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Original Article

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

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Aim The Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) showed that tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations in patients with transthyretin amyloid cardiomyopathy (ATTR-CM). This study aimed to estimate the impact of tafamidis on survival and quality-adjusted life-years (QALYs).

Methods and results A multi-state, cohort, Markov model was developed to simulate the disease course of ATTR-CM throughout a lifetime. For survival extrapolation, survival curves were fitted by treatment arm and New York Heart Association (NYHA) Class I/II (68% of patients) and NYHA Class III (32% of patients) cohorts using the individual patient-level data from both the ATTR-ACT and the corresponding long-term extension study. Univariate and multivariate sensitivity analyses were conducted. The predicted mean survival for the total population (NYHA Class I/II + III) was 6.73 years for tafamidis and 2.85 years for the standard of care (SoC), resulting in an incremental mean survival of 3.88 years [95% confidence interval (CI) 1.32–5.66]. Of the 6.73 life-years, patients on tafamidis spend, on average, 4.82 years in NYHA Class I/II, while patients on SoC spend an average of 1.60 life-years in these classes. The combination of longer survival in lower NYHA classes produced a QALY gain of 5.39 for tafamidis and 2.11 for SoC, resulting in 3.29 incremental QALYs (95% CI 1.21–4.74) in favour of tafamidis.

Conclusion Based on the disease simulation model results, tafamidis is expected to more than double the life expectancy and QALYs of ATTR-CM patients compared to SoC. Longer-term follow-up data from the ATTR-ACT extension study will further inform these findings.

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Keywords Amyloidosis • Mortality • Tafamidis • Transthyretin • Cardiomyopathy

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive infiltrative cardiomyopathy in which amyloid fibrils composed of misfolded transthyretin protein accumulate in the heart, impairing myocardial function over time and leading to progressive heart failure (HF) and death.[1,2] ATTR-CM is classified as a rare disease, and traditionally, treatments have been limited to supportive care and, in rare cases, heart transplant.[3,4]

Prior to 2019, there were no proven pharmacotherapies for the treatment of ATTR-CM, and prognosis has been typically poor, with a median survival of 2–6 years.[5–8] Tafamidis was recently approved and received orphan designation in several countries, including the USA, Japan, and the European Union (EU) for the treatment of ATTR-CM, based on the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT).[9–11]

ATTR-ACT was a global, phase III, placebo-controlled, randomized clinical trial assessing patients with hereditary and wild-type ATTR-CM.[12] The ATTR-ACT showed that tafamidis was associated with a reduction in all-cause mortality [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.51–0.96], decrease in cardiovascular (CV)-related hospitalizations (relative risk ratio 0.68, 95% CI 0.56–0.81), and reductions in the decline of functional capacity and quality of life when compared with standard of care (SoC).[13] After 30 months, all trial participants were allowed to continue or start tafamidis in an open-label extension study.[14]

Preliminary data from the ongoing open-label extension study showed continued survival improvements at 49 months in patients treated with tafamidis who had initiated treatment from ATTR-ACT [HR 0.64 (95% CI 0.47–0.85)].

Considering that the median overall survival has not been reached for the tafamidis arm and that the ATTR-ACT and extension studies showed continued separation of the overall survival curves for the two treatment arms, the shape of the survival curve predicting the full survival benefit for tafamidis is still unknown.[13–15] To examine the potential long-term outcomes associated with tafamidis treatment, we used a disease simulation model that was informed by patient-level data from ATTR-ACT and the open-label extension study to estimate the impact of tafamidis treatment (mean difference from SoC) over a patient's lifetime.[13,14]

Methods

Model structure

A flexible probabilistic multi-state Markov model was developed in Microsoft Excel to simulate the disease course and survival associated with tafamidis vs. SoC treatment in patients with ATTR-CM in the USA over a lifetime horizon (maximum of 30 years). The model was probabilistic such that it runs multiple iterations of a cohort (1000 patients) with randomly selected baseline characteristics to define the 'average' characteristics of that cohort. The model structure was developed in line with previously published reviews and models in the HF indication, which modelled different rates of progression by the New York Heart Association (NYHA) functional classification—a clinician-rated assessment intended to evaluate the impact of patient symptoms on functional capacity.[16–18] The prognosis of HF and ATTR-CM patients has been shown to worsen with higher NYHA functional classification stages.[13,19] As such, the NYHA functional classification is considered a predictor of health-related quality of life and survival, making it an excellent patient-centric measure of disease burden.[18,20,21]

The model simulates patients' transitions to three main disease-specific health states: (i) alive without (heart) transplant, (ii) alive with (heart) transplant, and (iii) dead. The 'alive without (heart) transplant' state is subdivided into the four NYHA class stages to model disease progression. In contrast, the 'alive with (heart) transplant' state is subdivided into the first month and subsequent months following a heart transplant (*Figure 1*).[22] Given the rarity of heart transplants in patients with ATTR-CM in the USA, the base case analysis did not allow patients to transition to the 'alive with (heart) transplant' state. Instead, the transplant probabilities were set to zero in the base case to reflect the real-world circumstances.[23] To test the impact of this assumption on outcomes, various probability values of receiving a transplant were assessed as part of the sensitivity analyses.

Patient characteristics

The characteristics of the modelled patient cohort reflect the average patient characteristics of those included in the ATTR-ACT.[13] An overview of patient characteristics is shown in *Table 1*.

Clinical data and survival modelling

Clinical inputs from two sources were included: (i) the 30-month follow-up data from ATTR-ACT assessing SoC ($n = 177$) vs. the pooled tafamidis cohorts (20 mg dose and 80 mg dose; $n = 264$) and (ii) the 49-month follow-up data from the open-label extension study of participants who continued tafamidis treatment since the start of ATTR-ACT ($n = 264$).[13,14] Since the research question concerned a lifetime survival comparison of tafamidis vs. SoC, using the SoC data from the extension study would produce biased results due to the crossover of all SoC-treated patients to tafamidis at Month 30.[14] Therefore, only data up to 30 months from the intent-to-treat analysis of ATTR-ACT were used for the SoC arm, and the 49-month extension study data were used for tafamidis.[13,14] Furthermore, given that NYHA classification is prognostic for survival, and previous HF models modelled disease progression based on NYHA classifications, the survival outcomes for NYHA Class I/II and NYHA Class III patients were assessed separately (*Figure 2*).

In-trial overall survival Kaplan–Meier (KM) curves from patient-level data for the tafamidis and SoC arms were extrapolated beyond observed time points from ATTR-ACT and its extension study by following international extrapolation guidelines.[24] To mimic reality, patients undergoing a transplant or receiving a left ventricular assist device (LVAD) were treated as censored at the time of the procedure, rather than treated as death as in the clinical trial statistical analysis. As noted earlier, patients undergoing transplants were considered separately in the model to capture transplant outcomes. The proportional hazard (PH) assumption was tested to determine whether

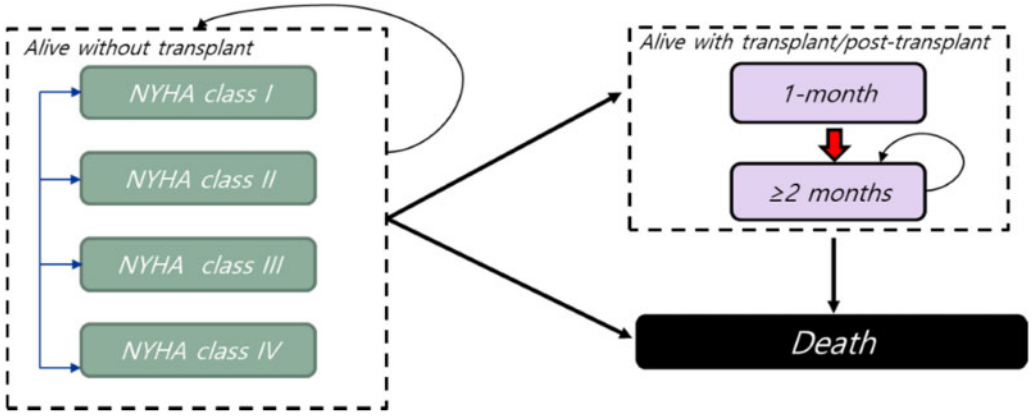

Figure 1 Model structure. NYHA, New York Heart Association Functional Classification.

Table 1 Overview of patient and model characteristics

Model parameter	Base case value	Source(s)
Model characteristics		
Setting	USA	NA
Time horizon	30 years	Caro *et al.* 2012[47]
Cycle length	1 month	Caro *et al.* 2012[47]
Patient characteristics		
% NYHA Class I/II at baseline	68%	ATTR-ACT[13]
% NYHA Class III at baseline	32%	ATTR-ACT[13]
% NYHA Class IV at baseline	0.00%	ATTR-ACT[13]
Age at model entry	74 years	ATTR-ACT[13]
Efficacy data		
All-cause mortality extrapolation function—tafamidis	NYHA Class I/II: Gompertz NYHA Class III: Weibull	ATTR-ACT[13]
All-cause mortality extrapolation function—SoC	NYHA Class I/II: Gompertz NYHA Class III: Weibull	ATTR-ACT[13]
NYHA class transition probabilities (by treatment)	Based on ATTR-ACT for 0–30 months, for extrapolations based on data from Months 24–30 for SoC or Months 30–48 for tafamidis	ATTR-ACT[13]
Utilities, mean (SE)		
Tafamidis	NYHA Class I: 0.874 (0.01) NYHA Class II: 0.832 (0.01) NYHA Class III: 0.707 (0.01) NYHA Class IV: 0.558 (0.06)	ATTR-ACT[13] and US value set[30]
SoC	NYHA Class I: 0.893 (0.02) NYHA Class II: 0.802 (0.01) NYHA Class III: 0.706 (0.01) NYHA Class IV: 0.406 (0.06)	ATTR-ACT[13] and US value set[30]

ATTR-ACT, Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; NA, not applicable; NYHA, New York Heart Association Functional Classification; SE, standard error; SoC, standard of care.

independent survival models should be applied in each treatment arm.[25] Based on the scaled Schoenfeld residuals, evidence of a violation of the PH assumption was found in the most prevalent NYHA Class I/II cohort; consequently, individual parametric models were fitted by treatment and NYHA class cohort for extrapolation (Supplementary material online, *Figure S5*).

For extrapolation purposes, the following seven commonly used parametric survival models were considered and fitted to the clinical data

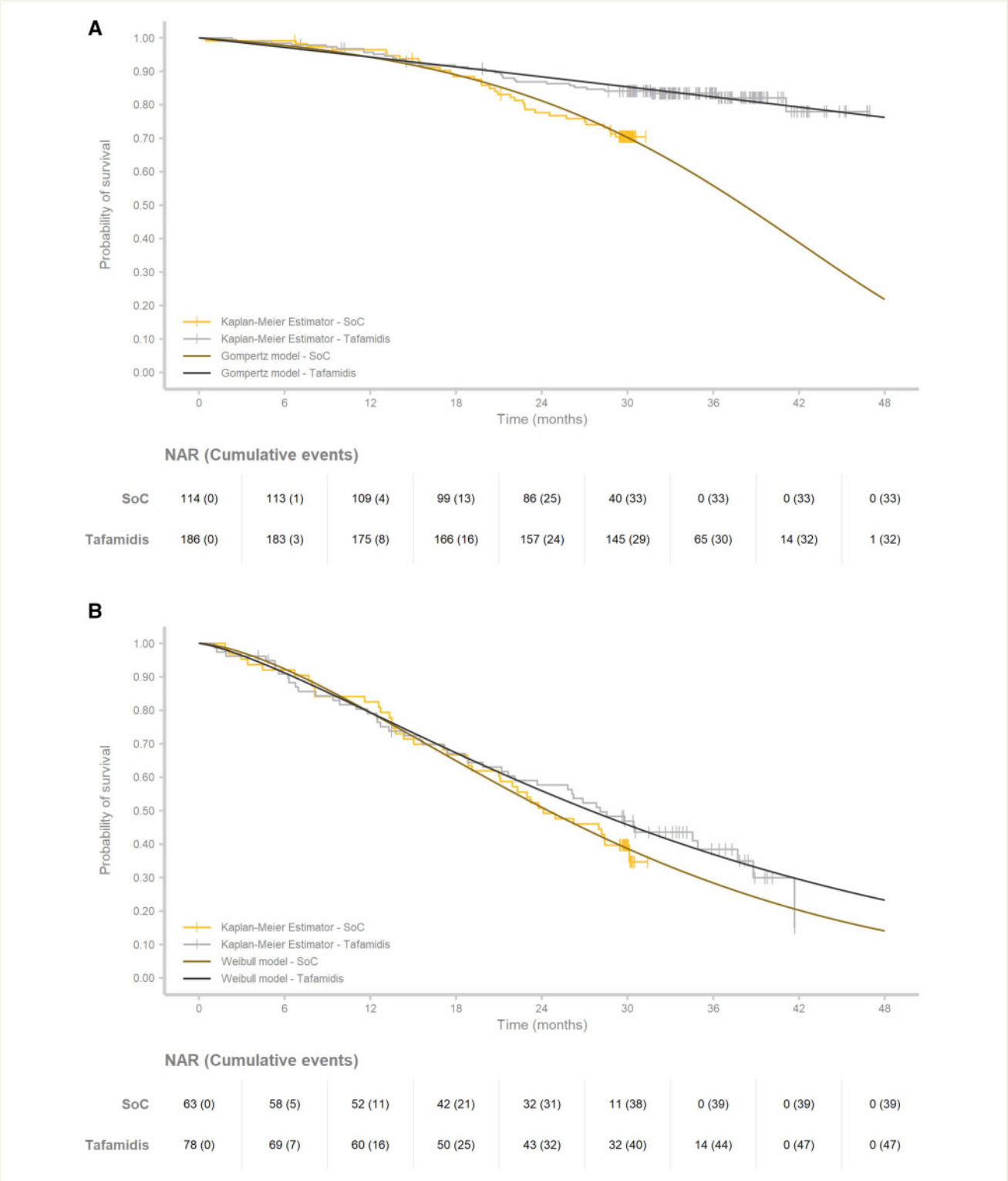

Figure 2 Overview of observed and predicted survival for standard of care and tafamidis for (*A*) New York Heart Association I/II patients and (*B*) New York Heart Association III. NAR, number at risk; SoC, standard of care.

following guidelines: exponential, generalized gamma, gamma, Gompertz, log-logistic, log-normal, and Weibull.[24] The parametric distribution analyses were conducted using the 'Survival' and 'Flexsurv' packages in R for Statistical Computing version 3.5.0.[26–28] The best fitting parametric distributions were selected based on visual inspection, goodness-of-fit statistics for survival analyses, including Akaike Information Criterion (AIC)

and Bayesian Information Criterion (BIC), as well as clinical plausibility.[24] The lifetime outcomes, in terms of survival and quality of life, were first estimated per NYHA Class I/II and NYHA Class III stratified cohorts, after which the weighted mean outcomes were calculated for the entire population of ATTR-ACT based on the underlying baseline NYHA class distribution in ATTR-ACT.

Utility estimates

The ATTR-ACT collected quality of life data from both the Kansas City Cardiomyopathy Questionnaire (KCCQ), a functional and clinical assessment tool for patients with HF, as well as the three-level version of the EQ-5D (EQ-5D-3L), a self-administered generic health status instrument.[13,29,30] Since the latter is a preferred tool by various health technology assessment bodies, the utility values with the EQ-5D-3L value set for the USA was used in the model.[13,30] The utility weights were stratified by treatment arm and NYHA class. As part of the sensitivity analyses, alternative utility assumptions were assessed. *Table 1* presents an overview of the model characteristics and parameters.

Outcomes

The primary outcomes of interest were (i) the mean and incremental survival in life-years gained and (ii) the mean and incremental quality-adjusted life-years (QALYs) gained. The means and their 95% CIs were estimated by bootstrapping from the distributions defined over the following parameters: utilities by health state and treatment; parametric survival extrapolation distributions by NYHA cohorts and treatment; the treatment-specific transition probabilities over the NYHA cohorts; and the distribution of mortality parameter alongside the transition probabilities to distribute alive patients into NYHA classes after Month 30.[31]

Sensitivity analyses

The effect of various parametric distributions, incremental mean life-years, and QALYs were assessed. Parametric distributions that increased the AIC/BIC for the SoC arm by more than 2 points compared to the best fitting distribution were disregarded from the analyses, as models with <2 points difference are well supported as suitable model selections.[32] The same distribution was applied for both treatment arms per NYHA cohort to limit the number of scenarios. If the predicted mortality hazards in the probabilistic sensitivity analysis were lower than the general population hazards, the general population hazards were applied in the model to avoid biased predictions.[33,34] Uncertainties regarding the impact of transplant rates were assessed through scenario analyses. The 30-month probabilities of transplant per treatment and NYHA stage cohort were set to reflect the rates observed in ATTR-ACT, which were 2.3% for SoC and 2.7% for tafamidis.[13]

With the introduction of tafamidis, it is expected that patients will be identified at earlier NYHA functional classification stages due to the increased awareness and adoption of non-invasive imaging modalities, such as bone scintigraphy and cardiac magnetic resonance imaging (MRI). In ATTR-ACT, 31.97% of the patients were categorized as NYHA Class III.[35–38] To assess the impact of earlier diagnosis, the percentage of NYHA Class I/II patients at model entry (base case 68.03%) ranged from 0% to 100% to assess the mean expected (incremental) survival and QALY.

Additional sensitivity analyses assessed the impact of utility values. In one scenario, we assumed no difference between treatments by applying the SoC arm's utility value from ATTR-ACT to both arms in the model.[13] In a second scenario, the utility used in the post-transplant setting was set at 0.76 in line with what has been reported for late-stage HF.[22]

Besides the tremendous burden for patients, there is also a burden for caregivers of patients with ATTR-CM.[39] In this scenario, a disutility of 0.01 was applied to the NYHA Class IV health state utility to consider the caregiver burden.[40]

Results

Extrapolations

In the base case, the Gompertz and the Weibull distributions were selected to extrapolate overall survival for the NYHA I/II and the NYHA III cohorts, respectively. The parametric survival distributions for the NYHA I/II and NYHA III cohorts fitted to the trial data are presented in *Figure 2*. Statistically, these distributions provided the best fits (Supplementary material online, *Tables S3–S6*) and clinically plausible estimates for both treatment groups. As determined by visual inspection, the survival extrapolations fit the overall survival KM plots observed in ATTR-ACT and extension study for both tafamidis and SoC (*Figure 3*).

Base case results

The model predicts a higher mean life expectancy for patients with ATTR-CM treated with tafamidis [6.73 years (95% CI 4.21–8.34)] compared to those treated with SoC [2.85 (95% CI 2.5–3.34)], resulting in an incremental life expectancy of 3.88 years (95% CI 1.32–5.66) in favour of tafamidis (*Figure 4A*). Of the total life-years, patients treated with tafamidis remain longer in the early NYHA stages (i.e. Class I and II), with an estimated life expenditure of 1.83 years (27.2%) in NYHA Class I, 2.99 years (44.4%) in NYHA Class II, 1.64 years (24.4%) in NYHA Class III, and 0.27 years in NYHA Class IV (4.0%) (*Figure 4A*). Compared to those receiving SoC, patients on tafamidis increased the total amount of time spent in NYHA Class I/II by 201% from 1.60 to 4.82 life-years.

Similarly, tafamidis provides more QALYs [5.39 QALYs (95% CI 3.35–6.79)] compared to the SoC arm [2.11 QALYs (95% CI 1.88–2.42)] in patients with ATTR-CM, resulting in an increment of 3.29 QALYs (95% CI 1.21–4.74). The QALYs spent in the NYHA Class I/II cohorts increased from 1.31 to 4.09 QALYs when comparing SoC with tafamidis (*Figure 4B*).

Sensitivity analyses

Based on the probabilistic sensitivity analyses conducted, the impact of different parametric distributions on the results was moderate. The most substantial reduction of incremental QALYs and life-years was observed when the gamma (NYHA Class I/II) and the Weibull (NYHA Class III) distributions were selected, which resulted in a 29.4% reduction in incremental life-years and 15.8% reduction in incremental QALYs when compared to the base case. The largest increase in incremental QALYs and life-years was observed after selecting the Gompertz (NYHA Class I/II) combined with the generalized gamma (NYHA Class III), which resulted in an 11.6% increase in incremental life-years and a 12.5% increase in incremental QALYs when compared to the base case. *Table 2* presents the results of the alternative parametric distributions tested in the probabilistic sensitivity analyses.

When assuming heart transplant probabilities of 2.3% for SoC and 2.7% for tafamidis in line with the 30-month data from ATTR-ACT, there was a decrease in incremental life-years gained from 3.88 to 3.82 (1.5% decrease) and in QALYs from 3.54 to 3.51 (0.85%

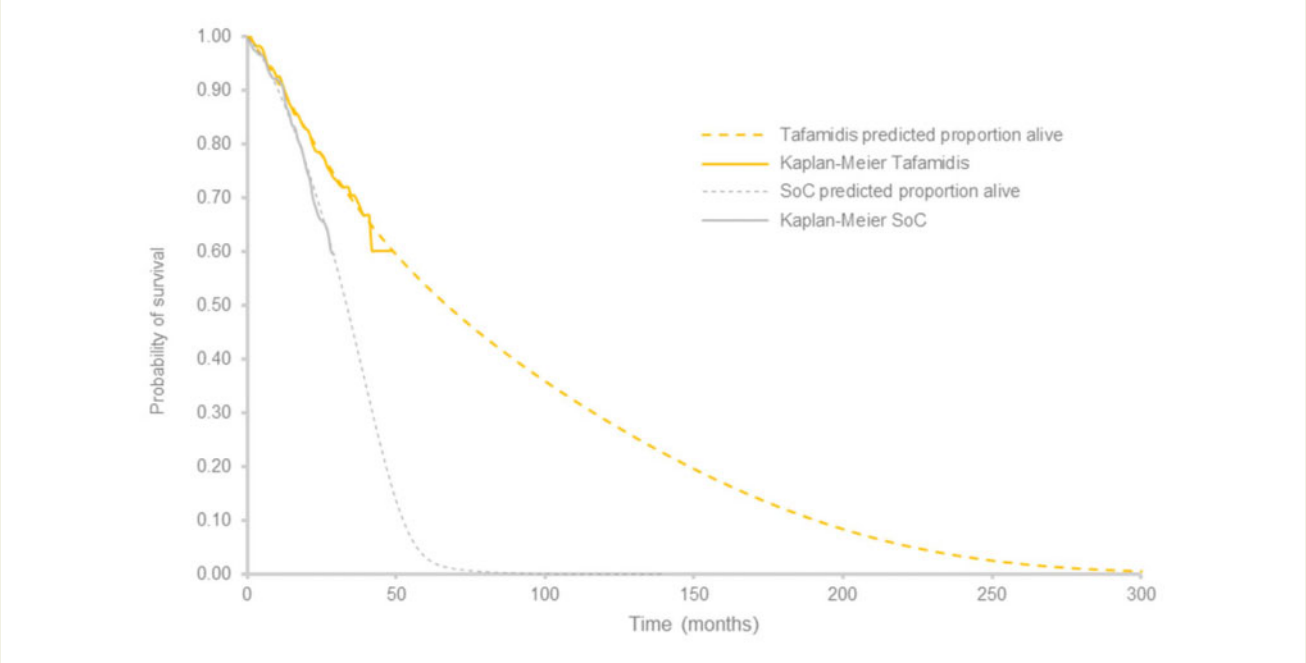

Figure 3 Predicted extrapolation and overall survival Kaplan–Meier for tafamidis and standard of care arms from Tafamidis in Transthyretin Cardiomyopathy Clinical Trial. SoC, standard of care.

decrease).[13] Assuming equal utilities by health state for tafamidis and SoC reduced the incremental QALYs from 3.29 to 3.19 (3.1% decrease). The impact of caregiver disutility did not affect incremental life-years or QALYs.

When assuming that 100% of patients would be diagnosed at NYHA Class I/II stages (vs. 68% in ATTR-ACT), the predicted incremental life-years for tafamidis improved from 3.88 to 5.49 years (41.5% increase), as well as the incremental QALYs from 3.29 to 4.62 (40.4% increase). Even if all patients were diagnosed and initiated treatment in NYHA Class III, tafamidis was still associated with a life-year gain of 0.44 (18.6% increase compared to SoC) and a corresponding gain in QALYs of 0.45, reflecting a 27.4% increase compared to SoC. *Table 2* presents the results of the alternative values tested in the scenario analyses.

Discussion

Tafamidis is the first-in-class transthyretin stabilizer approved for the treatment of ATTR-CM.[41] The pivotal study, ATTR-ACT, showed tafamidis improved survival and decreased CV-related hospitalizations.[13] In the present study using a flexible disease simulation model based on data from ATTR-ACT and its extension study, we show that tafamidis was associated with a mean survival of 6.73 years as compared to 2.85 years for SoC, resulting in an incremental mean survival of 3.88 years (95% CI 1.32–5.66).[13,14] Of the 6.73 life-years, patients treated with tafamidis spend an average of 4.82 years in NYHA Class I/II, while patients on SoC spend an average of only 1.60 life-years in these early NYHA stages. The combination of longer survival in NYHA classes I/II for tafamidis compared to SoC resulted in a QALY gain of 5.39 and 2.11, respectively, resulting in 3.29 incremental QALYs (95% CI 1.21–4.74) in favour of tafamidis.

Sensitivity analyses demonstrated moderate impact on the results based on the various parametric distributions selected for both SoC and tafamidis, with variations ranging from a reduction of 29.4% and an increase of 11.6% in incremental life-years, and a reduction of 15.8% to an increase of 12.5% for incremental QALYs when compared to the base case results. Similar conclusions were derived for scenario analyses with differing utility estimates and heart transplantation rates.

With the increased awareness of ATTR-CM and the adoption of non-invasive imaging modalities such as bone scintigraphy and cardiac MRI, the percentage of patients diagnosed in NYHA Class I/II will likely increase in the future. The scenario analysis showed that if 100% of the patients were detected in NYHA Class I/II and subsequently treated with tafamidis instead of SoC, the incremental survival would improve by 41.5%. We assumed that the age of treatment initiation would be unchanged for these analyses, and only the proportion of patients by NYHA class varied. Of course, this simplifies the clinical reality, as one would expect that earlier diagnosis would also result in an earlier age of diagnosis. We hypothesize that if the average age of diagnosis decreased, then the health benefits of tafamidis would probably increase; however, further research is needed to confirm these potential benefits.

In a recent publication by Kazi *et al.*[42], a cost-effectiveness model estimated mean survival for SoC and tafamidis at 3.46 and 5.43 years, respectively, resulting in an incremental mean survival of 1.97 years in favour of tafamidis. Although their survival estimate favours tafamidis, the lower incremental gain compared to our

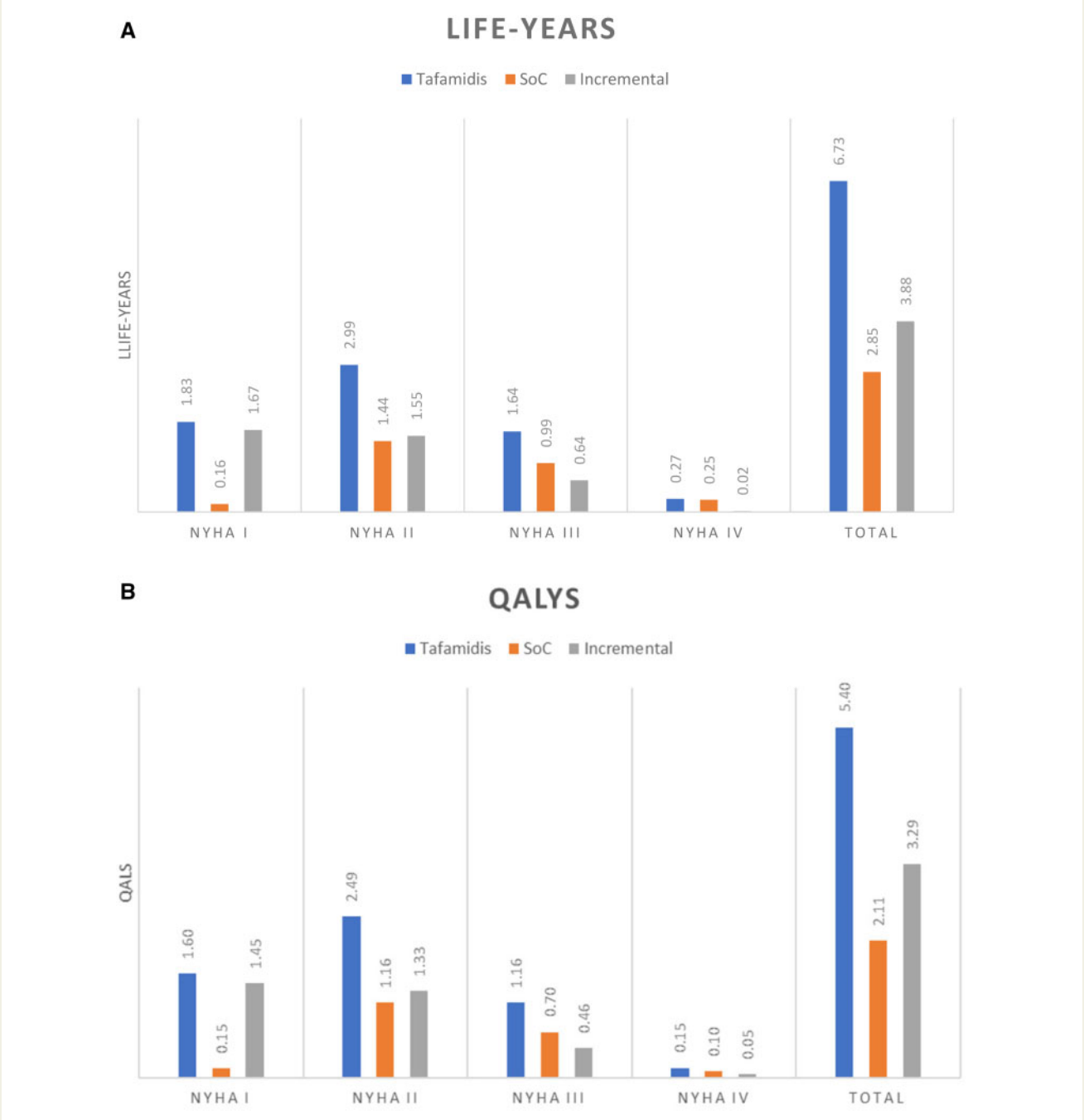

Figure 4 Overview of (*A*) the mean and incremental mean survival and (*B*) quality-adjusted life-years by health state as predicted by the model. NYHA, New York Heart Association Functional Classification; QALYs, quality-adjusted life-years; SoC, standard of care.

model can be explained by the different model structures, assumptions, and inputs. First, Kazi *et al.*[42] used the 30-month data-cut of ATTR-ACT for survival extrapolation, while our model benefitted from the availability of the open-label extension study data, which showed a continued overall survival divergence between both arms. Using survival data from a longer follow-up period reduced the uncertainty in the extrapolations for the tafamidis arm. The sensitivity analyses tested different extrapolation models, resulting in similar outcomes as those in the base case. Unlike our approach, Kazi *et al.*[42] assumed constant HRs to extrapolate survival of tafamidis, which likely underestimated the effect of tafamidis considering the observed separation of the overall survival curves for tafamidis and placebo in ATTR-ACT and its long-term extension studies. Furthermore, Kazi *et al.*[42] considered heart transplants and implantation of LVAD as deaths in their analyses, which may have underestimated survival in their extrapolations.

Table 2 Overview of the impact of the base case and scenario analyses on the outcomes

	Life-years (95% CI)			QALYs (95% CI)		
Base case	**Tafamidis**	**SoC**	**Incremental**	**Tafamidis**	**SoC**	**Incremental**
NYHA I/II—Gompertz	6.73	2.85	3.88	5.39	2.11	3.29
NYHA III—Weibull	(4.21–8.34)	(2.5–3.34)	(1.32–5.66)	(3.35–6.79)	(1.88–2.42)	(1.21–4.74)
Sensitivity analyses: parametric distributions by NYHA cohorts						
NYHA I/II—log-logistic	7.52	4.3	3.22	6.03	2.84	3.19
NYHA III—Weibull	(6.08–8.3)	(3.27–5.4)	(1.44–4.64)	(4.85–6.76)	(2.27–3.5)	(1.85–4.1)
NYHA I/II—Weibull	7.09	3.4	3.69	5.69	2.41	3.27
NYHA III—Weibull	(4.87–8.24)	(2.75–4.33)	(1.37–5.12)	(3.87–6.67)	(2.02–2.94)	(1.47–4.36)
NYHA I/II—gamma	6.95	4.2	2.74	5.57	2.81	2.77
NYHA III—Weibull	(3.08–8.69)	(1.78–8.31)	(-2.21 to 6.43)	(2.45–7.1)	(1.32–5.03)	(-0.67 to 5.32)
NYHA I/II—Gompertz	6.65	2.78	3.87	5.33	2.06	3.27
NYHA III—Gompertz	(4.15–8.24)	(2.47–3.28)	(1.34–5.61)	(3.32–6.71)	(1.84–2.39)	(1.21–4.7)
NYHA I/II—Gompertz	7.04	3.11	3.93	5.64	2.24	3.4
NYHA III—log-logistic	(4.5–8.75)	(2.69–3.65)	(1.32–5.78)	(3.6–7.07)	(1.97–2.57)	(1.3–4.86)
NYHA I/II—Gompertz	6.82	2.96	3.87	5.47	2.16	3.31
NYHA III—gamma	(4.18–8.93)	(2.29–4.12)	(0.86–6.18)	(3.34–7.19)	(1.72–2.84)	(0.94–5.11)
NYHA I/II—Gompertz	7.4	3.07	4.33	5.92	2.22	3.7
NYHA III—G. gamma	(3.87–10.86)	(2.52–4.69)	(0.49–8.02)	(3.13–8.7)	(1.88–3.07)	(0.79–6.56)
Sensitivity analyses: transplant rate						
Transplants as observed in the trial	7.1 (4.62–8.7)	3.28 (2.84–3.97)	3.82 (1.24–5.6)	5.7 (3.67–7.03)	2.45 (2.13–2.91)	3.25 (1.19–4.68)
Sensitivity analyses: utility estimates						
Equal utilities SoC and tafamidis	6.73 (4.21–8.34)	2.85 (2.5–3.34)	3.88 (1.32–5.66)	5.3 (3.3–6.7)	2.11 (1.88–2.42)	3.19 (1.15–4.66)
Considering caregiver disutility	6.73 (4.21–8.34)	2.85 (2.5–3.34)	3.88 (1.32–5.66)	5.39 (3.35–6.79)	2.11 (1.88–2.42)	3.29 (1.21–4.74)
Sensitivity analyses: NYHA class at diagnoses						
100% NYHA I/II	8.57 (4.95–10.91)	3.08 (2.64–3.78)	5.49 (1.75–8.04)	6.95 (4.01–8.97)	2.32 (2.02–2.75)	4.62 (1.62–6.7)
100% NYHA III	2.8 (2.19–3.57)	2.36 (1.86–2.97)	0.44 (-0.41 to 1.34)	2.09 (1.62–2.7)	1.64 (1.31–2.01)	0.45 (-0.15 to 1.11)

CI, confidence interval; G. gamma, generalized gamma; NYHA, New York Heart Association Functional Classification; SoC, standard of care; QALY, quality-adjusted life-years.

Another significant difference of the model by Kazi *et al.* is the model structure, which does not take NYHA classes into account and inadequately captures all potential benefits of the tafamidis treatment, such as delayed disease progression. Tafamidis is a stabilizer of ATTR-CM disease, and the timing of its initiation is crucial in determining its lifetime efficacy for the individual patient. In our model, the NYHA Class I/II and NYHA Class III patients were separately modelled since they are two distinct cohorts in ATTR-ACT and the extension study, whereas the Kazi *et al.* study pooled all patients regardless of NYHA class. There were two reasons for applying this approach. First and most importantly, a substantial difference was observed in the survival and disease progression of the NYHA Class I/II cohort at baseline compared to the NYHA Class III cohort at baseline. The present model simulated NYHA subgroups separately in line with ATTR-ACT findings and several published literature reviews on the HF modelling and health technology assessment survival extrapolation guidance.[17,24,43] Therefore, the present model should be considered a more comprehensive analysis of the impact of tafamidis treatment. Second, the proportion of patients in NYHA Class III was slightly lower for the tafamidis treatment arm compared to the SoC arm in ATTR-ACT.[13] Applying the weighted modelling approach resulted in an equal proportion of patients in NYHA Class III for both the SoC and tafamidis arm. Therefore, the subgroup analyses can be considered as a conservative approach for tafamidis.[8]

Our study has strengths and limitations. One advantage of the current model is the lifetime prediction of outcomes based on a 'hard' clinical endpoint, such as overall survival.[44–46] Another advantage of the disease simulation model is its structure, which explicitly modelled disease progression. This structure is in line with previously published HF models that have explicitly considered 'alive' and 'dead' and recommended using NYHA classes as health states when feasible.[16,17] Using different NYHA classes is a logical choice for utility purposes, given that utilities vary by classification and the effect of tafamidis on disease progression by NYHA class.

Despite these strengths, some limitations to the model should be emphasized. In the model base case, we did not include heart transplant rates as these are rare in ATTR-CM patients in the USA.[3,4] However, a scenario analysis including heart transplant rates showed results were not sensitive to this assumption. Moreover, the model relies on parametric extrapolations on data derived from tafamidis patients who had not reached the median survival for the NYHA I/II

cohort. Consequently, several different parametric distributions were tested as part of the sensitivity analyses, demonstrating that the base case results were relatively stable across the various parametric distributions. In general, the limited availability of data is a primary challenge to ATTR-CM modelling, as it is a rare, infrequently diagnosed condition. As such, the natural history of the condition has not been studied in large, longitudinal datasets. This poses limitations on the complexity of the model structure and the prediction of future events. A future research area will be the development of patient simulation models, which could better consider patient heterogeneity and predict the probability of events based on individual patient characteristics and history. Such a model structure requires comprehensive data sources not currently available, although possible in the future, as ATTR-CM is more frequently diagnosed and more considerable, long-term datasets are collected. Moreover, ATTR-ACT included a smaller percentage of patients with hereditary ATTR-CM (24%), limiting our ability to build separate models for each ATTR-CM genotype.

Finally, the current model used the pooled efficacy data from the two tafamidis arms (20 mg dose and 80 mg dose) vs. SoC as assessed in ATTR-ACT.[13,14] The extension study of ATTR-ACT showed good performance of both the 20 mg and the 80 mg dose, but overall, the 80 mg dose was found to be superior with reduced all-cause mortality without added side effects.[15] Using the pooled data of the 20 mg and 80 mg arms of ATTR-ACT to inform the model was considered a conservative approach.[15]

Conclusion

Based on the disease simulation model results, tafamidis is expected to more than double the life expectancy and QALYs of ATTR-CM patients compared to SoC. Longer-term follow-up data from the extension study to ATTR-ACT will further inform these findings.

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Conflict of interest: D.T. and D.G. are employees of EVERSANA, who were paid consultants for Pfizer Inc. in connection with the development of the model. B.L., R.B., M.S., and M.H.R. are employees of Pfizer and hold Pfizer stock and/or stock options. B.H. and A.G. are employees of Ingress-health and have received personal consulting fees from Pfizer Inc. in connection with the development of the model and manuscript. M.P. is an employee of the University of Groningen and director/sole stockholder of Pharmacoeconomics Advice Groningen and reports grants and honoraria for both entities. A.M. received research grants (paid to the Oregon Health & Science University) from Pfizer and Akcea Therapeutics and serves on a scientific advisory board with Ionis and Eidos.

Data availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results (accessed 20 January 2021) for more information.

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