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ORIGINAL RESEARCH

Cardiovascular-Related Mortality and Hospitalizations in Patients with Transthyretin Amyloid Cardiomyopathy Treated with Tafamidis: A Post Hoc Analysis of the Phase 3 ATTR-ACT and Long-Term Extension

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ABSTRACT

***Introduction*:** Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) are at high risk of cardiovascular (CV)-related hospitalizations (CVH), which are associated with higher mortality. In the phase 3 study ATTR-ACT, treatment with tafamidis significantly reduced CVH versus placebo.

***Methods*:** This post hoc analysis included patients from ATTR-ACT (30 months) and its long-term extension (LTE; 60 months) receiving tafamidis 80 mg ($n=176$) or placebo in ATTR-ACT and switched to tafamidis 80 mg in the LTE ($n=177$). CV-related events (CV-related mortality [CVM] and/or recurrent CVH) and CVM were evaluated. Liu–Wei–Yang–Ying and Cox proportional hazard models were used to evaluate time to recurrent CV-related events and CVM, respectively.

***Results*:** During ATTR-ACT, cumulative incidence of first and recurrent CV-related events in the tafamidis group was lower versus placebo from month 9 and incidence of CVM was lower from month 18. These trends continued throughout the LTE. At month 24, a significant 29% hazard reduction was observed for CV-related events with tafamidis 80 mg versus placebo (incidence 48% vs 61%; hazard ratio [HR] 0.713 [95% CI 0.524–0.970]; $p=0.0310$). Hazard reduction remained significant until month 90 with continuous tafamidis 80 mg and was 37% at month 90 (incidence 77% vs 79%; HR 0.629 [95% CI 0.491–0.806; $p=0.0002$]). Incidence of CVM with continuous tafamidis 80 mg was lower versus placebo(/tafamidis 80 mg) at month 24 (21% vs 29%) and month 90 (39% vs 47%), with significant hazard reductions of 38% (HR 0.618 [95% CI 0.401–0.954]; $p=0.0299$) and 39% (HR 0.607 [95% CI 0.436–0.843]; $p=0.0029$), respectively. Similar trends were

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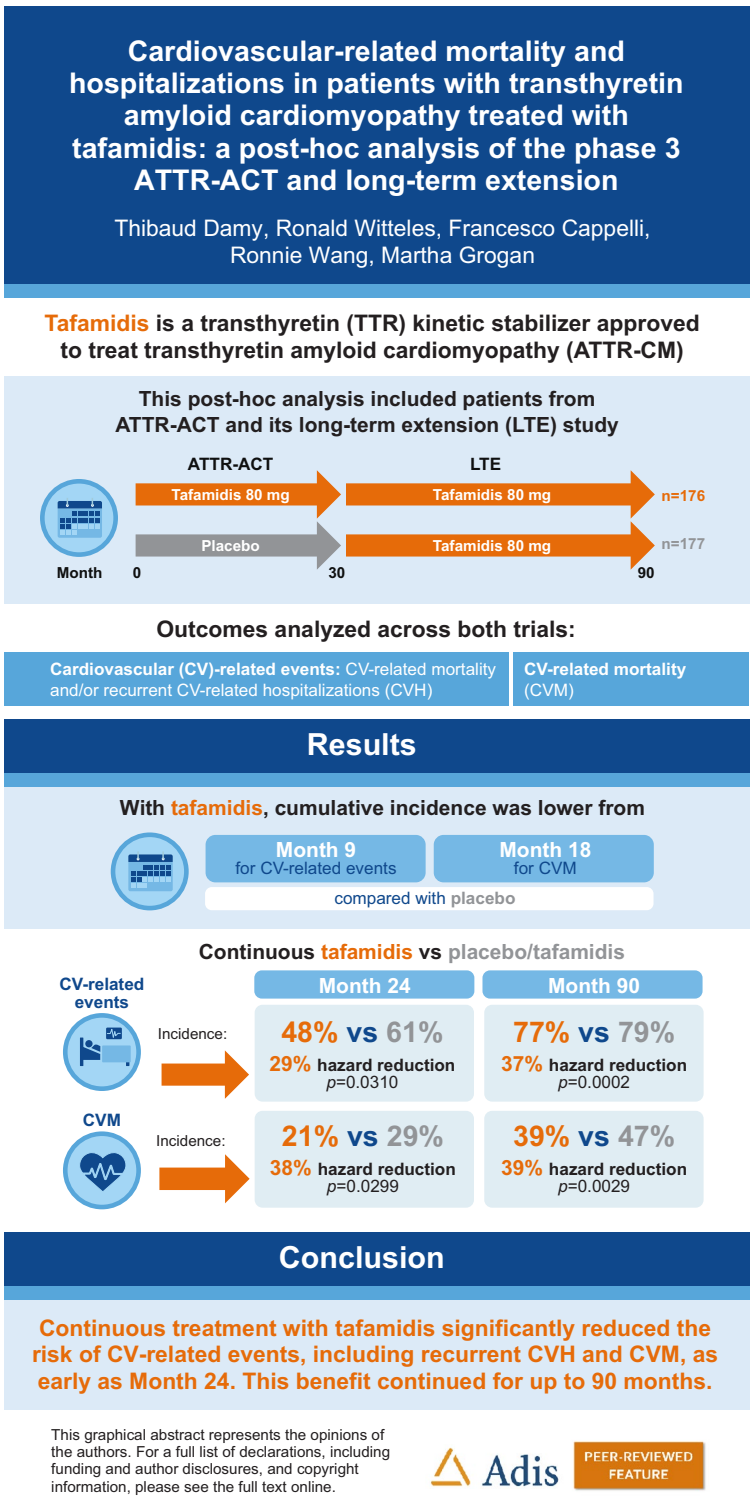
observed in patients with baseline New York Heart Association (NYHA) functional class I/II but not with baseline NYHA class III.
Conclusion: Treatment with tafamidis significantly reduced the risk of CV-related events, including recurrent CVH and CVM, as early as month 24. This benefit continued for ≤90 months. Graphical abstract available for this article.
Trial Registry: ClinicalTrial.gov identifiers: NCT01994889; NCT02791230.

PLAIN LANGUAGE SUMMARY

Transthyretin amyloid cardiomyopathy (called ATTR-CM) is a disease that affects the heart and can cause heart failure. Patients with ATTR-CM are frequently hospitalized as a result of cardiovascular problems. Tafamidis is approved for the treatment of ATTR-CM. In the phase 3 ATTR-ACT, patients treated with tafamidis were less likely to be hospitalized or die because of heart-related problems compared to those treated with placebo. In this analysis, the investigators looked at the frequency and risk of cardiovascular events (both hospitalizations and death) during ATTR-ACT and the long-term extension study that followed. This analysis included 176 patients who took tafamidis during ATTR-ACT (which lasted 2.5 years) and the long-term extension study (which lasted 5 years), and 177 patients who took placebo during ATTR-ACT switched to tafamidis during the long-term extension study. After 1.5 years of treatment and until the end of the long-term extension study, fewer patients taking tafamidis experienced cardiovascular-related events compared to patients who first took placebo and then switched to tafamidis. The risk for heart-related events and heart-related death was significantly lower after 2 years of treatment with tafamidis compared to placebo. The risk remained significantly lower until the end of the long-term extension study for patients who took tafamidis from the start compared to patients who switched from placebo to tafamidis. In summary, treatment with tafamidis reduced the risk of heart-related events and death for up to 7.5 years.

Graphical Abstract:



Keywords: ATTR-CM; Cardiovascular-related hospitalization; Cardiovascular-related mortality; CV-related events; Tafamidis; Transthyretin amyloid cardiomyopathy

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.32801490.

Key Summary Points

Why carry out this study?

Cardiovascular (CV)-related hospitalizations, which are associated with increased mortality, are common for patients with transthyretin amyloid cardiomyopathy (ATTR-CM).

In ATTR-ACT, treatment with the transthyretin tetramer stabilizer tafamidis reduced the risk of CV-related hospitalizations and CV-related mortality compared with placebo.

In this post hoc analysis, incidence and risk of CV-related events, including CV-related mortality and recurrent CV-related hospitalizations, during ATTR-ACT (30 months) and its 60-month open-label long-term extension (LTE) study were evaluated.

What was learned from this study?

Patients who received continuous tafamidis had a significantly lower risk of CV-related events and CV-related mortality alone from month 24 until the end of the LTE compared with patients who switched from placebo to tafamidis after 30 months. Similar results were also observed in patients with baseline New York Heart Association (NYHA) functional class I/II but not in patients with baseline NYHA class III.

Treatment with tafamidis reduces the risk of CV-related events, including CV-related mortality and recurrent CV-related hospitalizations in patients with ATTR-CM for up to 7.5 years.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) is characterized by misfolded transthyretin (TTR) monomers forming fibrils and accumulating in various tissues, including the myocardium, leading to ventricular stiffness and cardiac dysfunction. Left untreated, median survival is 3.5 years in patients with wild-type ATTR-CM and 2.5 years in patients with mutations in the *TTR* gene (variant ATTR-CM) [1]. As the disease progresses, severe heart failure is common [1, 2]. In patients with ATTR-CM, hospitalizations due to worsening heart failure were associated with significantly higher risk of mortality [3]. One study from several North European countries showed that patients with ATTR-CM have a higher risk and number of hospitalizations than patients with other types of heart failure [4]. The mean number of hospitalizations and hospitalization days increased steadily during the 3 years preceding diagnosis before rising sharply during the first year post diagnosis. Additional studies from the USA and South Korea also found increased rates and length of hospital stay for patients with ATTR-CM [5, 6]. In addition, hospitalizations (all-cause and related to worsening heart failure) were associated with an increased risk of mortality [3, 6]. A recent international consensus paper proposed the inclusion of CV-related hospitalizations to monitor disease progression [7].

Tafamidis is a once-daily, oral TTR kinetic stabilizer and was the first disease-modifying therapy approved to treat ATTR-CM. Tafamidis showed a statistically significant reduction in mortality and CV-related hospitalizations versus placebo over 30 months in the phase 3 ATTR-ACT trial [8]. Results from the open-label extension (LTE) and from an early-access cohort confirmed the beneficial effects of tafamidis on mortality and CV-related hospitalizations with a follow-up of up to 71 months [9–11].

The effect of tafamidis on reducing annual rates of and time to CV-related hospitalizations during the 30-month study period of ATTR-ACT was greater among patients with New York Heart Association (NYHA) functional class I/II versus those with class III symptoms at baseline [8, 12,

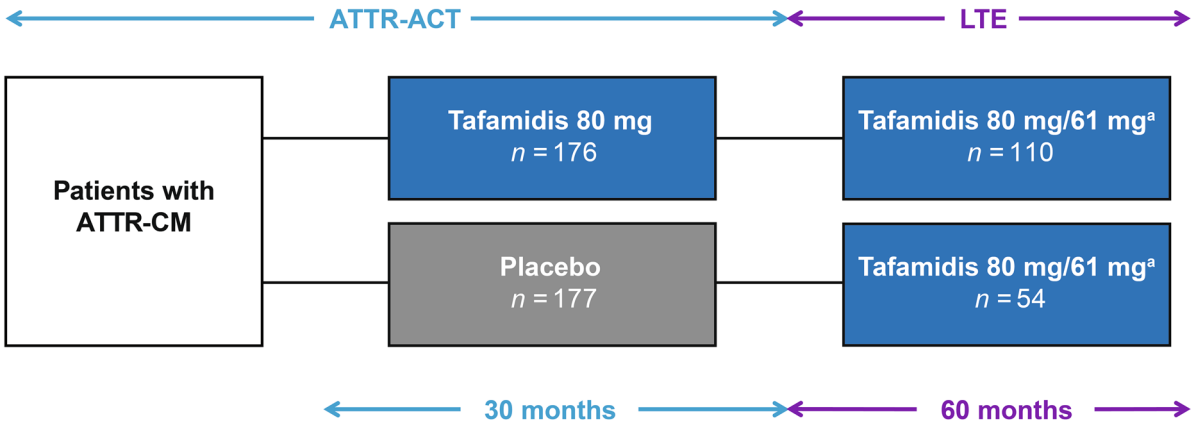


Fig. 1 Simplified trial design. [a]As of July 20, 2018, all patients receiving tafamidis in the LTE were switched to the bioequivalent tafamidis free acid 61 mg. *ATTR-ACT* Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *ATTR-CM* transthyretin amyloid cardiomyopathy, *LTE* long-term extension

13]. In ATTR-ACT, the predominant cause of CV-related death was due to heart failure compared with sudden death in patients with heart failure with preserved ejection fraction where sudden death appears to be the most common cause of death [2]. Patients receiving tafamidis in ATTR-ACT had lower rates of CV-related death (20% vs 28% with placebo), including death due to heart failure (16% vs 23%). A 31% reduction in the risk of CV-related death was observed with tafamidis compared with placebo.

In this exploratory, post hoc analysis of ATTR-ACT and the LTE, combined CV-related events of CV-related mortality and recurrent CV-related hospitalizations were evaluated with a follow-up of up to 90 months.

METHODS

Study Design

The design of ATTR-ACT and the LTE have been described previously and is summarized in Fig. 1 [8, 9, 14]. Briefly, patients aged 18–90 years with biopsy-confirmed ATTR-CM (wild-type or variant) and NYHA class I–III were included in ATTR-ACT [8, 14]. Patients were randomized 2:1:2 to tafamidis meglumine 80 mg (bioequivalent to tafamidis free acid 61 mg [15] and referred to as tafamidis 80 mg hereafter; $n = 176$), tafamidis 20 mg ($n = 88$), or placebo ($n = 177$) for up to 30 months. Following the double-blind study period, patients could enroll in the open-label LTE. Patients treated with tafamidis continued the dose to which they had been randomized at the start of ATTR-ACT (tafamidis 80 mg/tafamidis 80 mg arm) and patients who received placebo were randomized 2:1 to receive tafamidis 80 or 20 mg (placebo/tafamidis 80 mg arm) in the LTE for up to 60 months. Tafamidis 20 mg is the approved dose for the treatment of transthyretin amyloid polyneuropathy in the European Union [8] and 40 other countries outside the USA where 20 mg is not approved [9]. Therefore, this post hoc analysis excluded patients who received tafamidis 20 mg in ATTR-ACT. Following a protocol amendment from July 20, 2018, all patients who received tafamidis 80 or 20 mg transitioned to tafamidis free acid 61 mg.

CV-related mortality and CV-related hospitalizations were adjudicated in the ATTR-ACT trial. In the LTE, CV-related mortality and CV-related hospitalizations were defined as a non-elective admission to an acute care setting for medical therapy that resulted in ≥ 24-h stay with a discharge diagnosis that included a CV reason or relatedness for hospitalization, based on the clinical judgment of the selected preferred terms from the Medical Dictionary for Regulatory Activities FDA Medical Queries. CV-related

Table 1 Baseline characteristics

	Overall (NYHA class I–III)		NYHA class I + II		NYHA class III	
	Tafamidis 80 mg (*n* = 176)	**Placebo (*n* = 177)**	**Tafamidis 80 mg (*n* = 121)**	**Placebo (*n* = 114)**	**Tafamidis 80 mg (*n* = 55)**	**Placebo (*n* = 63)**
Age, years						
Mean (SD)	75.2 (7.2)	74.1 (6.7)	75.0 (7.1)*	73.1 (6.5)*	75.5 (7.6)	75.7 (6.8)
Median (min, max)	76.0 (46.0, 88.0)	74.0 (51.0, 89.0)	75.0 (56.0, 88.0)	74.0 (53.0, 86.0)	76.0 (46.0, 87.0)	76.0 (51.0, 89.0)
< 80, *n* (%)	125 (71.0)	140 (79.1)	87 (71.9)*	97 (85.1)*	38 (69.1)	43 (68.3)
≥ 80, *n* (%)	51 (29.0)	37 (20.9)	34 (28.1)*	17 (14.9)*	17 (30.9)	20 (31.7)
Sex, *n* (%)						
Male	158 (89.8)	157 (88.7)	113 (93.4)	105 (92.1)	45 (81.8)	52 (82.5)
Female	18 (10.2)	20 (11.3)	8 (6.6)	9 (7.9)	10 (18.2)	11 (17.5)
Genotype, *n* (%)						
ATTRwt	134 (76.1)	134 (75.7)	99 (81.8)	90 (78.9)	35 (63.6)	44 (69.8)
ATTRv	42 (23.9)	43 (24.3)	22 (18.2)	24 (21.1)	20 (36.4)	19 (30.2)
Medical history, *n* (%)						
AF/AFL	112 (63.6)	118 (66.7)	78 (64.5)	70 (61.4)	34 (61.8)	48 (76.2)
IHD	11 (6.3)	6 (3.4)	9 (7.4)	3 (2.6)	2 (3.6)	3 (4.8)
Stroke	0	2 (1.1)	0	1 (0.9)	0	1 (1.6)
COPD	8 (4.5)	11 (6.2)	2 (1.7)	7 (6.1)	6 (10.9)	4 (6.3)
Diabetes mellitus	23 (13.1)	33 (18.6)	12 (9.9)	17 (14.9)	11 (20.0)	16 (25.4)
NYHA class, *n* (%)						
I	16 (9.1)	13 (7.3)	16 (13.2)	13 (11.4)	N/A	N/A
II	105 (59.7)	101 (57.1)	105 (86.8)	101 (88.6)	N/A	N/A
III	55 (31.3)	63 (35.6)	N/A	N/A	55 (100.0)	63 (100.0)
NAC classification, *n* (%)						
Stage I	76 (43.2)	72 (40.7)	64 (52.9)	55 (48.2)	12 (21.8)	17 (27.0)
Stage II	66 (37.5)	70 (39.5)	43 (35.5)	43 (37.7)	23 (41.8)	27 (42.9)
Stage III	34 (19.3)	35 (19.8)	14 (11.6)	16 (14.0)	20 (36.4)	19 (30.2)
NT-proBNP, pg/mL						
Mean (SD)	3941.0 (3090.0)	3845.5 (2971.5)	3259.0 (2292.3)	3472.2 (2732.1)	5441.5 (3991.2)	4520.9 (3277.4)

Table 1 continued

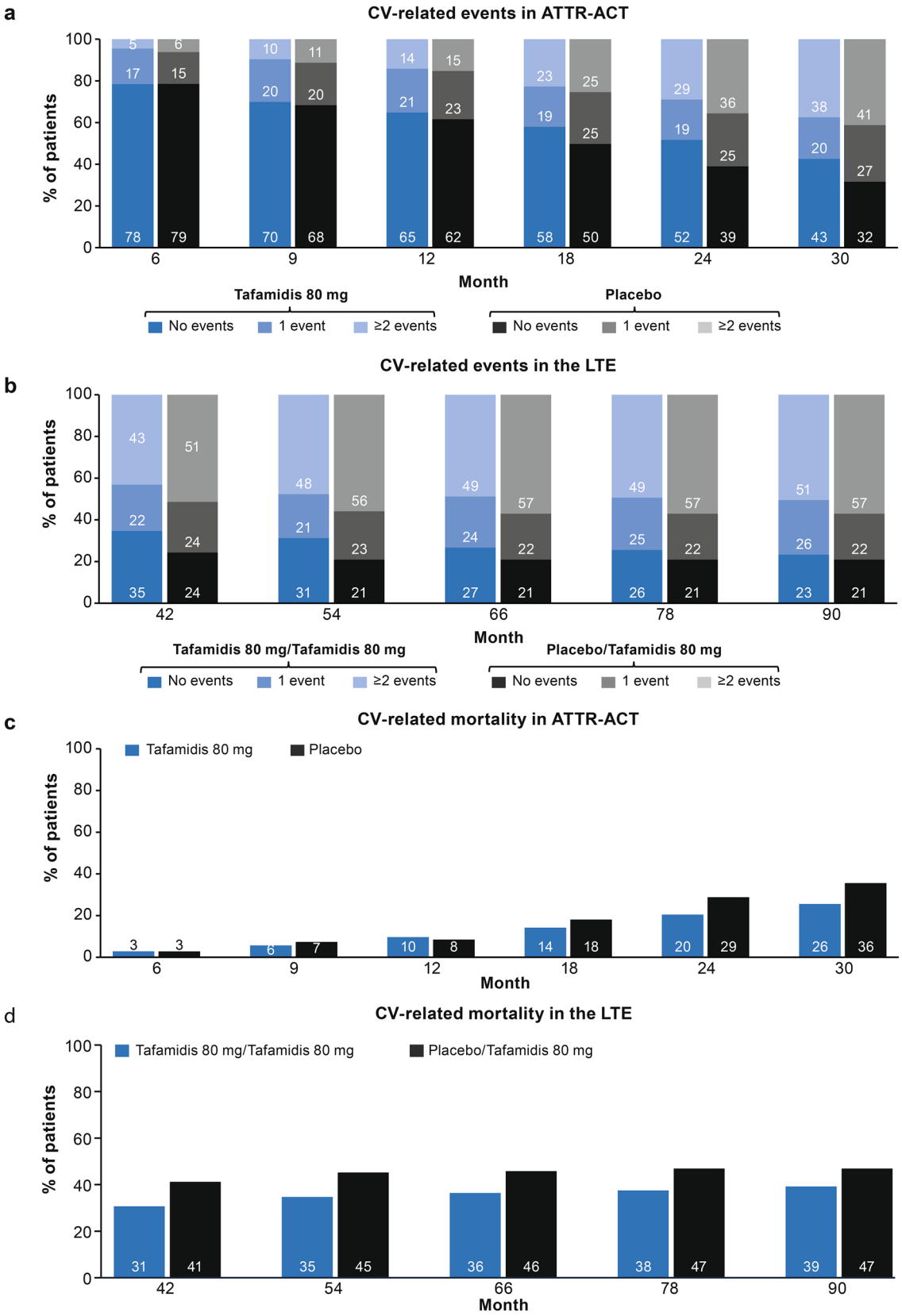
	Overall (NYHA class I–III)		NYHA class I + II		NYHA class III	
	Tafamidis 80 mg (*n* = 176)	Placebo (*n* = 177)	Tafamidis 80 mg (*n* = 121)	Placebo (*n* = 114)	Tafamidis 80 mg (*n* = 55)	Placebo (*n* = 63)
Median (min, max)	3122.0 (392.0, 22,019.8)	3161.0 (298.0, 16,786.8)	2672.0 (392.0, 12,379.9)	2816.3 (457.0, 16,599.9)	4410.0 (849.0, 22,019.8)	4079.0 (298.0, 16,786.8)
KCCQ-OSS						
Mean (SD)	67.1 (21.3)	65.9 (21.7)	74.4 (17.4)	73.4 (18.5)	51.1 (20.3)	52.4 (20.7)
Median (min, max)	71.0 (7.6, 100.0)	68.0 (13.8, 100.0)	77.1 (30.7, 100.0)	76.1 (29.9, 100.0)	50.4 (7.6, 85.4)	51.6 (13.8, 94.8)
eGFR, mL/min/1.73 m^2						
Mean (SD)	57.1 (17.1)	55.8 (16.9)	60.8 (16.0)	57.5 (15.6)	49.0 (17.0)	52.7 (18.6)
Median (min, max)	55.6 (23.0, 96.3)	54.1 (18.3, 96.6)	57.3 (27.3, 96.3)	55.5 (28.4, 96.6)	48.3 (23.0, 90.7)	50.8 (18.3, 93.7)
TTR concentration, mg/dL						
n	156	158	110	104	46	54
Mean (SD)	7.1 (4.6)	6.2 (3.2)	7.4 (5.0)	6.5 (2.9)	6.4 (3.4)	5.8 (3.6)
Median (min, max)	5.9 (2.4, 29.3)	5.4 (2.4, 23.9)	6.0 (2.5, 29.3)	5.6 (2.4, 17.5)	5.5 (2.4, 20.5)	5.1 (2.6, 23.9)
6MWT distance, m						
Mean (SD)	344.8 (120.3)	353.3 (126.0)	383.1 (107.8)	402.9 (106.4)	260.4 (102.6)	263.3 (108.1)
Median (min, max)	342.5 (61.0, 685.0)	346.0 (80.0, 822.0)	383.0 (133.0, 685.0)	408.5 (135.0, 822.0)	256.0 (61.0, 480.0)	250.0 (80.0, 544.0)
Follow-up, months						
Median (Q1, Q3)	54.8 (29.7, 78.1)	30.5 (24.5, 64.5)	64.7 (31.6, 80.3)	41.9 (29.5, 67.3)	30.0 (13.6, 62.3)	29.5 (15.0, 43.6)

AF/AFL atrial flutter/atrial fibrillation, *6MWT* 6-min walk test, *ATTRv* variant transthyretin amyloidosis, *ATTRwt* wild-type transthyretin amyloidosis, *COPD* chronic obstructive pulmonary disease, *eGFR* estimated glomerular filtration rate, *KCCQ-OSS* Kansas City Cardiomyopathy Questionnaire-overall summary score, *IHD* ischemic heart disease, *max* maximum, *min* minimum, *N/A* not applicable, *NAC* National Amyloidosis Centre, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *NYHA* New York Heart Association, *SD* standard deviation, *TTR* transthyretin, *Q1/3* 1st/3rd quartile

*$p < 0.05$

mortality was defined as death due to a CV event, heart transplant, or implantation of a cardiac mechanical assist device.

This study was approved by the independent review board or ethics committee at each participating center and was conducted in accordance with the concepts laid out in the Declaration of Helsinki of 1964 and later amendments, and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.


a
CV-related events in ATTR-ACT
% of patients
Month
Tafamidis 80 mg
Placebo
No events
1 event
≥2 events
b
CV-related events in the LTE
% of patients
Month
Tafamidis 80 mg/Tafamidis 80 mg
Placebo/Tafamidis 80 mg
No events
1 event
≥2 events
c
CV-related mortality in ATTR-ACT
Tafamidis 80 mg
Placebo
% of patients
Month
d
CV-related mortality in the LTE
Tafamidis 80 mg/Tafamidis 80 mg
Placebo/Tafamidis 80 mg
% of patients
Month

◂**Fig. 2** Cumulative incidence of CV-related events (mortality events, single or recurrent hospitalizations) during **a** ATTR-ACT and **b** LTE, **c** CV-related mortality during ATTR-ACT, and **d** in the LTE in the overall cohort. *ATTR-ACT* Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CV* cardiovascular, *LTE* long-term extension, *NYHA* New York Heart Association

Statistical Analyses

Patients were categorized by baseline NYHA functional class: class I–III (overall population), class I/II, or class III. The cumulative incidence of CV-related hospitalizations and CV-related mortality was evaluated throughout ATTR-ACT and the LTE. All analyses were based on the number of patients initially randomized to tafamidis 80 mg or placebo. Patients in the tafamidis 80 mg or placebo arm who completed ATTR-ACT but did not enroll into the LTE were included but censored, and patients who switched from placebo and randomized to tafamidis 20 mg in the LTE were censored as well.

A Liu–Wei–Yang–Ying (LWYY) model (or modified Andersen–Gill model) was used to evaluate time to recurrent CV events, including the combined endpoint of CV-related mortality (CVM) and/or recurrent (CV)-related hospitalizations (CVH), which employed a robust covariance matrix estimator to allow for arbitrary dependence structures among recurrent events within the same patient. A Cox proportional hazard model was used to evaluate time to CVM (single endpoint). Both models compared tafamidis 80 mg and placebo (during ATTR-ACT) or tafamidis 80 mg/tafamidis 80 mg and placebo/tafamidis 80 mg (during the LTE) with treatment as the main effect adjusted for baseline *TTR* genotype (variant, wild), natural log-transformed baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP; pg/mL), and baseline estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2). NYHA classification was adjusted in both models in the overall (NYHA class I–III) cohort, but not in the subset analysis models for NYHA class I/II or class III cohorts. Separate survival analysis datasets were structured for each analysis timepoint with corresponding censoring. No multiplicity adjustments were made as no multiple comparisons were performed in a single dataset.

Kaplan–Meier plots were provided for the associated LWYY models or Cox models for overall patients (baseline NYHA class I–III), baseline NYHA class I/II, and baseline NYHA class III. Frequencies and percentages of the CV events were summarized by visits and by treatment. Number needed to treat (NNT) was defined as the reciprocal of the absolute risk difference (incidence in placebo group – incidence in tafamidis group), rounded up to the nearest higher integer.

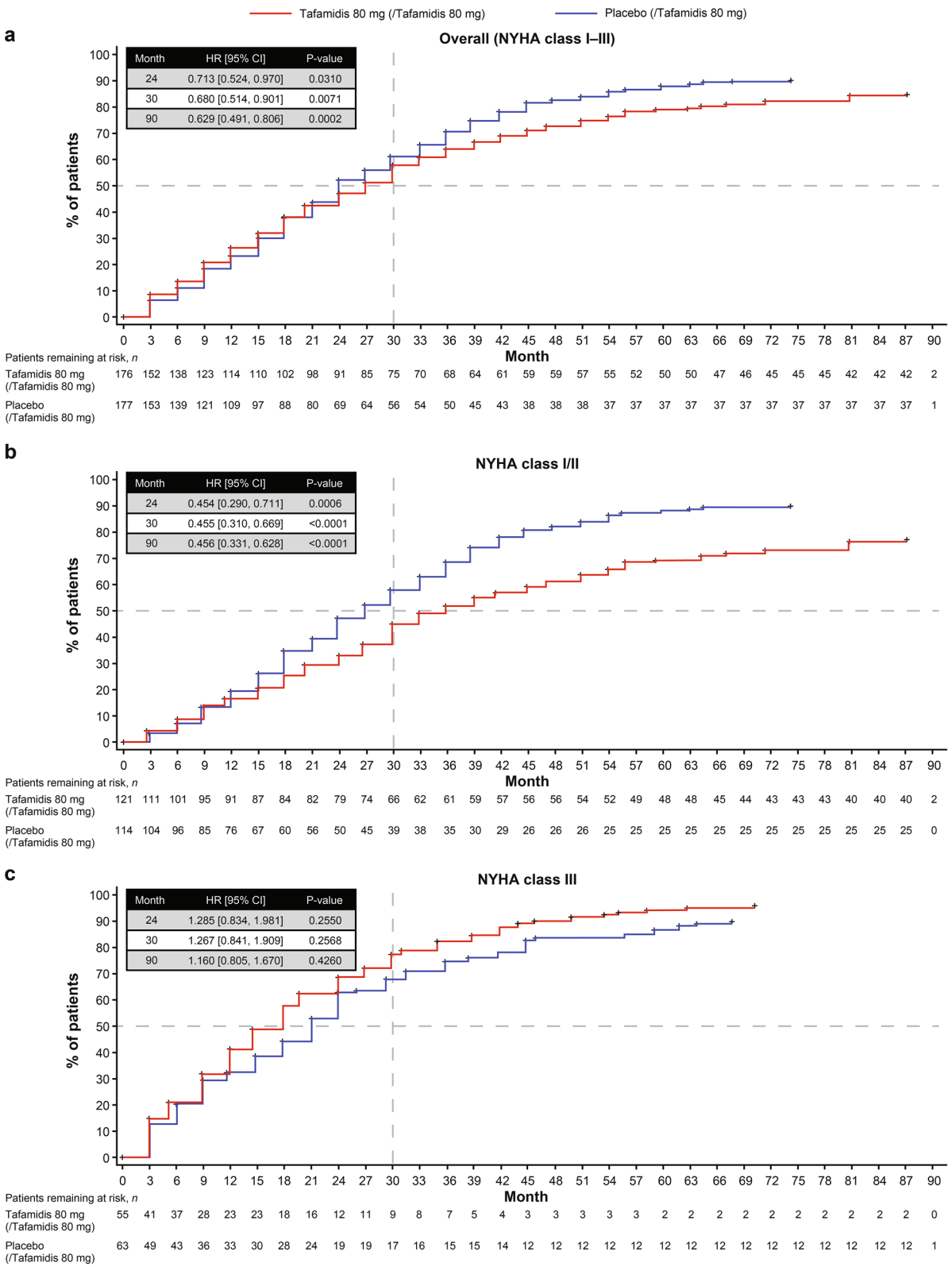
RESULTS

Patient Baseline Characteristics and Disposition

Of the 176 patients randomized to tafamidis 80 mg at the start of ATTR-ACT, 110 (63%) continued treatment in the LTE. In addition, 54 (31%) of the 177 patients randomized to placebo at the start of ATTR-ACT received tafamidis 80 mg (and then switched to the bioequivalent tafamidis free acid 61 mg) in the LTE (Fig. 1).

Overall, baseline characteristics at the start of ATTR-ACT were balanced across all subgroups (Table 1). Mean age was between 73 and 76 years and overall age ranged from 46 to 89 years across the subgroups. The proportion of patients aged ≥80 years ranged from 14.9% to 31.7%. In the NYHA class I/II cohort, significantly more patients receiving tafamidis 80 mg were aged ≥80 years (28.1%) compared with placebo (14.9%; $p=0.0142$). At least 81.8% of patients were male and the majority (63.6% to 81.8%) had wild-type ATTR-CM. Most patients (≥63.6%) had National Amyloidosis Centre stage I or II disease. The median follow-up time in the tafamidis 80 mg arm was approximately 24 months longer than in the placebo arm in the overall and NYHA class I/II cohorts, whereas the median follow-up time was similar between treatments in the NYHA class III category.

Baseline characteristics by continuation status are shown in Supplementary Table S1. Patients who did not enroll in the LTE were


Tafamidis 80 mg (/Tafamidis 80 mg)
Placebo (/Tafamidis 80 mg)
a
Overall (NYHA class I–III)
Month | HR [95% CI] | P-value
24 | 0.713 [0.524, 0.970] | 0.0310
30 | 0.680 [0.514, 0.901] | 0.0071
90 | 0.629 [0.491, 0.806] | 0.0002
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 176 152 138 123 114 110 102 98 91 85 75 70 68 64 61 59 59 57 55 52 50 50 47 46 45 45 45 42 42 42 2
Placebo (/Tafamidis 80 mg) 177 153 139 121 109 97 88 80 69 64 56 54 50 45 43 38 38 38 37 37 37 37 37 37 37 37 37 37 37 37 1
b
NYHA class I/II
Month | HR [95% CI] | P-value
24 | 0.454 [0.290, 0.711] | 0.0006
30 | 0.455 [0.310, 0.669] | <0.0001
90 | 0.456 [0.331, 0.628] | <0.0001
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 121 111 101 95 91 87 84 82 79 74 66 62 61 59 57 56 56 54 52 49 48 48 45 44 43 43 43 40 40 40 2
Placebo (/Tafamidis 80 mg) 114 104 96 85 76 67 60 56 50 45 39 38 35 30 29 26 26 26 25 25 25 25 25 25 25 25 25 25 25 25 0
c
NYHA class III
Month | HR [95% CI] | P-value
24 | 1.285 [0.834, 1.981] | 0.2550
30 | 1.267 [0.841, 1.909] | 0.2568
90 | 1.160 [0.805, 1.670] | 0.4260
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 55 41 37 28 23 23 18 16 12 11 9 8 7 5 4 3 3 3 3 3 2 2 2 2 2 2 2 2 2 2 0
Placebo (/Tafamidis 80 mg) 63 49 43 36 33 30 28 24 19 19 17 16 15 15 14 12 12 12 12 12 12 12 12 12 12 12 12 12 12 12 1

◂**Fig. 3** Time to CV-related events (CV-related mortality and/or recurrent CV-related hospitalizations) during ATTR-ACT and the LTE in **a** the overall cohort, **b** baseline NYHA class I/II, and **c** NYHA baseline class III. *ATTR-ACT* Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CV* cardiovascular, *LTE* long-term extension, *NYHA* New York Heart Association

more likely to be Black, have ATTRv-CM or NYHA class III at baseline. Patients with NYHA class II at baseline were more likely to enroll in the LTE.

CV-Related Events (Combined Endpoint)

During ATTR-ACT, the majority of patients (≥ 62%) in the tafamidis 80 mg and placebo arms experienced no CV-related events throughout the first year, decreasing until month 30 in both treatment arms (Fig. 2a). Between months 9 and 30, the proportion of patients with no CV-related events was larger in the tafamidis 80 mg arm (70% decreasing to 43%) compared with placebo (68% decreasing to 32%). The proportion of patients experiencing one event was smaller in the tafamidis 80 mg arm (19% to 21%) compared with placebo (23% to 27%) between months 12 and 30. The proportion of patients with recurrent (≥ 2) CV-related events between months 6 and 30 was consistently lower in the tafamidis 80 mg arm (5% to 38%) than in the placebo arm (6% to 41%).

Although more patients experienced recurrent (≥ 2) CV-related events throughout the LTE (during which all patients received tafamidis 80 mg) than ATTR-ACT in both treatment arms, continuous treatment with tafamidis 80 mg showed a greater benefit than switching from placebo to tafamidis 80 mg. The proportion of ≥ 2 CV-related events with continuous tafamidis was lower (43–51%) than with placebo/tafamidis 80 mg (51–57%), whereas the proportion of patients with no events was higher with continuous tafamidis than placebo/tafamidis 80 mg (Fig. 2b).

CV-Related Mortality

During the first year of ATTR-ACT, the cumulative incidence of CV-related mortality was similar between tafamidis- and placebo-treated patients (Fig. 2c). From month 18 onwards, the incidence of CV-related mortality was lower in the tafamidis 80 mg (14–26%) than the placebo (18–36%) arm (Fig. 2c). Throughout the LTE, CV-related mortality increased slightly in the tafamidis 80 mg/tafamidis 80 mg arm (31% to 39%) and placebo/tafamidis 80 mg arm (41% to 47%); however, the incidence remained lower with continuous tafamidis compared with placebo/tafamidis 80 mg (Fig. 2d).

Time to CV-Related Events (Combined Endpoint)

At month 24 in ATTR-ACT, the cumulative incidence of CV-related events in the overall patient cohort was 48% in the tafamidis 80 mg arm compared with 61% in the placebo arm, resulting in a 29% hazard reduction (hazard ratio [HR] 0.713 [95% CI 0.524–0.970]; $p=0.0310$; Fig. 3a; Table 2). Incidence of CV-related events increased throughout the remainder of ATTR-ACT and the LTE with continuous tafamidis (73%) and up to month 66 with placebo/tafamidis 80 mg (79%); however, hazard reduction (tafamidis 80 mg[/tafamidis 80 mg] vs placebo[/tafamidis 80 mg]) remained significant up until month 90 (37%; HR 0.629 [95% CI 0.491–0.806; $p=0.002$]). NNT remained relatively stable ranging from 8 to 10 until month 54 before increasing to ≤ 42 by month 90.

In patients with baseline NYHA class I/II, an increase in cumulative incidence of CV-related events was observed from month 24 to month 90, from 35% to 68% with tafamidis 80 mg(/tafamidis 80 mg) and from 56% to 78% with placebo(/tafamidis 80 mg) (Table 3). Hazard reduction with tafamidis 80 mg(/tafamidis 80 mg) was relatively constant at approximately 54–56% during the same time period (month 24: HR 0.454 [95% CI 0.290–0.711]; $p=0.0006$; month 90: HR 0.456 [95% CI 0.331–0.628]; $p<0.0001$; Fig. 3b; Table 3). NNT was ≤ 10

Table 2 Time to CV-related events (combined endpoint) and CV-related mortality in the overall cohort (NYHA class I–III)

Month	CV-related events (combined endpoint)[a]					CV-related mortality				
	Incidence, *n* (%)		NNT	HR [95% CI][b]	*p* value	Incidence, *n* (%)		NNT	HR [95% CI][c]	*p* value
	Tafamidis 80 mg (/tafamidis 80 mg) (*n* = 176)	Placebo (/ tafamidis 80 mg) (*n* = 177)				Tafamidis 80 mg (/tafamidis 80 mg) (*n* = 176)	Placebo (/ tafamidis 80 mg) (*n* = 177)			
ATTR-ACT										
24	85 (48.3)	108 (61.0)	8	0.713 [0.524, 0.970]	0.0310	36 (20.5)	51 (28.8)	12	0.618 [0.401, 0.954]	0.0299
30	101 (57.4)	121 (68.4)	10	0.680 [0.514, 0.901]	0.0071	45 (25.6)	63 (35.6)	10	0.609 [0.412, 0.899]	0.0125
LTE										
42	115 (65.3)	134 (75.7)	10	0.641 [0.490, 0.838]	0.0011	54 (30.7)	73 (41.2)	10	0.599 [0.419, 0.857]	0.0051
54	121 (68.8)	140 (79.1)	10	0.622 [0.481, 0.803]	0.0003	61 (34.7)	80 (45.2)	10	0.590 [0.419, 0.829]	0.0024
66	129 (73.3)	140 (79.1)	18	0.618 [0.481, 0.793]	0.0002	64 (36.4)	81 (45.8)	11	0.604 [0.432, 0.845]	0.0032
78	131 (74.4)	140 (79.1)	22	0.622 [0.485, 0.797]	0.0002	66 (37.5)	83 (46.9)	11	0.589 [0.423, 0.822]	0.0018
90	135 (76.7)	140 (79.1)	42	0.629 [0.491, 0.806]	0.0002	69 (39.2)	83 (46.9)	14	0.607 [0.436, 0.843]	0.0029

ATTR-ACT Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *LWYY* Lin–Wei–Yang–Ying, *NNT* number needed to treat, *NYHA* New York Heart Association, *LTE* long-term extension

[a]CV-related mortality and (recurrent) CV-related hospitalizations

[b]Calculated using LWYY model

[c]Calculated using Cox proportional hazard model

Table 3 Time to CV-related events (combined endpoint) and CV-related mortality in patients with baseline NYHA class I/II

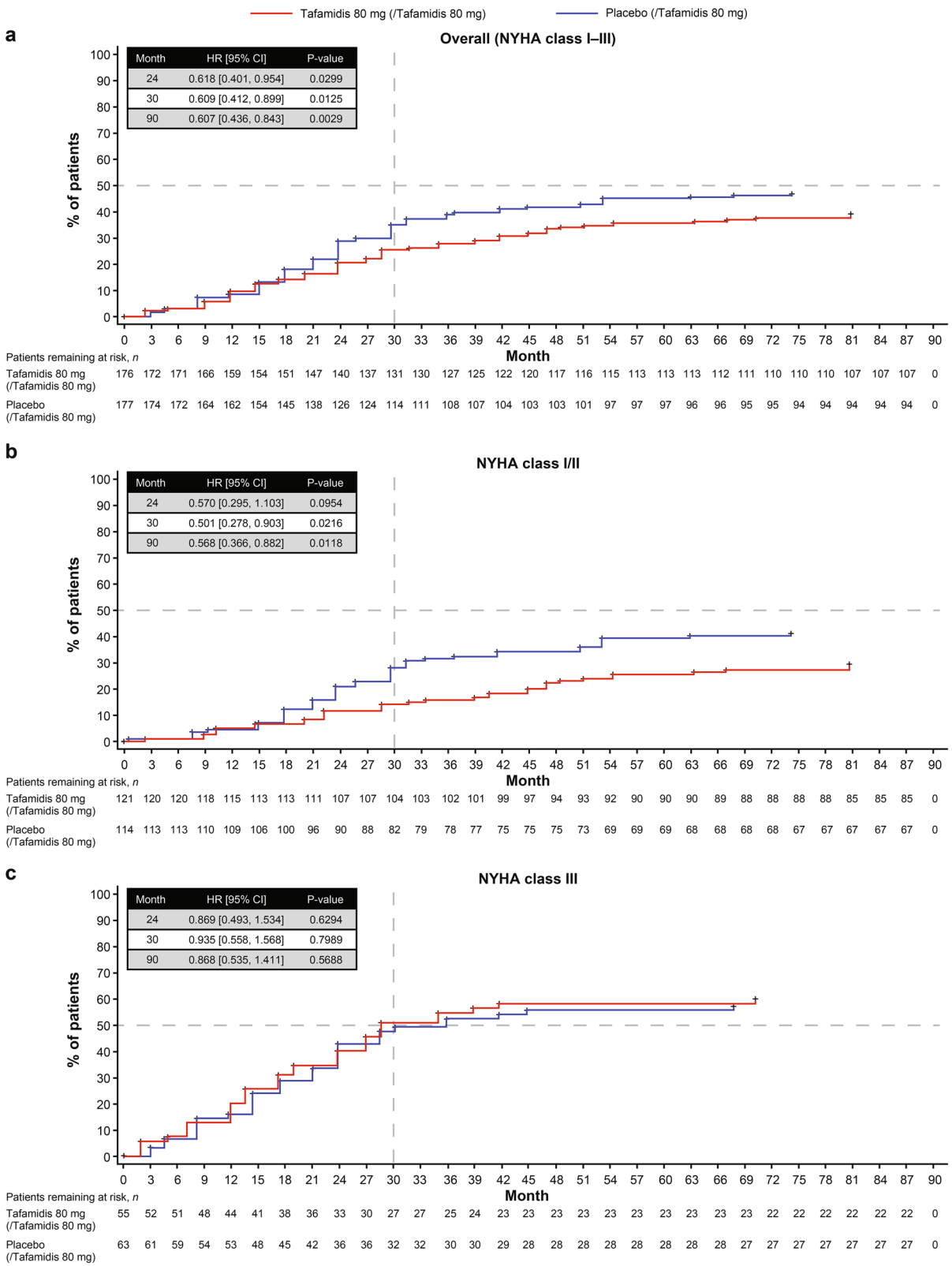
Month	CV-related events (combined endpoint)[a]					CV-related mortality				
	Incidence, *n* (%)		NNT	HR [95% CI][b]	*p* value	Incidence, *n* (%)		NNT	HR [95% CI][c]	*p* value
	Tafamidis 80 mg (/tafamidis 80 mg) (*n* = 121)	Placebo (/tafamidis 80 mg) (*n* = 114)				Tafamidis 80 mg (/tafamidis 80 mg) (*n* = 121)	Placebo (/tafamidis 80 mg) (*n* = 114)			
ATTR-ACT										
24	42 (34.7)	64 (56.1)	5	0.454 [0.290, 0.711]	0.0006	14 (11.6)	24 (21.1)	11	0.570 [0.295, 1.103]	0.0954
30	55 (45.5)	75 (65.8)	5	0.455 [0.310, 0.669]	< 0.0001	17 (14.0)	32 (28.1)	8	0.501 [0.278, 0.903]	0.0216
LTE										
42	64 (52.9)	85 (74.6)	5	0.420 [0.291, 0.605]	< 0.0001	22 (18.2)	39 (34.2)	7	0.489 [0.289, 0.826]	0.0075
54	69 (57.0)	89 (78.1)	5	0.420 [0.299, 0.590]	< 0.0001	29 (24.0)	45 (39.5)	7	0.516 [0.323, 0.825]	0.0058
66	76 (62.8)	89 (78.1)	7	0.440 [0.317, 0.609]	< 0.0001	32 (26.4)	46 (40.4)	8	0.546 [0.347, 0.860]	0.0091
78	78 (64.5)	89 (78.1)	8	0.447 [0.324, 0.617]	< 0.0001	33 (27.3)	47 (41.2)	8	0.542 [0.346, 0.850]	0.0075
90	82 (67.8)	89 (78.1)	10	0.456 [0.331, 0.628]	< 0.0001	36 (29.8)	47 (41.2)	9	0.568 [0.366, 0.882]	0.0118

ATTR-ACT Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *LWYY* Lin–Wei–Yang–Ying, *NNT* number needed to treat, *NYHA* New York Heart Association, *LTE* long-term extension

[a]CV-related mortality and (recurrent) CV-related hospitalizations

[b]Calculated using LWYY model

[c]Calculated using Cox proportional hazard model


Tafamidis 80 mg (/Tafamidis 80 mg)
Placebo (/Tafamidis 80 mg)
a
Overall (NYHA class I–III)
Month | HR [95% CI] | P-value
24 | 0.618 [0.401, 0.954] | 0.0299
30 | 0.609 [0.412, 0.899] | 0.0125
90 | 0.607 [0.436, 0.843] | 0.0029
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 176 172 171 166 159 154 151 147 140 137 131 130 127 125 122 120 117 116 115 113 113 113 112 111 110 110 110 107 107 107 0
Placebo (/Tafamidis 80 mg) 177 174 172 164 162 154 145 138 126 124 114 111 108 107 104 103 103 101 97 97 97 96 96 95 95 94 94 94 94 94 0
b
NYHA class I/II
Month | HR [95% CI] | P-value
24 | 0.570 [0.295, 1.103] | 0.0954
30 | 0.501 [0.278, 0.903] | 0.0216
90 | 0.568 [0.366, 0.882] | 0.0118
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 121 120 120 118 115 113 113 111 107 107 104 103 102 101 99 97 94 93 92 90 90 90 89 88 88 88 88 85 85 85 0
Placebo (/Tafamidis 80 mg) 114 113 113 110 109 106 100 96 90 88 82 79 78 77 75 75 75 73 69 69 69 68 68 68 68 67 67 67 67 67 0
c
NYHA class III
Month | HR [95% CI] | P-value
24 | 0.869 [0.493, 1.534] | 0.6294
30 | 0.935 [0.558, 1.568] | 0.7989
90 | 0.868 [0.535, 1.411] | 0.5688
% of patients
Month
Patients remaining at risk, n
Tafamidis 80 mg (/Tafamidis 80 mg) 55 52 51 48 44 41 38 36 33 30 27 27 25 24 23 23 23 23 23 23 23 23 23 22 22 22 22 22 22 0
Placebo (/Tafamidis 80 mg) 63 61 59 54 53 48 45 42 36 36 32 32 30 30 29 28 28 28 28 28 28 28 28 27 27 27 27 27 27 0

◂**Fig. 4** Time to CV-related mortality during ATTR-ACT and the LTE in **a** the overall cohort, **b** baseline NYHA class I/II, and **c** NYHA baseline class III. *ATTR-ACT* Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CV* cardiovascular, *LTE* long-term extension, *NYHA* New York Heart Association

throughout both studies and ranged from 5 to 8 until month 78. No significant hazard reduction for time to CV-related events was observed in patients with baseline NYHA class III (Fig. 3c).

Time to CV-Related Mortality

The cumulative incidence of CV-related mortality in the overall cohort at month 24 was 20% and 29% with tafamidis 80 mg(/tafamidis 80 mg) and placebo(/tafamidis 80 mg) arms, respectively, increasing to 39% and 47% at month 90 (Table 2, Fig. 2c, d). Hazard reduction with tafamidis 80 mg(/tafamidis 80 mg) compared with placebo/tafamidis 80 mg was 38% at month 24 (HR 0.618 [95% CI 0.401–0.954]; $p=0.0299$) and remained relatively stable at 39–41% until the end of ATTR-ACT and the LTE (Fig. 4a; Table 2). NNT remained relatively stable throughout both studies ranging from 10 to 14.

Cumulative incidence in patients with baseline NYHA class I/II was 12% and 21% at month 24 in the tafamidis 80 mg(/tafamidis 80 mg) and placebo(/tafamidis 80 mg) arms, respectively, and increased to 30% and 41% at month 90 (Fig. 4b; Table 3). A significant hazard reduction for tafamidis 80 mg/(tafamidis 80 mg) of 50% was observed at month 30 (HR 0.501 [95% CI 0.278–0.903]; $p=0.0216$), decreasing to 43% at month 90 (HR 0.568 [95% CI 0.366–0.882]; $p=0.0118$). NNT ranged from 7 to 11 throughout both studies. In patients with baseline NYHA class III, no significant hazard reduction for time to CV-related mortality was observed (Fig. 4c).

DISCUSSION

With a follow-up of up to 90 months, this current post hoc analysis represents the longest study of the effect of TTR inhibition currently available on CV-related events in patients with ATTR-CM. During ATTR-ACT, the risk of combined CV-related events (CV-related mortality and CV hospitalizations) was significantly lower for patients receiving tafamidis 80 mg versus placebo in the overall patient population and in patients with low disease burden (NYHA class I/II) from month 24 onwards. This effect continued throughout the LTE after patients who received placebo during ATTR-ACT were switched to tafamidis 80 mg, highlighting the positive impact of early treatment initiation. A similar benefit was seen for CV-related mortality alone. Incidence of CV-related events, including CV-related mortality, was generally higher in patients with higher disease burden (NYHA class III). The lack of observable treatment benefit in these patients is consistent with the survival bias previously observed in ATTR-ACT [12, 13].

Starting at month 9, the cumulative incidence of CV-related events (including CV-related mortality and recurrent CV hospitalizations) was consistently lower in patients in the overall patient population treated with tafamidis 80 mg(/tafamidis 80 mg) compared with placebo(/tafamidis 80 mg). A significant hazard reduction for CV-related events and CV-related mortality, respectively, was observed from month 24 (29% [$p=0.0310$] and 38% [$p=0.0299$]) up until month 90 (37% [$p=0.0002$] and 39% [$p=0.0029$]). Similar results were observed in patients with lower disease burden at baseline. These findings are in line with and expand on previous results from ATTR-ACT [2, 8] and the LTE [9, 10], and demonstrate that long-term treatment with tafamidis is effective in reducing CV-related events, including recurrent CV hospitalizations and CV-related mortality. Reducing recurrent hospitalizations and the associated reduction in burden for patients and caregivers is an important goal of treatment.

In comparison with other types of heart failure, patients with ATTR-CM experience higher rates of all-cause hospitalizations versus patients with other types of heart failure (3.3 vs 2.5 during the first year following diagnosis) as well as longer hospitalization duration (mean number of days of 21.7 vs 15.2 during the same time

period) as shown in a European study [4]. An analysis of the South Korean National Health Interview Survey database showed a 3.8-fold increase in hospital admissions, and a 5.1-fold increase in length of stay was observed following a diagnosis with ATTR-CM ($p<0.001$) [5]. Results from another study from the US National Inpatient Sample showed patients admitted to hospital with cardiac amyloidosis were more likely to die during their inpatient stay (7.4% compared with propensity-matched patients without a diagnosis of cardiac amyloidosis [$p<0.001$]) [6].

In ATTR-ACT, treatment with tafamidis reduced the annual rates of CV-related hospitalizations ($p<0.001$) and mean length of stay per CV-related hospitalization event (8.6 vs 9.6 days) versus placebo [16]. As a result, tafamidis prevented 2.6 CV-related hospitalization days per patient per year. Hospitalizations due to worsening heart failure have been associated with a significantly increased risk of mortality in patients with ATTR-CM ($p<0.001$) [3]. An increase in heart failure-related hospitalizations has been recommended as a measure of disease progression in ATTR-CM: ≥1 hospitalization event within a 6-month period was recommended in 2021 [17] and has recently been updated to ≥1 hospitalization event within a 12-month period [7].

Key strengths include the length of the follow-up, the adjudication of CV-related events during ATTR-ACT, and prespecified definition of CV-related events in the LTE. Analyses were based on the number of patients enrolled from the start of ATTR-ACT and a robust LWYY model assuming dependence in CV-related events was used. Limitations of this analysis include its post hoc nature and the small sample size, particularly toward the end of the LTE.

CONCLUSION

This analysis of the ATTR-ACT study found treatment with tafamidis significantly reduced the risk of CV-related events, including recurrent CV-related hospitalizations and CV-related mortality, as early as month 24. This benefit continued in the LTE for up to 90 months in patients who received tafamidis throughout both studies compared with those who switched from placebo to tafamidis after 30 months, underlining the importance of early treatment.

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Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information. Please direct any further enquiries to the corresponding author.

Declarations

Conflict of Interest. Thibaud Damy reports speaking fees, research grants, or consulting fees from Pfizer, Bridgebio, Ionis Pharmaceuticals, AKCEA, AstraZeneca, NovoNordisk, Alnylam Pharmaceuticals, and Alexion. Ronald Witteles served as a paid adviser to Alexion, Alnylam,

AstraZeneca, Bridge Bio, Intellia, Medison, Novo Nordisk, and Pfizer. Francesco Cappelli has acted as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, Bayer, AstraZeneca, BridgeBio (formerly Eidos Therapeutics), Novo Nordisk, and Pfizer. Ronnie Wang is an employee of and owns stock/options in Pfizer. Martha Grogan reports research funding from Alnylam, Eidos, Pfizer, Novo Nordisk, and Janssen; license/patent pending from Anumana (algorithm to detect cardiac amyloidosis using AI ECG); Advisory Boards for Janssen, Novo Nordisk, Alnylam, BridgeBio, and AstraZeneca.

Ethical Approval. These studies were approved by the independent review board or ethics committee at each participating center and was conducted in accordance with the concepts laid out in the Declaration of Helsinki of 1964, its later amendments, and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

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