Meta-Regression Analysis of the Association Between Change in Six Minute Walk Distance and Survival in Transthyretin-Mediated Amyloidosis With Cardiomyopathy

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Conclusions

- **This meta-regression analysis shows that more favorable changes from baseline in the 6-minute walk test (6MWT) are associated with better survival among patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM)**
- **The estimated odds ratio (OR) for survival per 15-meter advantage in change in 6MWT distance from baseline to 12 months was 1.302 (95% confidence interval [CI]: 1.280, 1.325)**
- **This analysis further supports the role of change in 6MWT as an early indicator of survival outcomes in ATTR-CM**

Background and Rationale

- Transthyretin amyloidosis (ATTR) is a progressive and fatal disease caused by accumulation of misfolded transthyretin (TTR) protein into toxic amyloid fibrils that deposit in multiple organs and tissues, including the heart and peripheral nerves[1–4]
- When TTR amyloid deposits in the heart, patients experience progressive cardiomyopathy (CM), ultimately leading to death, which typically occurs between 2.5 and 5 years after diagnosis of ATTR-CM[5–7]
- Given the survival duration in patients with ATTR-CM, it may not be feasible in some cases to detect treatment effects on a practical timescale in clinical trials of ATTR-CM therapies, especially in patients with less severe disease
- In contrast, due to the more rapidly emergent effects of ATTR-CM on physical function, treatment effects on 6MWT distance can be detected on a practical timescale, even in the early stages of disease progression in ATTR-CM
- The 6MWT is considered a clinically meaningful measure in cardiopulmonary diseases as it assesses patients' functional capacity. In such diseases, it is an indicator of clinical status and disease trajectory, and has been shown to be predictive of mortality and cardiovascular (CV) events[8–10]

Objective

- To assess the relationship between 12-month change in 6MWT distance and longer-term survival, and thus explore the potential prognostic value of changes in 6MWT in ATTR-CM specifically, given the sensitivity of 6MWT to treatment in this condition

Methods

Study Identification and Data Sources

- A systematic literature review (SLR) was conducted to identify observational or interventional studies examining 6MWT together with survival and/or hospitalization as outcomes in patients with ATTR-CM
  - Of the publications identified:
    - Eight publications, originating from two clinical trials (ATTR-ACT[10–15] and ENDEAVOUR[16]) and one observational study (TRACS[7]), reported study-specific data on 6MWT together with survival and/or hospitalization in patients with ATTR-CM. These were further assessed for potential inclusion in a meta-regression analysis assessing the relationship of 6MWT with survival and/or hospitalization in ATTR-CM
    - The remainder focused on patients with dilated CM, or synthesized data from multiple studies without providing sufficient details on outcomes of interest at the level of the individual study
- For the studies underlying the eight publications identified via the SLR for potential inclusion in the meta-regression analysis, feasibility assessment evaluated similarity and heterogeneity among study designs, along with availability of relevant data
  - Based on the feasibility assessment, a meta-regression analysis using summary-level longitudinal data on change from baseline in 6MWT distance and survival from ATTR-ACT and TRACS was identified as feasible
    - Change from baseline in 6MWT distance and survival probabilities were assessed longitudinally in ATTR-ACT and TRACS with overlap between the two studies in terms of the time points at which 6MWT was assessed and in terms of the time points at which survival was assessed (**Table 1**)
  - This meta-regression analysis excluded data from the ENDEAVOUR study, as ENDEAVOUR did not report data on change from baseline in 6MWT distance[16]
  - A meta-regression analysis estimating the association between changes in 6MWT and CV-related hospitalization risk was deemed not feasible, as cardiovascular-related hospitalization rates were not reported at any common time points between the ATTR-ACT and TRACS studies (**Table 1**)

Methods (cont.)

- For the meta-regression analysis, beta-regression with logit link was used to estimate the association between 12-month changes in 6MWT distance and longer-term survival probabilities (controlling for follow-up visit month at which survival was assessed) based on summary-level statistics from the included studies (**Figure 1**)
  - Survival probabilities were derived from summary-level death counts, assuming independent censoring
  - Sensitivity analyses were conducted in which other variables (in addition to 12-month change in 6MWT and visit month) that are potentially associated with survival were adjusted for as covariates; these included ATTR type and baseline 6MWT

Figure 1. Meta-regression Analysis Study Design

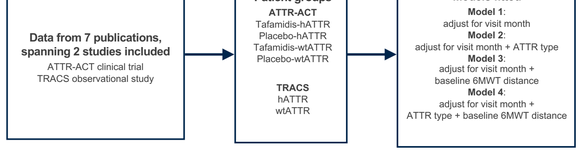

Table 1. Key characteristics of ATTR-ACT and TRACS studies

	ATTR-ACT[10–14]	TRACS[7]
Study description	Phase 3, multicenter, 3-arm, placebo-controlled, double-blind, randomized clinical trial	Prospective, observational natural history study
Key inclusion criteria	• Aged 18–90 years • Diagnosis of hATTR or wtATTR with CM • 6MWT distance >100 meters at baseline	• No age restriction • Diagnosis of hATTR (V1221) or wtATTR with CM
Follow-up	30 months	24 months
Cohort and sample size	441 patients randomized 2:1:2 to receive 80 mg tafamidis (n=176), 20 mg tafamidis (n=88), or placebo (n=177) for 30 months. The two tafamidis dosage groups were combined for primary analysis (n=176+88=264) • Tafamidis hATTR (n=63) • Tafamidis wtATTR (n=201) • Placebo hATTR (n=43) • Placebo wtATTR (n=134)	29 patients with ATTR-CM • hATTR (V1221 mutation) (n=11) • wtATTR (n=18)
Outcome assessment timepoints		
6MWT	Baseline, 6, 12, 18, 24, and 30 months	Baseline, 12 and 18 months
Survival	Probability at 6, 12, 18, 24, and 30 months	Probability at 6, 12, 18, and 24 months
Hospitalization	Proportion with CV-related hospitalizations at 30 months	Proportion with CV-related hospitalizations at 6, 12, 18, and 24 months
Association between 6MWT distance and survival or hospitalization	Association of baseline 6MWT distance with all-cause mortality and CV-related hospitalization was reported	Not reported

Results

Meta-regression Analysis Results

- Summary-level patient characteristics, changes in 6MWT distance, and survival probabilities from ATTR-ACT and TRACS that were used in the main meta-regression analysis or sensitivity analyses are summarized in (**Table 2**)

Table 2. Summary-level Patient Characteristics and Outcomes for Meta-regression Analysis of Change in 6MWT vs Survival

Study	Subgroup	Age (years)	Sex, n (%)	Race, n (%)	BMI or mBMI, mean ± SD	Visit	6MWT (mean ± SD)	% OS
ATTR-ACT (Rapezzi 2021)	Tafamidis - hATTR (n=63)	Mean ± SD: 71.6 ± 8.0 Median (range): 74.0 (46–85)	Male: 47 (74.6) Female: 16 (25.4)	White: 28 (44.4) Black: 34 (54.0) Asian: 1 (1.6) Other: 0 (0.0)	mBMI: 1006.0 ± 177.5	Baseline	297.1 ± 134.0 m	—
						6M	LS mean Δ: −37.4 m	87.3
						12M	LS mean Δ: −32.6 m	76.2
						18M	LS mean Δ: −49.5 m	66.7
						24M	LS mean Δ: −53.0 m	58.7
						30M	LS mean Δ: −80.2 m	52.8
	Tafamidis - wtATTR (n=201)	Mean ± SD: 75.5 ± 6.7 Median (range): 75.0 (56–88)	Male: 194 (96.5) Female: 7 (3.5)	White: 183 (91.0) Black: 3 (1.5) Asian: 12 (6.0) Other: 3 (1.5)	mBMI: 1075.3 ± 169.6	Baseline	367.3 ± 112.2 m	—
						6M	LS mean Δ: −7.6 m	98.0
						12M	LS mean Δ: −16.5 m	93.0
						18M	LS mean Δ: −28.6 m	86.6
						24M	LS mean Δ: −37.3 m	81.1
						30M	LS mean Δ: −43.1 m	73.1
	Placebo - hATTR (n=43)	Mean ± SD: 71.4 ± 8.1 Median (range): 73.0 (51–86)	Male: 29 (67.42) Female: 14 (32.6)	White: 22 (51.2) Black: 21 (48.8) Asian: 0 (0.0) Other: 0 (0.0)	mBMI: 1005.6 ± 225.1	Baseline	311.2 ± 117.1 m	—
						6M	LS mean Δ: −34.7 m	93.0
						12M	LS mean Δ: −61.9 m	81.4
						18M	LS mean Δ: −78.7 m	65.1
						24M	LS mean Δ: −120.6 m	48.8
						30M	LS mean Δ: −160.0 m	34.7
	Placebo - wtATTR (n=134)	Mean ± SD: 74.9 ± 6.0 Median (range): 75.0 (57–89)	Male: 128 (95.5) Female: 6 (4.5)	White: 124 (92.5) Black: 5 (3.7) Asian: 5 (3.7) Other: 0 (0.0)	mBMI: 1085.9 ± 180.2	Baseline	366.7 ± 126.2 m	—
						6M	LS mean Δ: −31.4 m	97.8
						12M	LS mean Δ: −50.7 m	94.0
						18M	LS mean Δ: −78.5 m	84.3
						24M	LS mean Δ: −100.9 m	72.4
						30M	LS mean Δ: −121.5 m	58.5
TRACS (Ruberg 2012)	wtATTR (n=18)	Mean ± SD: 76 ± 6	Male: 18 (100) Female: 0 (0.0)	Black: 0 (0.0) Other: 18 (100)	BMI: 25.0 ± 2.9	Baseline	368.5 ± 138.1 m	—
						12M	Δ from baseline: –24.9 ± 73.4 m	100.0
						18M	Δ from baseline: –43.9 ± 99.4 m	92.8
	hATTR (n=11)	Mean ± SD: 71 ± 5	Male: 9 (82.0) Female: 2 (18.0)	Black: 11 (100) Other: 0 (0.0)	BMI: 26.5 ± 3.7	Baseline	287.6 ± 173.5 m	—
						12M	Δ from baseline: –91.1 ± 43.9 m	100.0
						18M	Δ from baseline: –117.5 ± 72.5 m	90.5

Main Analysis

- In the main analysis (Model 1, adjusted for follow-up visit month only), the estimated OR for survival (95% CI) per 15-meter improvement in change in 6MWT distance from baseline to 12 months was 1.302 (1.280, 1.325) (**Table 3**)

Table 3. Main Analysis (Model 1); Estimated Association between 12-Month Change in 6MWT Distance (Per 15-Meter Improvement in Change from Baseline) and Survival Probability

Variable	Survival OR (95% CI)	p
Δ6MWT distance from baseline to 12 months, +15 m difference	1.302 (1.280, 1.325)	<0.001
Follow-up visit		
18 months	Reference	—
24 months	0.549 (0.520, 0.579)	<0.001
30 months	0.343 (0.326, 0.362)	<0.001

Sensitivity Analysis

- In sensitivity analyses (**Table 4**), the magnitude of association between 6MWT distance change from baseline to 12 months and survival slightly decreased when adjusting for ATTR type (Model 2), baseline 6MWT distance (Model 3), and ATTR type and baseline 6MWT distance (Model 4)

Table 4. Sensitivity Analyses (Models 2–4); Estimated Associations between 12-Month Change in 6MWT Distance (Per 15-Meter Improvement in Change from Baseline) and Survival Probability

Variable	Model 2		Model 3		Model 4	
	Survival OR (95% CI)	p	Survival OR (95% CI)	p	Survival OR (95% CI)	p
Δ6MWT distance from baseline to 12 months, +15 m difference	1.175 (1.162, 1.188)	<0.001	1.194 (1.181, 1.208)	<0.001	1.153 (1.141, 1.165)	<0.001

Discussion

- This study was the first to assess the association between changes in 6MWT, as a short-term measure, and survival, as a longer-term endpoint, in ATTR-CM
- Results were directionally consistent with prior work on the associations between baseline 6MWT distance and mortality,[9,10] and association between changes in 6MWT distance and survival in patients with chronic heart failure[8]
  - Based on the current analysis, at a given time point beyond 12 months, a patient whose 12-month change from baseline in 6-MWT was 15 meters better than that of another patient would be expected to have approximately 15–30% higher relative odds of survival compared with that patient
- The results of this analysis should be considered in context of the following limitations:
  - A limited number of studies were appropriate for inclusion in the analysis
  - Summary-level data on survival probabilities were used, assuming patients were censored at a constant rate during the follow-up period and across different studies
  - The model did not consider potential interactions between the variables included in the regression model
  - The range of covariates that could be adjusted for in the model was limited to those reported in the studies included in the analysis

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Abbreviations: 6MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR amyloidosis with cardiomyopathy; BMI, body mass index; CI, confidence interval; CM, cardiomyopathy; CV, cardiovascular; hATTR, hereditary transthyretin-mediated amyloidosis; LS, least squares; m, meters; M, months; mBMI, modified body mass index; OR, odds ratio; OS, overall survival; SD, standard deviation; SLR, systematic literature review; TTR, transthyretin; wt, wild type.

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