Relative Importance of Markers of Progression in Patients With Transthyretin Amyloid Cardiomyopathy Receiving Tafamidis: Post Hoc Analysis

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INTRODUCTION

- Tafamidis is the only transthyretin (TTR) kinetic stabilizer for treating transthyretin amyloid cardiomyopathy (ATTR-CM) that is administered orally once daily and has demonstrated a statistically significant reduction in mortality at 30 months compared with placebo.[1-3]
- The approval of tafamidis meglumine 80 mg and its bioequivalent tafamidis free acid 61 mg was based on the landmark phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT).[1]
  - This pivotal study demonstrated that tafamidis significantly improved clinical outcomes in patients with ATTR-CM, and slowed disease progression, as shown by 6-minute walking distance (6MWD) preservation and improved scores on the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) compared with placebo.[1]
- A 2025 expert consensus identified key markers strongly associated with prognosis and validated cut-offs for predicting all-cause mortality (ACM) and cardiovascular hospitalizations (CVH), including N-terminal pro–B-type natriuretic peptide (NT-proBNP), 6MWD distance, KCCQ-OS score, outpatient diuretic intensification (ODI), and estimated glomerular filtration rate (eGFR).[4]
- This post-hoc analysis aimed to rank the relative importance of individual markers of disease progression for predicting time to ACM and time to recurrent CVH.
  - This analysis also aimed to assess the impact of multiple markers of disease progression on ACM and CVH outcomes in patients.

METHODS

Statistical Analysis

- Patients who were enrolled and received tafamidis 80/61 mg and survived for the first 12 months of treatment were included.
  - The Cox proportional hazard model was used to analyze time to ACM, including heart transplant or cardiac mechanical-assisted device implantation from Month 12 onwards until the end of the long-term extension (LTE), and to compare marker stability vs marker progression.
  - The Liu-Wei-Yang-Ying (LWYY) model assumed arbitrary dependence structures among recurrent events within the same patient was implemented to analyze the time to recurrent CVH from Month 12 onwards, until the end of the LTE.

Cohorts and Evaluable Markers

- Two separate cohorts were used.
- ATTR-ACT[1]: patients who survived until Month 12 of ATTR-ACT, continued treatment until the end of the LTE study, and followed up for 78 months.
  - 6 markers of disease progression were included to evaluate time to ACM and time to recurrent CVH (**Table 1**):
    - 6MWD.
    - CVH in the first 12 months (to evaluate ACM).
    - KCCQ-OS.
    - eGFR.
    - New York Heart Association (NYHA) functional classification.
    - NT-proBNP.
- LTE[5]: patients who survived until Month 12 of the LTE study, continued treatment until the end of the study and were followed up for 48 months.
  - 5 disease markers were included to evaluate time to ACM and time to recurrent CVH (**Table 1**):
    - CVH in the first 12 months (to evaluate ACM).
    - ODI.
    - eGFR.
    - KCCQ OS.
    - NYHA functional classification.

Relative Importance of Markers of Disease Progression for Time to ACM and Time to Recurrent CVH

- Two models were used for each marker of disease progression.
  - Base model included *TTR* genotype (variant, wild-type).
  - Each marker (stable vs progression) was added one at a time to the base model to evaluate the gain in likelihood ratio Chi-square (LR χ^2) statistics.

Table 1: Description of datasets and markers of disease progression

	ATTR-ACT cohort (N=142, subsequent follow-up 78 months)	LTE cohort (N=895, subsequent follow-up 48 months)
Markers available	6WMD, KCCQ-OS, eGFR, NT-proBNP, NYHA	ODI, KCCQ-OS, eGFR, NYHA
Markers not available	ODI	6WMD, NT-proBNP (small sample size; therefore, not evaluated)
CVH as a marker for ACM	Yes	Yes

The progression status of the markers was considered the risk factor for worsening disease prognosis and defined as variations in NT-proBNP concentration (an absolute increase of >700 pg/mL with a relative increase >30%), 6MWD (an absolute reduction >35 m), KCCQ-OS score (>5-point decrease in score), ODI (initiation of any new oral loop diuretic or a sustained increase in dose for ≥30 days), NYHA classification (increase in classification), eGFR (a decrease with a threshold >20%, calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation).[5]
6MWD=6-minute walking distance; ACM=all-cause mortality; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CVH=cardiovascular hospitalization; eGFR=estimated glomerular filtration rate; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LTE=long-term extension; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; ODI=outpatient diuretic intensification

- In both Cox proportional hazards model and the LWYY model, markers with the greatest gain in LR χ^2 were ranked as the most important in predicting long-term ACM or CVH in ATTR-ACT and LTE cohort separately.

Comparison of the Number of Markers of Disease Progression on Time to ACM and Time to Recurrent CVH

- The number of risk factors (progression status of the marker) was determined for each patient in each cohort.
  - Pairwise comparison among the number of markers was conducted for the hazard ratio (HR) obtained from Cox model (time to ACM), and LWYY model (time to recurrent CVH).

RESULTS

- In the landmark analysis sets, 155 patients with available marker data were included in ATTR-ACT and 895 were included in the LTE cohort.

Relative Importance of Markers of Disease Progression for Time to ACM

ATTR-ACT Cohort (78-month follow-up, N=155)

- 6MWD had the strongest association with time to ACM (based on the gain in LR χ^2) with a 58% hazard reduction (**Figure 1A**). In descending order, the importance of markers was:
  - CVH within the first 12 months.
  - KCCQ-OS.
  - eGFR.
  - NYHA functional class.
  - NT-proBNP.

LTE Cohort (48-month follow-up, N=895)

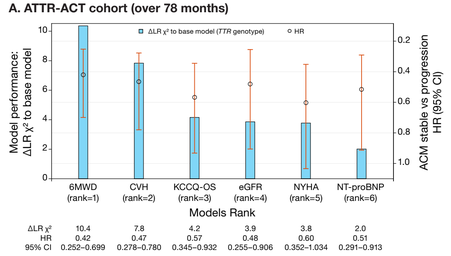
- CVH within the first 12 months had the strongest association with time to ACM (based on the gain in LR χ^2) with a 58% hazard reduction (**Figure 1B**). In descending order, the importance of markers was:
  - ODI.
  - eGFR.
  - KCCQ-OS.
  - NYHA functional classification.

Relative Importance of Markers of Disease Progression for Time to Recurrent CVH

ATTR-ACT Cohort (78-month follow-up, N=155)

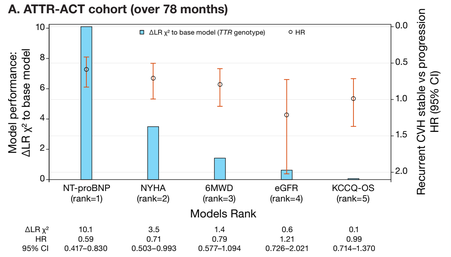
- NT-proBNP had the strongest association with time to recurrent CVH based on the gain in LR χ^2) with a 41% hazard reduction (**Figure 2A**). In descending order, the importance of markers was:
  - NYHA functional classification.
  - 6MWD.
  - eGFR.
  - KCCQ-OS.

Figure 1: Relative importance of markers of disease progression for time to ACM



Δ=change; 6MWD=6-minute walking distance; ACM=all-cause mortality; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CVH=cardiovascular hospitalization; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LTE=long-term extension; LR χ^2=likelihood ratio Chi-square; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; ODI=outpatient diuretic intensification; *TTR*=transthyretin

Figure 2: Relative importance of markers of disease progression for time to recurrent CVH



Δ=change; 6MWD=6-minute walking distance; ACM=all-cause mortality; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CVH=cardiovascular hospitalization; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LTE=long-term extension; LR χ^2=likelihood ratio Chi-square; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; ODI=outpatient diuretic intensification; *TTR*=transthyretin

Table 2: Pairwise comparison of the number of markers of disease progression on time to ACM and time to recurrent CVH over 78 months in the ATTR-ACT cohort (N=142)

	Cox model for time to ACM events				LWYY model for time to recurrent CVH[a]			
	n	Markers of disease progression	HR (95% CI)	P value	n	Markers of disease progression	HR (95% CI)	P value
1 vs 0 risk	40 vs 40	KCCQ-OS, 6MWD, eGFR, NT-proBNP, NYHA, CVH	2.00 (0.927–4.314)	0.0775	43 vs 46	KCCQ-OS, 6MWD, eGFR, NT-proBNP, NYHA[a]	1.27 (0.893–1.804)	0.1845
2 vs 0 risks	25 vs 40		1.70 (0.671–4.318)	0.2631	24 vs 46		1.35 (0.856–2.134)	0.1955
3 vs 0 risks	20 vs 40		2.51 (1.017–6.221)	0.0460	29 vs 46		1.31 (0.839–2.057)	0.2336
4+ vs 0 risks	17 vs 40		9.82 (4.075–23.659)	<0.0001	N/A[b]		N/A[b]	N/A[b]

[a] LWYY Model for time to recurrent CVH, 3+ risks vs 0 risk.
[b] N/A=no patients had 4 risk factors to evaluate time to recurrent CVH.
Poisson regression model to compare frequency of subsequent reoccurred CVH, with group as the main effect adjusted for baseline *TTR* genotype.
HR obtained from LWYY model, with group as the main effect adjusted for baseline *TTR* genotype as the covariate.
6MWD=6-minute walking distance; ACM=all-cause mortality; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CVH=cardiovascular hospitalization; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LWYY=Lin-Wei-Yang-Ying; N/A=not available; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; *TTR*=transthyretin

Table 3: Pairwise comparison of the number of markers of disease progression on time to ACM and time to recurrent CVH over 48 months in the LTE cohort (N=895)

	Cox model for time to ACM events				LWYY model for time to recurrent CVH[a]			
	n	Markers of disease progression	HR (95% CI)	P value	n	Markers of disease progression	HR (95% CI)	P value
1 vs 0 risk	273 vs 283	KCCQ-OS, ODI, eGFR, NYHA, CVH	0.84 (0.560–1.265)	0.4058	295 vs 302	KCCQ-OS, ODI, eGFR, NYHA	1.60 (1.041–2.469)	0.0324
2 vs 0 risks	196 vs 283		1.92 (1.322–2.782)	0.0006	209 vs 302		3.42 (2.247–5.190)	<0.0001
3 vs 0 risks	95 vs 283		2.43 (1.575–3.757)	<0.0001	74 vs 302		4.81 (2.916–7.936)	<0.0001
4 vs 0 risks	48 vs 283[b]		4.53 (2.742–7.472)	<0.0001	15 vs 302		3.36 (1.193–9.475)	0.0218

[a] In the LWYY Model for time to recurrent CVH, 2+ risks vs 0 risk.
[b] In the Cox Model for time to recurrent CVH, 4+ risks vs 0 risk.
Poisson regression model to compare frequency of subsequent reoccurred CVH, with group as the main effect adjusted for baseline *TTR* genotype.
HR obtained from LWYY model, with group as the main effect adjusted for baseline *TTR* genotype as the covariate.
ACM=all-cause mortality; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CVH=cardiovascular hospitalization; eGFR=estimated glomerular filtration rate; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LTE=long-term extension; LWYY=Lin-Wei-Yang-Ying; NYHA=New York Heart Association; ODI=outpatient diuretic intensification; *TTR*=transthyretin

LTE Cohort (48-month follow-up, N=895)

- ODI had the strongest association with time to recurrent CVH based on the gain in LR χ^2) (**Figure 2B**) with a 47% hazard reduction. In descending order, the importance of markers was:
  - KCCQ-OS.
  - eGFR.
  - NYHA functional classification.

Comparison of the Number of Markers of Disease Progression and Their Impact on Time to ACM and Time to Recurrent CVH

ATTR-ACT Cohort (78-month follow-up, N=142)

- Patients in ATTR-ACT with 2 or more markers of disease progression (n=25) had a greater ACM hazard compared with patients with no markers (n=40) (**Table 2**).
  - The presence of markers of disease progression in patients in ATTR-ACT was associated with only a small, nonsignificant increase in CVH risk compared with patients with no markers due to the small sample size in this cohort (**Table 2**).

LTE Cohort (48-month follow-up, N=895)

- Patients in the LTE with 2 or more markers (n=196) had a significantly greater ACM hazard compared with patients with no markers (n=283) (**Table 3**).
  - Patients in the LTE with 1 or more markers had a significantly greater CVH hazard compared with patients with no markers (**Table 3**). This was attributed to the large sample size in the LTE cohort.

CONCLUSIONS

- This analysis demonstrates that key markers of disease progression, including CVH, patient-reported health status, functional capacity, renal function, and biomarkers, show clinically meaningful associations with mortality and CVH across independent ATTR-CM cohorts and follow-up durations.
- Despite differences in study design, disease severity, and observation period, the relative importance of these markers remained largely concordant, supporting their robustness and relevance for risk stratification.
- These findings provide a strong foundation for the development of integrated risk-scoring approaches that combine multiple markers to guide clinical decision-making.

REFERENCES

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DISCLOSURES

PGP: Speaker fees: Alnylam, AstraZeneca, Bayer, BridgeBio, Intellia, Ionis, Novo Nordisk, Pfizer; scientific meeting expenses: Alnylam, Pfizer; consultancy fees: Alexion, Alnylam, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia, Ionis, Neuroimmune, Novo Nordisk, Pfizer; his institution has received research grants/educational support from Alnylam, AstraZeneca, Bayer, BridgeBio, Intellia, Novo Nordisk, and Pfizer. **MH:** Advisory boards for Alnylam, Eidos, Ionis, Alexion Pharmaceuticals, and Pfizer. **MG:** Research funding from Alnylam, Eidos, Pfizer, Novo Nordisk, and Janssen; license/patent pending from Anumana (algorithm to detect cardiac amyloidosis using AI ECG); Advisory boards for Janssen, Novo Nordisk, Alnylam, BridgeBio, and AstraZeneca. **RMW:** Paid adviser: Alexion, Alnylam, AstraZeneca, BridgeBio, Medison, and Pfizer. **VM, RW:** Employees of and hold stock or stock options in Pfizer.

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