

Natural history and progression of transthyretin amyloid cardiomyopathy: insights from ATTR-ACT

Jose Nativi-Nicolau^{1*}, Daniel P. Judge², James E. Hoffman³, Balarama Gundapaneni⁴, Denis Keohane⁵, Marla B. Sultan⁵ and Martha Grogan⁶

¹Department of Medicine, University of Utah Health Care, Salt Lake City, UT, USA; ²Medical University of South Carolina, Charleston, SC, USA; ³University of Miami, Miami, FL, USA; ⁴Pfizer Inc, Groton, CT, USA; ⁵Pfizer Inc, New York, NY, USA; and ⁶Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Abstract

Aims Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive, fatal disorder that remains underdiagnosed. The Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) was the first large clinical trial to include both wild-type (ATTRwt) and hereditary (ATTRv) patients. A description of the natural history of ATTR-CM, utilizing data from placebo-treated patients in ATTR-ACT, will provide a greater understanding of presentation and progression of ATTR-CM and may aid in disease awareness, earlier diagnosis and treatment monitoring.

Methods and results Changes in clinical endpoints (mortality, cardiovascular [CV]-related hospitalizations, 6-min walk test [6MWT] distance and Kansas City Cardiomyopathy Questionnaire Overall Summary [KCCQ-OS] score) from baseline to Month 30 in the 177 patients (134 ATTRwt, 43 ATTRv) who received placebo in ATTR-ACT were assessed. ATTRwt patients tended to have less severe disease at baseline. Over the duration of ATTR-ACT, there were 76 (42.9%) all-cause deaths, and 107 (60.5%) patients had a CV-related hospitalization. There was a lower proportion of all-cause deaths in ATTRwt (49, 36.6%) than ATTRv (27, 62.8%). There was a similar, steady decline in mean (SD) 6MWT distance from baseline to Month 30 in ATTRwt (93.9 [93.7] m) and ATTRv (89.1 [107.2] m) patients. The decline in mean (SD) KCCQ-OS score was less severe in ATTRwt (13.8 [20.7]) than ATTRv (21.0 [26.4]) patients.

Conclusions Patients with ATTR-CM experience a severe, progressive disease. In ATTR-ACT, placebo-treated patients with ATTRv, compared with ATTRwt, had more severe disease at baseline, and their disease progressed more rapidly as shown by mortality, hospitalizations and quality of life over time.

Keywords Transthyretin amyloid cardiomyopathy; Clinical trial; Progression; Variant; Hereditary; Wild-type

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*Correspondence to: Jose Nativi-Nicolau, Department of Medicine, University of Utah Health Care, 30N 1900 E, Salt Lake City, UT, USA. Phone: +1 801-587-2199. Email: jose.nativi-nicolau@hsc.utah.edu

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the accumulation of wild-type (ATTRwt) or variant (ATTRv) transthyretin amyloid fibrils in the myocardium, leading to cardiomyopathy and symptoms of heart failure.^{1–3} Onset of ATTRwt is typically later in life (>60 years of age) with the large majority of patients being male.² In contrast, symptom onset in patients with ATTRv can occur at a younger age.^{1–3}

ATTR-CM is a progressive, fatal disease, but it remains both underdiagnosed and misdiagnosed, and its prevalence remains unknown. In studies in older patients with heart

failure with preserved ejection fraction, as many as 15% of patients had evidence of previously undiagnosed ATTRwt.^{4–6} Median survival for patients with ATTR-CM varies with respect to genotype and disease stage at diagnosis.^{3,7} Without treatment, survival has been reported as approximately 2.5 years for patients with ATTRv caused by the Val122Ile mutation^{7–9} and 3.6 years for patients with ATTRwt.^{8,10} Greater awareness of ATTR-CM, and what to expect during the course of disease, could aid earlier diagnosis and improve patient management and treatment outcomes.¹¹

The Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) was the first large clinical trial to include

both patients with ATTRwt and patients with ATTRv and represents one of the largest, and longest, collections of natural history data in patients with ATTR-CM.¹² Patients were enrolled in ATTR-ACT for up to 30 months, providing a detailed assessment of patients over a meaningful period of time. Following on from prior publications showing the efficacy of tafamidis in patients with ATTR-CM,¹² in both patients with ATTRwt and patients with ATTRv,¹³ this analysis aims to describe the natural history of ATTR-CM utilizing data from placebo-treated patients in ATTR-ACT.

Methods

Trial design and patients

ATTR-ACT was a Phase 3, multicentre, international, three-arm, parallel-design, placebo-controlled, double-blind, randomized study (ATTR-ACT) for which the design has been previously published (NCT01994889).^{12,14} Briefly, those eligible to enrol were patients aged ≥ 18 and ≤ 90 years with ATTR-CM defined by the presence of either ATTRv or ATTRwt and a medical history of heart failure. The trial was approved by the independent review boards or ethics committee at each participating site and was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. This is the largest published clinical trial of placebo-treated patients with ATTR-CM to date. This analysis describes those patients who received placebo during the 30 months of the trial.

Clinical evaluations and statistical analyses

Clinical evaluations in ATTR-ACT included all-cause mortality, cardiovascular (CV)-related mortality, CV-related hospitalizations, functional capacity (assessed by 6-min walk test [6MWT] distance), health status and quality of life (assessed by Kansas City Cardiomyopathy Questionnaire Overall Summary [KCCQ-OS] score), changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and echocardiographic measures of cardiac structure and function (interventricular septal wall thickness, left ventricular [LV] posterior wall thickness, LV ejection fraction, LV stroke volume and LV strain). As prespecified in the study protocol, 6MWT distance and KCCQ-OS score were assessed at baseline and every 6 months for the duration of the trial. NT-proBNP was assessed at baseline and at Month 12 and Month 30. Echocardiographic measures were assessed at baseline and at Months 6, 18 and 30. Vital status was collected for every patient at Month 30. Heart transplant and implantation of a cardiac mechanical assist device were counted as

death/mortality for this description; actual deaths and heart transplants are also shown separately.

This is a descriptive analysis of the changes in clinical endpoints from baseline to Month 30 in patients who received placebo. Clinical endpoints are also described in patients by genotype (ATTRwt compared with ATTRv) and NYHA class at baseline (Class I and II compared with Class III). Some data on the effect of treatment with tafamidis (compared with placebo) on these outcomes have been previously published.^{12,13}

Results

Patient characteristics at baseline

A total of 177 patients received placebo; the majority were male, with a mean age of 74 years (*Table 1*). Genotypes of the 43 patients with ATTRv were Val122Ile (23 patients [53.5%]); Thr60Ala (6 [14.0%]); Val30Met (6 [14.0%]); Ile68Leu (4 [9.3%]); and Asp18Glu, Glu54Leu, Glu89Gln, and Pro24Ser (one patient each [2.3%]). At baseline, patients with ATTRwt tended to be older, but with less severe disease, as shown by the smaller proportion of patients in NYHA Class III and longer mean 6MWT distance (*Table 1*). In contrast, KCCQ-OS scores and NT-proBNP levels were similar in patients with ATTRwt and patients with ATTRv. Patients with ATTRwt tended to be more likely to have atrial fibrillation, coronary artery disease, sleep apnoea syndrome and Type 2 diabetes mellitus at enrolment than patients with ATTRv. The majority of patients were receiving diuretics at baseline (69.5% of patients), although use of beta blockers (29.9%) and agents acting on the renin-angiotensin system (27.1%) was less because they are poorly tolerated or considered harmful in patients with ATTR-CM.¹⁵

Mortality and hospitalizations

In total, there were 76 (42.9%) all-cause deaths, of which 63 (35.6% of all patients) were CV related (*Table 2* and *Figure 1*). There was a lower proportion of all-cause deaths in patients with ATTRwt than in patients with ATTRv (*Table 2* and *Figure 2A*). There was also a lower proportion of all-cause deaths in patients with baseline NYHA Class I and II than NYHA Class III (*Table 2* and *Figure 2B*). CV-related deaths were also less common in patients with ATTRwt and patients who were NYHA Class I and II (*Table 2* and *Figure 3*). Overall, all-cause mortality was greatest in patients with ATTRv who were NYHA Class III at baseline (78.9%), followed by patients with ATTRwt who were NYHA Class III (54.5%), patients with ATTRv who were NYHA Class

Table 1 Demographic and clinical characteristics at baseline

	ATTRwt (n = 134)	ATTRv (n = 43)
Age, years		
Mean (SD)	74.9 (6.0)	71.4 (8.1)
Median	75.0	73.0
Min, max	57, 89	51, 86
Sex, n (%)		
Male	128 (95.5)	29 (67.4)
Female	6 (4.5)	14 (32.6)
Race, n (%)		
White	124 (92.5)	22 (51.2)
Black	5 (3.7)	21 (48.8)
Asian	5 (3.7)	0
BMI, mean (SD)	26.6 (3.6)	25.4 (5.8)
mBMI ^a , mean (SD)	1085.9 (180.2)	1005.6 (225.1)
NYHA class, n (%)		
I	11 (8.2)	2 (4.7)
II	79 (59.0)	22 (51.2)
III	44 (32.8)	19 (44.2)
6MWT distance (metres), mean (SD)	366.7 (126.2)	311.2 (117.1)
KCCQ-OS score, mean (SD)	65.1 (21.3)	68.4 (23.1)
NT-proBNP (pg/mL), mean (SD)	3826.3 (2840.2)	3905.4 (3384.2)
Comorbidities ^b , n (%)		
Atrial fibrillation	71 (53.0)	18 (41.9)
Hypertension	61 (45.5)	23 (53.5)
Hyperlipidaemia	44 (32.8)	14 (32.6)
Cardiac failure, congestive	38 (28.4)	11 (25.6)
Chronic kidney disease	31 (23.1)	10 (23.3)
Coronary artery disease	35 (26.1)	5 (11.6)
Osteoarthritis	32 (23.9)	7 (16.3)
Benign prostatic hyperplasia	30 (22.4)	7 (16.3)
Sleep apnoea syndrome	32 (23.9)	4 (9.3)
Gastro-oesophageal reflux disease	26 (19.4)	6 (14.0)
Gout	21 (15.7)	4 (9.3)
Constipation	19 (14.2)	5 (11.6)
Insomnia	17 (12.7)	6 (14.0)
Hypothyroidism	15 (11.2)	6 (14.0)
Type 2 diabetes mellitus	19 (14.2)	0
Dyspnoea	13 (9.7)	6 (14.0)
Carpal tunnel syndrome	15 (11.2)	3 (7.0)
Fatigue	15 (11.2)	3 (7.0)
Echocardiography measures, mean (SD)		
IVST, mm	16.1 (3.3)	16.5 (4.1)
LV posterior wall thickness, mm	16.6 (3.9)	17.0 (4.8)
LV ejection fraction, %	48.9 (8.7)	47.9 (11.3)
LV stroke volume, mL	46.5 (16.4)	40.8 (17.9)
Circumferential mid-global strain, %	-17.2 (10.0)	-15.9 (8.5)
Radial mid-global strain, %	18.6 (10.8)	14.9 (9.0)
Global longitudinal strain, %	-9.6 (3.6)	-8.6 (3.6)

Some demographic data have been previously published.¹³

6MWT, 6-minute walk test; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; IVST, interventricular septal wall thickness; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LV, left ventricular; mBMI, modified body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

^amBMI is calculated by multiplying the BMI [weight (kg)/height (m²)] by serum albumin concentration (g/L).

^bComorbidities present at enrolment in >10% of all patients.

I and II (50.0%) and patients with ATTRwt who were NYHA Class I and II (27.8%) (Table 3).

In total, 107 (60.5%) patients had a CV-related hospitalization, with similar proportions in each genotype and NYHA group (Table 4). The frequency of CV-related hospitalizations per year was greater in patients with ATTRv and in NYHA Class III.

Functional capacity, health status and quality of life and cardiac measures

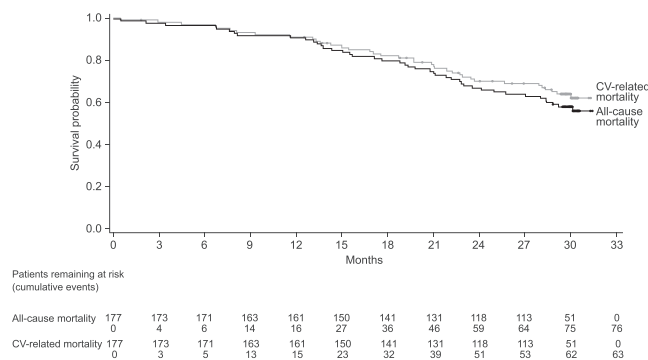
Functional capacity, as measured by 6MWT distance, declined markedly over time, with a mean (standard deviation [SD]) decline in all patients from baseline to Month 30 of 89.7 (105.2) m. The decline was similar in ATTRwt and ATTRv

Table 2 All-cause, and CV-related, mortality in all patients and by genotype and NYHA class at baseline

	All-cause mortality	CV-related mortality
All patients		
<i>n</i>	177	177
Mortality, <i>n</i> (%)	76 (42.9)	63 (35.6)
Deaths	72 (40.7)	59 (33.3)
Heart transplants	4 (2.3)	4 (2.3)
Median time to event, months	NE	NE
ATTRwt		
<i>n</i>	134	134
Mortality, <i>n</i> (%)	49 (36.6)	41 (30.6)
Deaths	46 (34.3)	38 (28.4)
Heart transplants	3 (2.2)	3 (2.2)
Median time to event, months	NE	NE
ATTRv		
<i>n</i>	43	43
Mortality, <i>n</i> (%)	27 (62.8)	22 (51.2)
Deaths	26 (60.5)	21 (48.8)
Heart transplants	1 (2.3)	1 (2.3)
Median time to event, months	23.5	28.4
NYHA Class I and II		
<i>n</i>	114	114
All-cause mortality, <i>n</i> (%)	37 (32.5)	32 (28.1)
Deaths	33 (28.9)	28 (24.6)
Heart transplants	4 (3.5)	4 (3.5)
Median time to event, months	NE	NE
NYHA Class III		
<i>n</i>	63	63
All-cause mortality, <i>n</i> (%)	39 (61.9)	31 (49.2)
Deaths	39 (61.9)	31 (49.2)
Heart transplants	0	0
Median time to event, months	24.1	28.4

Some data on all-cause mortality have been previously published.^{12,13}

ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CV, cardiovascular; NE, not estimable; NYHA, New York Heart Association.

Figure 1 All-cause mortality and CV-related mortality in all patients. (Some data on all-cause mortality have been previously published¹²).

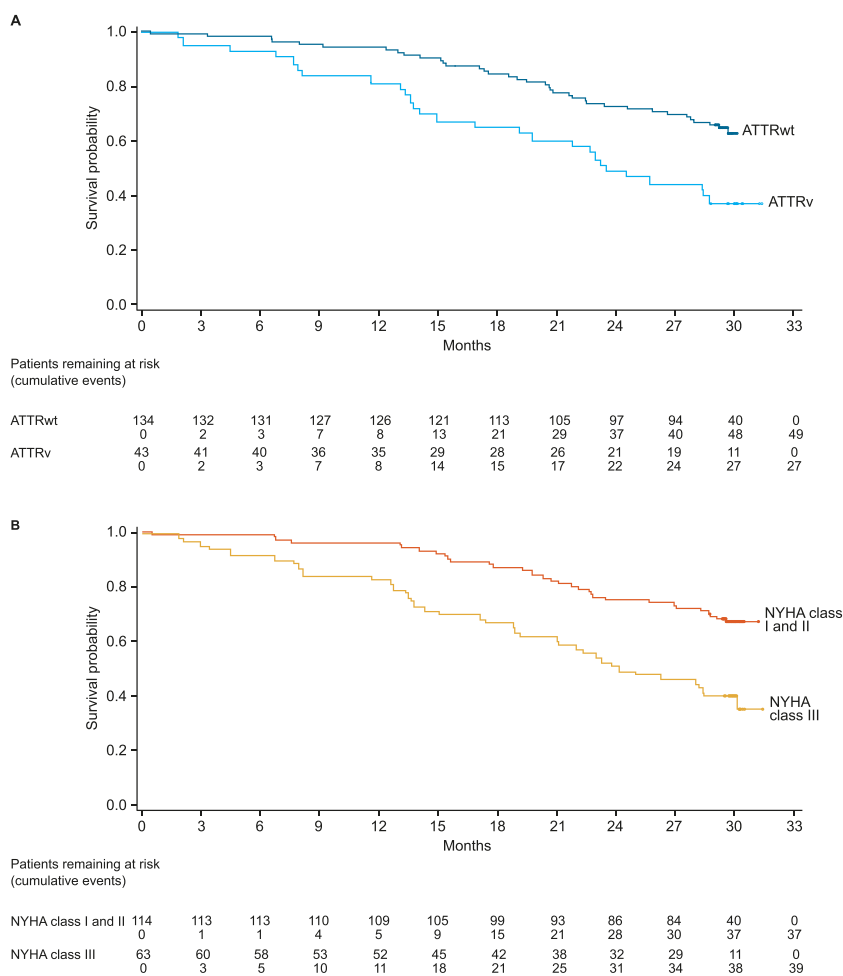
and in NYHA Class I and II and NYHA Class III (Figure 4). Health status and quality of life, as assessed by KCCQ-OS score, also declined markedly over time, with a mean (SD) decline in all patients from baseline to Month 30 of 14.6 (21.4). The decline was slightly less severe in ATTRwt than ATTRv and in NYHA Class I and II than NYHA Class III (Figure 5). NT-proBNP levels increased over the trial in all patients (Figure S1). Echocardiography measures worsened over time in all patients, with the worsening of radial and

circumferential strain in particular more rapid, and more severe, in patients with ATTRv (Figure S2).

Discussion

Patients with ATTR-CM experience a severe, progressive disease with high mortality and frequent hospitalizations. In ATTR-ACT, placebo-treated patients with ATTRv,

Figure 2 All-cause mortality by (A) genotype and (B) NYHA class at baseline. (Some data in patients with ATTRwt and patients with ATTRv have been previously published¹³).



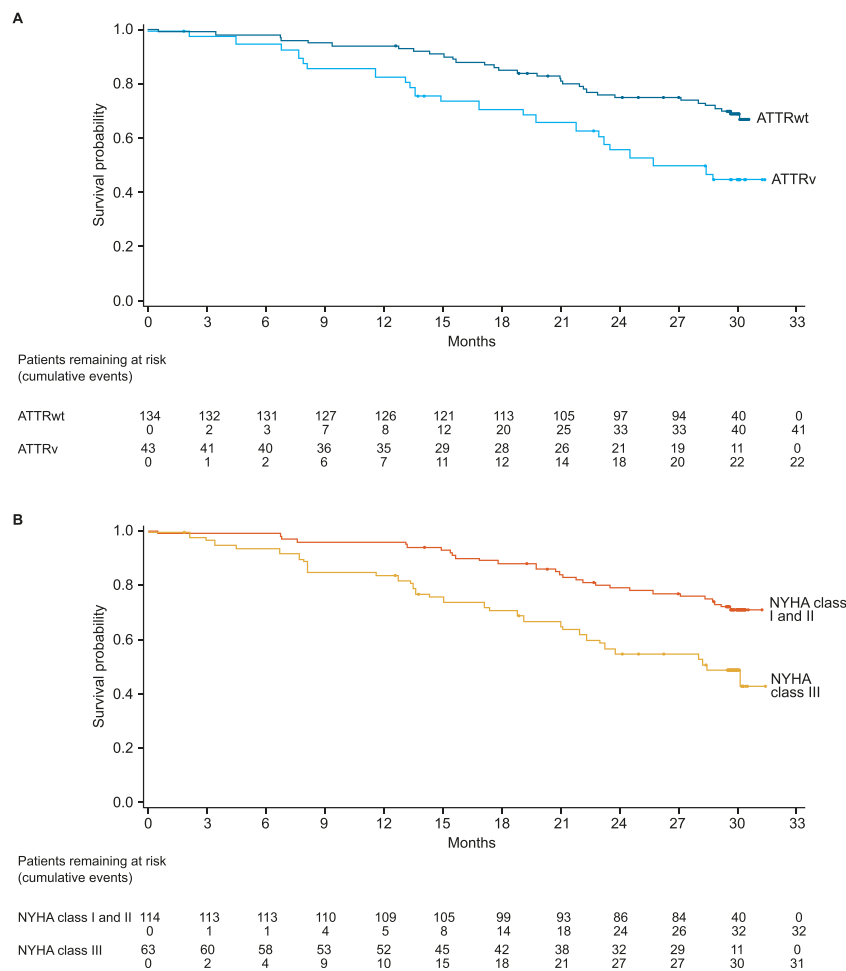
compared with patients with ATTRwt, had more severe disease at baseline, as measured by NYHA class and functional capacity (as assessed by 6MWT distance). In addition, in patients with ATTRv, disease progressed more rapidly as shown by mortality, decline in health status and quality of life (as assessed by KCCQ-OS score) and increase in NT-proBNP levels over time.

These data are consistent with prior observational studies in patients with ATTR-CM, which have demonstrated the poor prognosis of the disease, both for patients with ATTRwt (Table S1) and for patients with ATTRv (Table S2).^{7,10,16–20} As in ATTR-ACT, observational studies have shown that patients with ATTRv tend to have more severe disease, and poorer survival, than patients with ATTRwt. Collectively, these studies reveal a consistent population of patients with ATTRwt, the majority (>80%) male, aged approximately 75 years, with elevated NT-proBNP/BNP levels and preserved or mildly reduced ejection fraction. The approximately one-third

mortality over 30 months in patients with ATTRwt in ATTR-ACT was also consistent with the approximately one-quarter to one-third mortality over 24–48 months in observational studies.^{7,10,16–20}

There have been fewer studies, with fewer participants, in patients with ATTRv.^{7,17,19} The majority of patients in these studies (67%–76%) were male, with females potentially less likely to be diagnosed with cardiac disease.²¹ These studies have also demonstrated the poorer survival in patients with ATTRv, reporting median survival times consistent with the 23.5 months observed in ATTR-ACT. Together, these data suggest that genotype, along with baseline disease severity, contributes to the prognosis of patients with ATTR-CM.

The decline in KCCQ-OS score over time in ATTR-ACT was more severe in patients with ATTRv and NYHA Class III, although the difference was not large and, as with 6MWT distance, the rate of decline was largely consistent across all

Figure 3 CV-related mortality by (A) genotype and (B) NYHA class at baseline.**Table 3** All-cause mortality in patients with ATTRwt and patients with ATTRv by NYHA class at baseline

	ATTRwt (n = 134)	ATTRv (n = 43)
NYHA Class I and II		
n	90	24
All-cause mortality, n (%)	25 (27.8)	12 (50.0)
Deaths	22 (24.4)	11 (45.8)
Heart transplants	3 (3.3)	1 (4.2)
Median time to event, months	NE	NE
NYHA Class III		
n	44	19
All-cause mortality, n (%)	24 (54.5)	15 (78.9)
Deaths	24 (54.5)	15 (78.9)
Heart transplants	0	0
Median time to event, months	28.1	13.8

Some data in these patients have been previously published.¹³

ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; NE, not estimable; NYHA, New York Heart Association.

groups. In patients with ATTRwt, there was a decline of approximately 3.5 points every 6 months (i.e. ~0.6 per month). In patients with ATTRv, there was a decline of approximately

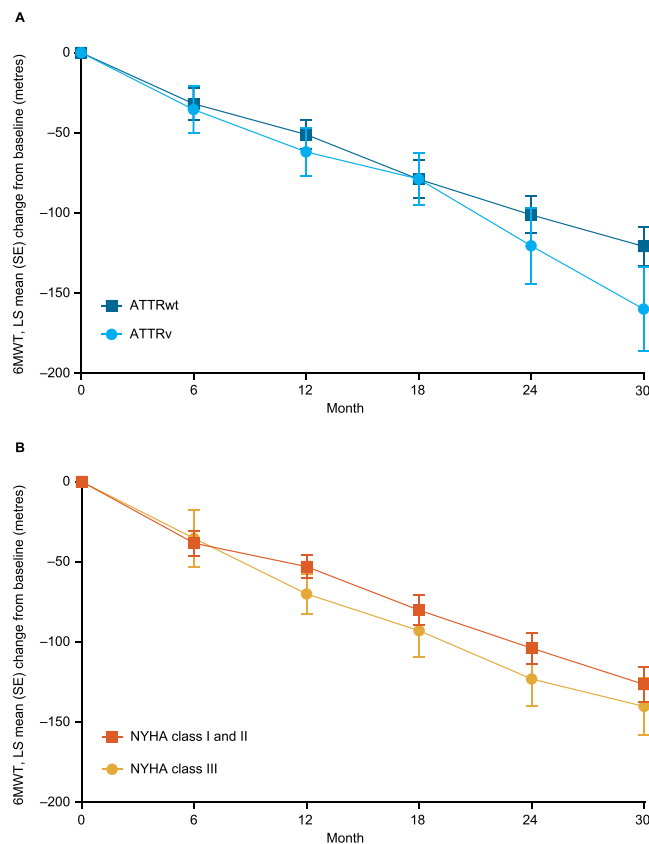
5.5 points each 6 months (i.e. ~0.9 per month). Patients with ATTR-CM have been shown to have poor overall quality of life and to experience a significant burden of disease with

Table 4 Hospitalizations by genotype and by NYHA class at baseline

	ATTRwt (n = 134)	ATTRv (n = 43)
Patients with CV-related hospitalizations, n (%)	81 (60.4)	26 (60.5)
Frequency of CV-related hospitalizations per year		
Mean (SD)	0.86 (1.20)	0.95 (1.21)
Median	0.40	0.56
Min, max	0, 7.23	0, 5.40
	NYHA Class I and II (n = 114)	NYHA Class III (n = 63)
Patients with CV-related hospitalizations, n (%)	70 (61.4)	37 (58.7)
Frequency of CV-related hospitalizations per year		
Mean (SD)	0.82 (1.06)	0.99 (1.42)
Median	0.40	0.45
Min, max	0, 5.39	0, 7.23

ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CV, cardiovascular; NYHA, New York Heart Association; SD, standard deviation.

Figure 4 Change in 6MWT distance over time by (A) genotype and (B) NYHA class at baseline. (Some data in patients with ATTRwt and patients with ATTRv have been previously published¹³).



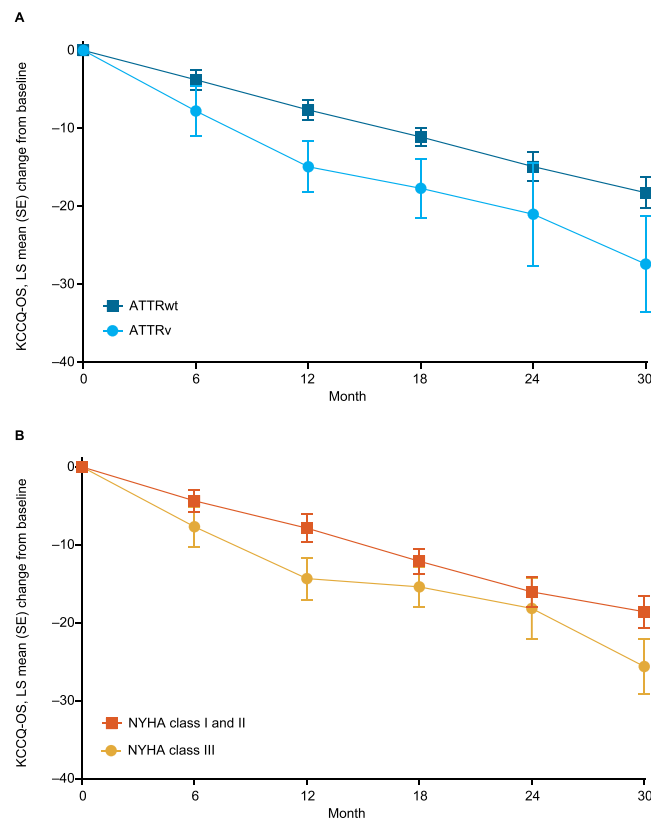
associated financial costs.^{11,22,23} The steady decline in KCCQ-OS score was consistent with an observational study in patients with ATTR-CM.²⁴

This analysis is limited by the fact that ATTR-ACT, as a clinical trial rather than an observational study, included only patients who met the trial’s inclusion criteria,¹⁴ which, as a result, may not have been representative of the general

population of patients with ATTR-CM. Nevertheless, the population in ATTR-ACT was broadly similar to those in observational studies (Tables S1 and S2) with similar demographics, but with a larger proportion of patients in NYHA Class ≥II than most observational studies.

Given the clear differences in both mortality and hospitalizations between patients with ATTRwt and patients

Figure 5 Change in KCCQ-OS score over time by (A) genotype and (B) NYHA class at baseline. (Some data in patients with ATTRwt and patients with ATTRv have been previously published¹³).



with ATTRv and between NYHA Class I and II and NYHA Class III, it was notable that there was no difference in the decline in 6MWT distance, despite differences in 6MWT distance at baseline. The rate of decline also appeared consistent over time, with each group experiencing a decline of 25–30 m every 6 months (i.e. ~5 m per month). Decline in 6MWT distance has been suggested as a measure of disease progression. However, it should be noted that there are a number of limitations with extrapolating the decline in one group of patients (the ATTR-ACT population) to all patients with ATTR-CM. Furthermore, the rate of decline observed in this analysis represents a group level change in least-squares mean and cannot necessarily be directly correlated to a specific change in any individual patient, either within the ATTR-ACT population or in patients with ATTR-CM more generally. The use of multiple measures will likely provide the clearest assessment of disease progression in patients with ATTR-CM.

Patients with ATTR-CM experience a severe, progressive disease. A greater understanding of the presentation and progression of ATTR-CM, together with the differences between patients with ATTRwt and patients with ATTRv, can help guide physicians in what to expect when treating these patients. Poorer outcomes in patients with more

severe disease emphasize the need for earlier diagnosis and treatment of patients with ATTR-CM.

Conflict of interest

JN-N has received research grants from Akcea, Eidos Therapeutics and Pfizer and consulting fees from Akcea, Alnylam, Eidos Therapeutics and Pfizer. DPJ has received grants and funding for the trial, travel expenses and consultancy fees from Pfizer; consultancy fees from ADRx, Cytokinetics and Tenaya Therapeutics; and clinical trial funding from Array BioPharma and Eidos Therapeutics. JEH reports membership of a speakers bureau for Celgene. BG, DK and MBS are full-time employees of Pfizer and hold stock and/or stock options. MG reports grants, advisory board and consultancy fees paid to her institution from Alnylam, Eidos Therapeutics, Prothena and Pfizer. Medical writing support was provided by Joshua Fink, PhD, of Engage Scientific Solutions and was funded by Pfizer.

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Data sharing

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 anonymized participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

Supporting information

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

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