Tafamidis Treatment Significantly Reduces The Risk of All-Cause Mortality, First and Recurrent Cardiovascular-related Hospitalization in Patients With Early Stage Transthyretin Amyloid Cardiomyopathy

A post-hoc analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT)

Martha Grogan (Mayo Clinic, Rochester, MN, USA)

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Background

- In the phase 3, multinational, randomized, placebo-controlled ATTR-ACT (NCT01994889) of patients with ATTR-CM, treatment with tafamidis was associated with improved clinical outcomes and quality of life vs placebo.[1]
- Compared with placebo, the combined primary endpoint of all-cause mortality and CV-related hospitalizations was significantly lower with tafamidis 80 mg[a] (P=0.003).[2]
- The risk of CV-related hospitalizations was reduced by 30% vs placebo: relative risk ratio 0.70 (95% CI: 0.57–0.85); P=0.0005.[2]
- The benefit of tafamidis treatment was greatest among patients with NYHA class I/II at baseline.[1,3,4]

Purpose of this post hoc analysis

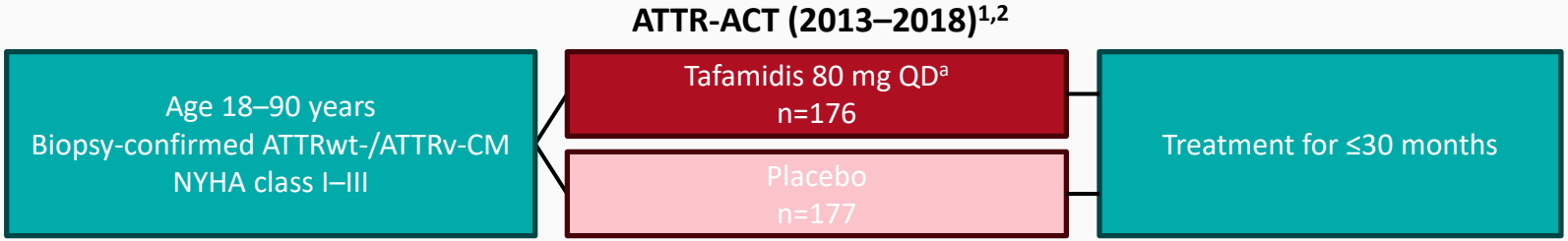
To evaluate the risk of first, recurrent (≥1) CV-related hospitalization and combined primary endpoint in patients with baseline NYHA class I/II in participants in ATTR-ACT taking the approved dose of tafamidis or placebo.

[a] Approved dose for the treatment of ATTR-CM.

ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM=transthyretin amyloid cardiomyopathy; CV=cardiovascular; NYHA=New York Heart Association

1. Maurer M, et al. N Engl J Med 2018;379:1007-16. **2.** Damy T, et al. Eur J Heart Fail 2021;23(2):277-85. **3.** Li H, et al. Cardiology 2022;147(4):398-405. **4.** Vong C, et al. Cardiovasc Drugs 2021;21(5):535-43.

Methods for this post hoc analysis



- Patients were categorized as:
  1. NYHA class I–III at baseline (overall population), or
  2. NYHA class I/II at baseline.
- The HR for first CV-related hospitalization was calculated using a Cox proportional hazards model.[b]
- The HR for recurrent CV-related hospitalization and the combined primary endpoint was calculated using the Liu-Wei-Yang-Ying (modified Anderson-Gill) model.[b]

[a] Approved dose for the treatment of ATTR-CM. The ATTR-ACT trial also included a tafamidis 20 mg cohort.
[b] Adjusted for transthyretin genotype (wild-type or variant) and for baseline NYHA class (overall population only).
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTRwt-/ATTRv-CM=wild-type/variant transthyretin amyloid cardiomyopathy; HR=hazard ratio; NYHA=New York Heart Association; QD=once daily

1. Maurer M, et al. N Engl J Med 2018;379:1007-16. **2.** Damy T, et al. Eur J Heart Fail 2021;23(2):277-85.

Baseline characteristics

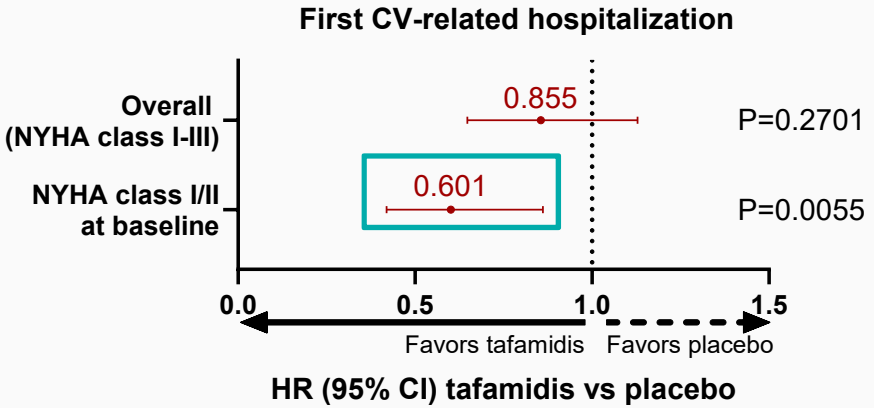
No notable differences between subgroups.

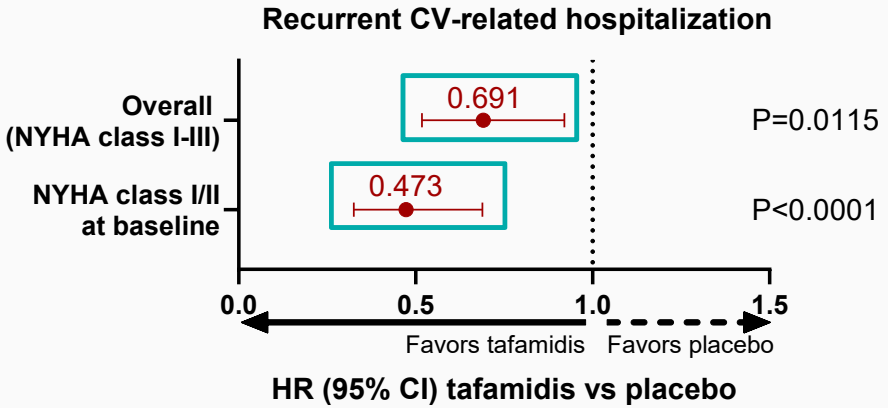
	Overall (NYHA class I–III)		NYHA class I/II at baseline	
	Tafamidis 80 mg n=176	Placebo n=177	Tafamidis 80 mg n=121	Placebo n=114
Age, median (SD), y	74.0 (6.7)	76.0 (7.2)	74.0 (6.5)	75.0 (7.1)
<80 y, n (%)	125 (71.0)	140 (79.1)	87 (71.9)	97 (85.1)
≥80 y, n (%)	51 (29.0)	37 (20.9)	34 (28.1)	17 (14.9)
Male, %	158 (89.8)	157 (88.7)	113 (93.4)	105 (92.1)
Genotype, n (%)				
Wild-type	134 (76.1)	134 (75.7)	99 (81.8)	90 (78.9)
Variant	42 (23.9)	43 (24.3)	22 (18.2)	24 (21.1)
Medical history, n (%)				
AF/AFL	112 (63.6)	118 (66.7)	78 (64.5)	70 (61.4)
IHD	11 (6.3)	6 (3.4)	9 (7.4)	3 (2.6)
Stroke	0	2 (1.1)	0	1 (0.9)
COPD	8 (4.5)	11 (6.2)	2 (1.7)	7 (6.1)
Diabetes mellitus	23 (13.1)	33 (18.6)	12 (9.9)	17 (14.9)
NYHA class				
I	16 (9.1)	13 (7.3)	16 (13.2)	13 (11.4)
II	105 (59.7)	101 (57.1)	105 (86.8)	101 (88.6)
III	55 (31.3)	63 (35.6)	n/a	n/a
NT-proBNP, median (range), pg/mL	3161 (298–16787)	3122 (392–22020)	2816 (457–16600)	2672 (392–12380)
Median follow-up, median (Q1, Q3), mo	29.9 (29.2, 30.2)	29.7 (21.1, 30.2)	30.0 (29.7, 30.2)	29.9 (24.0, 30.2)

AF/AFL=atrial flutter/atrial fibrillation; COPD=chronic obstructive pulmonary disease; IHD=ischemic heart disease; n/a=not applicable; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; Q=quartile

Risk of first and recurrent CV-related hospitalizations

In patients with NYHA class I/II at baseline, the risks of first and recurrent CV-related hospitalizations[a] were significantly lower with tafamidis vs placebo (40% and 53%, respectively).





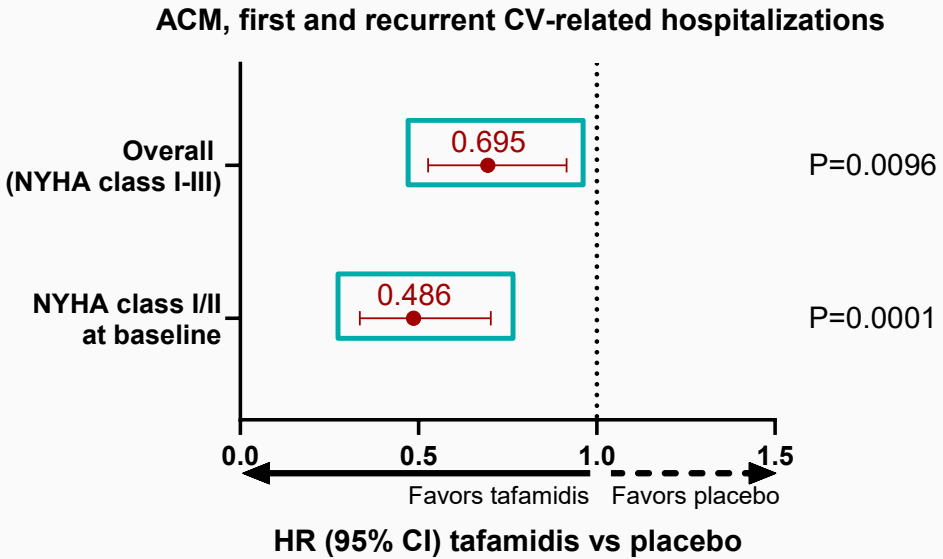
Median time to first CV-related hospitalization (Q1, Q3), months			
Overall		NYHA class I/II at baseline	
Tafamidis 80 mg n=176	Placebo n=177	Tafamidis 80 mg n=121	Placebo n=114
23.3 (6.6, 29.9)	14.3 (7.1, 28.6)	29.2 (11.2, 30.1)	16.5 (8.6, 29.6)

[a] On study.

CV=cardiovascular; HR=hazard ratio; NYHA=New York Heart Association; Q=quartile

Risk of ACM, first and recurrent CV-related hospitalization events

In the overall cohort and patients with NYHA class I/II at baseline, the risk of ACM[a], first and recurrent CV-related hospitalizations[b] (combined, hierarchical primary endpoint) were significantly lower with tafamidis vs placebo.



[a] Including heart transplants or implantation of a cardiac mechanical assist device during on study or during the follow-up period on study and during subsequent follow-up.

[b] On study.

ACM=all-cause mortality; CV=cardiovascular; HR=hazard ratio; NYHA=New York Heart Association

Summary and conclusions

- In ATTR-ACT, the risk of recurrent CV-related hospitalizations with tafamidis 80 mg was significantly lower vs placebo in the overall patient population.
- A significant reduction in first and recurrent CV-related hospitalizations was seen in patients with low disease burden (NYHA class I/II) at baseline treated with tafamidis vs placebo.
- In the overall patient population and those with low disease burden at baseline, the risk of all-cause mortality, first and recurrent CV-related hospitalizations was also significantly reduced with tafamidis vs placebo.

The risk of all-cause mortality, first and recurrent CV-related hospitalizations was lowest in patients with early stage ATTR-CM treated with tafamidis.

ATTR-CM=transthyretin amyloid cardiomyopathy; CV=cardiovascular; NYHA=New York Heart Association

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