noted within each domain and treatment assignment. Domains of the KCCQ favor acoramidis vs placebo, with numerical improvements noted in self-efficacy and quality of life (QoL) domains.

[a]SD is provided for summary scores.

Figure 3. Forest Plot for Change From Baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) to Month 30 by Subgroup

Subgroup	No. of participants[a] (%)	LSM difference (95% CI)	*P* value
Overall	606 (100)	9.9 (6.0 to 13.9)	<.001
ATTR-CM genotype			.09[b]
ATTRv-CM	59 (10)	20.3 (7.5 to 33.1)	.002
ATTRwt-CM	547 (90)	8.8 (4.6 to 13.0)	<.001
NT-proBNP, ng/L			.66[b]
≤3000	398 (66)	9.3 (4.5 to 14.1)	<.001
>3000	208 (34)	11.2 (4.4 to 18.0)	.001
eGFR, mL/min/1.73 m^2			.24[b]
<45	93 (15)	4.4 (−5.9 to 14.6)	.40
≥45	513 (85)	11.0 (6.7 to 15.3)	<.001
Age, y			.23[b]
<78	298 (49)	12.4 (6.9 to 18.0)	<.001
≥78	308 (51)	7.6 (2.0 to 13.2)	.008
Country			.85[b]
US	117 (19)	10.7 (1.8 to 19.6)	.02
Rest of world	489 (81)	9.7 (5.3 to 14.1)	<.001
NYHA class			.39[b]
I, II	507 (84)	10.8 (6.5 to 15.1)	<.001
III	99 (16)	6.0 (−4.3 to 16.2)	.25

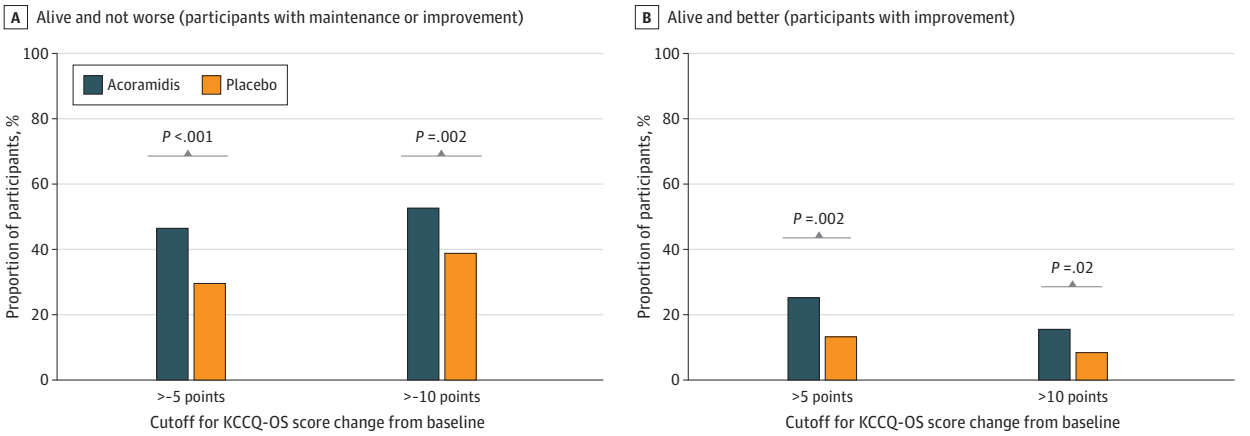


ATTR-CM indicates transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; LSM, least-squares mean; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association.

[a]Data are from participants with available values.

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

Figure 4. Bar Graphs Showing Proportions of Participants With Stable or Improved Kansas City Cardiomyopathy Questionnaire Overall Summary Scores (KCCQ-OS)



Rates of "alive and not worse" as defined by the proportion of participants who maintained or improved their KCCQ-OS at month 30 (A) and the proportion of participants who had an improved KCCQ-OS at month 30 (B). Participants with missing data were considered to be not "alive and not worse."

The proportion of participants who were "alive and not worse" at month 30 significantly favored acoramidis; 171 of 367 participants randomized to acoramidis (46.6%) vs 56 of 188 randomized to placebo (29.8%) were "alive and not worse" (<5-point decrease), which was a 16.8% difference with an odds ratio of 2.1 (95% CI, 1.44-3.09; $P < .001$) and an NNT of 6 (95% CI, 4.0-11.6) (**Figure 4**A). Using a less stringent cutoff of a less than 10-point decrease for "alive and not worse," 194 of 367 acoramidis recipients (52.9%) achieved this outcome vs 73 of 188 placebo recipients (38.8%), which was a 14.1% difference with an odds ratio of 1.8 (95% CI, 1.25-2.61; $P = .002$) and an NNT of 8 (95% CI, 4.5-18.3).

Participants were also more likely to be categorized as "alive and well" if randomized to acoramidis; 168 of 367 acoramidis recipients (45.8%) and 59 of 188 placebo recipients (31.4%) were considered "alive and well," resulting in a difference of 14.4% with an odds ratio of 1.9 (95% CI, 1.30-2.78; $P < .001$) and an NNT of 7 (95% CI, 4.5-16.2).

The proportion of participants who were "alive and better" are shown in Figure 4B, with 93 of 367 acoramidis recipients (25.3%) being alive and having at least a small, more than 5-point improvement in health status from baseline to month 30 vs 26 of 188 placebo recipients (13.8%) (difference, 11.5%; odds ratio, 2.1; 95% CI, 1.32-3.43; $P = .002$) with an NNT of 9 (95% CI, 5.5-20.4). When considering an at least moderate, more than 10-point improvement, 58 of 367 acoramidis recipients (15.8%) vs 16 of 188 placebo recipients (8.5%) met these criteria (difference, 7.3%; odds ratio, 2.0; 95% CI, 1.13-3.61; $P = .02$) with an NNT of 14.

Discussion

To our knowledge, this is the first comprehensive report of the effect of acoramidis on patient-reported HF-related health status in patients with ATTR-CM. In ATTRibute-CM, treatment with acoramidis resulted in meaningful and sustained benefits in HF-related health status through month 30 vs placebo. Although health status declined over time in both acoramidis and placebo groups, consistent with the progressive nature of ATTR-CM, acoramidis attenuated the decline in KCCQ-OS and in all subdomain scores vs placebo. Differences in health status between treatment groups emerged early (within 3 months of acoramidis initiation), becoming statistically significant at 9 months, and continued to diverge over time. Importantly, we observed a population-level 10-point difference in KCCQ-OS between treatment groups, which is larger than the treatment difference typically observed in many HF clinical trials.[22] This suggests that a greater proportion of participants experienced slowed worsening or improvement of their KCCQ-OS with acoramidis vs placebo and is of particular relevance given that one of the primary goals in ATTR-CM management is to preserve or improve health status. These findings were robust across both observed and imputed datasets. Furthermore, sensitivity analyses excluding participants who received concomitant tafamidis showed consistent benefits of acoramidis on HF-related health status. Collectively, these results highlight both the early onset and durability of benefit with acoramidis.

Treatment effects with acoramidis were consistent across prespecified subgroups, including TTR genotype, age, sex, and NYHA class, without evidence of heterogeneity, suggesting that acoramidis confers health status benefits relative to placebo across the entire ATTR-CM disease spectrum. These overall benefits with acoramidis were supported by attenuated decline across multiple KCCQ domains, with particularly pronounced differences observed in QoL and self-efficacy scores relative to placebo. The rapid and widening benefits of acoramidis on HF-related health provide a clearer framework for understanding the patient-centered benefits of acoramidis, demonstrating that improvements in survival and reducing the rate of clinical events are aligned with preservation and improvement of health status in ATTR-CM.[13]

This study also integrates survival and HF-related health status to demonstrate treatment benefits with acoramidis in patients with ATTR-CM. Participants receiving acoramidis were more likely to experience stabilization of their health status and had a higher likelihood of being "alive and not worse" (NNT = 6), "alive and well" (NNT = 7), or "alive and better" (NNT = 9) vs placebo. Taken together, these patient-reported benefits complement previously established reductions in mortality and CVH with acoramidis, indicating that treatment not only improves survival and reduces clinical events, but also attenuates the decline in patients' health status. The integration of survival and patient-reported health status reinforces the importance of early diagnosis and timely initiation of acoramidis for optimal management of this chronic and progressive condition.

Prior studies have shown that stabilization or silencing of the TTR protein with tafamidis or vutrisiran, respectively, attenuates the decline in HF-related health status.[23-25] Although the LSM differences between treatments and placebo in KCCQ-OS vary across studies (13.4 points with tafamidis, 8.7 points with vutrisiran vs 9.9 points with acoramidis), cross-trial comparisons remain difficult given differences in baseline health status, timing of diagnosis, event rates, and treatment availability. Collectively, the range of emerging therapeutic options for ATTR-CM is encouraging, and the magnitude of benefits observed with acoramidis (NNT of 6 to 7) supports its relevance to patient-centered outcomes.

Limitations

The findings from this study should be interpreted in the context of the following limitations. Although the inclusion and exclusion criteria of a trial can often limit generalizability, as clinical suspicion of ATTR-CM increases and patients are being diagnosed earlier in the disease course, their outcomes may differ from those observed in this trial. The KCCQ-OS assessment was added as a protocol amendment, so not all participants had a month 3 assessment. Since KCCQ scores often decline before clinical events occur, measuring the KCCQ only in those who survive may bias calculated scores toward those with better health status and could obscure real treatment effects; however, our "alive and well" analyses address this concern and represent the first time such an analysis has been applied to this population.[26,27] Finally, ATTRibute-CM included a relatively low proportion of certain subgroups, including women and participants with variant ATTR-CM. This may affect the generalizability of the health status outcomes reported here given that previous studies have found that KCCQ scores may vary between men and women and that participants with variant ATTR-CM show more rapid deterioration in health status than those with wild-type disease.[28-30]

Conclusions

In this secondary analysis of the ATTRibute-CM randomized clinical trial among patients with ATTR-CM, acoramidis attenuated the decline in patient-reported health status vs placebo, with sustained results that were consistent across prespecified subgroups. Moreover, a greater proportion of participants receiving acoramidis were considered "alive and not worse," "alive and well," or "alive and better" at 30 months vs placebo. These findings demonstrate that the survival and CVH benefits of acoramidis are accompanied by meaningful stabilization of patient-reported health status in ATTR-CM.

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