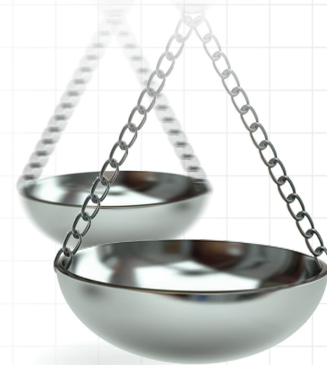




Estimating the health benefits of timely diagnosis and treatment of transthyretin amyloid cardiomyopathy

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Aim: Delayed diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) represents a missed opportunity for intervention. This study estimates the health benefits of timely diagnosis and treatment with tafamidis. **Methods:** A disease simulation model was developed to predict health outcomes under scenarios of timely and delayed diagnosis and treatment. Efficacy and quality of life (QoL) profiles were derived from the pivotal tafamidis trial and diagnostic delay durations from the literature. **Results:** Timely diagnosis and treatment were predicted to extend mean life expectancy by 5.46 and 7.76 years, relative to delayed diagnosis, for wild-type and hereditary ATTR-CM, respectively. Corresponding quality-adjusted life years gains were 4.50 and 6.22. **Conclusion:** Timely diagnosis and treatment with tafamidis are predicted to significantly improve survival and QoL for ATTR-CM patients.

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Keywords: ATTR-CM • diagnosis • disease simulation model • health outcomes • tafamidis • transthyretin amyloid cardiomyopathy

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and ultimately fatal disease caused by the accumulation of amyloid fibrils in the heart muscle [1,2]. This leads to restrictive cardiomyopathy, progressive heart failure and increased risk of conduction abnormalities and arrhythmias [1]. The more common wild-type form (ATTRwt-CM) is associated with aging, with symptom onset typically occurring at age 60 years or older, and is diagnosed predominantly in males [3–5]. The prevalence of ATTRwt-CM is not well characterized, but the condition is thought to be under recognized [1,2]. Hereditary ATTR-CM, also known as variant (ATTRv-CM), is caused by autosomal dominant mutations in the *TTR* gene [6]. ATTRv-CM is rarer and occurs in geographical and ethnic clusters [6]. In the USA, the most common mutation, Val122Ile (also reported as p.Val142Ile), is almost exclusively identified in the African-American population, where it has a prevalence of approximately 3–4% [7,8].

The prognosis for ATTR-CM is poor, with typical survival from diagnosis of 2–6 years [2]. As the disease progresses, patients experience worsening symptoms of heart failure, including fatigue, dyspnea (shortness of breath), reduced exercise capacity and impaired health-related quality of life (HRQoL) [2,9,10].

Diagnostic delay is common [6,11–13], with patients often not correctly diagnosed for several years after symptom onset. The reasons for this include low awareness of ATTR-CM among clinicians [6,11,14], symptom overlap with other more common causes of heart failure and the historical need for invasive diagnosis via cardiac biopsy [15,16].

In patients with mixed phenotype ATTRv-CM, diagnosis may also be complicated by the presence of neurological manifestations [2,17], with a multidisciplinary approach and close communication between cardiologists and neurologists often necessary. Since 2016, a range of recommendations on noninvasive diagnostic techniques have been published [2,15,18,19], as have suggested diagnostic ‘red flags’ for ATTR-CM [2,6]. Together, these have increased awareness and made diagnosis easier, although uptake outside of specialist centers remains inconsistent [20,21].

Another important contributing factor to diagnostic delay has been the absence of a disease-modifying treatment, which together with the need for invasive diagnosis, previously limited the incentive to refer patients for specialist investigation. This situation changed with the introduction of tafamidis, which was approved for the treatment of ATTR-CM by the US FDA in 2019 and by the EMA in 2020 [22,23]. In the pivotal Phase III trial (tafamidis in transthyretin cardiomyopathy clinical trial; ATTR-ACT), treatment with tafamidis reduced all-cause mortality compared with a placebo (HR: 0.70 [95% CI: 0.51–0.95]; $p = 0.0259$) [24]. Tafamidis was also associated with favorable effects on HRQoL and functional capacity [24].

With a disease-modifying treatment now available, diagnostic delay represents a missed opportunity for intervention to extend and improve life for patients with ATTR-CM through treatment. Furthermore, delayed diagnosis is likely to result in more advanced disease at treatment initiation than would otherwise be the case [25,26], reducing the potential to benefit from treatment. The objective of this study was to estimate the expected health benefits of timely diagnosis and treatment of ATTR-CM with tafamidis in the US setting, using a disease simulation model.

Methods

A disease simulation model was developed to characterize the natural history of disease for individuals with ATTR-CM and to predict long-term health outcomes under scenarios of timely and delayed diagnosis followed by treatment with tafamidis.

Model conceptualization

Model conceptualization was informed by relevant existing literature, including publicly available health technology assessment dossiers for chronic heart failure therapies (e.g., ivabradine [27] and sacubitril valsartan [28]). A panel of clinical experts also contributed to the model’s design to ensure face validity and that the model provided an accurate approximation of clinical practice.

Model overview

A discrete-time, cohort-level Markov state-transition model was developed to simulate the chronic burden of ATTR-CM over a lifetime horizon.

To capture the natural disease progression of ATTR-CM and the patient experience [29], model health states were characterized by the New York Heart Association (NYHA) functional classification of heart failure (NYHA classes I–IV). This widely used classification system is based on the degree to which physical activity is limited and the activity thresholds resulting in heart failure symptoms [29]. NYHA class is also a statistically significant predictor of both HRQoL and survival [30–32].

For a defined cohort of patients, disease progression, characterized by transitions through the NYHA classes, is simulated until death due to general or disease-related causes. Consistent with clinical expectations and in line with trial outcomes [33], the risk of death due to disease-related causes is conditional upon NYHA class, with patients with more advanced disease (i.e., higher NYHA class) subject to greater risk. The rate at which patients progress through NYHA classes in the model is governed by transition probabilities; these describe the probability that patients will move from one class to another over a given period of time. HRQoL is characterized by utility weights assigned to each NYHA class.

A schematic diagram of the model structure is presented in [Figure 1](#); technical specification of the model implementation is provided in the [Supplementary Material \(See S2.1\)](#).

Model application: primary analyses

The model was configured to predict outcomes for cohorts of patients under scenarios in which diagnosis and treatment with tafamidis were timely or delayed, with timely diagnosis and treatment defined by younger age and less severe disease (i.e., lower NYHA class) at initiation.

At model initiation, simulated patients were assumed to be in NYHA class I or II, with the applied distribution derived from the number of patients in each of these classes at baseline in ATTR-ACT [33]. Diagnostic delay

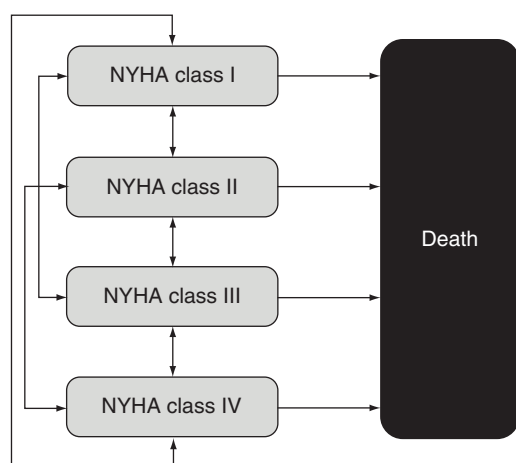


Figure 1. Schematic diagram of the structure of the model.
 NYHA: New York Heart Association.

durations and baseline demographic characteristics were informed by the findings of a targeted literature review characterizing the extent and consequences of delayed diagnosis and misdiagnosis for patients with ATTR-CM; the review identified 22 studies reporting on time from symptom onset to diagnosis in patients with ATTR-CM [13]. The clinical plausibility of the identified diagnostic delay durations and the representativeness of modeled patient demographics were verified by a panel of clinical experts. Independent analyses were conducted for ATTRwt-CM and ATTRv-CM patients to reflect the difference in diagnostic delay and demographic profiles seen between the two forms in the literature [13], and in line with clinical expectations. Treatment with tafamidis was assumed to commence at diagnosis.

Treatment efficacy, captured via the estimation of survival and NYHA class status, was based on analysis of individual patient-level data from ATTR-ACT and its LTE (preliminary August 2019 database lock) [24,33,34]. While on treatment, simulated patients assume efficacy profiles derived from the pooled tafamidis meglumine 20 and 80 mg dosing arms of ATTR-ACT and its LTE. Prior to commencing treatment (i.e., during the diagnostic delay period), patients assume efficacy profiles derived from ATTR-ACT's placebo arm. US preference weights [36] were used to derive treatment-specific NYHA class utility values from EuroQoL five-dimension 3-level (EQ-5D-3L) data collected directly from patients during the trial.

The expected benefits of timely diagnosis and treatment were quantified in terms of incremental gains in life expectancy and quality-adjusted life years (QALYs). A schematic diagram illustrating the modeling framework for a 5-year delay is presented in Figure 2. Baseline patient demographic, baseline NYHA class and delay duration profiles applied in the primary analysis are presented in Table 1, and a descriptive summary of all other modeled input profiles is provided in Table 2; further detail on the applied input profiles is provided in the Supplementary Material (see S2.2 and S2.3).

Model application: sensitivity & scenario analyses

Analyses were carried out to assess the sensitivity of model predictions to changes in the baseline age (± 5 years) and the sex distribution of the cohort (proportion female $\pm 20\%$). In addition, several scenario analyses were undertaken to evaluate the impact of key assumptions on modeled outcomes. The survival models used to characterize disease-related mortality in the primary analyses were chosen as they best represent the observed trial data and have underlying profiles consistent with clinical expectations. However, in line with best practice, scenario analyses evaluated the impact of employing alternative survival models to characterize disease-related mortality (see S2.3 for details). Patient NYHA class status was assessed at a frequency of 6 months in ATTR-ACT and its LTE. In the primary analyses, transition matrices governing movement between NYHA classes in the model were informed by transitions observed across all NYHA class assessment intervals. This approach was adopted to ensure optimal use of the data points (see S2.2 for details). However, progression rates for the early within-trial assessment intervals (months 0–6 and 6–12) showed some differences to those later in the trial. The impact of only modeling transitions observed over each of these 6-month intervals for these early periods was assessed via scenario analysis. Finally, a

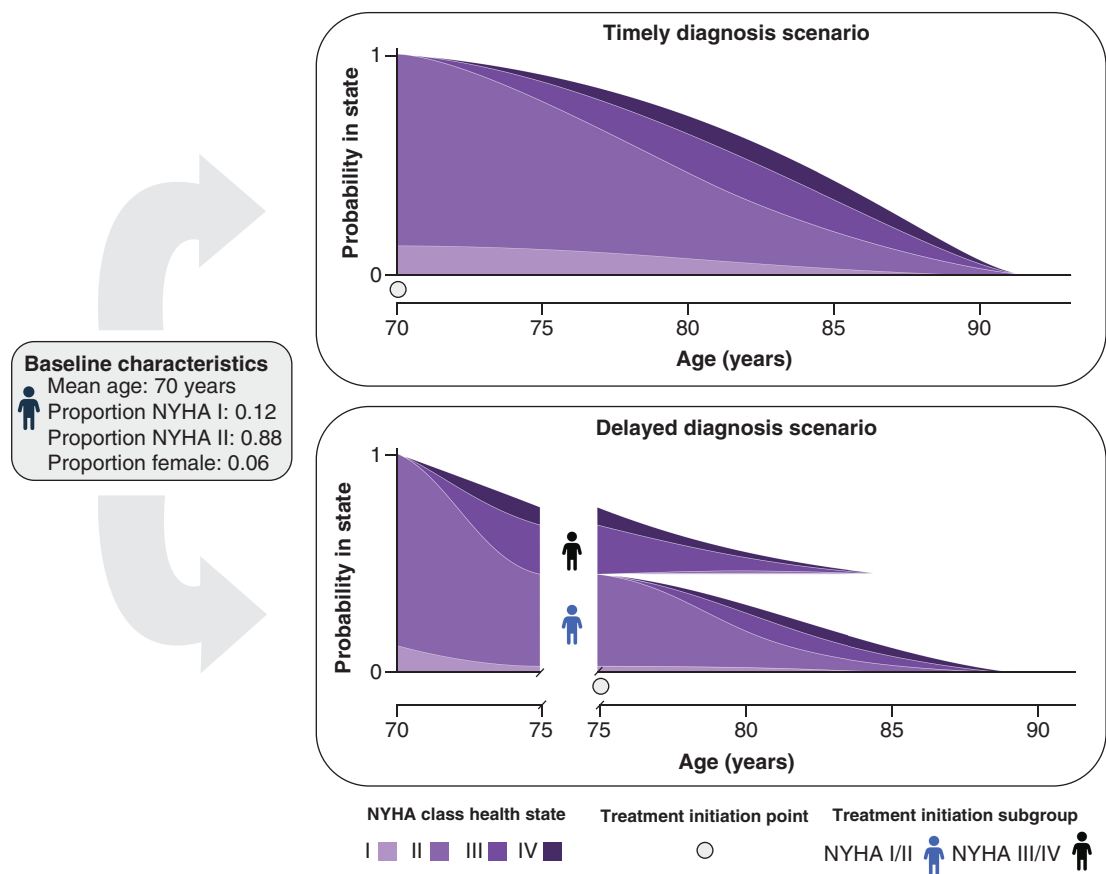


Figure 2. Schematic illustrating the applied modelling framework for a 5-year diagnostic delay. NYHA: New York Heart Association.

Table 1. Modeled baseline patient demographic, baseline New York Heart Association class and delay duration profiles by transthyretin amyloid cardiomyopathy type.

Parameter	Value	Source	Ref.
ATTRwt-CM			
Mean age at baseline (years)	70	Rozenbaum <i>et al.</i> [†]	[13]
Proportion female	0.06		
Baseline NYHA class distribution			
Proportion NYHA I	0.12	ATTR-ACT ATTRwt-CM population	[33]
Proportion NYHA II	0.88		
Mean delay duration (years)	6.08 (min: 1.25; max: 7.17)	Rozenbaum <i>et al.</i> [‡]	[13]
ATTRv-CM			
Mean age at baseline (years)	60	Rozenbaum <i>et al.</i> [†]	[13]
Proportion female	0.27		
Baseline NYHA class distribution			
Proportion NYHA I	0.12	ATTR-ACT ATTRv-CM population	[33]
Proportion NYHA II	0.88		
Mean delay duration (years)	5.67 (min: 1.75; max: 6.50)	Rozenbaum <i>et al.</i> [‡]	[13]

[†]Baseline age and proportion female values were derived from the studies employed to inform delay durations [13]; reported or derived mean age at onset was employed to inform baseline age, with values rounded to the nearest 5-year multiple.

[‡]To align with the model cycle length, reported diagnostic delay durations were rounded down to the nearest month.

ATTR-CM: Transthyretin amyloid cardiomyopathy; ATTRv: Variant ATTR amyloidosis; ATTRwt: Wild-type ATTR amyloidosis; NYHA: New York Heart Association.

Table 2. Descriptive summary of input profiles applied in the model.

Parameter group	Parameter	Description	Source	Ref.
Survival	Background (general population) mortality	US age- and sex-specific national life tables	Arias <i>et al.</i> (CDC)	[35]
	Disease-related mortality	Treatment-specific survival models	ATTR-ACT & LTE	[33,34]
	NYHA class mortality-relative risks [†]	Treatment specific NYHA class relative risks of mortality	ATTR-ACT & LTE	[33,34]
Disease progression	NYHA class transition probabilities	Treatment-specific NYHA class transition matrices	ATTR-ACT & LTE	[33,34]
Health-related quality of life	NYHA class health state utilities	Treatment and NYHA class specific utility values	ATTR-ACT; Shaw <i>et al.</i>	[33,36]

[†] Employed to inform NYHA class-specific disease-related mortality risk, only.
CV: Cardiovascular; NYHA: New York Heart Association.

scenario evaluated outcomes based on efficacy profiles derived from the tafamidis meglumine 80 mg dosing arm alone. The primary analysis of ATTR-ACT compared the pooled tafamidis arms (tafamidis meglumine 20 and 80 mg dosing) with the placebo arm [24], but the FDA- and EMA-recommended doses are tafamidis meglumine 80 mg and the 61 mg free acid bioequivalent dose, respectively [22,23]. *Post hoc* analysis of data from ATTR-ACT and its LTE confirmed that the 80 mg dose had a significantly greater survival benefit over placebo compared with the 20 mg dose, with no dose-related safety concerns [37].

Analytic software

The disease simulation model was developed in Microsoft Excel 2016® (Microsoft Corporation, WA, USA). R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct statistical analyses informing the model input profiles and for the production of results figures.

Results

Primary analysis

Per-patient health outcomes for the timely and delayed diagnosis and treatment scenarios modeled in the primary analyses are presented in Table 3. In ATTRwt-CM patients, timely diagnosis and treatment with tafamidis were

Table 3. Per-patient health outcomes by modeled timely and delayed diagnosis scenarios.

ATTR-CM type	Scenario	Life years	QALYs			
ATTRwt-CM	Timely diagnosis scenario	11.65	9.31			
	Delayed diagnosis scenario (6.08-year delay)	6.19	4.81			
	Incremental	5.46	4.50			
ATTRv-CM	Timely diagnosis scenario	12.62	10.01			
	Delayed diagnosis scenario (5.67-year delay)	4.86	3.80			
	Incremental	7.76	6.22			
		Time spent in NYHA class (years) [†]				
		NYHA I	NYHA II	NYHA III	NYHA IV	
ATTRwt-CM	Timely diagnosis scenario	1.31	7.01	3.14	0.20	
	Delayed diagnosis scenario (6.08-year delay)	0.53	3.64	1.84	0.18	
	Incremental	0.78	3.36	1.30	0.02	
ATTRv-CM	Timely diagnosis scenario	1.69	6.89	3.60	0.43	
	Delayed diagnosis scenario (5.67-year delay)	0.48	3.01	1.21	0.16	
	Incremental	1.21	3.88	2.40	0.27	

Apparent differences in the reported values are due to rounding.

[†] The time spent in each NYHA class is determined by the baseline NYHA class distribution of the modeled patient cohort, and the modeled NYHA class transition and mortality risk profiles. The majority of the modeled patient cohort (88%) were in NYHA class II at baseline with the remainder (12%) in NYHA class I, for both ATTRwt-CM and ATTRv-CM.

ATTR-CM: Transthyretin amyloid cardiomyopathy; ATTRv: Variant ATTR amyloidosis; ATTRwt: Wild-type ATTR amyloidosis; Inc.: Incremental; NYHA: New York Heart Association; QALY: Quality-adjusted life year.

predicted to extend mean life expectancy by 5.46 years relative to delayed diagnosis (mean delay: 6.08 years). For ATTRv-CM patients, timely diagnosis and treatment were predicted to result in life expectancy gains of 7.76 years relative to delayed diagnosis (mean delay: 5.67 years). Most of the benefit was accrued in the NYHA classes corresponding to less advanced heart failure (classes I and II). With timely diagnosis and treatment, ATTRwt-CM patients were predicted to spend approximately twice as long (4.14 additional years) in NYHA class I and II than if they had experienced the mean delay; ATTRv-CM patients were predicted to spend almost two and a half times longer (5.09 additional years) in these classes. Resultant QALY gains were predicted to be 4.50 and 6.22 for ATTRwt-CM and ATTRv-CM, respectively.

As expected, for both ATTRwt-CM (Figure 3) and ATTRv-CM (Figure 4) patients, predicted life expectancy and QALY gains associated with timely diagnosis and treatment were greater when compared with outcomes for more lengthy delays.

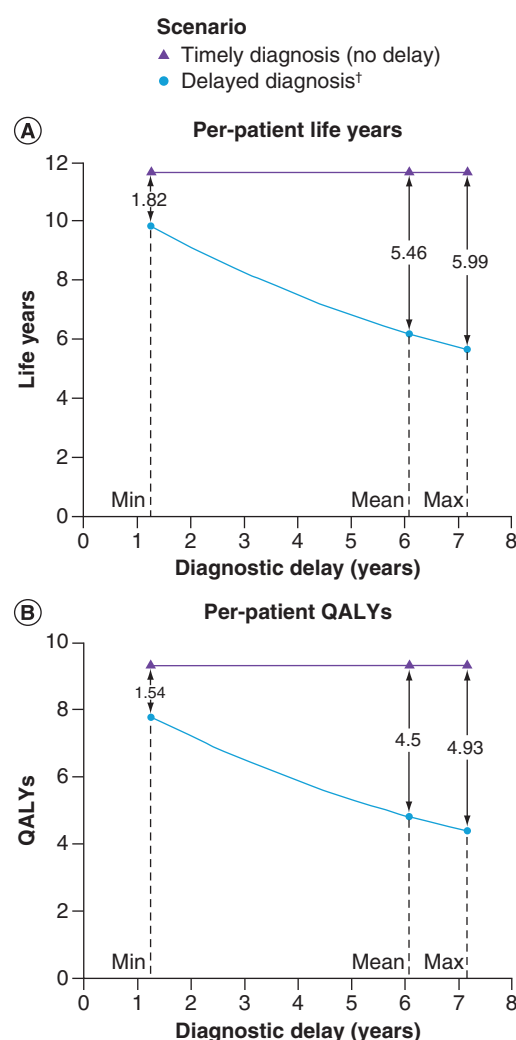


Figure 3. Per-patient health outcomes: ATTRwt-CM. (A) ▲ markers denote life year predictions under the scenario of timely diagnosis and treatment; ● markers denote life year predictions for scenarios considering the mean and range diagnostic delays. Gains associated with timely diagnosis and treatment are shown as the difference between the respective points. **(B)** Per A for QALYs.

[†]Diagnostic delays correspond to those presented in Table 1.

QALY: Quality-adjusted life year.

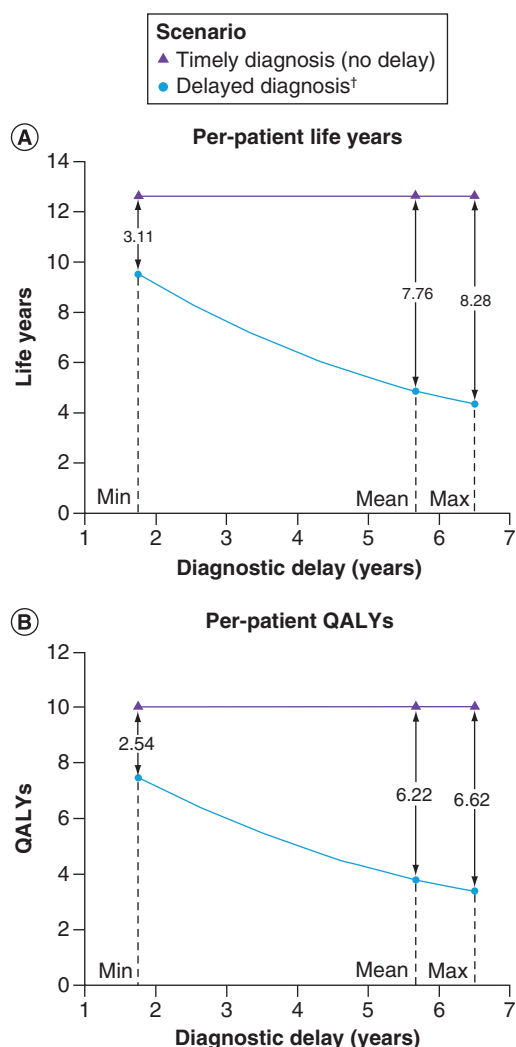


Figure 4. Per-patient health outcomes: ATTRv-CM. (A) ▲ markers denote life year predictions under the scenario of timely diagnosis and treatment; ● markers denote life year predictions for scenarios considering the mean and range diagnostic delays. Gains associated with timely diagnosis and treatment are shown as the difference between the respective points. (B) Per A for QALYs.

[†]Diagnostic delays correspond to those presented in Table 1.

QALY: Quality-adjusted life year.

Sensitivity & scenario analyses

Figure 5 summarizes the impact of sensitivity and scenario analysis variations on incremental health outcomes. For both ATTR-CM types, timely diagnosis and treatment were predicted to improve health outcomes across all sensitivity and scenario analyses conducted.

Model predictions were sensitive to baseline age variations (± 5 years), with greater health benefits predicted for younger patients and less benefit for older patients. Driven by improved survival outcomes, predicted health benefits were greater when tafamidis efficacy profiles were based on the 80 mg dosing arm alone; in the primary analysis, tafamidis efficacy profiles were based on the pooled (tafamidis meglumine 20 and 80 mg dosing) tafamidis arms. Variations to the sex distribution of the cohort (proportion female $\pm 20\%$) had limited impact for either ATTR-CM type; however, the model results indicate greater benefit for females, with the proportionally greater differences predicted for ATTRv-CM patients due in part to the fact that this cohort contained a greater proportion of females than the ATTRwt-CM cohort (Table 1).

The use of alternative survival models (see S2.3 for detail) to characterize disease-related mortality also influenced results, providing more conservative estimates of the expected health gains for timely diagnosis and treatment than

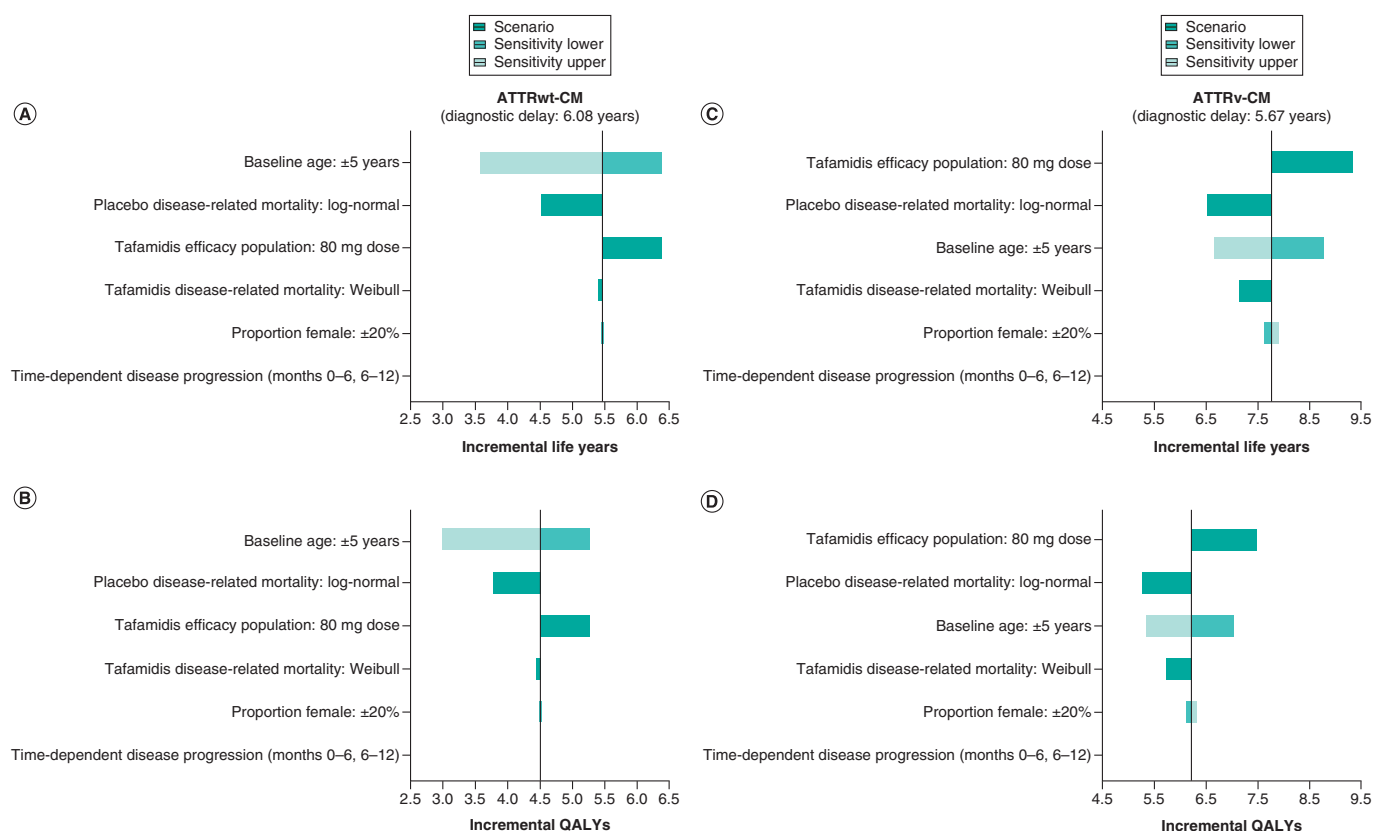


Figure 5. Sensitivity and scenario analyses: tornado plot of incremental health outcomes. Incremental life years (A) and QALYs (B) predicted for ATTRwt-CM patients in the primary analysis are denoted by the vertical lines with the impact of variations made for sensitivity and scenario analyses depicted by the horizontal bars. Sensitivity and scenario analyses are ranked in order of impact. (C & D) As above for ATTRv-CM.

ATTR-CM: Transthyretin amyloid cardiomyopathy; NYHA: New York Heart Association; QALY: Quality-adjusted life year.

the primary analyses. Modeling only NYHA class transitions observed in each 6-month assessment interval in ATTR-ACT for the early assessment phases (months 0–6 and months 6–12) had a negligible impact on results.

Discussion

Diagnostic delay for ATTR-CM is widely acknowledged in the literature as a clinical challenge [6,11–13]. However, until the advent of disease-modifying treatment, its consequences for patients' life expectancy and HRQoL were limited. To our knowledge, the benefits of timely diagnosis and treatment in the era of disease-modifying treatment have not previously been quantified.

This study demonstrates that lengthy diagnostic delays represent a foregone opportunity to extend and improve life for patients with ATTR-CM through treatment with a disease-modifying therapy, tafamidis. Relative to delayed diagnosis, timely diagnosis and treatment for ATTRwt-CM patients were predicted to result in a mean life expectancy gain of 5.46 years and a mean QALY gain of 4.50. For ATTRv-CM patients, mean life expectancy and QALY gains were 7.76 and 6.22, respectively. Most of the benefit was accrued in the NYHA classes corresponding to less advanced heart failure (NYHA class I and II), with patients from the modeled ATTRwt-CM and ATTRv-CM cohorts predicted to spend markedly greater amounts of time in these classes under conditions of timely diagnosis and treatment than if they had experienced delay. These findings reflect the observation that, due to its mechanism of action and ATTR-CM's progressive nature, tafamidis is expected to provide greater benefit, both in overall extension of life and extension of life in lower heart failure classes, to patients who are treated earlier in the disease course [24,38].

Sensitivity analyses found that estimated benefits were greater for younger patients and females. The prediction that younger patients derive greater benefit further underscores the need for earlier diagnosis in order to maximize treatment benefit. Consistent with the findings of published post-hoc analyses of ATTR-ACT and its LTE [37],

scenario analyses also found that estimated health benefits were greater when tafamidis efficacy was based on the ATTR-ACT 80 mg dosing arm alone. These findings suggest that estimates based on the efficacy of the pooled (tafamidis meglumine 20 and 80 mg) tafamidis dosing arms may be conservative, and further support FDA and EMA recommendations for use of the tafamidis meglumine 80 and the 61 mg free acid bioequivalent doses, respectively [22,23].

Our study did not consider the economic implications of diagnostic delay. However, there is evidence that patients with delayed diagnosis have high healthcare resource utilization during their diagnostic journey, typically making numerous healthcare visits, including inpatient hospitalizations, and undergoing a range of investigations for other conditions [12,26]. This cycling through different investigations and services would be largely avoided with prompt diagnosis. An economic evaluation by Pilgaard *et al.* of diagnostic and lifetime hospital costs of patients with ATTRwt-CM in the Danish healthcare setting concluded that healthcare resource use costs could be reduced through earlier diagnosis [39].

Our study has notable strengths. Treatment efficacy, quantified in terms of survival and NYHA class status, and HRQoL were informed by analyzing individual patient-level data from the pivotal trial (ATTR-ACT) and its LTE, which followed tafamidis-managed patients to a median treatment duration of 51.9 months [40]. This can be considered the best available evidence, given that ATTR-ACT was a Phase III randomized controlled trial providing direct evidence on the efficacy of tafamidis versus placebo. Modeled diagnostic delay and baseline demographic characteristic profiles were derived from a comprehensive literature review that captured reports of diagnostic delay from real-world clinical practice [13]. Furthermore, unlike studies evaluating the benefits of screening interventions, the findings of our study are not subject to lead time bias. Given that the evidence source informing outcome estimates in both the timely and delayed diagnosis and treatment scenarios is a single randomized controlled trial, and that survival predictions are made from a common point of disease development (as detailed in the baseline characteristics in Table 1), the confounding effects of the lead time associated with earlier diagnosis are not incurred.

Some limitations of the study should be noted. First, no evidence was available in the literature on diagnostic delay to inform NYHA class distributions at symptom onset, so the distributions observed at randomization in ATTR-ACT were assumed to be in place in the analyses. While benefits were seen across patients with baseline NYHA class I–III in ATTR-ACT, the current analyses considered only those patients with baseline NYHA class I or II. As such, the modeled outcomes can be considered representative for patients with early-stage disease. Second, it was necessary to extrapolate survival outcomes beyond the observed data, as many patients enrolled in ATTR-ACT were still alive at the time of data cut-off. Nevertheless, as survival extrapolations were based on ATTR-ACT and its LTE, the model predictions can be considered to be informed by the best available evidence.

Conclusion

Facilitating timely diagnosis is a key element in the drive to improve the management of patients with ATTR-CM, and this study adds further evidence to support the urgency of reducing diagnostic delay. Timely diagnosis and treatment with tafamidis are predicted to significantly improve survival and health-related quality of life outcomes for ATTRwt-CM and ATTRv-CM patients compared with the historical scenario of delayed diagnosis and lack of a disease-modifying treatment.

Future perspective

The availability of a disease-modifying treatment, together with recent consensus recommendations on non-invasive diagnostic techniques and suggested diagnostic ‘red flags’, are leading to increased awareness of ATTR-CM among clinicians. This trend is expected to continue, with the result that patients will, on average, be diagnosed earlier in the disease process, increasing the benefit derived from treatment.

Summary points

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and ultimately fatal disease caused by the accumulation of amyloid fibrils in the heart muscle.
- Diagnostic delay is common, with patients often not correctly diagnosed for several years after symptom onset.
- Since the recent introduction of the first disease-modifying treatment, tafamidis, diagnostic delay represents a missed opportunity for intervention to extend and improve life for patients with ATTR-CM.
- This study evaluated the expected health benefits of timely diagnosis and treatment of ATTR-CM with tafamidis in the US setting, using a disease simulation model.
- Analyses were underpinned by the findings of a targeted literature review and individual patient-level data from the pivotal Phase III trial, Tafamidis in Transthyretin cardiomyopathy Clinical Trial (ATTR-ACT).
- Timely diagnosis and treatment were predicted to substantially improve survival and health-related quality of life outcomes for ATTRwt-CM and ATTRv-CM patients, compared with the historical scenario of delayed diagnosis and lack of a disease-modifying treatment.
- Estimated benefits were greater for younger patients, underscoring the need for treatment earlier in the disease course in order to maximize benefit.
- Facilitating timely diagnosis is a key element in the drive to improve the management of patients with ATTR-CM.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/visit/10.2217/cer-2021-0071

Financial & competing interests disclosure

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