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## Cost-Effectiveness of Tafamidis Therapy for Transthyretin Amyloid Cardiomyopathy

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### Abstract

**Background:** In patients with transthyretin amyloid cardiomyopathy (ATTR-CM), tafamidis reduces all-cause mortality and cardiovascular hospitalizations, and slows decline in quality-of-life compared with placebo. In May 2019, tafamidis received expedited approval from the US FDA as a breakthrough drug for a rare disease. However, at \$225,000 per year, it is the most expensive cardiovascular drug ever launched in the US, and its long-term cost-effectiveness and budget impact are uncertain. We therefore sought to estimate the cost-effectiveness of tafamidis and its potential effect on US health care spending.

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**Methods:** We developed a Markov model of patients with wild-type or variant ATTR-CM and heart failure (mean age 74.5 years) using inputs from the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), published literature, US Food and Drug Administration review documents, healthcare claims, and national survey data. We compared no disease-specific treatment (“usual care”) with tafamidis therapy. The model reproduced 30-month survival, quality-of-life, and cardiovascular hospitalization rates observed in ATTR-ACT; future projections used a parametric survival model in the control arm, with constant hazards reduction in the tafamidis arm. We discounted future costs and quality-adjusted life years (QALYs) by 3% annually, and examined key parameter uncertainty using deterministic and probabilistic sensitivity analyses. The main outcomes were lifetime incremental cost-effectiveness ratio (ICER) and annual budget impact, assessed from the US healthcare sector perspective. This study was independent of the ATTR-ACT trial sponsor.

**Results:** Compared with usual care, tafamidis was projected to add 1.29 (95% uncertainty interval, 0.47–1.75) QALYs at an incremental cost of \$1,135,000 (872,000–1,377,000), resulting in an ICER of \$880,000 (697,000–1,564,000) per QALY gained. Assuming a threshold of \$100,000 per QALY gained and current drug price, tafamidis was cost-effective in 0% of 10,000 probabilistic simulations. A 92.6% price reduction from \$225,000 to \$16,563 would be necessary to make tafamidis cost-effective at \$100,000/QALY. Results were sensitive to assumptions related to long-term effectiveness of tafamidis. Treating all eligible patients with ATTR-CM in the US with tafamidis (n = 120,000) was estimated to increase annual healthcare spending by \$32.3 billion.

**Conclusions:** Treatment with tafamidis is projected to produce substantial clinical benefit but would greatly exceed conventional cost-effectiveness thresholds at the current US list price. Based on recent US experience with high-cost cardiovascular medications, access to and uptake of this effective therapy may be limited unless there is a large reduction in drug costs.

### Keywords

Tafamidis; Amyloidosis; Heart Failure; Cost-Effectiveness; Economics

### Background

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome that accounts for approximately 50% of all heart failure and lacks effective treatments. Transthyretin amyloid cardiomyopathy (ATTR-CM), caused by the accumulation in the myocardium of amyloid fibrils composed of misfolded transthyretin, is an underrecognized cause of HFpEF in older adults.<sup>1</sup> In addition to causing heart failure, it increases the risk of conduction abnormalities, atrial fibrillation, embolic stroke, and cardiovascular death, and results in a median survival of 2.5 to 3.5 years from diagnosis if untreated.<sup>1, 2</sup>

Tafamidis is a drug that binds to and stabilizes transthyretin, thereby preventing transthyretin tetramer dissociation, the rate-limiting step in transthyretin amyloid deposition. In the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), patients with ATTR-CM and heart failure who received tafamidis experienced lower all-cause mortality, fewer cardiovascular hospitalizations, and a slower decline in quality-of-life and functional

capacity compared with patients who received placebo.<sup>2</sup> In May 2019, tafamidis received expedited approval from the US Food and Drug Administration (FDA) as a breakthrough drug, a designation reserved for therapies “intended to treat a serious or life-threatening disease” with preliminary evidence to suggest “a substantial improvement over existing therapies.”<sup>3</sup> However, at a list price of \$225,000 per year, it is the most expensive cardiovascular drug ever launched in the US, raising concerns about cost-effectiveness, affordability, and access. A timely and rigorous cost-effectiveness evaluation would help inform clinical and policy discussions regarding uptake of tafamidis and may influence drug pricing as the drug enters the market. We therefore sought to perform an independent cost-effectiveness analysis of tafamidis for ATTR-CM, with the goal of better understanding the potential effects of this high-priced therapy on US healthcare spending.

## Methods

The simulation model and key inputs used to conduct this research are available to interested researchers who submit a 1- to 2-page research proposal and collaboration plan to Dr. Kazi (e-mail, dkazi@bidmc.harvard.edu) and sign a Creative Commons agreement, pending approval by the model team. Data used to generate the inputs for this study come from health care claims, surveys, and publications detailed in Table 1 and the Supplemental Material and may be requested directly from their primary source. Data on health surveys, vital statistics, and health care costs are publicly available from government sources as described. Because the study relied on publicly available de-identified data, this was deemed to not be human subjects research and institutional review board approval was therefore not required.

## Model Structure

We developed a state-transition Markov model of patients with wild-type or variant (i.e., hereditary) ATTR-CM and heart failure using inputs from the ATTR-ACT trial, published literature, FDA review documents, national claims data, and the Medical Expenditure Panel Survey (MEPS).<sup>2, 4, 5, 9, 10, 12–17</sup> In monthly cycles, patients could continue to live with heart failure (with declining quality-of-life related to advancing disease), experience cardiovascular hospitalizations, or die from cardiovascular or non-cardiovascular causes (Figure 1). We adopted the US healthcare sector perspective, including all healthcare-related expenditures regardless of who incurs them, and a lifetime analytic horizon. Future costs and benefits were discounted at 3% per year. We adhered to the guidelines recommended by the Second Panel for Cost-Effectiveness in Health and Medicine.<sup>6</sup>

## Target Population

The simulated population reflected the characteristics of patients in ATTR-ACT, a phase 3, multicenter, placebo-controlled, double-blind, randomized trial that enrolled patients between 18 and 90 years of age who had wild-type or variant ATTR-CM, a history of heart failure, and at least one prior hospitalization for heart failure or clinical evidence of heart failure.<sup>2</sup> Patients with New York Heart Association Class IV symptoms, an implanted left ventricular assist device, or severe renal insufficiency (estimated glomerular filtration rate

<25 ml/min/m<sup>2</sup>) were excluded. The mean age at study entry was 74.5 years and 11% were women.

### Treatment Strategies

We evaluated the effect of tafamidis compared with no disease-specific ATTR-CM treatment (“usual care”).

### Transition Probabilities for the first 30 months

The model was calibrated to reproduce 30-month survival, quality-of-life, and cardiovascular hospitalization rates observed in ATTR-ACT, based on published data and publicly available FDA review documents.<sup>2, 4</sup> In ATTR-ACT, compared with patients receiving placebo, patients receiving tafamidis had lower all-cause mortality at 30 months (hazard ratio 0.70, 95% confidence interval [CI] 0.56–0.81) and a lower rate of cardiovascular hospitalizations (relative risk 0.68, 95% CI 0.56–0.80). In order to estimate survival in both arms, we fit separate parametric Weibull models to the observed survival in the control and intervention arms of the trial (Figure 1). The Weibull was chosen because it is a flexible class of distributions that allows for increasing or decreasing hazard over time (e.g., increasing cardiovascular mortality with age), and also covers simpler distributions like the exponential distribution.<sup>18</sup> We used parametric bootstrapping to estimate the uncertainty of the Weibull curve, assuming a bivariate normal joint distribution of the estimates of its sigma and k parameters (Table 1). As observed in ATTR-ACT, we assumed that survival in the intervention arm was identical to that in the control arm for the first 18 months. We then used the Weibull models described above – based on the published survival curves from the trial – to model the reduction in all-cause mortality in the intervention arm relative to the control arm between months 18 and 30.

We assumed that patients in the control arm would have an average of 0.70 cardiovascular hospitalizations a year (95% CI 0.62–0.80) as observed in ATTR-ACT, and applied a 32% hazard reduction in the tafamidis arm (Table 1).<sup>2</sup>

### Extrapolation Beyond Trial Duration

Since patients enrolled in ATTR-ACT were only followed for 30 months, we used the Weibull model described above to project survival in the control arm beyond 30 months. In the base case, we made the optimistic assumption that the benefits of tafamidis would be sustained beyond 30 months, so that the hazard ratio for survival observed in month 30 would continue throughout the duration of therapy. We also assumed that the monthly rate of decline in mean quality-of-life in each arm would continue unchanged beyond 30 months. These assumptions favored tafamidis and represented a “best-case scenario” for the cost-effectiveness of tafamidis compared with usual care (Supplemental Table 1). In sensitivity analyses, we modeled: 1) an “intermediate-case scenario” that assumed that the effectiveness of tafamidis waned over the 60 months after trial completion so that there was no difference between the intervention and control arms beyond month 90; and 2) a “worst-case scenario” that assumed that tafamidis becomes completely ineffective after month 30.

## Adverse Events

In ATTR-ACT, the safety profile of tafamidis appeared to be similar to placebo at 30 months. We therefore did not include any costs and quality-of-life penalties related to medication-related adverse events in the model.

## Costs

We assumed that one year of tafamidis therapy would cost \$225,000, its wholesale acquisition cost in September 2019 (Supplement, *Tafamidis Dose and Pricing*).<sup>7</sup> We varied this assumption in sensitivity analyses. The cost of cardiovascular hospitalizations was estimated from the 2014 Healthcare Cost and Utilization Project data using Ninth Revision of International Classification of Diseases (ICD-9) codes, adjusted to include physician fees (Supplemental Table 2, *Estimating Costs of Cardiovascular and Non-Cardiovascular Care*).<sup>9, 10</sup> Because ATTR-CM has substantial prognostic implications for patients and, in the case of hereditary ATTR-CM, for family members, we assumed that patients with heart failure with preserved ejection fraction would be tested for ATTR-CM regardless of the decision to initiate tafamidis therapy. We therefore did not incorporate diagnostic costs in this analysis as their inclusion would not be expected to alter the incremental cost-effectiveness of tafamidis therapy. Background healthcare costs (defined as all direct medical costs, excluding cardiovascular hospitalizations and tafamidis drug costs) were estimated as the adjusted, survey-weighted mean total expenditures for individuals with history of heart failure and without any cardiovascular hospitalizations in the year prior or during the survey year from the 2006–2015 MEPS, stratified by age.<sup>8</sup> We included long-term care costs by multiplying the proportion of all US adults using each type of long-term care service by published annual long-term care cost estimates from the US Department of Health and Human Services (Supplemental Tables 3 and 4).<sup>14, 15</sup> All costs were inflated to 2019 US dollars using the Personal Consumption Expenditure index.<sup>16</sup> Additional modeling details are available in the online Supplemental Material.

## Quality-of-Life Estimates

ATTR-ACT used the overall score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-OS) to measure study participants' heart failure-specific health status at baseline and throughout follow-up.<sup>17</sup> We used observed changes in the KCCQ-OS from ATTR-ACT (placebo  $20.81 \pm 1.97$  vs tafamidis  $7.16 \pm 1.42$ ) in the first 30 months of the model and linearly extrapolated these afterward. To map KCCQ-OS scores to quality-of-life weights, we developed a mapping algorithm using individual-level data from a prospective, 14-center cohort of 476 outpatients with heart failure (Supplement, *Estimating Quality-of-Life Parameters*, Supplemental Table 5, and Supplemental Table 6).<sup>19</sup> To capture the uncertainty in this mapping process, we used parametric bootstrapping to generate 1000 paired values for the mapping parameters, which we incorporated into probabilistic sensitivity analyses.<sup>20</sup> Since patients with HFpEF typically receive other oral medications like diuretics, we did not model any additional pill-related disutility related to tafamidis therapy.

## Main Outcome Measures

The primary outcome was the incremental cost-effectiveness ratio (ICER) of tafamidis compared with usual care, assessed in terms of both cost per life year and cost per quality-adjusted life year (QALY). We assumed a cost-effectiveness threshold of \$100,000 per QALY, and examined alternative thresholds in sensitivity analyses (high value, <\$50,000; intermediate value, \$50,000 to <\$150,000, and low value, \$150,000 per QALY gained).<sup>21</sup> We also evaluated the impact on annual healthcare spending if all US patients eligible for tafamidis were to receive the drug. For this budget impact analysis, we estimated a target population of 120,000 US adults, based on a conservative estimate that 4% of adults older than 60 years who have HFpEF have ATTR-CM, but varied this number between 100,000 to 200,000 in sensitivity analyses (Supplemental Material, *Approach to the Budget Impact Analysis*). We first estimated total change in healthcare spending over 5 years and then generated annualized estimates of budget impact.

## Sensitivity Analyses

We performed deterministic and probabilistic sensitivity analyses to reflect uncertainty in the key parameters. In deterministic analyses, we varied input parameters one-at-a-time across the range shown in Table 1 while holding all other parameters at their base-case value. Probabilistic sensitivity analyses were performed by drawing (with replacement) 10,000 sets of input parameters from pre-specified statistical distributions in order to generate 95% uncertainty intervals (UI) for key clinical and economic outcomes as well as acceptability curves.

## Software

Modeling was performed using TreeAge Pro 2019 (TreeAge Software Inc, Williamstown, Massachusetts) and Microsoft Excel version 16 (Microsoft Corporation, Redmond, Washington), and statistical analyses were performed using R version 3.6.1 (Vienna, Austria).

## Funding and Role of the Sponsor

This study was independent of the commercial sponsor of the ATTR-ACT trial, and was funded by the Richard A. and Susan F. Smith Center for Cardiovascular Outcomes Research and a Northwestern University Multidisciplinary Amyloidosis Program pilot grant. Dr. Bellows is supported by K01-HL140170 from the National Heart, Lung, and Blood Institute. The funders had no role in study design, data collection and analysis, or preparation of the manuscript, or the decision to submit it for publication.

## Results

### Model Calibration

The mean age of the simulated cohort was 74.5 years and 11% were women. The model accurately replicated the all-cause mortality and cardiovascular hospitalization rates observed in ATTR-ACT over 30 months of follow-up (Supplemental Table 7). For instance, all-cause mortality at 30 months among patients receiving tafamidis was 29.6% in the model

and 29.5% in ATTR-ACT. At 30 months, the hazard ratio for all-cause mortality (tafamidis vs. usual care) was 0.68 (95% UI 0.51 to 0.86) in the model compared with 0.70 (95% CI 0.51 to 0.96), and the relative risk ratio for cardiovascular hospitalizations was 0.70 [95% UI 0.59 to 0.83] in the model vs 0.68 (95% CI 0.56 to 0.81) in ATTR-ACT (Supplemental Table 7).

### Base-Case Analysis

Mean survival in the usual care arm was 3.46 (95% UI, 2.88–4.25) years; this was prolonged to 5.43 (95% UI, 4.17–6.76) years in the tafamidis arm (Table 2). Patients receiving tafamidis were projected to have fewer cardiovascular hospitalizations over the first 30 months compared with patients receiving usual care, but this was offset by additional hospitalizations over the long-term due to increased survival, resulting in a higher total number of lifetime cardiovascular hospitalizations in patients receiving tafamidis (Table 2 and Supplemental Table 8). Compared with usual care, treatment with tafamidis over the lifetime horizon was projected to generate 1.29 (95% UI, 0.60–1.89) additional QALYs at an incremental cost of \$1,135,000 (95% UI, 872,000–1,377,000), resulting in an ICER of \$880,000 (95% UI, 697,000–1,553,000) per QALY gained (Table 2). The incremental cost in the intervention arm was almost entirely comprised of the cost of tafamidis (\$1,086,000 [95% UI, 861,000–1,303,000]), with a small contribution from increased background costs related to prolonged survival (Table 2). There was no meaningful reduction in lifetime costs of cardiovascular care because savings from fewer cardiovascular hospitalizations per year were offset by increased cardiovascular costs in the added years of life.

### Sensitivity Analyses

In deterministic analyses, our findings were sensitive to three key parameters. First, an increase in the discount rate to 8% increased the ICER to \$977,000 per QALY gained. Second, assuming a lower effectiveness of tafamidis with regard to reduction in all-cause mortality would increase the ICER to \$1,321,000 per QALY gained. Third, the ICER was very sensitive to the annual cost of tafamidis. A 92.6% price reduction from \$225,000 to \$16,563 would make tafamidis cost-effective at a threshold of \$100,000 per QALY gained, while an 87% price reduction to \$29,925 would make it cost-effective at \$150,000 per QALY gained (Figure 2). Additionally, shortening the time horizon to 30 months, the duration of ATTR-ACT, increased the ICER to \$3,903,000 per QALY gained (Supplemental Table 8). The model was relatively insensitive to other parameters (altering the ICER by less than 20%).

In probabilistic sensitivity analyses, tafamidis was cost-effective in 0% of the 10,000 probabilistic simulations at a cost-effectiveness threshold of \$100,000 per QALY gained (Figure 3 and Supplemental Figure 1).

### Scenario Analyses

The results were sensitive to the long-term durability of effectiveness of tafamidis. Assuming that the effectiveness of tafamidis wanes over 5 years after trial completion (intermediate-case scenario) reduced the incremental benefit of tafamidis to 0.63 QALYs and increased the ICER to \$1,517,000 per QALY gained (Supplemental Table 9). Assuming

complete loss of tafamidis effectiveness beyond 30 months (worst-case scenario) increased the ICER to \$3,122,000 per QALY gained. In the intermediate-case and worst-case scenarios, the price of tafamidis would need to be 95.7% and 97.4% lower, respectively, for the therapy to be cost-effective at a threshold of \$100,000 per QALY gained (Supplemental Table 10).

### Budget Impact Analysis

Treating all eligible US patients with ATTR-CM with tafamidis (n = 120,000) was projected to increase annual healthcare spending by \$32.3 billion. Nearly all of the budget impact (\$31.9 billion) was due to the cost of tafamidis. The change in healthcare spending varied with estimated prevalence of ATTR-CM, ranging from \$26.9 billion if the prevalence was assumed to be 100,000 to \$53.8 billion if the prevalence was assumed to be 200,000.

### Discussion

In a simulation model calibrated to the results of the ATTR-ACT trial, we found that tafamidis therapy for patients with ATTR-CM would increase quality-adjusted life expectancy by an average of 1.29 QALYs, but the ICER of \$880,000 per QALY gained would be substantially higher than conventional cost-effectiveness thresholds. A 92.6% reduction in the annual price of tafamidis – from \$225,000 to \$16,563 – would be needed for the drug to be cost-effective at a commonly accepted threshold of \$100,000 per QALY gained. Savings from fewer cardiovascular hospitalizations per patient per year would be offset by increases in healthcare costs related to prolonged survival, such that U.S. healthcare spending would increase by \$32.3 billion a year if all eligible patients were to receive tafamidis therapy. This includes a \$31.9 billion increase in annual prescription drug expenditures, which would increase the total US spending for all prescription drugs by 9.3% (from \$344 billion in 2018 to \$375.9 billion).<sup>22</sup> As diagnosis rates increase – as a result of greater awareness about ATTR-CM, increased use of nuclear scintigraphy for accurate diagnosis, and more widespread uptake of genetic tests to screen family members of individuals with variant ATTR-CM – the budget impact of tafamidis is expected to increase as well.<sup>23</sup> The challenge for health systems and payers is therefore likely to grow over time. Our findings are concordant with those of two prior analyses that found that tafamidis was not cost-effective for ATTR familial amyloid polyneuropathy in Europe.<sup>24, 25</sup> However, our analysis is the to examine tafamidis from a US healthcare sector perspective and include the survival benefits observed in ATTR-ACT.

Over the past 3 decades, numerous cost-effective and potentially life-saving therapies have been approved and implemented for heart failure with reduced ejection fraction, but pharmaceutical innovation for HFpEF has largely been disappointing. One potential explanation for the difficulty in developing effective therapies for HFpEF is that it represents a heterogeneous group of conditions that are unlikely to all respond to a single therapy, arguing against a “one-size-fits-all” approach. Given this heterogeneity, HFpEF is an ideal syndrome for the application of precision medicine, and recent efforts have focused on identifying subgroups of HFpEF to tailor therapy accordingly. The recognition of ATTR-CM as a distinct phenotype of HFpEF, the use of nuclear scintigraphy to noninvasively and



accurately diagnose ATTR-CM, and the development of tafamidis to inhibit a key step in the pathogenesis of ATTR-CM are therefore major advances in the targeted treatment of the HFpEF syndrome.<sup>2</sup> Our study suggests that for patients similar to those in the ATTR-ACT trial, tafamidis therapy for ATTR-CM will prolong quality-adjusted survival by 1.29 QALYs, a relatively large health gain compared with other contemporary cardiovascular therapies, justifying its designation as a “breakthrough therapy” that addresses an important unmet clinical need.<sup>26, 27</sup> For comparison, the use of sacubitril-valsartan in heart failure with reduced ejection fraction is projected to yield 0.62 QALYs over a patient’s lifetime.<sup>26</sup>

But these substantial health benefits of tafamidis are projected to come at a high cost. Our study demonstrates that, at current drug prices, widespread uptake of tafamidis would produce a large increase in healthcare spending, with an ICER that is greatly exceeds US thresholds for high or even intermediate economic value. Although manufacturers typically offer discounts and rebates amounting to 25–30% of the wholesale acquisition cost, our findings suggest that massive discounts or price reductions would be needed in order to make tafamidis economically attractive at conventional thresholds. It should be noted, however, that manufacturers of rare drugs have substantial pricing power, so that these drugs are often discounted less than 5% if at all. Moreover, manufacturers’ discounts do little to alleviate the financial burden for Medicare Part D beneficiaries (who, given the natural history of the disease, are likely to represent the majority of US patients eligible for this novel therapy) because their copayments are calculated from the list price of the drug before the application of any rebates or discounts. As a result, Medicare Part D beneficiaries without secondary insurance may be responsible for tens of thousands of dollars per year in out-of-pocket costs. This would put the drug out of reach for many fixed-income seniors.

In many ways, tafamidis is emblematic of contemporary challenges in rewarding pharmaceutical innovation – it is a highly personalized therapy that is effective, safe, and unaffordable. Its expedited FDA approval in May 2019 relied on several regulatory and financial incentives available to manufacturers of “orphan drugs” that target rare diseases without pre-existing treatments.<sup>28,29</sup> These incentives, embedded in the Orphan Drug Act and designed to help patients gain expedited access to transformative therapies, have been spectacularly successful in spurring pharmaceutical innovation: 58% of all new drugs approved in 2018 were for a rare-disease indication.<sup>30</sup> But once approved, drugs that receive “orphan drug status” typically enter the market at a very high price: the 100 best-selling rare disease drugs in 2017 cost an average of \$116,000 more than 100 best-selling drugs for other indications.<sup>31</sup> Innovators have argued that these higher prices are necessary to recoup large investments in research and development when only a small number of patients are eligible for therapy. But the high price tag defeats the very purpose of the expedited approval process, as it makes the drug unaffordable for the target population. The case of tafamidis lends further credence to recent calls to reform the Orphan Drug Act to ensure access to the rare-disease drugs that utilize its incentives. For instance, regulatory and financial incentives could be conditioned on the manufacturer setting a value-based price, based on an appropriate cost-effectiveness threshold for rare-disease drugs.<sup>30</sup> In return, payers would cover these drugs without onerous pre-authorization requirements or large co-payments, eliminating financial barriers to access and adherence. While the details would need to be

worked out, it is clear that a framework for the responsible pricing of novel therapies guided by rigorous and timely value-based assessments is urgently needed to ensure broad access.

Recent experience with other high-price cardiovascular medications such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may foretell the adoption patterns for tafamidis. Launched in 2016 at an average price of \$14,350 per year and with a potential target population of 10 million US adults, PCSK9 inhibitors saw their uptake stymied due to a combination of onerous pre-authorization requirements (related to high drug costs for payers) and frequent prescription abandonment (related to high out-of-pocket costs for patients).<sup>32, 33</sup> Subsequently, a series of independent cost-effectiveness analyses argued for a 70–80% price-reduction to meet conventional cost-effectiveness thresholds; other studies showed that average annual out-of-pocket costs for a Medicare Part D beneficiary receiving a PCSK9 inhibitor and a generic statin was \$5000.<sup>33, 34</sup> Finally, in 2019, both manufacturers announced an unprecedented 60% price reduction in an effort to increase uptake. We suspect that the widespread adoption of tafamidis is likely to face similar hurdles. Unless the price of the drug falls substantially, onerous pre-authorization requirements and high out-of-pocket costs are likely to present substantial hurdles to widespread adoption. Consequently, the projected population health gains with tafamidis are unlikely to be achieved at 2019 prices.

### Limitations

Our study has a few limitations. Our estimates of the efficacy and safety of tafamidis were based on a single randomized clinical trial with a mean follow-up of 30 months and should be updated when longer follow-up data and information regarding high-risk subgroups become available. We have previously argued that the “life-cycle approach” advocated by the National Academy of Medicine to evaluate the safety and effectiveness of drugs based on new data should be extended to cost-effectiveness evaluations.<sup>34</sup> Our base-case analysis assumed an annual drug price equivalent to the wholesale acquisition cost of tafamidis before any discounts or rebates offered by the manufacturer. However, our findings suggest that the typical discounts are not likely to make the drug cost-effective. We did not incorporate the cost of provider time spent on meeting onerous pre-authorization requirements often introduced by payers to limit uptake of expensive medications, the clinician time spent appealing initial denials, or the effect of delays in initiating treatment. We did not model the costs or consequences of cardiac transplantation and cardiac-assist devices, which are uncommon in patients with ATTR-CM because the average age at diagnosis in the US is 70–75 years. If future diagnostic advances facilitate the diagnosis of amyloid cardiomyopathy at younger ages, and should tafamidis therapy in younger patients alter the rates of transplantation or implantation of cardiac-assist devices during follow-up, this cost-effectiveness analysis would need to be updated to include the high cost of these procedures. Health-related quality-of-life data were not directly available for trial participants in ATTR-ACT; we therefore estimated quality-of-life data from published KCCQ-OS estimates. Our budget impact evaluation was based on current estimates of the prevalence of ATTR-CM, which several experts believe to be an underestimate of its true prevalence. If rates of diagnosis of ATTR-CM substantially increase due to more widespread application of nuclear scintigraphy and genetic testing, as well as from greater awareness of

the condition, the impact of tafamidis therapy on total health spending would exceed our projections.

## Conclusions

In a disease-simulation model calibrated to the results of the ATTR-ACT trial, treatment with tafamidis is projected to produce substantial clinical benefit but would greatly exceed conventional cost-effectiveness thresholds at the current list price. Based on recent US experience with high-cost cardiovascular medications, access to and uptake of this effective therapy may be limited unless there is a large reduction in drug costs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments and Author Contributions:

Dr. Kazi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## Non-standard Abbreviations and Acronyms

<b>ATTR-ACT</b>	Transthyretin Amyloidosis Cardiomyopathy Clinical Trial
<b>ATTR-CM</b>	transthyretin amyloid cardiomyopathy
<b>FDA</b>	Food and Drug Administration
<b>HFpEF</b>	heart failure with preserved ejection fraction

<b>ICER</b>	incremental cost-effectiveness ratio
<b>KCCQ-OS</b>	Kansas City Cardiomyopathy Questionnaire Overall Score
<b>MEPS</b>	Medical Expenditure Panel Survey
<b>PCSK9</b>	proprotein convertase subtilisin/kexin type 9
<b>UI</b>	uncertainty interval

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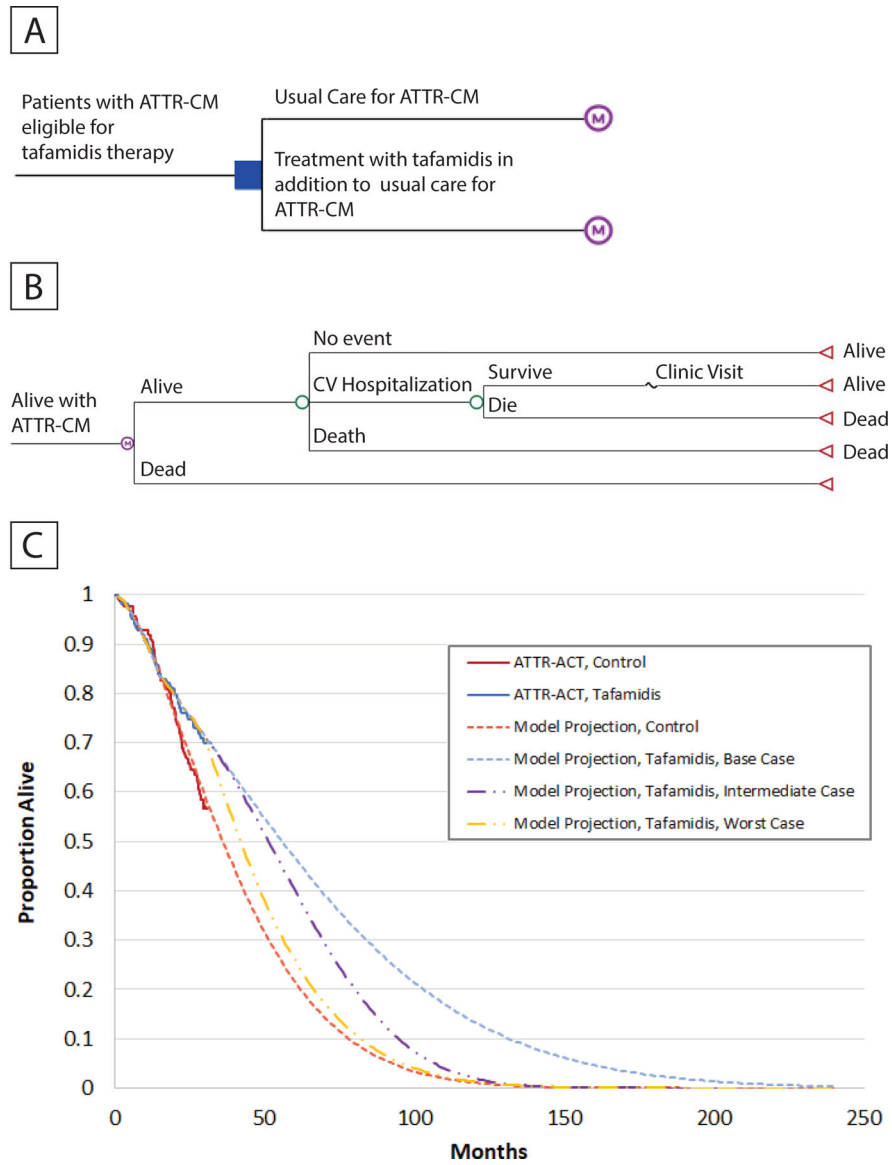
## Clinical Perspective

### What is new?

- In patients with transthyretin amyloid cardiomyopathy (ATTR-CM), tafamidis reduces all-cause mortality and slows decline in quality-of-life compared with placebo, but it is the most expensive cardiovascular drug ever launched in the US.
- In this simulation model of US adults, tafamidis therapy for ATTR-CM was estimated to cost \$880000 per quality-adjusted life-year gained compared with usual care and increased annual health care costs by \$32.3 billion (including a 9.3% increase in total spending on all prescription drugs over 2018 levels).
- A 92.6% reduction in drug price from \$225000 annually to \$16,563 would be necessary to meet a \$100000 per QALY threshold.

### What are the clinical implications?

- Assuming 2019 prices, tafamidis use does not meet generally accepted cost-effectiveness thresholds and is estimated to increase US health care costs substantially.
- Based on recent US experience with high-cost cardiovascular medications, access to and uptake of this potentially life-saving therapy may be limited unless there is a large reduction in drug costs.



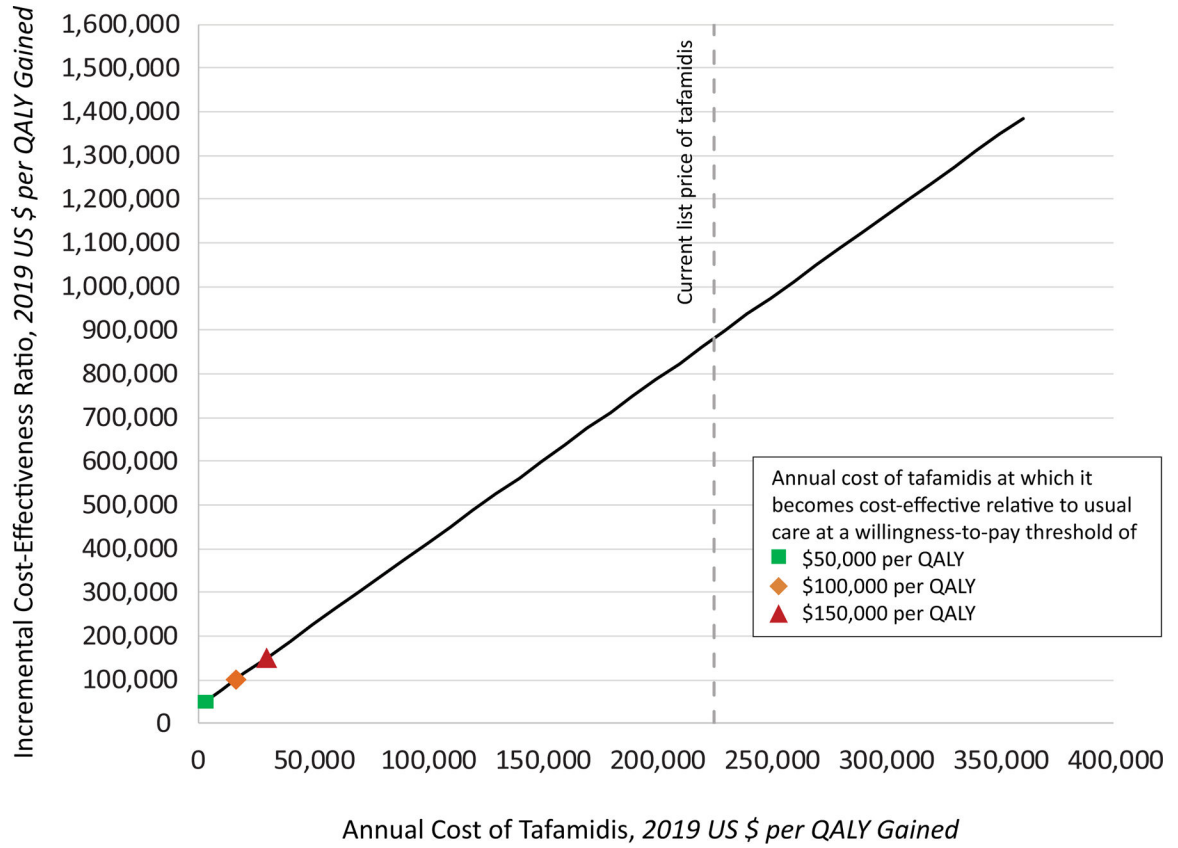
**Figure 1. Schematic of Model and Model Calibration.**

We developed a state-transition Markov model to evaluate the cost-effectiveness of tafamidis therapy compared with usual care among patients with symptomatic heart failure due to transthyretin amyloid cardiomyopathy (ATTR-CM, panel A). In monthly cycles, patients could experience cardiovascular hospitalizations (some proportion of which were fatal), or die from other causes (Panel B). In the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), treatment with tafamidis compared with usual care reduced the risk of cardiovascular hospitalizations throughout the course of therapy, and the risk of death after the first 18 months of treatment. Over the initial 30 months, the model reproduced survival rates seen in the tafamidis and control arms in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT, Panel C). The model used a parametric (Weibull) model to project long-term survival in the control arm beyond 30 months. The base case assumed that the effectiveness of tafamidis would be preserved beyond 30 months



(best-case scenario). In sensitivity analyses, we modeled an intermediate-case scenario that assumed that the effectiveness of tafamidis gradually would wane beyond 30 months so that there would be no meaningful differences between the control and intervention groups beyond 90 months, and a worst-case scenario that assumed a complete loss of effectiveness of tafamidis beyond 30 months (Panel C). See text for additional modeling details.

Abbreviations: ATTR-ACT = Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, ATTR-CM = transthyretin amyloid cardiomyopathy.



**Figure 2. One-Way Sensitivity Analysis by Price of Tafamidis.**

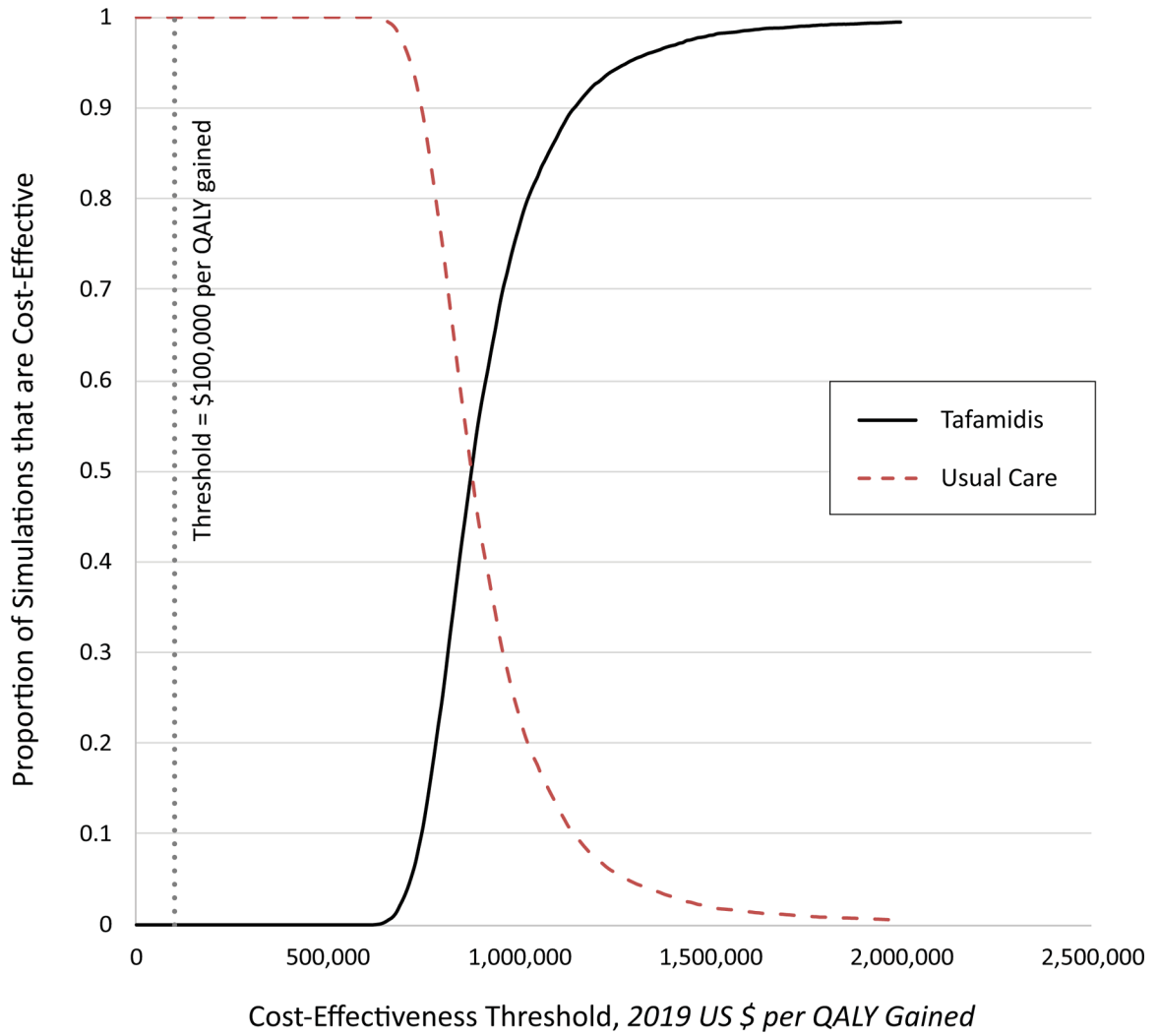
We evaluated the effect of varying the annual cost of tafamidis on the incremental cost-effectiveness ratio (ICER) of tafamidis compared with usual care, holding all other input parameters at their base-case value. At the 2019 annual price of \$225,000, tafamidis does not meet conventional cost-effectiveness thresholds. An 86.7% reduction in price to \$29,925 would be needed to achieve a threshold of \$150,000 per quality-adjusted life year (QALY) gained, a 92.6% reduction in price to \$16,563 would be needed to meet a cost-effectiveness threshold of \$100,000 per QALY gained, and a 98.6% reduction to \$3,200 would be needed to achieve a cost-effectiveness threshold of \$50,000 per QALY gained.

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**Figure 3. Cost-Effectiveness Acceptability Curves.**

In probabilistic sensitivity analyses, we ran 10,000 iterations of the model after sampling key input parameters from pre-specified statistical distributions (with replacement). The results are shown below as acceptability curves, which indicate the proportion of simulations (y-axis) in which a given strategy is the optimal strategy at various cost-effectiveness thresholds (x-axis). Under our base case assumptions and assuming a societal cost-effectiveness threshold of \$100,000 per quality-adjusted life year (QALY), treatment with tafamidis was cost-effective compared with usual care in 0% of the simulations.

Table 1.

## Input Parameters

Parameter	Base-Case Value	Range in Sensitivity Analyses	Distribution for Probabilistic Analyses	Source
<b>Transition Probabilities</b>				
Rate of CV hospitalizations, <i>per person per year</i>	0.70	0.62 – 0.80	Log-normal	Maurer et al. 2018 <sup>2</sup> , CDER 2019 <sup>4</sup>
Proportion of CV hospitalizations that are fatal	0.0954	0.035 – 0.105	Beta	Wadhwa 2018 <sup>5</sup> , range assumed
Rate of death from any cause in the control arm, <i>per person per year</i>	Weibull distribution estimated from control arm of ATTR-ACT, with the following parameters: Sigma: 0.644 (SE 0.1081) k: 3.820 (SE 0.0887)		Weibull *	Maurer et al. 2018 <sup>2</sup>
Discount rate, <i>per year</i>	0.03	0.01 – 0.08	-	Sanders et al. 2016 <sup>6</sup>
<b>Effectiveness of Tafamidis</b>				
Hazard Ratio for CV hospitalizations, compared with usual care	0.68	0.56 – 0.81	Log-normal	Maurer et al. 2018 <sup>2</sup>
Rate of death from any cause in the tafamidis arm, <i>per person per year</i>	Months 0–18: Identical to the control arm		-	Maurer et al. 2018 <sup>2</sup>
	Months 18–30: Weibull distribution estimated from pooled tafamidis arm of ATTR-ACT, with the following parameters: Sigma: 0.939 (SE 0.1628) k: 4.429 (SE 0.3116)		Weibull *	
	Months >30: Hazard ratio relative to usual care as observed in month 30 of the simulation		-	
<b>Costs</b>				
Tafamidis therapy, <i>USD per year</i>	225,000	2,250 – 500,000	-	Truven Health Analytics <sup>7</sup> , Range assumed
Background healthcare costs, <i>USD</i>			Normal	MEPS <sup>8</sup>
Age <75 years	19,785	19,050 – 20,520		
Age 75–85 years	18,462	17,967 – 18,958		
Age >85 years	17,417	16,945 – 17,889		
CV hospitalization, <i>USD</i>			Normal	HCUP <sup>9</sup> , Peterson et al. 2015 <sup>10</sup>
Age <75 years	20,219	16,256 – 24,182		
Age 75–85 years	20,219	16,256 – 24,182		
Age >85 years	13,716 <sup>§</sup>	11,028 – 16,404		
Clinic visit, <i>USD</i>	148	120 – 175	Normal	CMS <sup>11</sup>
<b>Quality of Life</b>				
Baseline KCCQ-OS	66.72	62.62 – 70.82	Normal	Maurer et al. 2018 <sup>2</sup>
Change in KCCQ-OS at 30 months in the control arm	-20.81	-24.67 to 16.95	Normal	CDER 2019 <sup>4</sup>
Change in KCCQ-OS at 30 months in the tafamidis arm	-7.16	-9.94 to -4.38	Normal	CDER 2019 <sup>4</sup>

Abbreviations: CDER = Center for Drug Evaluation and Research, CMS = Centers for Medicare and Medicaid Services, CV = cardiovascular, HCUP = Healthcare Cost and Utilization Project, KCCQ-OS = Kansas City Cardiomyopathy Questionnaire – Overall Score, MLM = Medical Expenditure Panel Survey, SE = standard error, USD = United States dollar.

\* For the purpose of the probabilistic sensitivity analysis, we assumed that the underlying sigma and k parameter estimates of the Weibull survival curve had a bivariate normal distribution.

§ The small decline in mean hospitalization costs has been previously described, and may relate to lower rates of utilization, on average, of high-cost invasive procedures in adults over the age of 85 years.

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**Table 2.**

## Base Case Results

	Usual Care	Tafamidis
<b>Healthcare Outcomes</b>		
Survival, <i>life years (undiscounted)</i>	3.46 (2.88 – 4.25)	5.43 (4.17 – 6.76)
Survival, <i>life years (discounted)</i>	3.23 (2.73 – 3.84)	4.83 (3.82 – 5.79)
Incremental <i>life years (discounted)</i>	Comparator	1.60 (0.48 – 2.47)
Quality-adjusted survival, <i>QALYs (discounted)</i>	2.19 (1.94 – 2.56)	3.48 (2.85 – 4.15)
Incremental QALYs ( <i>discounted</i> )	Comparator	1.29 (0.47 – 1.75)
Cardiovascular Hospitalizations, <i>number</i>	2.36 (1.87 – 3.02)	2.53 (1.78 – 3.43)
<b>Direct Healthcare Costs</b>		
Lifetime Healthcare Costs, <i>2019 USD (discounted)</i>	126,000 (105,000 – 157,000)	1,262,000 (996,000 – 1,515,000)
Spending on Tafamidis	-	1,086,000 (861,000 – 1,303,000)
Spending on CV Hospitalizations	34,000 (26,000 – 46,000)	34,000 (23,000 – 47,000)
Background Healthcare Costs	92,000 (77,000 – 113,000)	142,000 (110,000 – 174,000)
Incremental healthcare costs, <i>2019 USD (discounted)</i>	Comparator	\$1,135,000 (872,000–1,377,000)
<b>ICER, USD per life-year gained</b>	Comparator	\$709,000 (547,000 – 1,943,000)
<b>ICER, USD per QALY gained</b>	Comparator	\$880,000 (697,000–1,564,000)

Abbreviations: ICER = incremental cost-effectiveness ratio; USD = United States Dollar; QALY = quality-adjusted life year.