wild-type TTR. Most of the patients had either New York Heart Association (NYHA) class II symptoms (72.0%) or class III symptoms (17.2%). The distribution of National Amyloidosis Centre stages[15] was 57% in stage I, 32% in stage II, and 11% in stage III. The last patient completed the 30-month assessments on April 28, 2023. The demographic and clinical characteristics of the patients are summarized in Table 1. The trial population was representative of the broader patient population with transthyretin amyloid cardiomyopathy (Table S2).[18] The disposition of all the patients who provided informed consent is shown in Figure S2.

HIERARCHICAL EFFICACY ANALYSES

The four-step primary hierarchical analysis (which included death from any cause, cardiovascular-related hospitalization, the change from baseline in the NT-proBNP level, and the change from baseline in the 6-minute walk distance) showed a better outcome in the acoramidis group than in the placebo group (Finkelstein–Schoenfeld test statistic, 5.015; P<0.001) and yielded a win ratio of 1.8 (95% CI, 1.4 to 2.2) (Fig. 1). A sensitivity analysis of the primary outcome in the intention-to-treat population showed a similar outcome (Finkelstein–Schoenfeld test statistic, 5.045; P<0.001).

Prespecified secondary analyses performed according to either the two-component hierarchy of death from any cause and cardiovascular-related hospitalization or the three-component hierarchy of death from any cause, cardiovascular-related hospitalization, and 6-minute walk distance are also shown in Figure 1; the associated win ratios were 1.5 (95% CI, 1.1 to 2.0) and 1.4 (95% CI, 1.1 to 1.8), respectively. Additional details regarding the win ratio complement to the primary outcome are shown in Figure 2.

Of the four components in the win ratio, the NT-proBNP pairwise comparisons yielded both the highest ratio of wins to losses (23.3% vs. 7.0%) as well as the greatest marginal number of potential ties broken (30.3%). Owing to the hierarchical nature of the win ratio, these comparisons were not considered until after most potential ties (58.0%) had already been determined by the two clinical outcomes of death from any cause (28.8%) and cardiovascular-related hospitalization (29.3%). For the potential ties in the Finkelstein–Schoenfeld test, 28.1% of results of pairwise comparisons were determined by death from any cause, 27.0% by cardiovascular-related hospitalization, 30.2% by NT-proBNP, and 14.3% by 6-minute walk distance; 0.4% remained as ties at the end of the procedure. Results of prespecified subgroup analyses are shown in Figure S3. The relative risk ratio for frequency of cardiovascular-related hospitalization per year was 0.496 (95% CI, 0.355 to 0.695) in favor of acoramidis. The 30-month change from baseline in the NT-proBNP level (ratio of adjusted geometric mean factor change) was 0.529 in favor of acoramidis (95% CI, 0.463 to 0.604) (Fig. 3A).

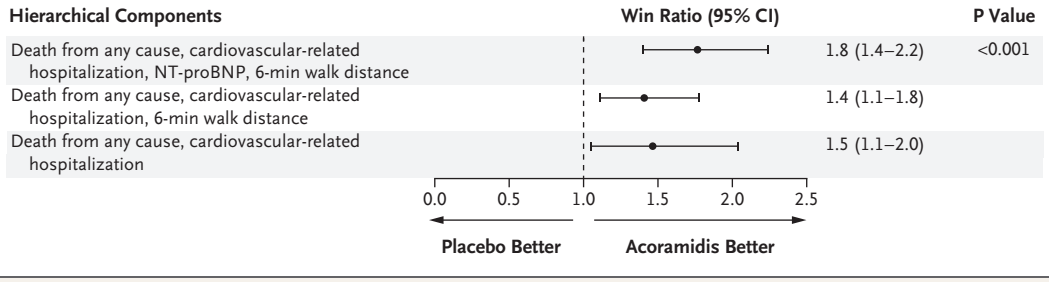


Figure 1. Primary Efficacy Analysis and Prespecified Secondary Analyses.

The four-step primary hierarchical analysis included death from any cause, cardiovascular-related hospitalization, the change from baseline in the level of N-terminal pro–B-type natriuretic peptide (NT-proBNP), and the change from baseline in the 6-minute walk distance. Also shown are the results of prespecified secondary analyses for the three-component hierarchy of death from any cause, cardiovascular-related hospitalization, and 6-minute walk distance and the two-component hierarchy of death from any cause and cardiovascular-related hospitalization. The P value for the win ratio was calculated with the use of the Finkelstein–Schoenfeld method.

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SECONDARY OUTCOMES

Key secondary outcomes that were included in the hierarchical plan to adjust for multiple comparisons were the 30-month change from baseline in the 6-minute walk distance, the change from baseline in the KCCQ-OS score, TTR serum level, and death from any cause. In the acoramidis group, the decrease from baseline in the 6-minute walk distance was less than that in the placebo group, with a least-squares mean difference of 39.6 m in favor of acoramidis (95% CI, 21.1 to 58.2; P<0.001) (Fig. 3B). Patients in the acoramidis group also had a better quality of life, as assessed by the KCCQ-OS score, with a least-squares mean difference of 9.94 points (95% CI, 5.97 to 13.91; P<0.001) (Fig. 3C). The serum TTR level, which is typically below normal or in the low-normal range among patients with transthyretin amyloid cardiomyopathy, was consistently higher throughout the trial in the acoramidis group than in the placebo group (Fig. 3D). At 30 months, the change from baseline in the least-squares mean difference in the serum TTR level was 7.01 mg per deciliter in favor of acoramidis (95% CI, 5.79 to 8.40; P<0.001).

The estimates from the prespecified analysis

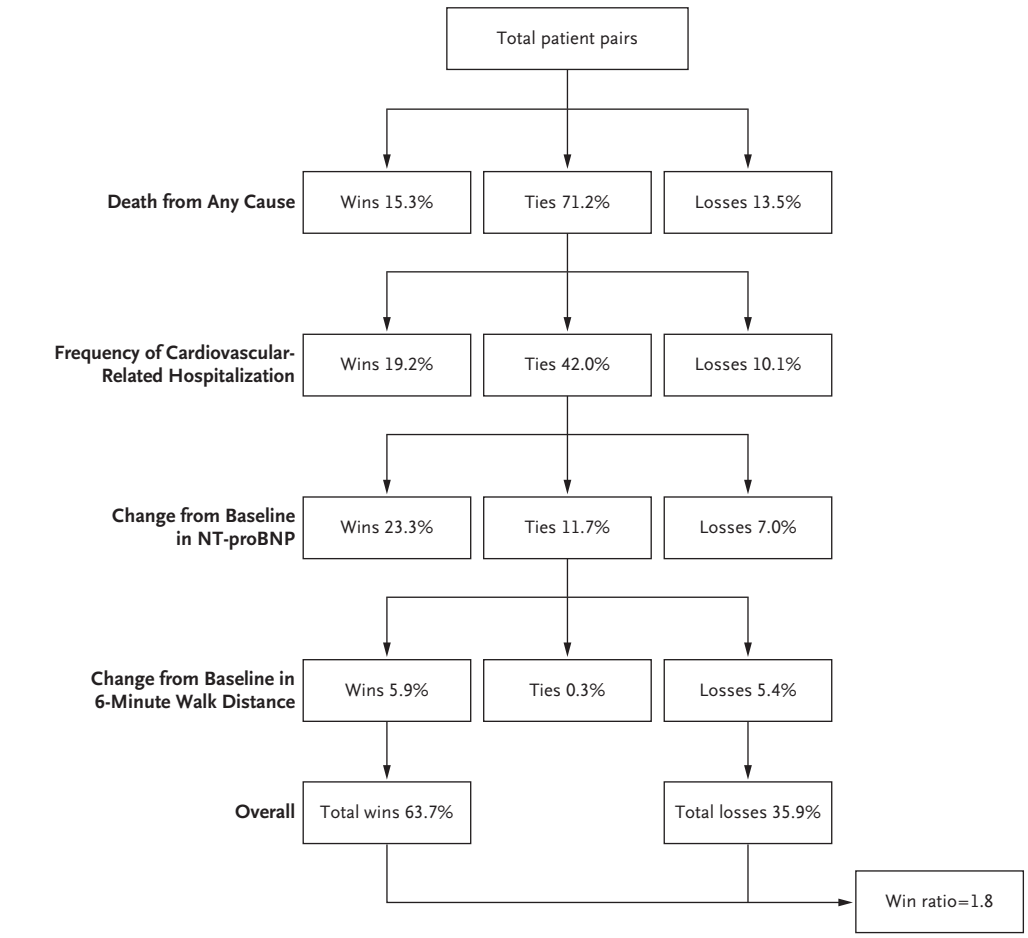


Figure 2. Paired Comparisons in the Four-Step Hierarchical Analysis of the Primary Outcome.

The stratified win ratio can be expressed as the proportion of pairwise comparisons for which active treatment wins over placebo divided by the proportion of pairwise comparisons for which placebo wins, taking into account both the hierarchical ordering of the comparisons and the strata in which the comparisons are performed. For each element of the hierarchical analysis, percentages of the total pairs that are determined to be wins, ties, or losses are shown. In each subsequent row, the wins, ties, and losses were all categorized as ties in the previous row. Percentages in several categories may not sum to the stated values because of rounding.

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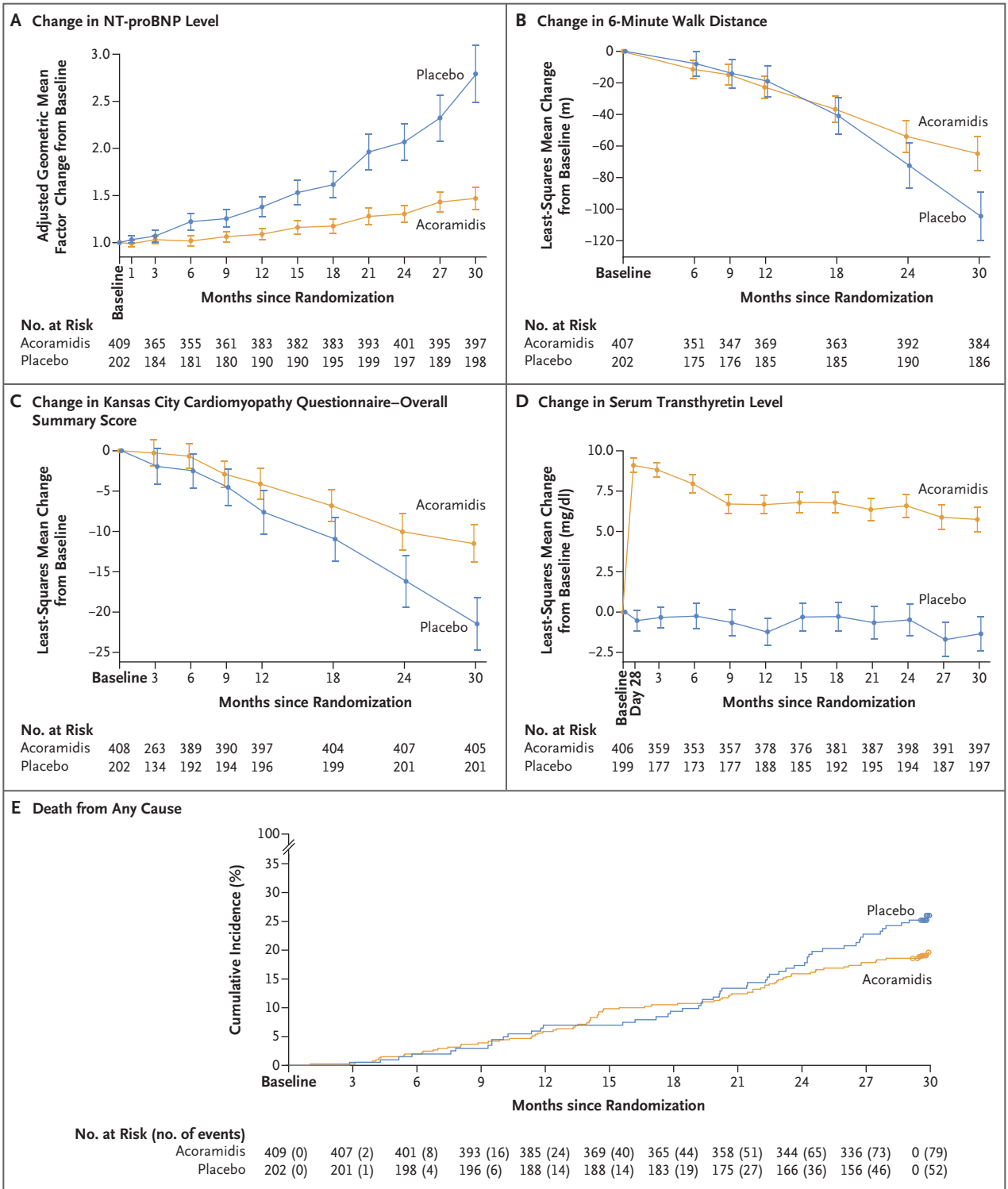


Figure 3. Key Secondary Outcomes.

Shown are the change from baseline in the NT-proBNP level (Panel A), the 6-minute walk distance (Panel B), the score on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (Panel C), and the serum transthyretin level (Panel D) in the acoramidis group as compared with the placebo group. Panel E shows the cumulative incidence curve for death from any cause.

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of the Cox proportional-hazards model for death from any cause (the final secondary outcome in the testing hierarchy) are not reported here because of deviations from model assumptions (see the Supplementary Appendix). In the cumulative incidence plot, the curves are observed to cross multiple times early in the trial before their eventual separation starting at approximately 19 months (Fig. 3E). In a prespecified sensitivity analysis of death from any cause, the result of log-rank testing was not significant. Prespecified subgroup analyses of cardiovascular-related hospitalization are shown in Figure S4.

RECEIPT OF TAFAMIDIS

A total of 107 patients received tafamidis (61 of 409 [14.9%] in the acoramidis group and 46 of 202 [22.8%] in the placebo group), which represented 17.5% of the 611 patients who were included in the primary analysis. The median time until the initiation of tafamidis was 17.2 months, and the median duration of exposure was 11.4 months. These values were similar in the acoramidis group and the placebo group (17.8 and 16.1 months, respectively, for the time until initiation and 11.6 and 10.8 months, respectively, for exposure duration).

SAFETY

The overall incidence of adverse events during treatment was similar in the acoramidis group and the placebo group (98.1% and 97.6%, respectively) and favored acoramidis with respect to serious adverse events (54.6% and 64.9%, respectively). All adverse events, those with a fatal outcome, those leading to hospitalization, and those leading to discontinuation of acoramidis or placebo are provided in Table S3. The most frequently reported adverse events in each trial group are provided in Table S4.

DISCUSSION

In this trial, we found a significant treatment effect for acoramidis in the four-step primary hierarchical analysis with respect to death from any cause, cardiovascular-related hospitalization, NT-proBNP, and 6-minute walk distance. One advantage of the hierarchical-analysis design is that all possible paired comparisons are made only at the initial step (i.e., death from any cause in this trial). At each subsequent step, only those ties remaining after the previous step are subject to a paired comparison. This approach places greater weight on the steps at the top of the hierarchy, a weighting that diminishes in the lower steps in the hierarchy. This design can be compared with the use of a time-to-first-event clinical outcome (e.g., a composite of major adverse cardiovascular events that includes cardiovascular death, recurrent myocardial infarction, or stroke), in which an equal weight is assigned to each component.

The majority of comparisons in the primary hierarchical analysis (55% in the Finkelstein–Schoenfeld test and 58% in the associated win ratio) were determined after the first two hierarchical components of death from any cause and cardiovascular-related hospitalization were considered, and the win ratio for a hierarchical outcome that included only these two components favored acoramidis (Fig. 1). Among the four key secondary outcomes that were included in the hierarchical plan to control for multiple testing, the between-group difference was significant for the 6-minute walk distance, KCCQ-OS score, and TTR serum level but not for death from any cause. It is possible that the mortality results were affected, at least in part, by a lower risk of death in our trial than the risks observed in previous studies, a difference that could reflect an evolution in disease awareness, earlier diagnosis, and thus better prognosis within the recently diagnosed target patient population.[18,19]

To place this finding into context, the observed 30-month survival of 74.3% in the placebo group in our trial was greater than the corresponding percentage of 70.5% in the combined tafamidis treatment groups in ATTR-ACT (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial), a cardiovascular outcomes trial involving patients with this condition. As a contemporary benchmark for placing the survival of 80.7% in the acoramidis group in the current trial into context, recent data from the U.S. Social Security Administration estimated 30-month survival at 85% in an age-matched cohort of the general population.[20] Similarly, the annualized rate of cardiovascular-related hospitalization of 0.29 in the acoramidis group in our trial can be viewed in the context of data regarding the annual overall hospitalization rate of 0.26 in the U.S. Medicare population.[21] During the past 10 years, awareness of transthyretin amyloid

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cardiomyopathy has increased in the clinical cardiology community, coupled with a noninvasive diagnostic algorithm,[22] such that the condition is being diagnosed at an earlier stage of disease. Coupled with improvements in heart failure management in patients with this condition, these developments have contributed to better survival, including among patients without access to tafamidis, the only currently approved, targeted therapy for transthyretin amyloid cardiomyopathy.[18]

In this trial, we found treatment-related benefits with respect to the primary outcome that included death from any cause, cardiovascular-related hospitalization, NT-proBNP level, and 6-minute walk distance. The overall frequencies of adverse events were similar in the two groups, as were discontinuations because of adverse events for reasons other than death. Fewer serious adverse events were associated with acoramidis than with placebo. These data support the use of acoramidis as an effective and safe treatment option for patients with transthyretin amyloid cardiomyopathy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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