

Improved long-term survival with tafamidis treatment in patients with transthyretin amyloid cardiomyopathy and severe heart failure symptoms

Perry Elliott^{1*}, Balarama Gundapaneni², Marla B. Sultan³, Monica Ines⁴, and Pablo Garcia-Pavia^{5,6,7}

¹University College London, London, UK; ²Pfizer Inc, Groton, CT, USA; ³Pfizer Inc, New York, NY, USA; ⁴Pfizer Inc, Porto Salvo, Portugal; ⁵Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain; ⁶Universidad Francisco de Vitoria, Madrid, Spain; and ⁷CNIC, Madrid, Spain

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Aim

The value of disease-modifying therapies (such as tafamidis) in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) and severe heart failure symptoms has been debated. This study assessed long-term all-cause survival in patients with New York Heart Association (NYHA) class III symptoms in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) long-term extension (LTE) study.

Methods and results

At the baseline of ATTR-ACT, 55/176 (31.3%) patients receiving tafamidis 80 mg and 63/177 (35.6%) receiving placebo had NYHA class III symptoms. After 30 months of treatment, patients could join an ongoing LTE study to receive open-label tafamidis. In an interim analysis of the LTE study (August 2021), all-cause mortality was lower among patients with NYHA class III symptoms who received continuous tafamidis in ATTR-ACT and the LTE study (hazard ratio 0.64; 95% confidence interval 0.41–0.99; median follow-up: 60 months), as compared with those who received placebo in ATTR-ACT and tafamidis in the LTE study (median follow-up: 56 months). Similar findings were observed in patients with NYHA class I/II symptoms at baseline (0.50; 0.35–0.73; tafamidis 80 mg $n = 121$; placebo $n = 114$; median follow-up of 61 and 60 months, respectively).

Conclusion

We observed reduced all-cause mortality with continuous tafamidis treatment compared with delayed tafamidis treatment (placebo then tafamidis) in patients with NYHA class III symptoms at baseline over a median follow-up of ~5 years. These findings demonstrate the value of tafamidis treatment in patients with ATTR-CM and severe heart failure symptoms, and emphasize the importance of early treatment.

Clinical Trial Registrations: ClinicalTrials.gov NCT01994889 and NCT02791230.

Keywords

Amyloidosis • Survival rate • ATTR-ACT • Prognosis • Trial

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by myocardial deposition of variant or wild-type transthyretin amyloid.¹ It is a progressive condition that leads to heart failure.¹ While outcomes can be improved with early diagnosis and treatment,

median untreated survival is reported to be between 2 and 6 years.^{2–7}

Tafamidis is the first disease-modifying therapy approved for the treatment of patients with ATTR-CM.^{8,9} This approval was based on favourable findings from the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), for which a long-term

*Corresponding author: Institute of Cardiovascular Science, University College London, Paul O’Gorman Building, 72 Huntley St, London WC1E 6DD, UK. Tel: +44 20 76796500, Email: perry.elliott@ucl.ac.uk

extension (LTE) study is ongoing.^{9–12} ATTR-ACT showed significantly reduced all-cause mortality in patients treated with tafamidis versus placebo over 30 months of treatment.¹⁰ Subsequent real-world studies have also shown an early and persistent difference in survival outcomes between patients treated with tafamidis versus placebo across various age groups, disease severities, and transthyretin genotypes.^{13–15}

Severe heart failure symptoms are associated with shorter median survival in patients with ATTR-CM.^{16–18} While ATTR-ACT was not powered for subgroup analyses, trends for improved survival with tafamidis treatment were evident in patients with New York Heart Association (NYHA) class I–III symptoms at baseline, and were most pronounced in those with class I or II (i.e. less severe disease).^{10,19} Exploratory analyses also showed an inverse relationship between all-cause mortality and 6-min walk test distances at baseline.²⁰ In ATTR-ACT, cardiovascular-related hospitalizations were reduced in patients with NYHA class I/II symptoms at baseline but increased in those who had NYHA class III symptoms.¹⁰ This was unexpected considering the improved survival and disease severity measures in this group, and has since been shown to be at least partially due to the confounding effect of reduced mortality, where patients with severe disease live longer and have more opportunity to experience cardiovascular-related hospitalization.²¹ Use of a survivor average causal effect method to adjust for the confounding effect of death found a 24% lower risk of cardiovascular-related hospitalizations in patients with NYHA class III symptoms treated with tafamidis.²¹ Together, these findings have raised questions around the value of tafamidis in patients with late-stage ATTR-CM.

In order to determine the efficacy of tafamidis in patients with ATTR-CM and severe heart failure, we analysed long-term all-cause mortality data from the most recent interim analysis of the ongoing ATTR-ACT LTE study (August 2021) in patients with NYHA class III symptoms.

Methods

Studies

ATTR-ACT was a multicentre, international, double-blind, placebo-controlled, parallel design, randomized, phase 3 trial (NCT01994889).¹⁰ In brief, patients with confirmed ATTR-CM and a history of heart failure were randomized 2:1:2 to receive daily tafamidis meglumine 80 mg, tafamidis meglumine 20 mg, or placebo for 30 months. Randomization was stratified by genotype and NYHA class (I or II/III).

Patients completing ATTR-ACT could enrol in an LTE study to receive up to an additional 60 months of tafamidis treatment (NCT02791230).¹² Patients receiving tafamidis (80 or 20 mg meglumine) in ATTR-ACT initially continued this dose in the LTE study. Those who had received placebo in ATTR-ACT were randomized 2:1 to tafamidis meglumine 80 or 20 mg, stratified by genotype. Following a protocol amendment in July 2018, patients transitioned to the approved tafamidis dosage of once-daily tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg. The LTE study is ongoing.

Both studies were approved by the independent review board or ethics committee at each participating centre and were conducted

in accordance with the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

All-cause mortality

All-cause mortality was a co-primary outcome in ATTR-ACT.¹⁰ This post-hoc analysis includes data on all-cause mortality from the latest interim data cut from the ongoing ATTR-ACT LTE study taken on 1 August 2021. Two groups were compared: (1) patients who received continuous tafamidis (tafamidis meglumine 80 mg in ATTR-ACT and then tafamidis free acid 61 mg in the LTE study); and (2) those who received placebo in ATTR-ACT and then tafamidis in the LTE study (termed the placebo to tafamidis group). Data from patients who received tafamidis meglumine 20 mg in ATTR-ACT are not included in any part of this analysis, as this dose has not been approved for the treatment of patients with ATTR-CM.

All-cause mortality was assessed for each NYHA group (I/II or III) using a Cox proportional hazards model with treatment and genotype included in the model. Heart transplantation or implantation of a mechanical ventricular assist device were considered equivalent to death.

Results

Overall, 110/176 patients treated with tafamidis 80 mg and 82/177 treated with placebo in ATTR-ACT subsequently enrolled and received tafamidis in the LTE study. Median follow-up time from ATTR-ACT baseline to the LTE study interim analysis was 61 months for patients in the continuous tafamidis group and 59 months for those in the placebo to tafamidis group.

NYHA class III patients

At the baseline of ATTR-ACT, 55/176 (31.3%) patients receiving tafamidis meglumine 80 mg and 63/177 (35.6%) patients receiving placebo had NYHA class III symptoms (Table 1). The median age of patients with NYHA class III symptoms was 76 years. Of those who received tafamidis, 82% of patients were male, 62% were White, and 64% had a wild-type transthyretin genotype. Of those who received placebo, 83% of patients were male, 83% were White, and 70% had a wild-type transthyretin genotype.

At the interim LTE study analysis, all-cause mortality was 64% in the continuous tafamidis group and 81% in the placebo to tafamidis group (Table 2). A Kaplan–Meier curve of observed all-cause mortality over time is presented in the Figure 1. The hazard ratio (HR) for all-cause mortality in the continuous tafamidis versus the placebo to tafamidis group was 0.64 (95% confidence interval [CI] 0.41–0.99; $p = 0.0460$).

NYHA class I/II patients

At the baseline of ATTR-ACT, 121/176 (68.8%) patients receiving tafamidis meglumine 80 mg and 114/177 (64.4%) patients receiving placebo had NYHA class I/II symptoms (Table 1). Among patients receiving tafamidis, the median age was 75 years, 93% were male,

Table 1 Patient characteristics at baseline by New York Heart Association class

| | NYHA class I/II | | NYHA class III | |
|---|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| | Continuous tafamidis (n = 121) | Placebo to tafamidis (n = 114) | Continuous tafamidis (n = 55) | Placebo to tafamidis (n = 63) |
| Age, years | | | | |
| Mean (SD) | 75 (7.1) | 73 (6.5) | 76 (7.6) | 76 (6.8) |
| Median (range) | 75 (56–88) | 74 (53–86) | 76 (46–87) | 76 (51–89) |
| Male sex, n (%) | 113 (93.4) | 105 (92.1) | 45 (81.8) | 52 (82.5) |
| Race, n (%) | | | | |
| White | 102 (84.3) | 94 (82.5) | 34 (61.8) | 52 (82.5) |
| Black | 9 (7.4) | 16 (14.0) | 17 (30.9) | 10 (15.9) |
| Asian | 8 (6.6) | 4 (3.5) | 3 (5.5) | 1 (1.6) |
| Other | 2 (1.7) | 0 | 1 (1.8) | 0 |
| Transthyretin genotype, n (%) | | | | |
| Wild-type | 99 (81.8) | 90 (78.9) | 35 (63.6) | 44 (69.8) |
| Variant | 22 (18.2) | 24 (21.1) | 20 (36.4) | 19 (30.2) |
| NT-proBNP, pg/ml, median (UQ–LQ) | 2672 (1722.0–4235.6) | 2816 (1766.0–4360.0) | 4410 (2625.0–7166.0) | 4079 (2321.0–5269.0) |
| Troponin I ^a , ng/ml, median (UQ–LQ) | 0.13 (0.08–0.18) | 0.13 (0.08–0.18) | 0.18 (0.13–0.30) | 0.14 (0.08–0.22) |
| 6MWT distance, m, median (UQ–LQ) | 383 (310–451) | 409 (327–475) | 256 (195–340) | 250 (180–333) |

6MWT, 6-min walk test; LQ, lower quartile; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; UQ, upper quartile.

Patients continuously treated with tafamidis meglumine 80 mg/free acid 61 mg, or placebo then tafamidis. *n* denotes number of patients.

^aTroponin I level missing for one placebo-treated patient with NYHA I/II symptoms (*n* = 113).

Table 2 All-cause mortality with tafamidis by baseline New York Heart Association class at interim analysis of the ATTR-ACT long-term extension study

| | NYHA class I/II | | NYHA class III | |
|---|--------------------------------|--------------------------------|-------------------------------|-------------------------------|
| | Continuous tafamidis (n = 121) | Placebo to tafamidis (n = 114) | Continuous tafamidis (n = 55) | Placebo to tafamidis (n = 63) |
| Interim LTE study analysis dated 1 August 2021 | | | | |
| Follow-up ^a , months, median (95% CI) | 61 (60–66) | 60 (56–65) | 60 (48–75) | 56 (51–74) |
| All-cause mortality after treatment initiation | | | | |
| <i>n</i> (%) | 49 (40.5) | 70 (61.4) | 35 (63.6) | 51 (81.0) |
| Due to: | | | | |
| Death | 42 (34.7) | 64 (56.1) | 33 (60.0) | 51 (81.0) |
| Heart transplant | 6 (5.0) | 6 (5.3) | 1 (1.8) | 0 |
| Mechanical ventricular assist device implantation | 1 (0.8) | 0 | 1 (1.8) | 0 |

CI, confidence interval; LTE, long-term extension; NYHA, New York Heart Association.

Patients continuously treated with tafamidis meglumine 80 mg/free acid 61 mg, or placebo then tafamidis.

^aMedian follow-up duration from Kaplan–Meier method.

84% were White, and 82% had a wild-type transthyretin genotype. Among patients receiving placebo, the median age was 74 years, 92% were male, 83% were White, and 79% had a wild-type transthyretin genotype.

At the interim LTE study analysis, all-cause mortality was 41% in the continuous tafamidis group and 61% in the placebo to tafamidis group, with an HR that remained favourable towards continuous

tafamidis treatment (HR 0.50; 95% CI 0.35–0.73; *p* = 0.0003; Table 2; Figure 1).

Safety

Adverse events reported in patients receiving continuous tafamidis are presented in online supplementary Table S1. The overall safety

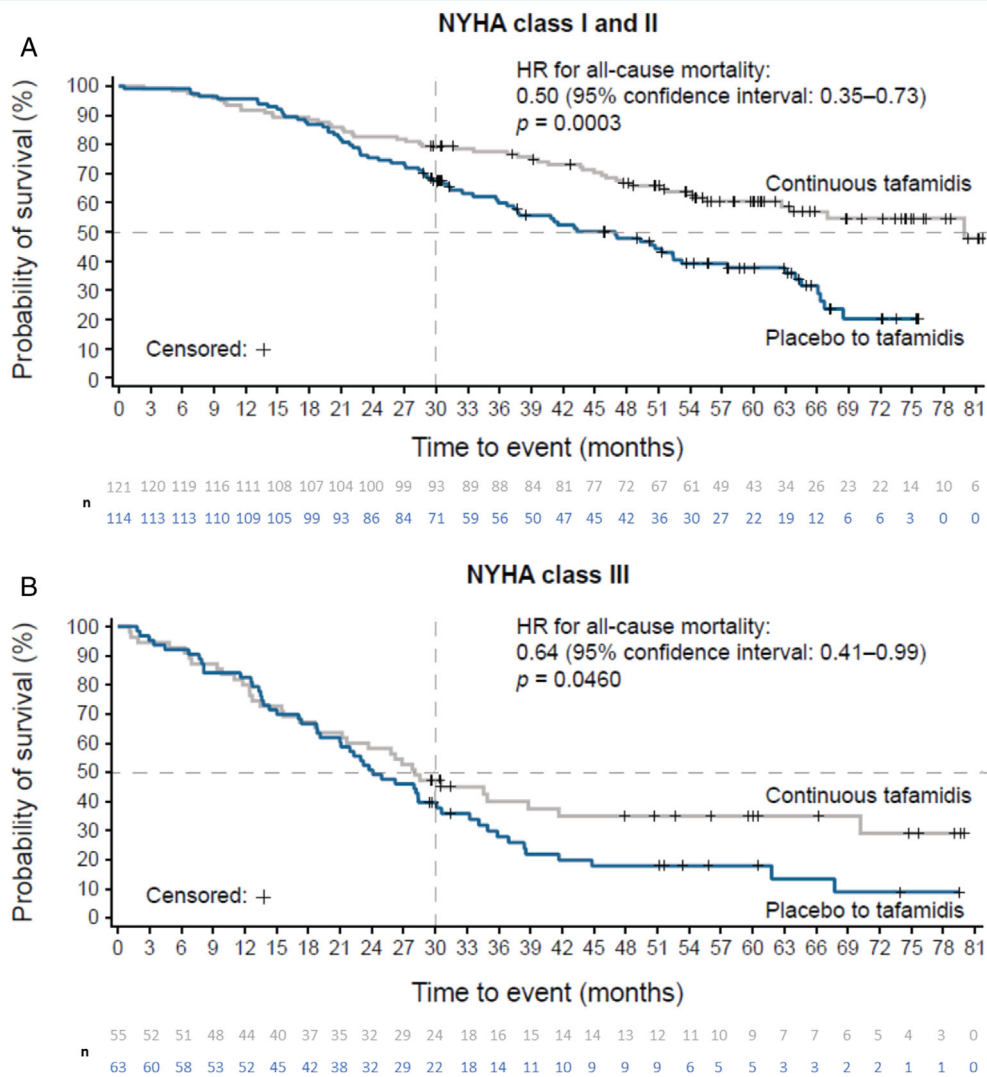


Figure 1 Kaplan–Meier curve of observed all-cause mortality in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the long-term extension study by baseline New York Heart Association (NYHA) class. Hazard ratio (HR) provided for patients continuously treated with tafamidis meglumine 80 mg/free acid 61 mg versus placebo then tafamidis.

profile of tafamidis was consistent with that previously reported in ATTR-ACT and at earlier time points in the LTE study.^{10,12}

Discussion

Our findings show that, among patients with ATTR-CM and NYHA class III symptoms at baseline, those continuously treated with tafamidis for a median of ~5 years had a lower risk of all-cause mortality than those initially treated with placebo.

Previous analyses have demonstrated the value of long-term tafamidis treatment.^{12,22–24} These latest findings support previous data demonstrating that patients who received placebo in ATTR-ACT continued to have poorer survival in the LTE than those who initially received tafamidis.^{11,12} Tafamidis treatment in the LTE study improved the probability of survival in patients who

had previously been treated with placebo in ATTR-ACT; however, delayed treatment had a long-term impact on the survival of patients with ATTR-CM. Data from this most recent interim data cut showed no new safety signals for tafamidis over long-term use.

ATTR-ACT was not designed to assess efficacy in NYHA subgroups; however, pre-specified exploratory analyses have previously indicated a reduction in all-cause mortality with pooled tafamidis (80 and 20 mg) versus placebo in NYHA subgroups I–III.^{10,19} Survival benefit was most pronounced in patients who were class I, compared with those who were class III.^{10,19} Further limitations of this analysis include the low numbers of patients in each group (particularly in the later stages of the LTE study), the potential for confounding changes in background heart failure therapy over the course of the analysis, and the lack of hospitalization data collected in the LTE study; which might have added

another dimension to our mortality findings. We also note the fragility of our findings, given that the CI for the all-cause mortality HR approaches 1 in the NYHA class III comparison. Additional real-world analysis has indicated that long-term tafamidis treatment significantly improved survival over 5 years in subsets of patients at the Columbia University Irving Medical Center with wild-type ATTR-CM who were Mayo stage I or II, but not stage III.¹³

In this study, though not designed or powered to precisely assess time to separation, treatment differences in the rate of mortality started to emerge during ATTR-ACT in both NYHA class I/II and III patients. In the most recent interim analysis of the LTE study, we observed a reduced risk of all-cause mortality across NYHA classes I/II (HR 0.50; 95% CI 0.35–0.73) and III (HR 0.64; 95% CI 0.41–0.99) in patients with ATTR-CM receiving continuous tafamidis (80 mg/61 mg) from the start of ATTR-ACT, as compared with those receiving placebo in ATTR-ACT and then tafamidis in the LTE study. These findings support the use of tafamidis in patients with early and advanced ATTR-CM, and further emphasize the importance of prompt diagnosis and treatment initiation.

Supplementary Information

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

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Conflict of interest: P.E. has received consultancy fees from Pfizer and Alnylam and educational grants from Pfizer. B.G., M.B.S., and M.I. are employees of Pfizer and own stock/stock options. P.G.P. has served as a speaker in scientific meetings for Alnylam, BridgeBio, Ionis, AstraZeneca, Novo Nordisk and Pfizer; received funding from Alnylam and Pfizer for scientific meeting expenses; consultancy fees from Alnylam, Attralus, BridgeBio, Neuroimmune, AstraZeneca, Novo Nordisk, Alexion, Intellia, and Pfizer; and his institution has received research grants/educational support from Alnylam, BridgeBio, AstraZeneca, Novo Nordisk, Intellia, and Pfizer.

References

- Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**73**:2872–2891. <https://doi.org/10.1016/j.jacc.2019.04.003>
- Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;**39**:2799–2806. <https://doi.org/10.1093/eurheartj/ehx589>
- Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation* 2019;**140**:16–26. <https://doi.org/10.1161/CIRCULATIONAHA.118.038169>
- Patel KS, Hawkins PN. Cardiac amyloidosis: Where are we today? *J Intern Med* 2015;**278**:126–144. <https://doi.org/10.1111/joim.12383>
- Rozenbaum MH, Large S, Bhabri R, Stewart M, Young R, Doornewaard AV, et al. Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy. *J Comp Eff Res* 2021;**10**:927–938. <https://doi.org/10.2217/ceer-2021-0071>
- Rozenbaum MH, Large S, Bhabri R, Stewart M, Whelan J, van Doornewaard A, et al. Impact of delayed diagnosis and misdiagnosis for patients with transthyretin amyloid cardiomyopathy (ATTR-CM): A targeted literature review. *Cardiol Ther* 2021;**10**:141–159. <https://doi.org/10.1007/s40119-021-00219-5>
- Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: A position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2021;**42**:1554–1568. <https://doi.org/10.1093/eurheartj/ehab072>
- European Medicines Agency. Vyndaqel (tafamidis) summary of product characteristics. 2021 https://www.ema.europa.eu/documents/product-information/vyndaqel-epar-product-information_en.pdf. Accessed 2 September 2021
- Pfizer Laboratories Division, Pfizer Inc. VYNDAQEL and VYNDAMAX highlights of prescribing information. 2020 <http://labeling.pfizer.com/ShowLabeling.aspx?id=11685>. Accessed 2 September 2021
- Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al.; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016. <https://doi.org/10.1056/NEJMoa1805689>
- Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail* 2021;**23**:277–285. <https://doi.org/10.1002/ehf.2027>
- Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail* 2022;**15**:e008193. <https://doi.org/10.1161/CIRCHEARTFAILURE.120.008193>
- Amaka S, Bhattacharya PT, Maurer MS, Griffin J. Tafamidis effectiveness in wild-type transthyretin cardiac amyloidosis by Mayo staging. *J Am Coll Cardiol* 2022;**79**:306. [https://doi.org/10.1016/S0735-1097\(22\)01297-9](https://doi.org/10.1016/S0735-1097(22)01297-9)
- Sarkar A, Miranda D, Sleiman J, Liang H, Ives L, Asher CR, et al. Does tafamidis benefit octogenarians with transthyretin amyloid cardiomyopathy? Analysis of the Cleveland Clinic Amyloid Registry. *J Am Coll Cardiol* 2022;**79**:300. [https://doi.org/10.1016/S0735-1097\(22\)01291-8](https://doi.org/10.1016/S0735-1097(22)01291-8)
- Hussain K, Macrinici V, Wathen L, Minga I, Gaznabi S, Kwak E, et al. Impact of tafamidis on survival in a real-world community based cohort. *J Am Coll Cardiol* 2022;**79**:517. [https://doi.org/10.1016/S0735-1097\(22\)01291-8](https://doi.org/10.1016/S0735-1097(22)01291-8)
- Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, et al. Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. *Eur J Heart Fail* 2021;**23**:895–905. <https://doi.org/10.1002/ehf.2198>
- Nativi-Nicolau J, Judge DP, Hoffman JE, Gundapaneni B, Keohane D, Sultan MB, et al. Natural history and progression of transthyretin amyloid cardiomyopathy: Insights from ATTR-ACT. *ESC Heart Fail* 2021;**8**:3875–3884. <https://doi.org/10.1002/ehf2.13541>
- Feng KY, Loungani RS, Rao VN, Patel CB, Khouri MG, Felker GM, et al. Best practices for prognostic evaluation of a patient with transthyretin amyloid cardiomyopathy. *JACC CardioOncol* 2019;**1**:273–279. <https://doi.org/10.1016/j.jacc.2019.11.006>
- Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, et al. Efficacy of Tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: Further analyses from ATTR-ACT. *JACC Heart Fail* 2021;**9**:115–123. <https://doi.org/10.1016/j.jchf.2020.09.011>
- Maurer MS, Adler E, Gundapaneni B, Sultan MB, Rapezzi C. Efficacy of tafamidis by baseline 6-minute walk test distance in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT). *J Card Fail* 2020;**26**:S10. <https://doi.org/10.1016/j.cardfail.2020.09.037>
- Li H, Rozenbaum M, Casey M, Sultan MB. Estimating the effect of tafamidis on cardiovascular-related hospitalization in NYHA class III patients with transthyretin amyloid cardiomyopathy in the presence of death. *Cardiology* 2022;**147**:398–405. <https://doi.org/10.1159/000525883>
- Rozenbaum M, Ines M, Young R. Long-term time varying survival treatment effect in the presence of scheduled switch from placebo to active treatment. *Value Health* 2022;**25**:S275. <https://doi.org/10.1016/j.jval.2021.11.1337>
- Rozenbaum M, Tran D, Li B, Bhabri R, Postma M, Masri A. Modelling lifetime survival gain in patients with transthyretin amyloid cardiomyopathy and baseline NYHA III: An analysis of ATTR-ACT and long-term extension study. *J Card Fail* 2022;**28**:S44. <https://doi.org/10.1016/j.cardfail.2022.03.116>
- Rozenbaum MH, Garcia A, Grima D, Tran D, Bhabri R, Stewart M, et al. Health impact of tafamidis in transthyretin amyloid cardiomyopathy patients: An analysis from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and the open-label long-term extension studies. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:529–538. <https://doi.org/10.1093/ehjqcco/qcab031>