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RESEARCH ARTICLE

Long-term tafamidis efficacy in patients with transthyretin amyloid cardiomyopathy by baseline left ventricular ejection fraction

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Aims Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) present with diverse left ventricular ejection fraction (LVEF). This study assessed tafamidis efficacy by baseline LVEF in the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and its long-term extension (LTE) study.

Methods and results Patients were randomized to 30 months of tafamidis or placebo treatment in ATTR-ACT. On completion, patients could join an LTE study to receive tafamidis. All-cause mortality (death, heart transplant, or cardiac mechanical assist device implantation) from baseline to the end of follow-up was assessed in patients continuously treated with tafamidis (80 mg meglumine or 61 mg free acid) or delayed tafamidis treatment (placebo in ATTR-ACT; tafamidis in the LTE study) according to baseline LVEF (<50% or ≥50%). Supportive outcomes were evaluated over a shorter follow-up. Patients with baseline LVEF <50% ($n = 177$: 88 tafamidis- and 89 placebo-treated) had signs of more severe heart failure, a higher proportion were Black, and had variant ATTR-CM than those with LVEF ≥50% ($n = 171$: 85 tafamidis- and 86 placebo-treated). At the end of follow-up (median 60–64 months), all-cause mortality was numerically higher in patients with baseline LVEF <50%; however, consistent with supportive findings, continuous tafamidis treatment was associated with a 47% reduction in mortality risk compared with delayed tafamidis treatment in patients with LVEF <50% and ≥50% (hazard ratio 0.53 [95% confidence interval 0.367–0.758]; $p < 0.001$, and 0.53 [0.344–0.818]; $p < 0.01$, respectively).

Conclusions Early initiation of tafamidis is associated with reduced mortality in patients with ATTR-CM, irrespective of initial LVEF value.
Clinical Trial Registration: ClinicalTrials.gov NCT01994889, NCT02791230.

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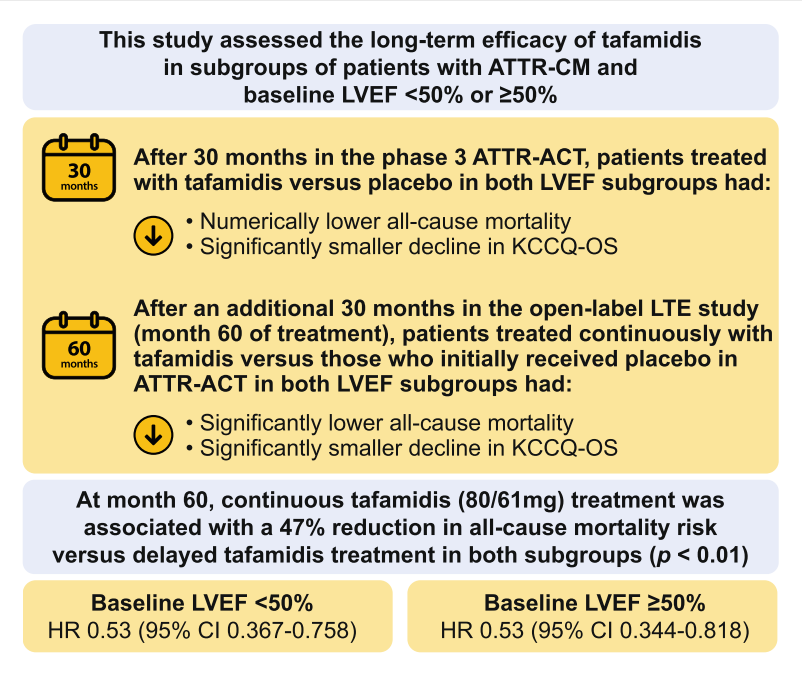
[Correction added on 4 December 2024, after first online publication: The copyright line was changed.]

Graphical Abstract



ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM, transthyretin amyloid cardiomyopathy; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LTE, long-term extension; LVEF, left ventricular ejection fraction.

Keywords Heart failure • Reduced ejection fraction • Mildly reduced ejection fraction • Preserved ejection fraction • 6-min walk test • Quality of life

Introduction

Tafamidis is approved for the treatment of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) in numerous countries worldwide.[1] This approval was largely based on efficacy and safety findings from the 30-month, phase 3, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT).[2] A long-term extension (LTE) study enabled patients who completed ATTR-ACT to receive open-label tafamidis for up to 5 years or until commercially available in their region.[3–6] The LTE study additionally provided data on long-term tafamidis treatment. Findings from these studies continue to demonstrate the clinical benefits of tafamidis meglumine 80 mg and free acid 61 mg in patients with ATTR-CM, including subgroups with wild-type ATTR-CM (ATTRwt-CM) and variant ATTR-CM (ATTRv-CM); mild, moderate, and severe clinical severities; and patients under and over the age of 80 years.[6–9]

Patients with chronic heart failure are typically grouped by their left ventricular ejection fraction (LVEF) to guide therapeutic recommendations and accurate prognosis estimates.[10–12] Heart failure can occur with preserved ejection fraction (defined as an LVEF ≥50%), mildly reduced (LVEF 41–49%), or reduced (LVEF ≤40%) ejection fraction. Although ATTR-CM was classically thought of as a condition presenting with LVEF ≥50%, several studies have since shown that a proportion of patients exhibit LVEF <50% at diagnosis.[13,14] Although ATTR-ACT excluded patients with New York Heart Association (NYHA) functional class IV, it did not select patients according to LVEF and, subsequently, 50% of enrolled patients with data had LVEF <50% (mildly reduced ejection fraction: 27%; reduced ejection fraction: 22%).[15] A high proportion of patients were also found to have mildly reduced or reduced ejection fraction, respectively, at ATTR-CM diagnosis in two recent US retrospective record review studies (17% or 28% and 13% or 42%), each comprising >500 patients.[16,17] In these studies, reduced ejection fraction was generally found to be more common in Black or African American patients, those with ATTRv-CM, and NYHA functional class III or IV.[15–17]

Tafamidis modifies the underlying cause of ATTR-CM and has been shown to be efficacious across patient groups comprising all three LVEF subsets.[2] Current treatment guidelines recommend tafamidis for the treatment of patients with ATTR-CM

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independently of their LVEF grouping, but despite this, there remains uncertainty around the relative value of tafamidis treatment in patients with mildly reduced or reduced ejection fractions versus preserved ejection fraction.[10,11] Moreover, tafamidis is currently not reimbursed in some countries (such as Spain) in patients with LVEF <50%.[18]

This *post-hoc* analysis assessed long-term all-cause survival in patients with ATTR-CM and mildly reduced or reduced ejection fraction (LVEF <50% at baseline) or preserved ejection fraction (LVEF ≥50% at baseline) treated with placebo or the approved tafamidis dose (80/61 mg) in ATTR-ACT and its LTE study.

Methods

Study design

ATTR-ACT (NCT01994889) was a multicentre, international, double-blind, placebo-controlled, parallel-design, randomized, phase 3 trial of tafamidis in patients with ATTR-CM.[2] Patients were randomized 2:1:2 to receive tafamidis meglumine 80 mg, 20 mg, or placebo for 30 months, stratified by transthyretin (*TTR*) genotype (wild-type or variant) and NYHA functional class (I or II/III). Patients completing ATTR-ACT were eligible to join the open-label LTE study (NCT02791230) and receive tafamidis for up to 60 months, or until it became commercially available in their region.[3–6] Those who received tafamidis in ATTR-ACT continued their treatment, and those who received placebo in ATTR-ACT were subsequently randomized 2:1 to tafamidis meglumine 80 or 20 mg, stratified by *TTR* genotype. Dose reduction was permitted in both trials. Following a protocol amendment (July 2018; median of 39 months into follow-up), all patients in the LTE study were switched to tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg. Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT are not included in any part of this analysis, as this dose has not been approved for the treatment of patients with ATTR-CM.

The studies were approved by the independent review board or ethics committee at each participating centre and conformed with the principles outlined in the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

To enrol in ATTR-ACT, patients must have been 18–90 years old with biopsy-confirmed ATTR-CM and an end-diastolic intraventricular septal thickness >12 mm, assessed by echocardiography.[2] All patients were required to have a history of heart failure with at least one associated hospitalization or clinical signs and symptoms consistent with heart failure, NYHA functional class I–III symptoms, an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/ml, a 6-min walk test (6MWT) distance >100 m, and an estimated glomerular filtration rate ≥25 ml/min/1.73 m^2.

Patients received standard of care therapy for heart failure alongside study treatment and were stable on this therapy, with no cardiovascular-related hospitalizations in the 2 weeks prior to baseline. Patients had not received a liver or heart transplant or had a cardiac mechanical assist device implant. There were no inclusion or exclusion criteria based on LVEF.

Analyses

This *post-hoc* analysis evaluated the efficacy of the approved dose of tafamidis (meglumine 80 mg or free acid 61 mg) in patients who took part in ATTR-ACT or the LTE study according to LVEF at baseline (<50% or ≥50%). Patients without a baseline LVEF measurement were excluded from the analysis. Data were pooled from ATTR-ACT and the completed LTE study.

Demographic and clinical characteristics for the four subgroups were summarized descriptively. The groups were: (1) patients with LVEF <50% at baseline and treated with tafamidis 80/61 mg continuously; (2) patients with LVEF <50% at baseline and treated with placebo in ATTR-ACT, then tafamidis in the LTE study; (3) patients with LVEF ≥50% at baseline and treated with tafamidis 80/61 mg continuously; and (4) patients with LVEF ≥50% at baseline who were treated with placebo in ATTR-ACT and tafamidis in the LTE study. Efficacy findings are compared between treatment groups within each LVEF category. This was a *post-hoc* analysis performed on a subgroup of patients in ATTR-ACT. No power calculations were performed.

Median follow-up time was calculated using Kaplan–Meier methods. Time to all-cause mortality (all-cause death, with heart transplant and implantation of a cardiac mechanical assist device treated as death events) was analysed using a Cox proportional hazards model with treatment and *TTR* genotype as covariates and visualized using Kaplan–Meier plots.

The least squares mean change from baseline in Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score was summarized for all patients with data at each time point out to Month 60. The overall summary score is the mean of physical limitation, symptom frequency, symptom burden, quality of life, and social limitation scores. The least squares mean changes from baseline in 6MWT distance and NT-proBNP concentration were summarized for all patients with data at each time point through to the end of ATTR-ACT (Month 30), as they were not required assessments in the LTE study. The *p*-values between treatments were obtained from a mixed model for repeated measures with fixed effects of treatment, visit, *TTR* genotype, and visit-by-treatment interaction, in an unstructured covariance matrix.

Results

ATTR-ACT enrolled 441 patients with ATTR-CM in 13 countries between December 2013 and August 2015 (*Figure 1*).[2] Of these, 176 patients were randomized to tafamidis meglumine 80 mg and 177 to placebo. Among patients treated with tafamidis 80 mg in ATTR-ACT, 88 (50%) had a baseline LVEF <50%, 85 (48%) LVEF ≥50%, and LVEF was missing for 3 (2%) patients. Similarly, among patients treated with placebo in ATTR-ACT, 89 (50%) had a baseline LVEF <50%, 86 (49%) LVEF ≥50%, and LVEF was missing for 2 (1%) patients. Among all patients with baseline data, 51% had an LVEF <50%.

After completing 30 months of treatment in ATTR-ACT, of the 108 patients continuing tafamidis meglumine 80 mg in the LTE study, 47 had started ATTR-ACT with an LVEF <50% (44%) and 61 (56%) with an LVEF ≥50%. Of the 82 patients switching from placebo to tafamidis meglumine in the LTE study, 35 (43%) had started ATTR-ACT with an LVEF <50%, and 47 (57%) with an LVEF ≥50%. Among all patients joining the LTE study, 43% had an LVEF <50%.

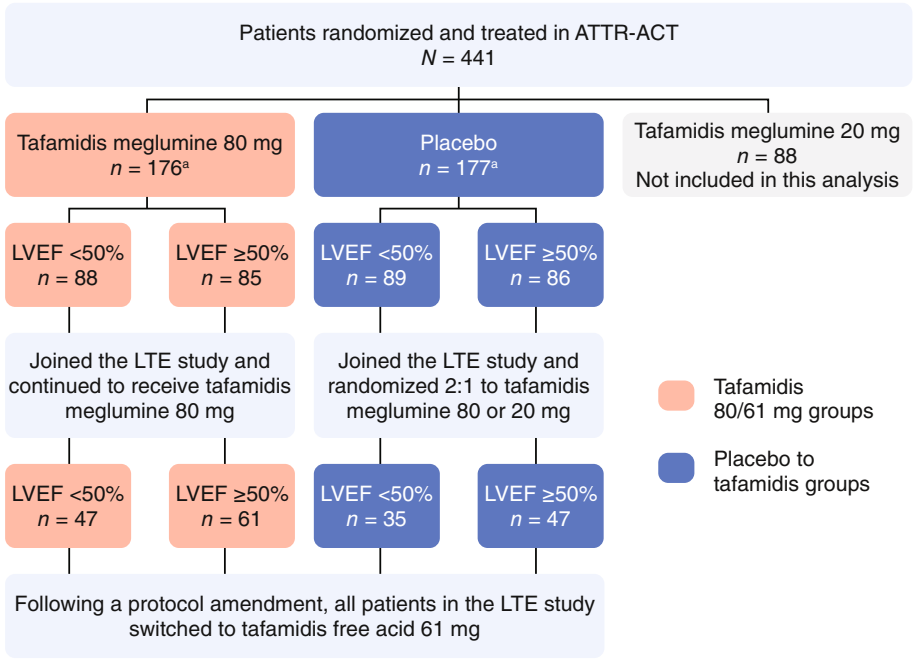

Figure 1 Patient groups and treatments. ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; LTE, long-term extension; LVEF, left ventricular ejection fraction. [a]LVEF missing for three patients who received tafamidis meglumine 80 mg in ATTR-ACT and two patients who received placebo.

Patients with left ventricular ejection fraction <50%

There were similar baseline demographics and clinical characteristics among patients with a baseline LVEF <50% in the two treatment groups (*Table 1*). In the tafamidis 80/61 mg and placebo to tafamidis groups, respectively, mean age was 75 and 73 years; 90% and 89% of patients were male, and 19% in each treatment group were Black or African American (73% and 80% White). Most patients in the tafamidis 80/61 mg and placebo to tafamidis groups had a baseline NYHA functional class of II or III (92% and 90%) and just over a quarter of patients had ATTRv-CM (30% and 27%). The most common *TTR* variant was V122I (p.V142I; $n = 34/50$ patients with ATTRv-CM; online supplementary *Table S1*). Median follow-up duration in patients with a baseline LVEF <50% in the tafamidis 80/61 mg group was 60 months (95% confidence interval [CI] 55.7–74.9) and in the placebo to tafamidis group was 64 months (95% CI 54.3–not estimable).

A numerically higher proportion of patients with LVEF <50% were Black and had ATTRv-CM compared with patients with LVEF ≥50% at baseline (online supplementary *Table S2*). There were higher proportions of patients with NYHA class III at baseline among those with an LVEF <50% versus ≥50%. Patients with an LVEF <50% also had a numerically higher median NT-proBNP concentration and a slightly lower median estimated glomerular filtration rate than those with an LVEF ≥50%.

The change from baseline in 6MWT distance was not significantly different between tafamidis and placebo groups with a baseline LVEF <50% at any timepoints in ATTR-ACT, whereas the increase from baseline in NT-proBNP was significantly smaller at 12 months, but not 30 months, in tafamidis-treated patients (online supplementary *Figure S1*). As anticipated in patients with a severe and progressive disease, KCCQ-OS score declined over the course of ATTR-ACT and the LTE study in both treatment groups with a baseline LVEF <50% (*Figure 2A* and *Graphical Abstract*). The reduction from baseline was statistically smaller in the tafamidis 80/61 mg versus the placebo to tafamidis group from Month 12. At Month 60, patients in the placebo to tafamidis group had a 21.6-point (95% CI 10.32–32.96; $p < 0.001$) larger reduction from baseline in least squares mean KCCQ-OS score compared with those in the continuous tafamidis group. At later time points, there were too few remaining patients for comparison.

At the end of ATTR-ACT (Month 30), all-cause mortality was 38% and 52% in the tafamidis and placebo groups with baseline LVEF <50% (hazard ratio [HR] 0.67 [95% CI 0.425–1.041]; $p = 0.07$). After an additional 30 months of treatment in the LTE study (Month 60; all patients had been receiving tafamidis), all-cause mortality was 53% and 74% in the tafamidis 80/61 mg and placebo to tafamidis groups, respectively (HR 0.57 [95% CI 0.391–0.832]; $p < 0.01$). Overall all-cause mortality to the end of follow-up in patients with a baseline LVEF <50% was 59% in the tafamidis 80/61 mg group and 82% in the placebo to tafamidis group (*Table 2* and *Graphical Abstract*). These proportions were numerically higher than in matching treatment groups with a baseline LVEF ≥50%. Most first events were all-cause death (45/52 events in the tafamidis 80/61 mg group and 69/73 events in the placebo to tafamidis group) and few were heart transplants or implantation of a cardiac mechanical assist device (7 and 4 in each group,

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Table 1 Baseline demographics and clinical characteristics

	LVEF <50%		LVEF ≥50%	
	Tafamidis 80/61 mg	Placebo/tafamidis	Tafamidis 80/61 mg	Placebo/tafamidis
n	88	89	85	86
Age, years, mean (SD)	75 (7.7)	73 (6.2)	75 (6.9)	74 (7.1)
Sex, *n* (%)				
Male	79 (89.8)	79 (88.8)	76 (89.4)	76 (88.4)
Female	9 (10.2)	10 (11.2)	9 (10.6)	10 (11.6)
Race, *n* (%)				
White	64 (72.7)	71 (79.8)	69 (81.2)	73 (84.9)
Black or African American	17 (19.3)	17 (19.1)	9 (10.6)	9 (10.5)
Asian	6 (6.8)	1 (1.1)	5 (5.9)	4 (4.7)
Other[a]	1 (1.1)	0	2 (2.4)	0
Modified BMI, $kg/m^2 \times g/L$, mean (SD)	1054 (172.2)	1059 (191.0)	1069 (168.5)	1073 (193.4)
Transthyretin genotype, *n* (%)				
Wild-type	62 (70.5)	65 (73.0)	69 (81.2)	67 (77.9)
Variant	26 (29.5)	24 (27.0)	16 (18.8)	19 (22.1)
NYHA class, *n* (%)				
I	7 (8.0)	9 (10.1)	9 (10.6)	4 (4.7)
II	50 (56.8)	40 (44.9)	53 (62.4)	60 (69.8)
III	31 (35.2)	40 (44.9)	23 (27.1)	22 (25.6)
NT-proBNP, ng/L, mean (SD)	4644 (3537)	4298 (2868)	3222 (2351)	3396 (3047)
Troponin I, ng/ml, mean (SD)	0.36 (1.32) (*n* = 88)	0.19 (0.18) (*n* = 89)	0.15 (0.10) (*n* = 85)	0.17 (0.18) (*n* = 85)
eGFR, ml/min/1.73 m^2, mean (SD)	55 (16.6) (*n* = 72)	52 (15.1) (*n* = 73)	58 (14.7) (*n* = 76)	58 (16.8) (*n* = 75)
LVEF, %, mean (SD)	39.9 (7.9)	41.1 (6.3)	56.5 (4.2)	56.5 (4.7)

BMI, body mass index; eGFR, estimated glomerular filtration rate (by Modification of Diet in Renal Disease equation); LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.
[a]Other includes American Indian or Alaskan Native.

respectively). At the end of the LTE study, the HR of all-cause mortality was significantly in favour of tafamidis 80/61 mg treatment (HR 0.53 [95% CI 0.367–0.758]; $p < 0.001$; *Figure 2B* and *Graphical Abstract*).

Patients with left ventricular ejection fraction ≥50%

There were similar baseline demographics and clinical characteristics among patients with a baseline LVEF ≥50% in the tafamidis 80/61 mg and placebo to tafamidis groups (*Table 1*). Mean age was 75 and 74 years, respectively; 89% and 88% of patients were male, and 11% in each group were Black or African American (81% and 85% White). The majority of patients had a baseline NYHA functional class II or III (89% and 95%), and just less than a quarter of patients in each group had ATTRv-CM (19% and 22%). The most common *TTR* variant was V122I (p.V142I; *n* = 16/35 patients with ATTRv-CM; online supplementary *Table S1*). Median follow-up duration in patients with a baseline LVEF ≥50% in the tafamidis 80/61 mg group was 63 months (95% CI 60.0–68.7) and in the placebo to tafamidis group was 61 months (95% CI 55.6–67.4).

There was a significantly smaller change from baseline in 6MWT distance and NT-proBNP concentration at all timepoints throughout ATTR-ACT in patients with a baseline LVEF ≥50% who received tafamidis versus placebo (online supplementary *Figure S2*). KCCQ-OS score declined over the course of ATTR-ACT and the LTE study in both treatment groups (*Figure 3A* and *Graphical Abstract*). The reduction from baseline was statistically smaller in the tafamidis 80/61 mg group versus the placebo to tafamidis group from Month 6. At Month 60, patients in the placebo to tafamidis group had a 30.4-point (95% CI 19.55–41.27; $p < 0.0001$) larger reduction from baseline in least squares mean KCCQ-OS score compared with those in the continuous tafamidis group.

At the end of ATTR-ACT (Month 30), all-cause mortality was 24% in the tafamidis and 33% in the placebo groups with a baseline LVEF ≥50% (HR 0.71 [95% CI 0.400–1.259]; $p = 0.24$). After an additional 30 months of treatment in the LTE study (Month 60; all patients had been receiving tafamidis), all-cause mortality was 36% and 53% in the tafamidis 80/61 mg and placebo to tafamidis groups, respectively (HR 0.57 [95% CI 0.359–0.899]; $p < 0.05$). Overall all-cause mortality during ATTR-ACT and the LTE study in patients with a baseline LVEF ≥50% was 41% in the tafamidis 80/61 mg group and 60% in the placebo to tafamidis group (*Table 2* and *Graphical Abstract*). Most first events were all-cause death, with two heart transplants reported in each treatment group, and no cardiac mechanical assist device implantations. At the end of the LTE study, the HR of all-cause mortality was significantly in favour of tafamidis 80/61 mg treatment (HR 0.53

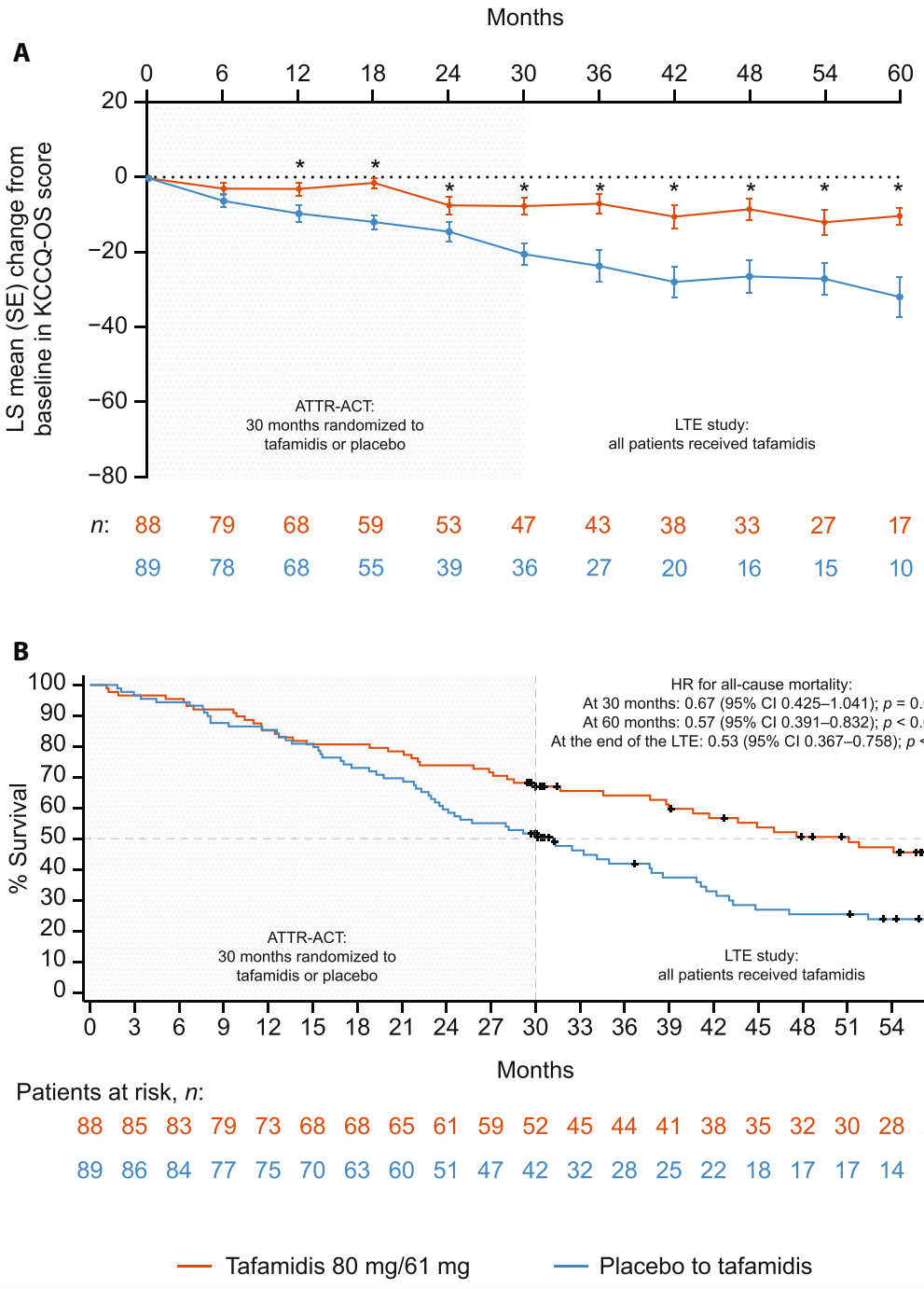

Figure 2 Health-related quality of life (*A*) and Kaplan–Meier plot of all-cause mortality (*B*) in patients with baseline left ventricular ejection fraction <50%. End of survival defined as death, heart transplant, or implantation of a cardiac mechanical assist device. ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CI, confidence interval; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LS, least squares; LTE, long-term extension; SE, standard error. *$p < 0.05$; + = censored.

Table 2 Observed all-cause mortality by left ventricular ejection fraction at baseline

	LVEF <50%		LVEF ≥50%	
	Tafamidis 80/61 mg	Placebo/tafamidis	Tafamidis 80/61 mg	Placebo/tafamidis
n	88	89	85	86
All-cause mortality, *n* (%)	52 (59.1)	73 (82.0)	35 (41.2)	52 (60.5)
First event, *n* (%)				
All-cause death	45 (51.1)	69 (77.5)	33 (38.8)	50 (58.1)
Heart transplant	5 (5.7)	4 (4.5)	2 (2.4)	2 (2.3)
Implantation of a cardiac mechanical assist device	2 (2.3)	0	0	0

LVEF, left ventricular ejection fraction.
Heart transplant and implantation of a cardiac mechanical assist device were treated as death. Statistical analyses were conducted using the Kaplan–Meier method and are shown in *Figures 2* and *3*.

[95% CI 0.344–0.818]; $p < 0.01$; *Figure 3B* and *Graphical Abstract*). This is the same HR as observed in patients with a baseline LVEF <50%.

Discussion

While tafamidis is recommended for the treatment of patients with ATTR-CM independently of LVEF, it is not yet reimbursed for patients with LVEF <50% in all regions.[10,11,18] This may be due to lower disease awareness and uncertainty around the relative value of tafamidis treatment in patients with heart failure and mildly reduced or reduced ejection fraction versus preserved ejection fraction. In this *post-hoc* analysis of patients with ATTR-CM who took part in the phase 3 ATTR-ACT and LTE studies, we found that around half (51%) had an LVEF <50% at baseline. As enrolment criteria were independent of LVEF, this demonstrates that a large proportion of patients with ATTR-CM present with heart failure with mildly reduced or reduced ejection fraction. Despite finding that patients with a baseline LVEF<50% had more severe disease than those with LVEF ≥50%, we observed similar efficacy of tafamidis in both groups.

Results of this study are consistent with previous reports that mildly reduced and reduced ejection fraction heart failure are common presentations of ATTR-CM, particularly in Black patients and those with advanced stage ATTRv-CM.[15–17] More serious symptoms and the more progressive nature of some genotypes associated with ATTRv-CM are likely to have contributed towards the numerically higher long-term all-cause mortality and larger declines in KCCQ-OS score in patients with a baseline LVEF <50% compared with ≥50%.[6,19] Numerically larger treatment differences in all-cause mortality rate were observed at Months 30 and 60 and at the end of follow-up (~5 years), respectively, in patients with LVEF <50% (14%, 21%, and 23%) compared with those with LVEF ≥50% (9%, 17%, and 19%); however, in both groups, the risk of all-cause mortality was reduced by 47% ($p < 0.01$) over the course of ATTR-ACT and the LTE study. The difference between continuous tafamidis and placebo to tafamidis treatment is consistent with that reported in an interim analysis of pooled data from ATTR-ACT and the LTE (median follow-up ~58 months versus 60–64 months in this study), with a 41% reduction in the risk of all-cause mortality.[4] The efficacy of tafamidis treatment on 6MWT distance and NT-proBNP concentration during the 30 months of ATTR-ACT was more evident in patients with an LVEF ≥50% versus <50%, likely because they had less advanced disease at baseline. However, it must be noted that this *post-hoc* analysis was performed in a subset of patients participating in ATTR-ACT, with the limitations that this entails. Despite this, continuous tafamidis treatment significantly and consistently reduced the decline in health-related quality of life in both LVEF groups during ATTR-ACT and the LTE study. Given the efficacy of tafamidis observed across LVEF in patients with ATTR-CM, in terms of both mortality and quality of life, decisions to initiate tafamidis treatment should not be determined by LVEF.

In this study, limitations included the reduced number of patients, with few remaining in the LTE study towards the end of follow-up, which created limited power to compare between groups. Further sub-analyses, for example by genotype, were not performed due to the limited sample size. Additionally, outcomes from the 6MWT and NT-proBNP assessments were not available for some patients during the first 30 months of follow-up. The baseline differences in disease severity also make comparisons between LVEF groups challenging, since patients with the more advanced heart failure are likely to be less responsive to treatment. Lastly, although these findings are encouraging, the treatment effect of tafamidis demonstrated here is likely an underestimate of its efficacy against placebo, as patients in the comparator group (placebo to tafamidis) also received tafamidis when they transitioned to the LTE study. Further studies on the efficacy of tafamidis in patients with different LVEFs would be of value to confirm our findings. In particular, though the current report does not provide data on cardiovascular-related hospitalizations, this would be a valuable measure of clinical deterioration with which to assess the long-term efficacy of tafamidis.

In conclusion, presentation with reduced or mildly reduced ejection fraction heart failure was common in patients with ATTR-CM enrolled in ATTR-ACT and the LTE study. The reduction in long-term all-cause mortality and deterioration of quality of life with early tafamidis treatment was significant and consistent in those with LVEF <50% or ≥50% at baseline. These findings

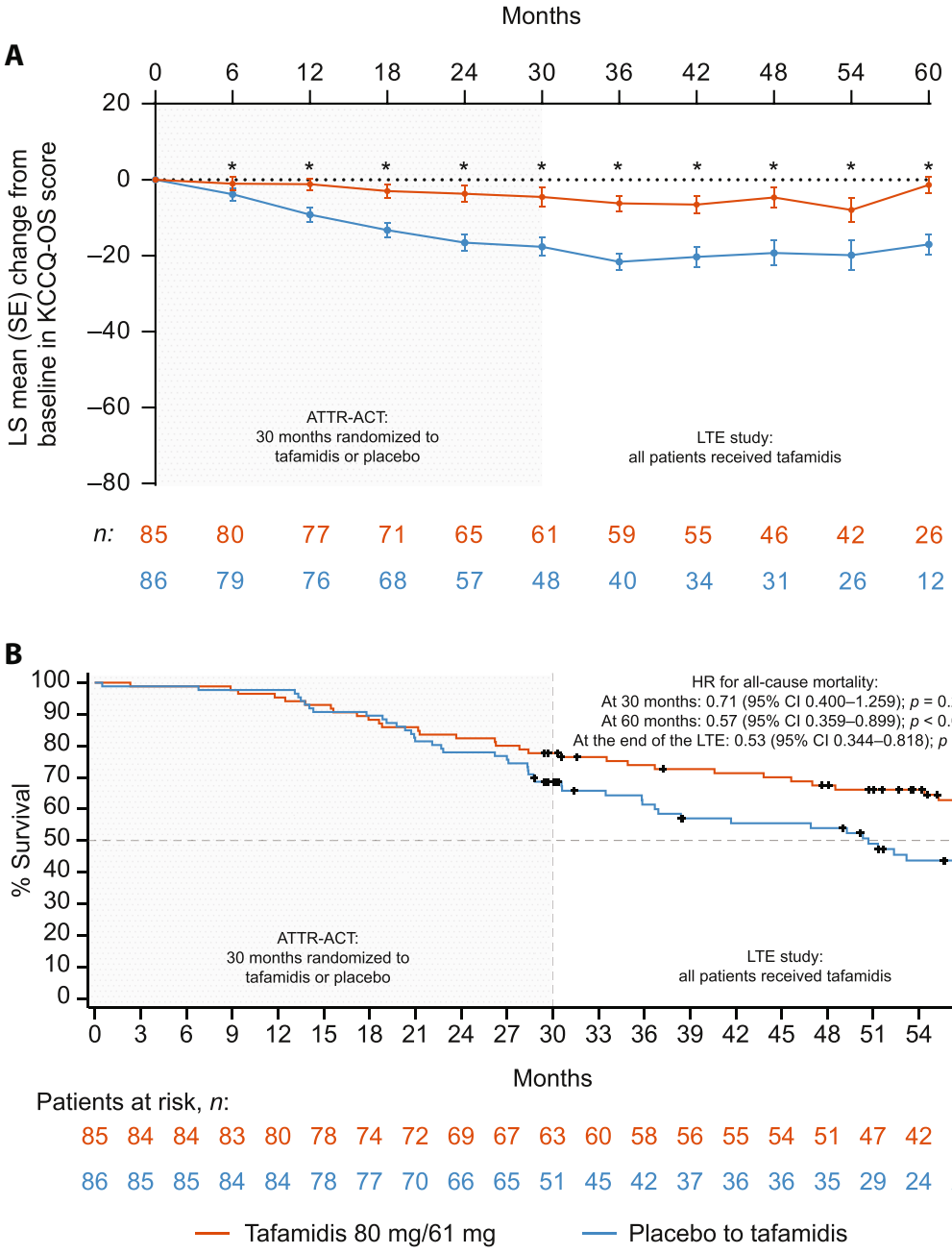

Figure 3 Health-related quality of life (*A*) and Kaplan–Meier plot of all-cause mortality (*B*) in patients with baseline left ventricular ejection fraction ≥50%. End of survival defined as death, heart transplant, or implantation of a cardiac mechanical assist device. ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CI, confidence interval; HR, hazard ratio; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LS, least squares; LTE, long-term extension; SE, standard error. *$p < 0.05$; + = censored.

demonstrate the efficacy of tafamidis in patients with ATTR-CM, irrespective of LVEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Burton A, Castaño A, Bruno M, Riley S, Schumacher J, Sultan MB, *et al.* Drug discovery and development in rare diseases: Taking a closer look at the tafamidis story. *Drug Des Devel Ther* 2021;**15**:1225–1243. https://doi.org/10.2147/DDDT.S289772
2. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.*; for the ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016. https://doi.org/10.1056/NEJMoa1805689
3. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, *et al.* Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail* 2021;**23**:277–285. https://doi.org/10.1002/ejhf.2027
4. Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, *et al.* Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail* 2022;**15**:e008193. https://doi.org/10.1161/CIRCHEARTFAILURE.120.008193
5. Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, *et al.* Long-term survival in people with transthyretin amyloid cardiomyopathy who took tafamidis: A plain language summary. *Future Cardiol* 2023;**19**:7–17. https://doi.org/10.2217/fca-2022-0096
6. Elliott P, Gundapaneni B, Sultan MB, Ines M, Garcia-Pavia P. Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms. *Eur J Heart Fail* 2023;**25**:2060–2064. https://doi.org/10.1002/ejhf.2974
7. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, *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**:115–123. https://doi.org/10.1016/j.jchf.2020.09.011
8. Li H, Rozenbaum M, Casey M, Sultan MB. Estimating the effect of tafamidis on cardiovascular-related hospitalization in NYHA class III patients with transthyretin amyloid cardiomyopathy in the presence of death. *Cardiology* 2022;**147**:398–405. https://doi.org/10.1159/000525883
9. Garcia-Pavia P, Sultan MB, Gundapaneni B, Sekijima Y, Perfetto F, Hanna M, *et al.* Tafamidis efficacy among octogenarian patients in the phase 3 ATTR-ACT and ongoing long-term extension study. *JACC Heart Fail* 2024;**12**:150–160. https://doi.org/10.1016/j.jchf.2023.08.032
10. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
11. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
12. Curtis JP, Sokol SI, Wang Y, Rathore SS, Ko DT, Jadbabaie F, *et al.* The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol* 2003;**42**:736–742. https://doi.org/10.1016/S0735-1097(03)00789-7
13. López-Sainz Á, Hernandez-Hernandez A, Gonzalez-Lopez E, Domínguez F, Restrepo-Cordoba MA, Cobo-Marcos M, *et al.* Clinical profile and outcome of cardiac amyloidosis in a Spanish referral center. *Rev Esp Cardiol (Engl Ed)* 2021;**74**:149–158. https://doi.org/10.1016/j.rec.2019.12.020
14. González-López E, Gagliardi C, Dominguez F, Quarta CC, de Haro-del Moral FJ, Milandri A, *et al.* Clinical characteristics of wild-type transthyretin cardiac amyloidosis: Disproving myths. *Eur Heart J* 2017;**38**:1895–1904. https://doi.org/10.1093/eurheartj/ehx043
15. Garcia-Pavia P, Fine N, Weissman NJ, Castano A, Gundapaneni B, Sultan MB, *et al.* Patients with transthyretin amyloid cardiomyopathy may have preserved, mildly reduced, or reduced ejection fraction. *Eur Heart J* 2021;**42**:717. https://doi.org/10.1093/eurheartj/ehab724.0717
16. Martyn T, Saef J, Dey AR, Khedraki R, Jain V, Collier P, *et al.* Racial and genetic differences in presentation of transthyretin amyloid cardiomyopathy with impaired left ventricular function. *JACC Heart Fail* 2022;**10**:689–691. https://doi.org/10.1016/j.jchf.2022.06.006
17. Cavalier JS, Bhattacharya P, Patolia H, Chandramouli S, Sen S, Karra R, *et al.* Multicenter transthyretin cardiac amyloidosis study demonstrates differences in phenotype and outcomes by race. *J Card Fail* 2023;**29**:699–700. https://doi.org/10.1016/j.cardfail.2022.10.381
18. Spanish Ministry of Health. Medication information. https://www.sanidad.gob.es/profesionales/medicamentos.do?metodo=verDetalle&cn=728101 (16 November 2023)
19. Nativi-Nicolau J, Judge DP, Hoffman JE, Gundapaneni B, Keohane D, Sultan MB, *et al.* Natural history and progression of transthyretin amyloid cardiomyopathy: Insights from ATTR-ACT. *ESC Heart Fail* 2021;**8**:3875–3884. https://doi.org/10.1002/ehf2.13541