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ORIGINAL RESEARCH

Atrial Fibrillation as a Prognostic Factor for All-Cause Mortality in Patients With Transthyretin Amyloid Cardiomyopathy

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ABSTRACT

BACKGROUND Atrial fibrillation/atrial flutter (AF/AFL) are common manifestations of transthyretin amyloid cardiomyopathy (ATTR-CM) but have not been found to be predictive of mortality.

OBJECTIVES This analysis aimed to examine whether baseline or historical AF/AFL at enrollment was prognostic for all-cause mortality.

METHODS In the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial), a 30-month study of tafamidis vs placebo for ATTR-CM, AF/AFL was evaluated as an independent prognostic factor for all-cause mortality using Cox proportional hazards modelling. The impact of AF/AFL on tafamidis efficacy was explored by adding an interaction term for AF/AFL status and treatment.

RESULTS ATTR-ACT enrolled 441 patients with ATTR-CM (median age 75 years; 90% male); 314 (71.2%) had baseline or historical AF/AFL at enrollment. AF/AFL was an independent prognostic factor for all-cause mortality after adjusting for covariates prespecified in the ATTR-ACT model (treatment, genotype, New York Heart Association functional class; HR: 0.550; 95% CI: 0.368-0.821) but not in an expanded stepwise model selection analysis including 23 covariates (blood urea nitrogen and N-terminal pro–B-type natriuretic peptide concentration, 6-minute walk test distance, genotype, treatment, and global longitudinal strain were prognostic [$P < 0.01$]). The interactions between tafamidis treatment and AF/AFL for all-cause mortality ($P = 0.33$) and changes in Kansas City Cardiomyopathy Questionnaire Overall Summary score ($P = 0.83$) and 6-minute walk test distance ($P = 0.82$) were not significant.

CONCLUSIONS In ATTR-ACT, baseline or historical AF/AFL was prognostic for all-cause mortality in analyses with limited adjustment but not after accounting for additional indicators of disease severity. Baseline or historical AF/AFL did not impact the efficacy of tafamidis treatment. (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy [ATTR-ACT]; NCT01994889) (JACC CardioOncol 2024;6:592-598) © 2024 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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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a fatal condition caused by the accumulation of misfolded transthyretin (TTR) in the extracellular matrix of the heart, leading to progressive heart failure, conduction system disease, and arrhythmias.[1-3] ATTR-CM can be classified as wild-type, in which no mutation in the *TTR* gene is identified, or variant, in which a mutation is present.[1-3] Atrial fibrillation (AF) and atrial flutter (AFL) are among the most common manifestations of ATTR-CM,[1,4] occurring in up to 70% of patients,[5-7] and the prevalence of these conditions increases with severity of ATTR-CM.[5,8] AF/AFL can be poorly tolerated in patients with ATTR-CM owing to diastolic dysfunction and is associated with a significantly increased risk of thromboembolic events.[5,9] However, prior studies suggest that AF/AFL is not predictive of mortality in patients with ATTR-CM.[5,6,10,11]

Tafamidis is a transthyretin kinetic stabilizer that inhibits tetramer dissociation, the initial step in amyloid formation, of wild-type and variant transthyretin.[12] The phase III ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) evaluated the efficacy and safety of tafamidis (20 or 80 mg) vs placebo in patients with wild-type and hereditary ATTR-CM.[13] Primary results showed that tafamidis reduced all-cause mortality and the rate of cardiovascular-related hospitalizations over 30 months (combined primary outcome).[13] The aim of this analysis of ATTR-ACT data was to evaluate baseline or historical AF/AFL at the time of enrollment as a potential prognostic factor for all-cause mortality.

METHODS

STUDY DESIGN AND PATIENTS. ATTR-ACT (NCT01994889) was a multicenter, international, randomized, double-blind, placebo-controlled, parallel-design, phase III trial of tafamidis in patients with ATTR-CM. The full design and primary results of ATTR-ACT have been published.[13,14] Briefly, 441 patients between 18 and 90 years of age with a biopsy-confirmed diagnosis of ATTR-CM and a history of heart failure were randomized 2:1:2 to receive tafamidis meglumine 80 mg, tafamidis meglumine 20 mg, or placebo for 30 months. All-cause mortality was assessed as a primary outcome in 264 patients treated with tafamidis (20 mg and 80 mg pooled) compared with 177 patients treated with placebo.[13]

In this post hoc analysis, patients with baseline or historical AF/AFL at enrollment in ATTR-ACT were identified based on: 1) a comprehensive review of their medical history; 2) the use of medication at enrollment (antiarrhythmics, beta-blockers, anticoagulant agents, or other medications) specifically designated as being prescribed for the treatment of AF/AFL; or 3) electrocardiogram (ECG) findings of AF/AFL before randomization. Patients who did not have baseline or historical AF/AFL at enrollment but developed AF/AFL during the study remained in the no baseline or historical AF/AFL group for this analysis; groups were not changed by the occurrence of new-onset AF/AFL during the study.

ATTR-ACT was approved by the independent review board or ethics committee at each site and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All participants provided written informed consent.

STATISTICAL ANALYSIS. Baseline demographic and clinical characteristics are summarized as mean ± SD, median with 25th and 75th percentiles (Q1, Q3), or count (percentage).

The chi-square test was used to explore the association of baseline or historical AF/AFL with baseline NYHA functional class (class I/II vs III) and baseline left ventricular (LV) ejection fraction category (preserved: ≥50%, mid-range: 41%-49%, reduced: ≤40%).

Baseline or historical AF/AFL was evaluated as an independent prognostic factor for all-cause mortality. The all-cause mortality analysis in ATTR-ACT used a Cox proportional hazards model with treatment, *TTR* genotype, and baselin NYHA functional class as prespecified covariates.[13] Heart transplantation, heart and liver transplantation, and implantation of a mechanical cardiac-assist device were treated as death for the purpose of these analyses. A stepwise Cox proportional hazards model examined 23 baseline

ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walk test
AF = atrial fibrillation
AFL = atrial flutter
ATTR-CM = transthyretin amyloid cardiomyopathy
BUN = blood urea nitrogen
ECG = electrocardiogram
GLS = global longitudinal strain
LV = left ventricular
NT-proBNP = N-terminal pro-B-type natriuretic peptide
TTR = transthyretin

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Demographic and Clinical Characteristics in Patients With or Without Baseline or Historical AF/AFL

	Baseline or Historical AF/AFL at Enrollment	
	Yes (n = 314)	No (n = 127)
Age, y	74.9 ± 6.8	73.0 ± 7.3
Sex		
Male	286 (91.1)	112 (88.2)
Female	28 (8.9)	15 (11.8)
Race		
White	270 (86.0)	87 (68.5)
Black	33 (10.5)	30 (23.6)
Asian	8 (2.5)	10 (7.9)
Other	3 (1.0)	0
Ethnicity	312	127
Not Hispanic or Latino	304 (97.4)	121 (95.3)
Hispanic or Latino	8 (2.6)	6 (4.7)
TTR genotype		
Wild-type	253 (80.6)	82 (64.6)
Variant	61 (19.4)	45 (35.4)
NYHA functional class		
I or II	205 (65.3)	95 (74.8)
III	109 (34.7)	32 (25.2)
6MWT distance, m	335.0 (259.0-435.0)	390.0 (303.0-451.0)
NT-proBNP, pg/mL	3,414.5 (2,075.0-5,213.6)	2,222.0 (1,274.0-3,873.7)
Troponin I	313	127
ng/mL	0.14 (0.08-0.20)	0.14 (0.09-0.19)
BUN, mg/dL	27.9 (21.8-35.0)	24.0 (19.0-30.0)
LVEF	310	126
%	49.1 (41.4-55.5)	52.0 (43.0-57.3)
Category		
≥50%	148 (47.7)	72 (57.1)
41%-49%	89 (28.7)	30 (23.8)
≤40%	73 (23.5)	24 (19.0)
LVEDD	307	124
mm	41.6 (37.0-46.2)	42.2 (37.0-46.6)
LV mass	307	123
g	281.1 (230.4-352.2)	282.1 (221.9-343.4)
GLS	307	126
%	−8.9 (−11.0 to −6.9)	−9.8 (−11.9 to −7.5)

Values are mean ± SD, n (%), or median (Q1-Q3).

6MWT = 6-minute walk test; AF = atrial fibrillation; AFL = atrial flutter; BUN = blood urea nitrogen; GLS = global longitudinal strain; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; *TTR* = transthyretin.

demographic and clinical covariates[15] as potential independent prognostic factors for all-cause mortality. Initial covariates were treatment group, *TTR* genotype, NYHA functional class, AF/AFL, sex, race, ethnicity, country, age, height, weight, 6-minute walk test (6MWT) distance, troponin I concentration, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, blood urea nitrogen (BUN) concentration, respiratory rate, LV end-diastolic interventricular septal wall thickness, LV posterior wall thickness, LV ejection fraction, LV stroke volume, global circumferential strain, global radial strain, and global longitudinal strain (GLS). A P value <0.10 was required to enter the model, and a P value <0.05 was required to stay in the model. A sensitivity analysis was conducted to examine the results of the these models without the assumption of heart transplantation, heart and liver transplantation, and implantation of a mechanical cardiac-assist device as death (patients were censored at the time of these procedures). Cox proportional hazards results are presented as HRs with 95% CIs.

The potential impact of baseline or historical AF/AFL on tafamidis efficacy was explored by adding an interaction term for AF/AFL status and treatment to prespecified models for all-cause mortality, quality of life (measured as change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary [KCCQ-OS] score), and functional capacity (measured as change from baseline in 6MWT distance).[13]

SAS Studio software (SAS Institute) was used to conduct the analyses.

RESULTS

BASELINE PATIENT CHARACTERISTICS. Of the 441 patients treated in ATTR-ACT (median age: 75 [Q1-Q3: 71-79] years; 90% male), 314 (71.2%) had baseline or historical AF/AFL at enrollment. Of these 314 patients, 198 were identified based on the use of medication indicated for the treatment of AF/AFL, including anticoagulant agents (n = 157), antiarrhythmic agents (n = 57), and beta-blockers (n = 37); 196 of these 198 patients also had a supportive medical history or ECG findings. The remaining 116 patients were identified based on medical history and/or ECG findings: 56 were identified based on both medical history and ECG, 18 based on ECG only, and 42 based on medical history only.

Patients with baseline or historical AF/AFL were more likely to be White and to have a wild-type *TTR* genotype compared with those without AF/AFL (Table 1). Patients with baseline or historical AF/AFL also had a shorter median 6MWT distance and higher median NT-proBNP and BUN concentrations (Table 1). There was no significant association between

historical or baseline AF/AFL and NYHA functional class ($P = 0.052$) or LV ejection fraction category ($P = 0.205$) at baseline.

AF/AFL AS A PROGNOSTIC FACTOR FOR ALL-CAUSE MORTALITY. As previously reported,[15] 154 of 441 patients (34.9%) in ATTR-ACT had died as of month 30, including 13 patients who underwent a heart transplantation or implantation of a mechanical cardiac-assist device. All variables in the Cox proportional hazards model (*TTR* genotype, treatment, baseline or historical AF/AFL, and NYHA functional class) were found to be significant independent prognostic factors for all-cause mortality (**Central Illustration**). The risk of mortality was 45% lower (HR: 0.550; 95% CI: 0.368-0.821) in patients without vs with baseline or historical AF/AFL. In the expanded stepwise selection analysis that included 23 baseline demographic and clinical covariates, baseline or historical AF/AFL was not a statistically significant independent prognostic factor for all-cause mortality. Significant prognostic factors in the expanded analysis were *TTR* genotype (variant vs wild-type), NT-proBNP concentration (log-transformed), GLS, BUN concentration, 6MWT distance, and treatment (tafamidis vs placebo) (**Central Illustration**).

Results were the same when the assumption of heart transplantation, heart and liver transplantation, and implantation of a mechanical cardiac-assist device as death was removed. AF/AFL was a significant prognostic factor for mortality in the original model (HR: 0.577; 95% CI: 0.382-0.874; $P = 0.009$) but not in the broader model. The final factors in the broader model were the same: *TTR* genotype (variant vs wild-type; HR: 1.677; 95% CI: 1.178-2.387; $P = 0.004$), log-transformed NT-proBNP concentration (HR: 1.628; 95% CI: 1.247-2.126; $P < 0.001$), GLS (HR: 1.060; 95% CI: 1.005-1.118; $P = 0.032$), BUN concentration (HR: 1.024; 95% CI: 1.013-1.035; $P < 0.001$), 6MWT distance (HR: 0.994; 95% CI: 0.992-0.996; $P < 0.001$), and treatment (tafamidis vs placebo; HR: 0.539; 95% CI: 0.384-0.757; $P < 0.001$).

AF/AFL INTERACTION WITH TAFAMIDIS TREATMENT. There was no significant interaction between the treatment effect in ATTR-ACT and baseline or historical AF/AFL for all-cause mortality ($P = 0.33$), change from baseline in KCCQ-OS ($P = 0.83$), or change from baseline in 6MWT distance ($P = 0.82$).

DISCUSSION

In this post hoc analysis from ATTR-ACT, baseline or historical AF/AFL at enrollment was common in patients with ATTR-CM. The rate of AF/AFL observed here (71%) was similar to prior studies that reported AF rates of approximately 70% in various populations of patients with ATTR-CM,[5-7] with a higher incidence in patients with wild-type vs hereditary disease.[5] The presence of AF in patients with ATTR-CM has been linked to more advanced disease,[5,8] which is consistent with our finding that patients in ATTR-ACT with baseline or historical AF/AFL had a higher median NT-proBNP concentration and lower median 6MWT distance compared with those without AF/AFL. Baseline or historical AF/AFL did not impact the beneficial effects of tafamidis on all-cause mortality, quality of life, or functional capacity measures in ATTR-ACT.

Although AF and AFL are among the most common manifestations of ATTR-CM, prior studies suggest that AF is not predictive of mortality.[5,6,10,11] The current analysis initially identified AF/AFL as an independent prognostic factor for all-cause mortality in patients with ATTR-CM using a Cox proportional hazards model that included treatment, *TTR* genotype, and NYHA functional class. However, in an expanded stepwise selection model that included 23 variables, baseline or historical AF/AFL no longer reached significance as an independent prognostic factor for all-cause mortality; variables that were prognostic factors were treatment, *TTR* genotype, 6MWT distance, NT-proBNP concentration, BUN concentration, and GLS. Although there was no independent association between AF/AFL and mortality after extensive adjustment for several variables, there was a relationship between AF/AFL and morality as indicated by the analyses with limited adjustment. The latter finding could prove useful in the clinical setting where only limited data such as LV ejection fraction or NYHA functional class may be available, in which case AF/AFL could be a valuable indicator of disease severity for the clinician.

This analysis was performed in a cohort of patients before the existence of any approved ATTR-CM therapies, and it provides information on the natural history of arrhythmias in the ATTR-CM population. This analysis also represents one of the largest

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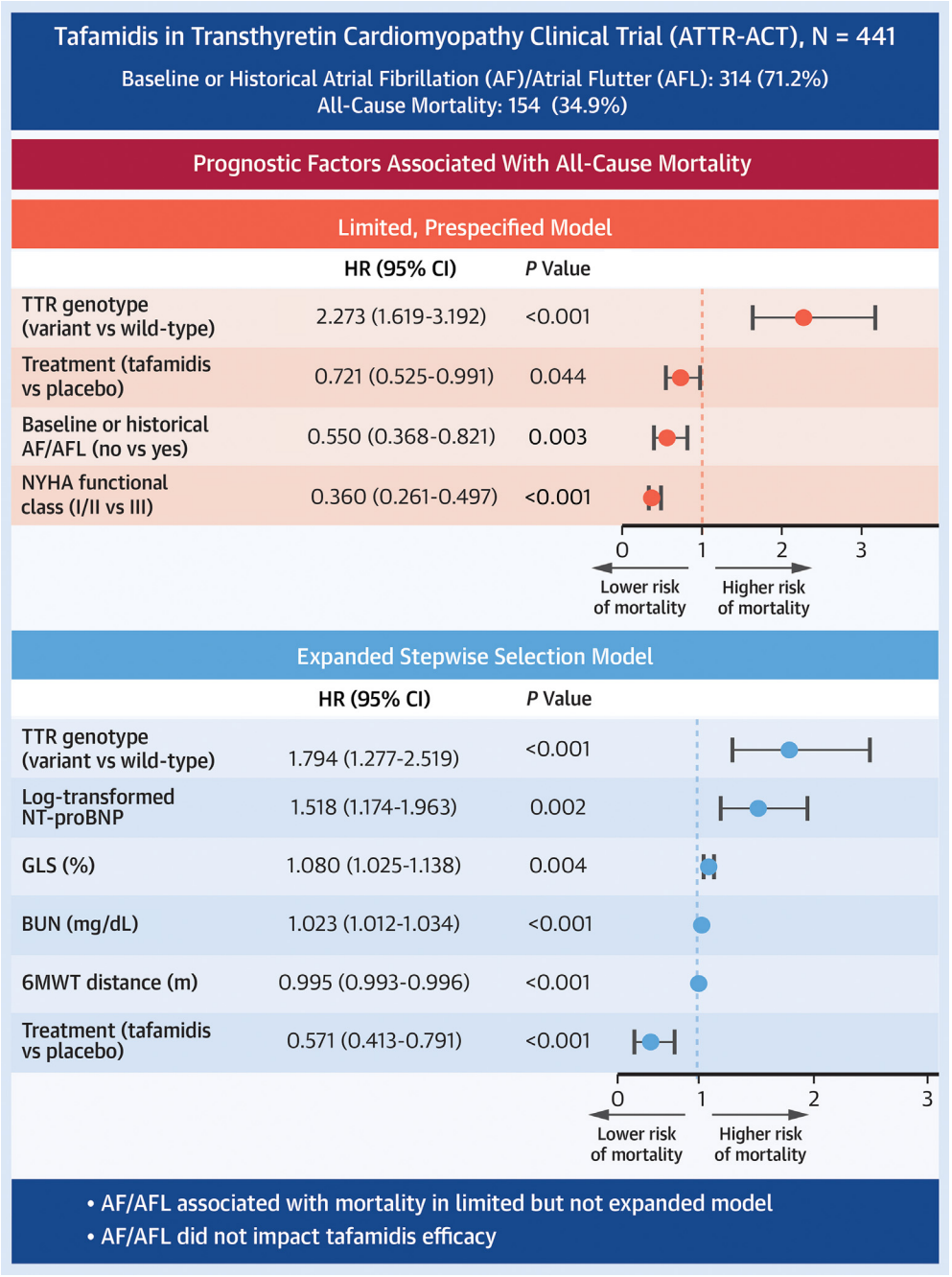
CENTRAL ILLUSTRATION **Cox Proportional Hazards Model for Prognostic Factors of All-Cause Mortality**



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Models replicated the primary outcome in the ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) with the addition of baseline or historical atrial fibrillation/atrial flutter (AF/AL) as a covariate. All variables in the limited model were found to be significant independent prognostic factors for all-cause mortality. The risk of mortality was 45% lower in patients without vs with baseline or historical AF/AFL. In the expanded model of 23 baseline and demographic covariates, AF/AFL not significant. This expanded stepwise Cox proportional hazards model selection analysis examined 23 baseline and demographic covariates as potential independent prognostic factors for all-cause mortality and identified transthyretin (TTR) genotype, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration (log-transformed), global longitudinal strain (GLS), blood urea nitrogen (BUN) concentration, 6-minute walk test (6MWT) distance, and treatment as significant prognostic factors. HRs correspond to a 1-U increase in value for log-transformed NTproBNP concentration, GLS, BUN concentration, and 6MWT. *TTR* = transthyretin.

studies to date on the prevalence and prognostic implications of AF/AFL in ATTR-CM.

STUDY LIMITATIONS. Limitations of this study are that this was a post hoc analysis that was not prespecified, and the study was not powered to evaluate outcomes in these subpopulations. In addition, the proportionality assumption for each covariate in the Cox models was not evaluated, so there may have been some modest deviation from this assumption. Also, a small number of patients (n = 2) were identified as having AF/AFL based on medication alone without supportive medical history or ECG findings; however, for these 2 patients, the medications were specifically listed as being prescribed for AF/AFL. Furthermore, this analysis focuses on the impact of baseline or historical AF/AFL rather than the development of incident AF/AFL during the course of the trial. Lastly, the majority patients in the study had a history of AF/AFL or had AF/AFL at baseline; therefore, the size of the no AF/AFL group was relatively small and further limited the power of this analysis.

CONCLUSIONS

In ATTR-ACT, baseline or historical AF/AFL was common among patients with ATTR-CM, and those with AF/AFL were more likely to have advanced disease. AF/AFL was prognostic of all-cause mortality in analyses with limited adjustment but not with extensive adjustment for other measures of disease severity. A similar treatment benefit with tafamidis was observed in all patients with ATTR-CM, regardless of their AF/AFL status.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF and AFL are common manifestations of ATTR-CM and are more prevalent in advanced stages of the disease, but they do not appear to be predictive of mortality when accounting for other markers of disease severity. Current or historical AF/AFL does not impact the efficacy of tafamidis treatment for ATTR-CM.

TRANSLATIONAL OUTLOOK: Tafamidis treatment benefits patients with ATTR-CM presenting with and without AF/AFL. Future studies may look at the impact of tafamidis treatment on the development and course of AF/AFL in patients with ATTR-CM.

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