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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Early Access to Tafamidis for Patients With Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND Tafamidis is a standard of care treatment for patients with transthyretin amyloid cardiomyopathy (ATTR-CM). While evidence was being assessed by regulatory authorities, a new, independent, and inclusive cohort of the phase 3 long-term extension study offered early access to tafamidis.

OBJECTIVES The purpose of this study was to present safety, mortality, and hospitalization findings for patients who received early access tafamidis.

METHODS Patients with ATTR-CM and who had not taken part in the phase 3 study were able to receive tafamidis free acid 61 mg (the dose later approved) for up to 60 months or until commercial availability in their region. Enrollment criteria were minimal.

RESULTS Among the 1,476 patients initiating tafamidis in the study between 2018 and 2023, mean (SD) age at enrollment was 76.5 (7.8) years, 88.8% were male, 85.6% had wild-type ATTR-CM, and 52.9% had NYHA functional class II symptoms (I: 14.9%, III: 30.8%, IV: 1.3%). Median exposure and follow-up were 12 (range: 0-55) and 19 (95% CI: 18.4-20.7) months, respectively. Overall, 7.6% of patients reported treatment-related adverse events, with 0.6% considered serious and 0.6% leading to study discontinuation. No new safety signals were identified. In Kaplan-Meier analyses, all-cause and cardiovascular (CV)-related mortality occurred in 23.4% and 13.8% of patients over the study period. Furthermore, 43.3% and 26.5% of patients had all-cause and CV-related hospitalizations. The total annual CV-related hospitalization rate was 0.26.

CONCLUSIONS In an inclusive patient cohort receiving early access to tafamidis, safety findings were consistent with those reported from other trials and real-world studies. (Long-term Safety of Tafamidis in Subjects With Transthyretin Cardiomyopathy; NCT02791230) (JACC Adv. 2025;4:102122) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv-CM = variant transthyretin amyloid cardiomyopathy

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy

CV = cardiovascular

KCCQ-CS = Kansas City Cardiomyopathy Questionnaire Clinical Summary

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary

LTE = long-term extension

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and often fatal condition caused by deposition of transthyretin (TTR) amyloid in the myocardial extracellular matrix.[1] This leads to restrictive cardiomyopathy, conduction disorders, arrhythmias, and heart failure.[1] The formation of TTR amyloid can occur spontaneously (usually associated with aging) or can be caused by inherited *TTR* gene variants with substitutions that promote amyloidogenesis.[1]

Tafamidis is a TTR stabilizer that inhibits the formation of TTR amyloid and is an approved treatment for patients with ATTR-CM in several countries worldwide.[2,3] Regulatory approvals of tafamidis have been largely based on findings from the international, phase 3, ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; NCT01994899), which was completed in 2018.[4] In ATTR-ACT, tafamidis-treated patients with ATTR-CM had a 30% lower risk of all-cause mortality over 30 months and a 32% lower annual risk of cardiovascular (CV)-related hospitalization compared with placebo-exposed patients.[4] On completion of ATTR-ACT, patients could join an open-label, long-term extension (LTE) study to receive tafamidis for up to 60 months or until available commercially in their region (NCT02791230).[5] Interim findings from the LTE study after a median of ~58 months of treatment showed a 41% lower risk of mortality in patients who had taken tafamidis in both ATTR-ACT and the LTE study compared with those who received placebo in ATTR-ACT and tafamidis in the LTE study.[6]

Following a protocol amendment in 2018, a new cohort was added to the LTE study to allow early access to tafamidis for patients who had not taken part in ATTR-ACT. The enrollment criteria were minimal, allowing an inclusive cohort of patients with all severities of ATTR-CM to enroll. The primary aim of the cohort was to assess the safety of the approved tafamidis dose in an inclusive population with ATTR-CM. This manuscript summarizes outcomes from this independent cohort, including the incidence of adverse events, mortality, and hospitalization during treatment. Exploratory analyses looked at mortality and hospitalization in subgroups of patients by baseline NYHA subgroups (I/II vs III/IV) and by *TTR* genotype.

METHODS

STUDY. This study was an independent arm of the international, multicenter, open-label, LTE study of tafamidis treatment in patients with ATTR-CM, formed following a protocol amendment in 2018 (NCT02791230).[5,6] Patients could receive early access to the approved dose of tafamidis treatment for up to 60 months, until it became commercially available by prescription in their region or the study was terminated by the sponsor. Baseline refers to screening assessments carried out in the 30 days prior to tafamidis initiation in the study. Treatment was initiated on day 0, after which patients were invited to clinic visits every 6 months, with additional telephone contact at months 3, 9, 15, 21, 27, 33, 39, 45, 51, and 57. Patients were followed for 28 days after their last dose of tafamidis.

PATIENTS. Inclusion and exclusion criteria were minimal to allow an unrestricted population of patients with ATTR-CM to receive early access to tafamidis treatment. Full inclusion and exclusion criteria are provided in Supplemental Table 1. The study was inclusive of patients with all NYHA functional classifications. Patients must have been aged ≥18 years (or the country-specific age of consent if >18 years) with a documented diagnosis of ATTR-CM (no specific testing regimens were required). Patients must have had *TTR* genotyping and appropriate laboratory testing to rule out light chain amyloidosis. Assessments were completed at screening for those without prior documentation. Female patients with childbearing potential could enroll if using appropriate contraception and not pregnant or breastfeeding. Patients with a history of liver or heart transplantation, an implanted mechanical left ventricular assist device, heart failure not predominantly due to ATTR-CM, urinary retention requiring self-catheterization, who required treatment with calcium-channel blockers, had used a TTR stabilizer (other than tafamidis), diflunisal, tauroursodeoxycholate, doxycycline, digitalis, patisiran, calcium-channel blockers or other investigational drugs in the last 30 days, or inotersen in the last 6 months were not permitted to enroll. As tafamidis was not approved for the treatment of patients with ATTR-CM in any region at the start of the study, most of these criteria were implemented as safety precautions.

All patients received once-daily, open-label tafamidis free acid 61 mg, or tafamidis meglumine 80 mg where 61 mg was unavailable. These bioequivalent formulations have since been approved in many countries for the treatment of patients with ATTR-CM.[2,3] Dose reduction to tafamidis meglumine 20 mg was permitted to address tolerability. Aside from prohibited medications (per exclusion criteria), standard of care therapies could continue alongside study treatment.

ETHICS AND CONSENT. The 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 and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

OUTCOMES. The primary objective of the study was to descriptively evaluate the safety of tafamidis treatment in an inclusive early access cohort. Primary outcomes were incidence of adverse events, and all-cause mortality, among all patients who received treatment. Other outcomes included the incidence of CV-related mortality, all-cause hospitalizations, and CV-related hospitalizations.

In exploratory analyses, the incidences of all-cause mortality, CV-related mortality, all-cause hospitalizations, and CV-related hospitalizations were evaluated by the patient's NYHA class (I/II vs III/IV) at baseline and by the patient's *TTR* genotype (wild-type or variant).

ANALYSES. As all patients received the same treatment, descriptive analyses were planned.

Dosing compliance was calculated per patient as n days dosed/n days in the study.

Data were summarized for adverse events reported by the investigator at any time during the treatment period and in the 28 days after final dosing. Relatedness to treatment was as reported by the investigator.

For statistical purposes, mortality assessments included heart transplantation and implantation of a left ventricular assist device as death. This reflects handling of these outcomes in the tafamidis clinical development program and that patients in receipt of a transplant or assist device required these interventions to avoid death. Causality of deaths was algorithmically assessed using study data reported by the investigator. Deaths recorded as being related to ATTR-CM were considered CV-related. For all other deaths, CV-relatedness was determined by association with a predefined list of preferred terms (Supplemental Table 2). Deaths associated with these terms were considered CV-related. Time to mortality was visualized using Kapan-Meier curves.

Hospitalization was defined as a nonelective admission and ≥24 hours stay in an acute care setting. CV causality was defined by the nature of the discharge diagnosis and relatedness of the hospitalization to the predefined preferred terms discussed above (Supplemental Table 2). Hospitalizations with a CV-related cause and associated with a serious adverse event were considered CV-related. The total rate of CV-related hospitalizations per year was calculated among all patients in the study as the total number of hospitalizations/total follow-up duration.

In exploratory analyses comparing baseline NYHA functional class subgroups (I/II vs III/IV), time to mortality was visualized using Kaplan-Meier curves, and HRs for all-cause and CV-related mortality were calculated using Cox Proportional Hazards models with NYHA class and *TTR* genotype in the model. Risk ratios for all-cause and CV-related hospitalizations were also calculated for patients who were NYHA functional class I/II vs III/IV at baseline. Findings for patients with wild-type and variant ATTR-CM (ATTRwt-CM and ATTRv-CM) were visualized but found not to be substantially different and did not warrant exploratory statistical testing.

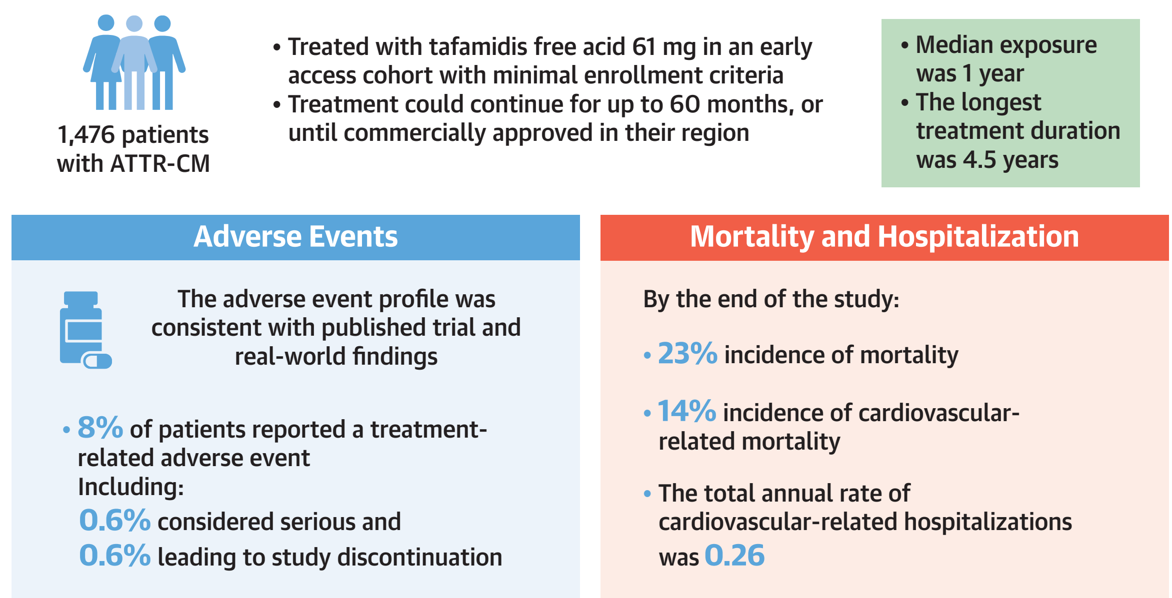
RESULTS

A plain language summary of the main findings is included in the Supplemental Material. A summary of the findings is also shown in the **Central Illustration**.

PATIENTS. Of 1,507 patients screened for the early access cohort, 1,476 received tafamidis between 2018 and 2023 and were included in the analysis (**Figure 1**). The most common reasons screened patients did not receive treatment were not meeting the entrance criteria ($n = 13$) and patient withdrawal or death ($n = 9$). Untreated patients were not included in the analysis as they could not contribute to safety assessments.

Treated patients were from 47 centers in 12 countries, across 5 continents: Argentina, Australia, Belgium, Canada, China (Hong Kong), Czechia, France, Japan, the Netherlands, Spain, Taiwan, and the United States. Mean (SD) patient age was 76.5 (7.8) years, and 37.5% (553/1,476) were ≥80 years of age (**Table 1**). Most patients were White (84.8%; 1,252/1,476), male (88.8%; 1,311/1,476), and had ATTRwt-CM (85.6%; 1,264/1,476). Of the 1,475 patients with NYHA classifications at baseline, 14.9% (220/1,475) were class I, 52.9% (781/1,475) class II, 30.8% (455/1,475) class III, and 1.3% (19/1,475) class IV (**Table 2**). Medical history conditions in >20% of patients were hypertension (in 61.4% of patients; 907/1,476), atrial fibrillation (57.9%; 854/1,476), carpal tunnel

CENTRAL ILLUSTRATION **Early Access to Tafamidis for Patients With Transthyretin Amyloid Cardiomyopathy**



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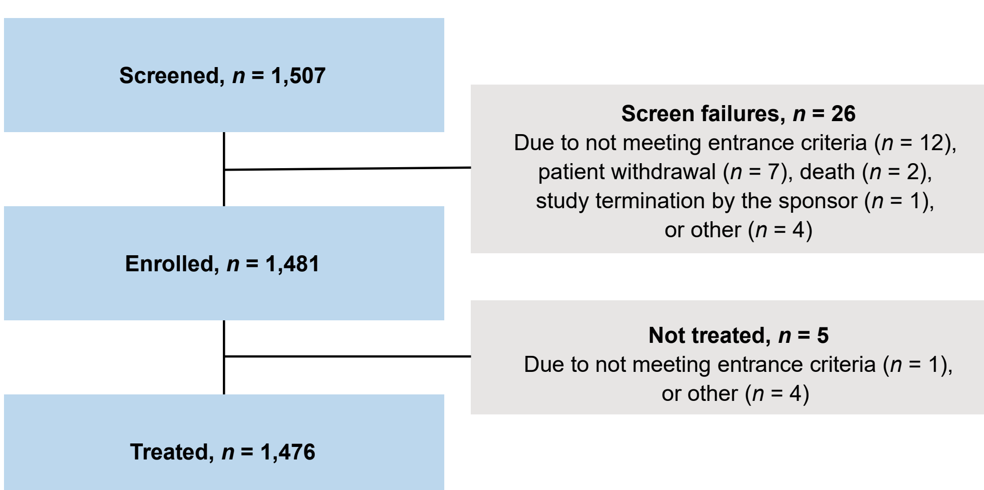
ATTR-CM = transthyretin amyloid cardiomyopathy.

syndrome (47.1%; 695/1,476), osteoarthritis (26.0%; 384/1,476), benign prostatic hyperplasia (25.2%; 372/1,476 [28.4% of males; 372/1,311]), hyperlipidemia (24.8%; 366/1,476), coronary artery disease (23.0%; 339/1,476), and dyslipidemia (22.0%; 324/1,476). Among all patients, medications of relevance taken during the study and coded using the World Health Organization Drug Dictionary included diuretics

FIGURE 1 **Patient Disposition**



Shows numbers of patients screened, enrolled, and treated as part of the early access study

(89.8%; 1,326/1,476), antithrombotic agents (87.9%; 1,297/1,476), cardiac therapy (62.0%; 915/1,476), beta-blocking agents (43.6%; 643/1,476), agents acting on the renin-angiotensin system (39.5%; 583/1,476), and antihypertensives (13.2%; 195/1,476). The median (range) N-terminal pro-B-type natriuretic peptide concentration among patients with data was 1,669 ng/L (51, 28,061), and modified body mass index was 1,097 g/dL × kg/m^2 (468.8, 2,147.6). Median (range) Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) and KCCQ-Clinical Summary (CS) scores among those with data were 71 (0.8, 100.0) and 75 (1.6, 100.0), respectively. The median (range) time since first diagnosis of ATTR-CM based on genotype testing was 0.7 (−0.4, 9.9) years.

ADVERSE EVENTS. Median (range) exposure to treatment was 379 days (1-1,659 days [0-4.5 years]); 95.5% (1,410/1,476) of all patients had ≥80% dosing compliance. Few patients (0.5%; 8/1,476) had a dosing reduction during the study. Of the 1,476 patients treated with tafamidis, 33.1% (488) discontinued the study. The most common reasons were death (12.5%; 184/1,476), withdrawal by the patient (11.7%; 172/1,476), and adverse event (4.5%; 66/1,476).

Overall, 87.7% (1,294/1,476) of all patients had ≥1 adverse event, 49.9% (736/1,476) had a serious adverse event, 37.7% (556/1,476) a severe adverse event, and 6.6% (97/1,476) an adverse event that led to study discontinuation. Adverse events in ≥10% of patients were cardiac failure (19.8%; 292/1,476), atrial fibrillation (12.7%; 187/1,476), and fall (10.9%; 161/1,476) (Table 3). The nature of reported events were similar to those in ATTR-ACT and interim analyses from the LTE study.[4,6] No new safety signals were identified.

A total of 112 patients reported adverse events considered by the investigator to be potentially treatment-related (Table 4). This represented 7.6% (112/1,476) of all treated patients. The most frequently reported treatment-related adverse events were diarrhea (1.8% of all treated patients; 26/1,476) and fatigue (0.7%; 10/1,476). Nine patients (0.6%) had serious treatment-related adverse events, and 9 patients (0.6%) had treatment-related adverse events leading to discontinuation from the study. Four patients (0.3%) reported treatment-related adverse events considered by the investigator to be severe in intensity.

ALL-CAUSE AND CV-RELATED MORTALITY. Median (95% CI) follow-up calculated by Kaplan-Meier methods was 19 months (18.4, 20.7). At study months 12, 24, and 30, the incidences of all-cause mortality were 10.4% (154/1,476), 18.2% (269/1,476), and 20.4% (301/1,476), respectively, and at the end of the study was 23.4% (345/1,476). At study months 12, 24, and 30, the incidences of CV-related mortality were 7.7% (114/1,476), 11.2% (166/1,476), and 12.1% (179/1,476), respectively, and at the end of the study was 13.8% (204/1,476) (Table 5, Figure 2). Seven patients had heart transplants and 2 had implantation of a left ventricular assist device, all of which were counted as CV-related deaths.

HOSPITALIZATIONS. Overall, 43.3% (639/1,476) of all patients had ≥1 all-cause hospitalizations during the study. The total annual rate among all patients was 0.52 (Table 5). Furthermore, 26.5% (391/1,476) of all patients had ≥1 CV-related hospitalization. The total annual rate of CV-related hospitalizations among all patients was 0.26.

EXPLORATORY ANALYSES BY BASELINE NYHA CLASSIFICATION. Patients (N = 1,001) with NYHA I/II classifications at baseline appeared to be younger, and less likely to be female and Black, than patients (n = 474) with NYHA III/IV classifications (Table 1). Aside from carpal tunnel syndrome and dyslipidemia, all the most common medical history conditions were less prevalent in patients who had an NYHA class of I/II vs III/IV (Table 2). The proportion of patients with ATTRv-CM was broadly similar among NYHA subgroups (13.9% [139/1,001] class I/II vs 15.4% [73/474] III/IV). Median N-terminal pro-B-type natriuretic peptide concentration was around half in patients with NYHA classifications of I/II vs III/IV (1,436 vs 2,816 ng/L). Among patients with data, median KCCQ-OS and KCCQ-CS scores were

TABLE 1 Patient Demographics

	Treated Patients (N = 1,476)	NYHA Classification at Baseline[a] I/II (n = 1,001)	NYHA Classification at Baseline[a] III/IV (n = 474)	*TTR* Genotype Wild-Type (n = 1,264)	*TTR* Genotype Variant (n = 212)
Age, y					
Mean (SD)	76.5 (7.8)	75.6 (7.9)	78.4 (7.0)	77.6 (7.0)	70.2 (9.0)
Median (range)	77 (32-96)	76 (32-95)	79 (41-96)	78 (41-96)	71 (32-90)
Sex, n (%)					
Male	1,311 (88.8)	903 (90.2)	407 (85.9)	1,164 (92.1)	147 (69.3)
Female	165 (11.2)	98 (9.8)	67 (14.1)	100 (7.9)	65 (30.7)
Race, n (%)					
White	1,252 (84.8)	865 (86.4)	386 (81.4)	1,189 (94.1)	63 (29.7)
Black	139 (9.4)	75 (7.5)	64 (13.5)	27 (2.1)	112 (52.8)
Asian	66 (4.5)	48 (4.8)	18 (3.8)	36 (2.8)	30 (14.2)
Other	19 (1.3)	13 (1.3)	6 (1.3)	12 (0.9)	7 (3.3)

Characterizes the patient population at enrollment in the early access study. The table further describes the demographic characteristics of subpopulations by baseline NYHA class and *TTR* genotype. [a]NYHA class was not fully documented in 1 patient.
TTR = transthyretin.

TABLE 2 Patient Clinical Characteristics

	Treated Patients (N = 1,476)	NYHA Classification at Baseline[a] I/II (n = 1,001)	NYHA Classification at Baseline[a] III/IV (n = 474)	*TTR* Genotype Wild-Type (n = 1,264)	*TTR* Genotype Variant (n = 212)
NYHA classification, n (%)					
I	220 (14.9)	220 (22.0)	0 (0.0)	186 (14.7)	34 (16.0)
II	781 (52.9)	781 (78.0)	0 (0.0)	676 (53.5)	105 (49.5)
III	455 (30.8)	0 (0.0)	455 (96.0)	387 (30.6)	68 (32.1)
IV	19 (1.3)	0 (0.0)	19 (4.0)	14 (1.1)	5 (2.4)
Missing	1 (<0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
TTR genotype, n (%)					
Wild-type	1,264 (85.6)	862 (86.1)	401 (84.6)	1,264 (100)	0 (0.0)
Variant	212 (14.4)	139 (13.9)	73 (15.4)	0 (0.0)	212 (100)
V122I (p. V142I)	132 (8.9)	75 (7.5)	57 (12.0)	0 (0.0)	132 (62.3)
A97S (p. A117S)	25 (1.7)	21 (2.1)	4 (0.8)	0 (0.0)	25 (11.8)
V30M (p. V50M)	13 (0.9)	10 (1.0)	3 (0.6)	0 (0.0)	13 (6.1)
T60A (p. T80A)	11 (0.7)	8 (0.8)	3 (0.6)	0 (0.0)	11 (5.2)
Others[b]	31 (2.1)	25 (2.5)	6 (1.3)	0 (0.0)	31 (14.6)
Most common medical history,[c] n (%)					
Hypertension	907 (61.4)	609 (60.8)	298 (62.9)	777 (61.5)	130 (61.3)
Atrial fibrillation	854 (57.9)	544 (54.3)	310 (65.4)	785 (62.1)	69 (32.5)
Carpal tunnel syndrome	695 (47.1)	488 (48.8)	206 (43.5)	598 (47.3)	97 (45.8)
Osteoarthritis	384 (26.0)	257 (25.7)	127 (26.8)	351 (27.8)	33 (15.6)
Benign prostatic hyperplasia	372 (25.2)	229 (22.9)	143 (30.2)	331 (26.2)	41 (19.3)
Hyperlipidemia	366 (24.8)	230 (23.0)	136 (28.7)	314 (24.8)	52 (24.5)
Coronary artery disease	339 (23.0)	220 (22.0)	119 (25.1)	305 (24.1)	34 (16.0)
Dyslipidemia	324 (22.0)	234 (23.4)	89 (18.8)	293 (23.2)	31 (14.6)
NT-proBNP, ng/L	n = 124	n = 103	n = 21	n = 106	n = 18
Mean (SD)	2,832 (4,036)	2,439 (3,587)	4,762 (5,466)	2,832 (3,977)	2,833 (4,495)
Median (range)	1,669 (51, 28,061)	1,436 (51, 28,061)	2,816 (534, 24,900)	1,785 (51, 28,061)	1,334 (51, 18,433)
mBMI, g/dL × kg/m^2	n = 1,263	n = 858	n = 405	n = 1,077	n = 186
Mean (SD)	1,108 (198.6)	1,114 (180.4)	1,094 (232.3)	1,120 (193.5)	1,037 (213.5)
Median (range)	1,097 (468.8, 2,147.6)	1,110 (468.8, 1,857.6)	1,064 (579.0, 2,147.6)	1,109 (579.0, 1,973.3)	1,032 (468.8, 2,147.6)
KCCQ-OS score	n = 1,468	n = 999	n = 468	n = 1,256	n = 212
Mean (SD)	68 (23.4)	76 (19.5)	50 (20.9)	68 (22.8)	64 (26.3)
Median (range)	71 (0.8, 100.0)	81 (6.0, 100.0)	48 (0.8, 100.0)	72 (2.9, 100.0)	69 (0.8, 100.0)
KCCQ-CS score	n = 1,468	n = 999	n = 468	n = 1,256	n = 212
Mean (SD)	71 (22.7)	79 (18.3)	53 (20.6)	71 (22.2)	68 (25.6)
Median (range)	75 (1.6, 100.0)	83 (12.0, 100.0)	53 (1.6, 100.0)	75 (5.7, 100.0)	74 (1.6, 100.0)

Characterizes the patient population at enrollment in the early access study. The table further describes the clinical characteristics of subpopulations by baseline NYHA class and *TTR* genotype. [a]NYHA class was not fully documented in one patient. [b]24 other variants were each identified in ≤4 patients. [c]In >20% of all treated patients and coded per MedDRA v26.1.

KCCQ-CS = Kansas City Cardiomyopathy Questionnaire Clinical Summary; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary; mBMI = modified body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviation as in Table 1.

numerically higher in patients with NYHA I/II vs III/IV classifications (81 vs 48 and 83 vs 53, respectively). Only 19 patients had an NYHA classification of IV at baseline. These patients had a median (range) age of 81 (41, 95) years, 73.7% were male (14/19), 78.9% (15/19) White, and 73.7% (14/19) had ATTRwt-CM.

Median (95% CI) follow-up calculated by Kaplan-Meier methods was 19 (18.2-20.7) months in patients who had an NYHA classification of I/II at baseline and 20 (18.2-21.5) months in those who had a classification of III/IV. Incidences of all-cause mortality at months 12, 24, 30, and at the end of study were 4.5% (45/1,001), 10.1% (101/1,001), 11.9% (119/1,001), and 15.0% (150/1,001), respectively, in patients who had an NYHA classification of I/II at baseline. Respective incidences in patients who had a classification of III/IV were 23.0% (109/474), 35.4% (168/474), 38.4% (182/474), and 41.1% (195/474) (Table 5, Figure 3). Incidences of CV-related mortality at months 12, 24, 30, and at the end of study were 2.7% (27/1,001), 4.5% (45/1,001), 5.0% (50/1,001), and 6.9% (69/1,001) in those with class I/II symptoms at

TABLE 3 Adverse Events in ≥5% of Patients (N = 1,476)

Cardiac failure	292 (19.8)
Atrial fibrillation	187 (12.7)
Fall	161 (10.9)
Dyspnea	120 (8.1)
Constipation	119 (8.1)
Gout	118 (8.0)
Peripheral edema	104 (7.0)
Dizziness	102 (6.9)
Diarrhea	99 (6.7)
Anemia	90 (6.1)
Urinary tract infection	89 (6.0)
Arthralgia	86 (5.8)
Cough	83 (5.6)
Hypotension	82 (5.6)
Hypovolemia	81 (5.5)
Fatigue	80 (5.4)
Acute kidney injury	78 (5.3)
COVID-19	75 (5.1)

Values are n (%). Describes the most reported adverse events in the early access study from the start of treatment until 28 days after the patient's last dose of tafamidis. Events coded per MedDRA v26.1.

TABLE 4 Incidence of Treatment-Related Adverse Events (N = 1,476)

Any treatment-related adverse event	112 (7.6)
Serious	9 (0.6)
Severe	4 (0.3)
Caused study discontinuation	9 (0.6)
Caused treatment discontinuation (patient remained in the study)	0 (0.0)
Caused a dose reduction	5 (0.3)

Values are n (%). Describes the incidence and nature of adverse events that were determined by the investigator to be related (or potentially related) to study treatment. Includes adverse events reported from the start of treatment until 28 days after the patient's last dose of tafamidis.

baseline, and 18.4% (87/474), 25.5% (121/474), 27.2% (129/474), and 28.5% (135/474) in those with class III/IV, respectively. Exploratory analyses confirmed a significantly lower ($P < 0.0001$) risk of all-cause (HR: 0.268; 95% CI: 0.216-0.332) and CV-related mortality (HR: 0.184; 95% CI: 0.138-0.246) over the study period in patients who had an NYHA classification of I/II vs III/IV at baseline.

Of the 19 patients who had an NYHA class of IV at baseline, 14 (73.7%) reached the all-cause mortality endpoint during the study. Twelve of these deaths were considered CV-related.

Among patients who had an NYHA classification of I/II at baseline, 38.6% (386/1,001) had ≥1 all-cause hospitalizations during the study and 22.0% (220/1,001) had ≥1 CV-related hospitalizations (Table 5). The total annual rate of all-cause and CV-related hospitalizations among all patients who had a classification of I/II at baseline were 0.40 and 0.19, respectively. Among patients who had an NYHA classification of III/IV at baseline, 53.4% (253/474) had ≥1 all-cause hospitalizations during the study and 36.1% (171/474) had ≥1 CV-related hospitalizations. The total annual rates among all patients who had a classification of III/IV at baseline were 0.86. and 0.47, respectively. The risk ratios (95% CI) for all-cause hospitalization and CV-hospitalization in patients who had an NYHA classification of I/II vs III/IV were 0.632 (0.581-0.687; $P < 0.0001$) and 0.640 (0.569-0.720; $P < 0.0001$), respectively.

DESCRIPTIVE SUMMARIES BY TTR GENOTYPE. Among the 1,476 treated patients, 1,264 (85.6%) had wild-type *TTR* and 212 (14.4%) had a *TTR* variant. The most common *TTR* variants were V122I (p. V142I; 8.9% [132/1,476]), A97S (p. A117S; 1.7% [25/1,476]), V30M (p. V50M; 0.9% [13/1,476]), and T60A (p. T80A; 0.7% [11/1,476]) (Tables 1 and 2). Twenty-four other variants were each present in ≤4 patients. Patients with ATTRv-CM were younger, and more likely to be female and Black or Asian, than those with ATTRwt-CM (Table 1). All the most common medical history conditions were less prevalent in patients with ATTRv-CM vs ATTRwt-CM, with the largest differences in the proportions with atrial fibrillation (32.5% [69/212] vs 62.1% [785/1,264]) and osteoarthritis (15.6% [33/212] vs 27.8% [351/1,264]) (Table 2). Though data were not available for all patients, median N-terminal pro-B-type natriuretic peptide concentrations were slightly lower among those with ATTRv-CM vs ATTRwt-CM, but NYHA classification profiles were similar. Median baseline KCCQ-OS and KCCQ-CS scores among those with data appeared slightly lower in patients with ATTRv-CM vs ATTRwt-CM (69 vs 72 and 74 vs 75, respectively).

Median (95% CI) follow-up calculated by Kaplan-Meier methods among patients with ATTRv-CM was 18 (15.9-21.4) and among patients with ATTRwt-CM was 20 (18.4-20.8) months. Incidences of all-cause mortality at months 12, 24, 30, and at the end of study were 8.0% (17/212), 16.0% (34/212), 17.9% (38/212), and 19.3% (41/212) in patients with ATTRv-CM. Respective incidences in patients with ATTRwt-CM were 10.8% (137/1,264), 18.6% (235/1,264), 20.8% (263/1,264), and 24.1% (304/1,264) (Table 5, Figure 4). Incidences of CV-related mortality at months 12, 24, 30, and at the end of study were 5.7% (12/212), 9.4% (20/212), 9.9% (21/212), and 10.4% (22/212) in patients with ATTRv-CM. Respective incidences in patients

TABLE 5 Mortality and Hospitalizations

		NYHA Classification at Baseline[a]		*TTR* Genotype	
	Treated Patients (N = 1,476)	I/II (n = 1,001)	III/IV (n = 474)	Wild-Type (n = 1,264)	Variant (n = 212)
All-cause mortality	345 (23.4)	150 (15.0)	195 (41.1)	304 (24.1)	41 (19.3)
Death as first event	336 (22.8)	148 (14.8)	188 (39.7)	296 (23.4)	40 (18.9)
Heart transplant as first event	7 (0.5)	1 (0.1)	6 (1.3)	6 (0.5)	1 (0.5)
LVAD implantation as first event	2 (0.1)	1 (0.1)	1 (0.2)	2 (0.2)	0 (0)
Censored	1,131 (76.6)[b]	851 (85.0)	279 (58.9)	960 (75.9)	171 (80.7)
CV-related mortality	204 (13.8)	69 (6.9)	135 (28.5)	182 (14.4)	22 (10.4)
Death as first event	195 (13.2)	67 (6.7)	128 (27.0)	174 (13.8)	21 (9.9)
Heart transplant as first event	7 (0.5)	1 (0.1)	6 (1.3)	6 (0.5)	1 (0.5)
LVAD implantation as first event	2 (0.1)	1 (0.1)	1 (0.2)	2 (0.2)	0 (0)
Censored	1,272 (86.2)[c]	932 (93.1)	339 (71.5)	1,082 (85.6)	190 (89.6)
≥1 all-cause hospitalization	639 (43.3)	386 (38.6)	253 (53.4)	549 (43.4)	90 (42.5)
Total annual rate among all patients[d]	0.52	0.40	0.86	0.52	0.50
≥1 CV-related hospitalization	391 (26.5)	220 (22.0)	171 (36.1)	324 (25.6)	67 (31.6)
Total annual rate among all patients[d]	0.26	0.19	0.47	0.25	0.31

Values are n (%). Describes the incidence of all-cause and CV-related mortality events, and all-cause and CV-related hospitalization events through the end of the early access study. The table further describes these outcomes in subpopulations by baseline NYHA class and *TTR* genotype. Data are n (%) unless otherwise stated. [a]NYHA class was not fully documented in 1 patient. [b]Reasons for censoring in ≥1 patient overall included study completion, withdrawal by patient, adverse event leading to discontinuation, failure to meet randomization criteria, lost to follow-up, study termination by sponsor, protocol violation, medication error without adverse event, insufficient clinical response, and other. [c]As for all-cause mortality, but additionally includes death for other reason. [d]Total hospitalization across all patients divided by total years of study participation.

CV = cardiovascular; LVAD = left ventricular assist device; other abbreviation as in Table 1.

with ATTRwt-CM were 8.1% (102/1,264), 11.6% (146/1,264), 12.5% (158/1,264), and 14.4% (182/1,264).

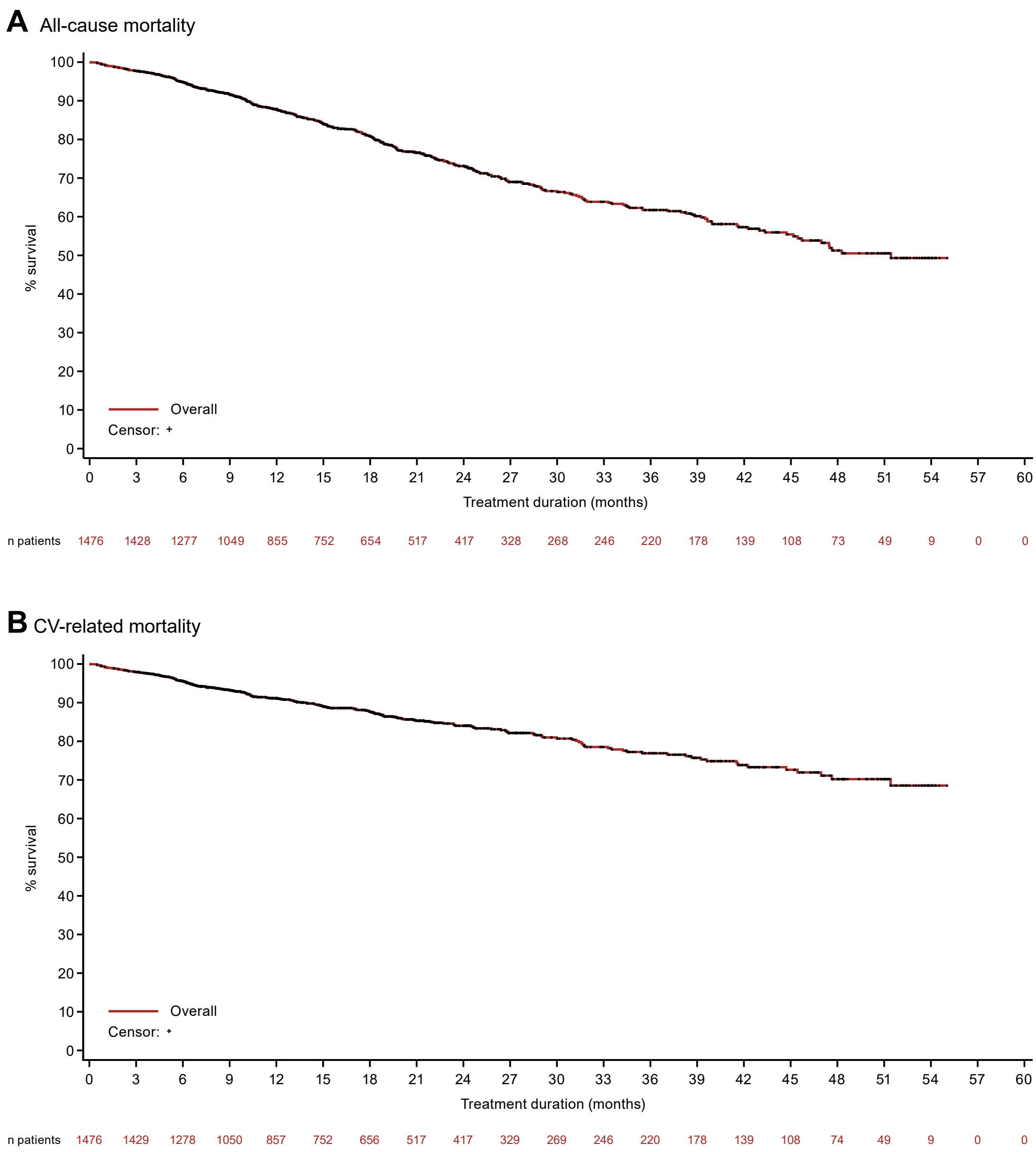
During the study, 42.5% (90/212) of patients with ATTRv-CM had ≥1 all-cause hospitalization during the study and 31.6% (67/212) had ≥1 CV-related hospitalization (Table 5). The total annual rates among all patients were 0.50 and 0.31, respectively. Overall, 43.4% (549/1,264) of patients with ATTRwt-CM had ≥1 all-cause hospitalization during the study and 25.6% (324/1,264) had ≥1 CV-related hospitalization. The total annual rates among all patients were 0.52 and 0.25, respectively.

DISCUSSION

In this international and inclusive population of patients with ATTR-CM receiving early access treatment, the safety profile of the approved tafamidis dose was similar to that reported in other trials and real-world studies.[4-10] After a maximum of 4.5 years treatment, all-cause mortality was observed in 23% of patients and CV-related mortality in 14%. The total annual rates of all-cause and CV-related hospitalizations among all patients were 0.52 and 0.26, respectively. Exploratory analyses showed a significantly lower risk of mortality and hospitalizations (both all-cause and CV-related) in patients who had an NYHA classification of I/II vs III/IV at baseline. Numerically similar outcomes were observed in patients with ATTRv-CM vs ATTRwt-CM.

Changes in the real-world population with ATTR-CM occur over time, influenced by evolving clinical management.[11-13] This study provided early access to tafamidis while it was being considered by regulatory authorities. Enrollment criteria were minimal, and adults with all severities of ATTR-CM were permitted to join. Therefore, this study population is perhaps less selective than compared to other clinical trials of tafamidis.[4,6] Study findings offer safety and supportive data from a large, inclusive, and relatively contemporary patient cohort treated with tafamidis between 2018 and 2023. As mortality and hospitalizations due to ATTR-CM are not linear over follow-up, and highly dependent on clinical characteristics and management, it is challenging to directly compare findings from treated cohorts from other trial and real-world studies. Though several previous analyses have demonstrated that initiation of disease-modifying therapy early in the disease course provides the best outcomes, the low proportion of patients with advanced disease (ie, NYHA IV symptoms) in this and other studies means it is a topic of ongoing interest.[6,14-20] Patients with class IV symptoms were not permitted to enroll in the earlier phase 3 ATTR-ACT, and despite being eligible for inclusion in this study, only 19 were enrolled.[4]

FIGURE 2 **Kaplan-Meier Curves for All-Cause and CV-Related Mortality**

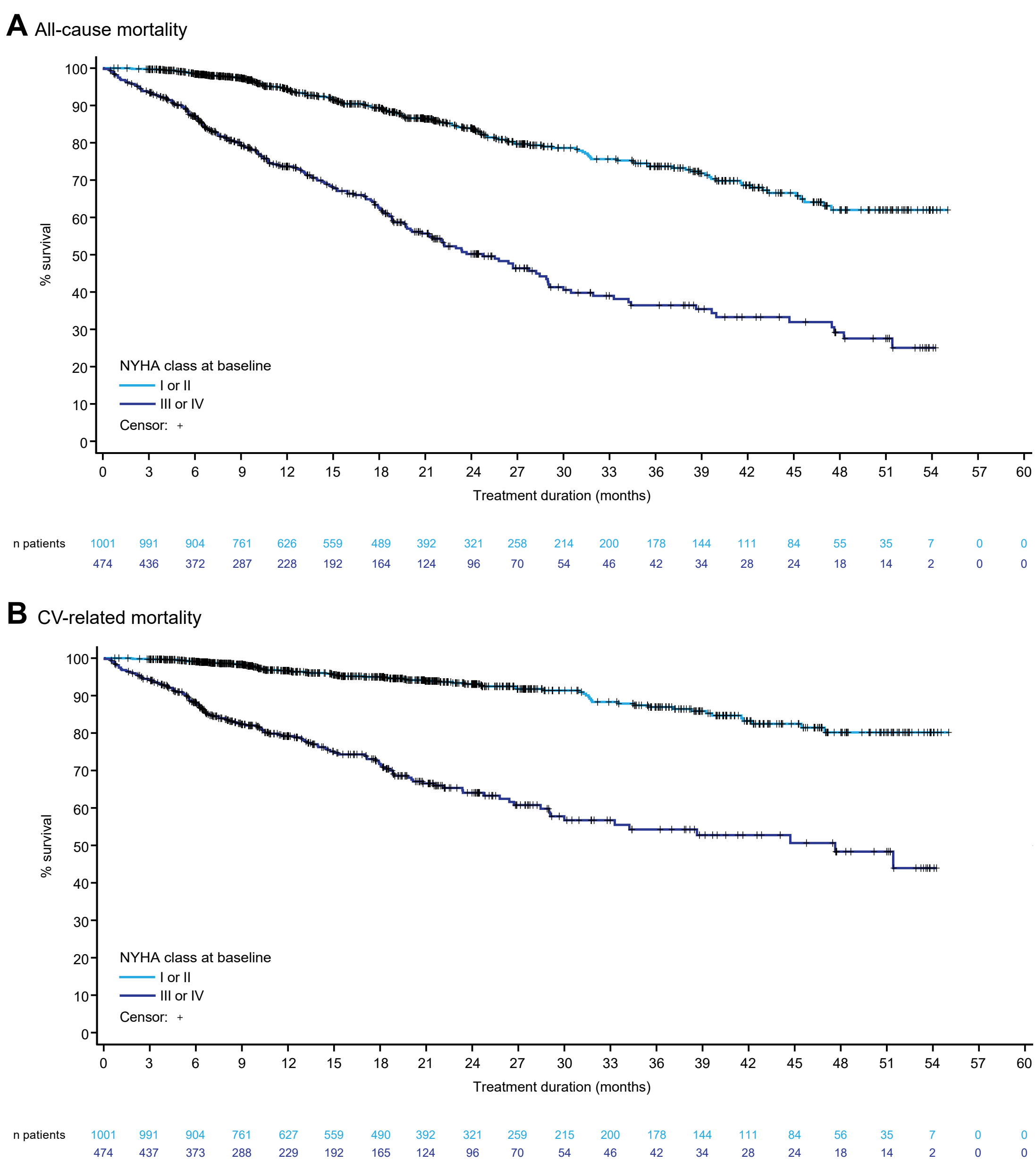


Curves show time to all-cause (A) and CV-related (B) mortality in the overall population of the early access study. CV = cardiovascular.

In this study, 14% of patients had ATTRv-CM, with over half holding a V122I (p. V142I) *TTR* genotype. Post hoc analyses from ATTR-ACT have shown that tafamidis treatment is beneficial in patients with ATTRv-CM and ATTRwt-CM.[21] As differences in outcomes between genotype subgroups in this study were small, they most likely reflected minor imbalances in the morbidity of ATTRv-CM and ATTRwt-CM patients at enrollment.

STUDY LIMITATIONS. The main limitation of this open-label, single-arm study is that there was no control group with which to compare treatment outcomes. This study was designed to provide early access to disease-modifying treatment and did not include an untreated group for ethical reasons.

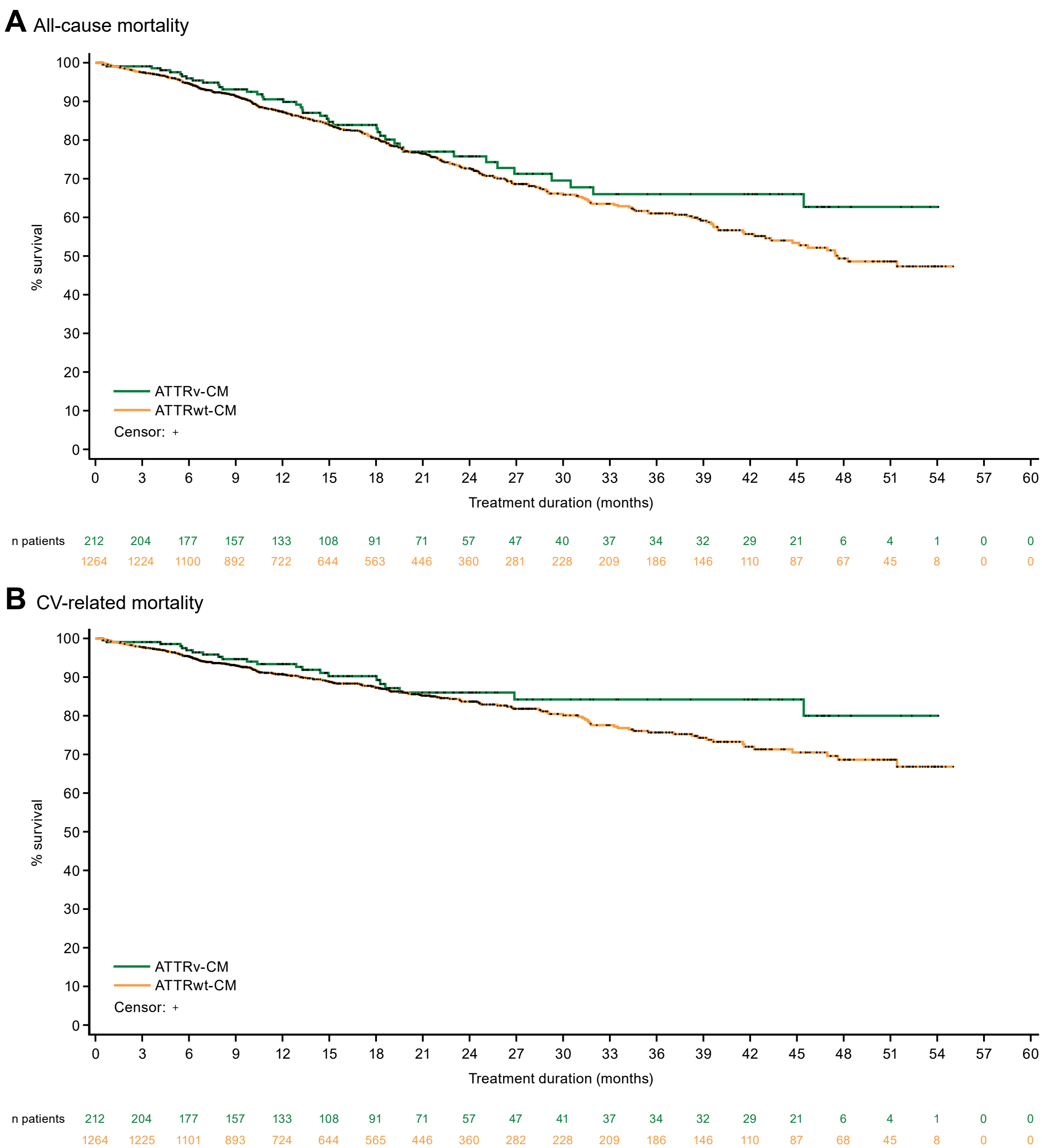
FIGURE 3 **Kaplan-Meier Curves for All-Cause and CV-Related Mortality by NYHA Subgroup**



Curves show time to all-cause (A) and CV-related (B) mortality in subgroups with NYHA functional class I/II or III/IV symptoms at baseline. Abbreviation as in **Figure 2**.

Further studies could make use of time-matched registry data to form a control arm and allow the assessment of efficacy. Another limitation is the median follow-up time of 19 months by Kaplan-Meier analysis. The study started in 2018, and tafamidis was approved and available in nearly all included regions by the end of 2020. In these regions, patients left the study to obtain tafamidis by prescription, reducing the median follow-up duration and potentially leading to regional bias in the longer-term data. An additional minor limitation is around overall generalizability. Though this study enrolled an inclusive population compared to clinical trials, a few remaining entrance criteria were required for safety

FIGURE 4 Kaplan-Meier Curves for All-Cause and CV-Related Mortality by *TTR* Genotype



Curves show time to all-cause (A) and CV-related (B) mortality in subgroups with a wild-type or variant TTR genotype. ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; TTR = transthyretin; other abbreviation as in Figure 2.

precautions. These excluded a small number of patients that may now be eligible for treatment in clinical practice. Entry required a documented diagnosis of ATTR-CM, but the methodology was not specified. Another minor limitation is the lack of N-terminal pro-B-type natriuretic peptide data with which to determine National Amyloidosis Staging. Finally, though there are many studies describing tafamidis use, it is challenging to compare efficacy outcomes between them due to differences in populations, follow-up times, and outcome definitions. For example, in this study, the causation of death and hospitalization events was not externally adjudicated (as in ATTR-ACT) but utilized an algorithm based on associated terms.[4] We suggest that direct comparisons between studies should be made with caution.

CONCLUSIONS

Findings from this study characterize the safety profile of tafamidis in an inclusive and relatively contemporary population of patients with ATTR-CM. The observed safety profile was consistent with that reported in other trials and real-world studies. Over a maximum exposure duration of 4.5 years, the incidence of all-cause mortality was 23% and CV-related mortality was 14%. The total annual rate of CV-related hospitalization among all patients was 0.26.

DATA AVAILABILITY STATEMENT 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.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The safety and efficacy of tafamidis have been characterized in several clinical and real-world studies. Findings from this independent and inclusive arm of a phase 3 LTE study support the previously reported safety profile of tafamidis in patients with ATTR-CM and provide additional data on the incidence of mortality and hospitalizations over the course of treatment.

TRANSLATIONAL OUTLOOK: The prognosis of patients with ATTR-CM is greatly improved with disease-modifying therapy. Characterizing and understanding treatment outcomes is important in supporting optimal clinical decision-making with patients.

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KEY WORDS amyloidosis, genotype, heart failure, multicenter trial, NYHA, survival rate

APPENDIX For supplemental tables and a plain language summary of findings, please see the online version of this paper.