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ORIGINAL RESEARCH

Modeling the Cost and Health Impacts of Diagnostic Strategies in Patients with Suspected Transthyretin Cardiac Amyloidosis

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BACKGROUND: Transthyretin cardiac amyloidosis (ATTR-CMP) is an increasingly recognized and treatable cause of heart failure with preserved ejection fraction. Multimodality cardiac imaging is recommended for ATTR-CMP diagnosis, but its cost-effectiveness in current clinical practice has not been well studied.

METHODS AND RESULTS: Using a microsimulation model, we compared the cost-effectiveness of a combination of strategies involving ^{99m}technetium pyrophosphate (PYP), cardiac magnetic resonance imaging, and endomyocardial biopsy for the diagnosis of ATTR-CMP. We developed a decision analytic model to project health care costs and lifetime quality-adjusted life years for symptomatic, older patients who present with congestive heart failure, with an increased left ventricular wall thickness and a 13% prevalence of ATTR-CMP. Rates of clinical events, costs, and quality-of-life values were estimated from published literature. The analysis was conducted from a US health care system perspective with health and cost outcomes discounted annually at 3%.

In the base-case scenario, using a fixed tafamidis price of $16 000 annually (previously identified cost-effective price), total health care costs per person were lowest for the PYP-only strategy ($209 415) and highest for endomyocardial biopsy strategy ($215 881). Of the 7 strategies examined, the PYP-only strategy had the highest net monetary benefit using a willingness-to-pay threshold of $100 000/quality-adjusted life year. Results were sensitive to variations in model inputs for PYP and cardiac magnetic resonance imaging specificity, cost of tafamidis, and willingness-to-pay thresholds.

CONCLUSIONS: Our model-based analyses showed that a PYP-only strategy to diagnose ATTR-CMP is the most cost-effective strategy, at willingness-to-pay threshold of $100 000/quality-adjusted life year. At higher threshold ($150 000/quality-adjusted life year), sequential tests involving PYP and cardiac magnetic resonance imaging may be considered cost effective.

Key Words: cardiac amyloidosis ■ cost–benefit analysis ■ multimodal imaging

Cardiac amyloidosis due to transthyretin amyloidosis (ATTR-CMP) has been perceived as a rare and inevitably fatal infiltrative cardiomyopathy that requires endomyocardial biopsy (EMB) for a definitive diagnosis. Advances in imaging and breakthrough therapies have remarkably changed our understanding of the evaluation, management, and prevalence of ATTR-CMP. Notably, radionuclide imaging with bone avid tracers (^{99m}technetium pyrophosphate [PYP], 3,3-diphosphono-1,2-propanodicarboxylicacid [DPD] and hydroxymethylene diphosphonate [HMDP]) has emerged as a highly specific tool to diagnose ATTR-CMP. A large international

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CLINICAL PERSPECTIVE

What Is New?

- In older patients presenting with heart failure and left ventricular thickening, a decision analytic model projects ^{99m}technetium pyrophosphate only as the most cost-effective modality to diagnose transthyretin cardiac amyloidosis, compared with other noninvasive imaging strategies or invasive endomyocardial biopsy.

What Are the Clinical Implications?

- Transthyretin cardiac amyloidosis has emerged as a treatable cause of heart failure with preserved ejection fraction increasing the urgency for its early diagnosis.
- The current results will form the basis for prospective comparative effectiveness studies to evaluate the cost-effectiveness of a noninvasive diagnostic strategy to screen older adults with heart failure with preserved ejection fraction for transthyretin cardiac amyloidosis.

Nonstandard Abbreviations and Acronyms

ATTR-CMP	transthyretin cardiac amyloidosis
EMB	endomyocardial biopsy
HFpEF	heart failure with preserved ejection fraction
ICER	incremental cost-effectiveness ratio
PYP	^{99m}technetium pyrophosphate

study has shown that EMB can be avoided in patients with heart failure (HF) and typical infiltrative phenotype on echocardiography or CMR (cardiac magnetic resonance imaging), with grade 2/3 PYP/DPD/HMDP uptake, if a clonal process is excluded by serum and urine immunofixation electrophoresis.[1]

Tafamidis, a transthyretin stabilizer therapy, has been proven to slow the progression of ATTR-CMP, reduce HF hospitalization and improve survival, and is now Food and Drug Administration approved.[2] The availability of targeted therapy for ATTR-CMP has increased the urgency for early diagnosis. Tafamidis has been shown to be less effective in patients with advanced HF (New York Heart Association class III) from ATTR-CMP further emphasizing the need for early diagnosis. However, until recently, the initial diagnosis of ATTR-CMP has been substantially delayed.[3]

Several studies using ^{99m}Tc-PYP/DPD/HMDP have identified ATTR-CMP in 13% to 18% of the elderly with HF with preserved ejection fraction (HFpEF) and increased left ventricular (LV) wall thickness[4,5] and in 13% to 16% of patients with severe aortic stenosis.[6–8] It can be estimated that currently only a small fraction of patients with ATTR-CMP are clinically diagnosed. Noninvasive imaging, as opposed to EMB, is likely to substantially improve underdiagnosis of ATTR-CMP. In a recent multisocietal consensus document, experts have rated echocardiography, CMR, and ^{99m}Tc-PYP/DPD/HMDP as appropriate in individuals over age 60 years with HFpEF and unexplained increased LV wall thickness.[9] HF is highly prevalent (~6 000 000 adults in the United States)[10] and approximately half of the patients with HF have preserved ejection fraction. Consequently, a large number of adults with HFpEF may be candidates for imaging-based screening for ATTR-CMP. However, the cost-effectiveness of the various imaging-based diagnostic approaches for ATTR-CMP has not been studied. The primary aim of this study was to compare the cost-effectiveness of multiple strategies to evaluate and manage ATTR-CMP in adults over age of 65 years presenting with HFpEF and increased LV wall thickness, an appropriate test per expert consensus recommendations.

METHODS

Model Overview

We performed a computer simulated state-transition model that projected cardiovascular events, life expectancy, quality-adjusted life years (QALYs), and lifetime health care costs for a symptomatic patient cohort at risk for ATTR-CMP, using inputs from the ATTR-ACT (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial)[2] and published literature. Our patient cohort included age >65 years, HFpEF, as per European Society of Cardiology definition, and increased LV wall thickness (end-diastolic wall thickness≥12 mm) at initial clinical presentation. As the role of PYP imaging is limited in patients with amyloid light chain amyloidosis, we assumed that serum-free light chain concentration and serum and urine immunofixation electrophoresis would be performed before advanced imaging as discussed in an AHA scientific statement.[11] The annual risk of clinical events depended on presence or absence of ATTR-CMP, initiation of therapy (tafamidis), and risk of EMB. Death could occur as result of cardiovascular events, noncardiovascular events, or complications arising from invasive diagnostic procedures. Depending on the clinical diagnostic strategy, patients in the model received tafamidis therapy immediately following diagnosis or never. All patients, however, were assumed to receive routine guideline-based medical therapy for HF, and these costs were also factored into the model. Base-case model inputs and sensitivity

analysis ranges are reported in Table 1. We will make the data, methods used in the analysis, and materials used in these models available to any researcher for purposes of reproducing the results or replicating the procedure. An institutional review board approval was not applicable for this paper on cost-effectiveness modeling as no human subject data were used.

For each strategy, health care costs and QALYs were projected to derive incremental cost-effectiveness ratios (ICERs). We used $100 000/QALY as a threshold for willingness to pay for health threshold[12] to determine the optimal strategy from our incremental cost-effectiveness analysis and to calculate net monetary benefit (monetized QALYs minus cost).[13] Net monetary benefit gives the same results as ICERs with a different decision rule: the strategy with the highest net monetary benefit is optimal.[13] At current pricing of $225 000 per year, tafamidis is not cost effective for the treatment of ATTR-CMP. A previous study has suggested that the cost-effective price point in the US system would be ~$16 000 annually.[14] This was simulated in our model as the cost of treatment ($16 000 per year) in the base-case study, as the focus of this paper is to evaluate the cost-effectiveness of imaging strategies. We also included, as a supplemental analysis, a scenario using contemporary ($225 000 per year) pricing for tafamidis. The analyses were conducted from a health system perspective over a lifetime horizon, with all costs projected to 2019 dollars, and future health care costs and QALYs discounted at 3% annually.[15] The model was programmed in TreeAge Pro 2012 (TreeAge Software Inc., Williamstown, MA).

Clinical Strategies Evaluated

We evaluated a combination of strategies that could lead to the diagnosis of ATTR-CMP. Detailed structure of the Markov model for each diagnostic strategy is shown in Figure S1. In the PYP-based strategies, we included PYP only (strategy 1) and PYP followed by

Table 1. Key Model Variables With Base-Case Values and Ranges Used in 1-Way and Probabilistic Sensitivity Analysis

Variable	Base-case value	Sensitivity analysis range	Distribution for probabilistic sensitivity analysis	Source
Discount rate	0.03	0–0.03	Not included	[32]
Probability of patient having ATTR-CMP	0.13	0–0.25	Gamma	[5]
Sensitivity of PYP	0.74	0.7–0.77	Beta	[1]
Specificity of PYP	1.0	0.96–1.0	Beta	[1]
Sensitivity of CMR	0.89	0.5–1.0	Beta	[17]
Specificity of CMR	0.89	0.5–1.0	Beta	[17]
Annual mortality rate in ATTR-CMP	0.138	0–0.138	Not included	[20]
Mortality hazard rate ratio for ATTR-CMP patients who received tafamidis	0.70	0.51–0.96	Lognormal	[2]
Annual cardiovascular hospitalization rate in ATTR-CMP	0.70	0–0.7	Lognormal	[14]
Cardiovascular hospitalization hazard rate ratio for ATTR-CMP patients who received tafamidis	0.68	0.56–0.81	Lognormal	[2]
Annual mortality rate in non ATTR-CMP CHF patients	0.08	0.05–0.15	Not included	[19]
Annual cardiovascular hospitalization rate in non ATTR-CMP CHF patients	0.084	0.06–0.092	Lognormal	[18]
Probability of dying from EMB	0.0003	0–0.0003	Not included	[16]
Cost of PYP ($)	509	0–508.87	Not included	CMS
Cost of CMR ($)	517	0–516.8	Not included	CMS
Cost of EMB ($)	1324	0–1324.28	Not included	CMS
Cost of ATTR genetic testing ($)	2225	0–5000	Not included	CMS
Background annual cost of CHF care ($)	19 785	19 050–20 520	Gamma	[14]
Cost of cardiovascular hospitalization ($)	20 129	16 256–24 182	Gamma	[14]
Cost of tafamidis ($)	16 000	0–20 000	Not included	
Utility in non ATTR-CMP CHF	0.81	0.75–0.87	Not included	[23]
Utility in treated ATTR-CMP CHF	Time-based table	±10%	Not included	[14]
Utility in untreated ATTR-CMP CHF	Time-based table	±10%	Not included	[14]

ATTR-CMP indicates transthyretin cardiac amyloidosis; CHF, congestive heart failure; CMR, cardiac magnetic resonance imaging; CMS, Centers for Medicare & Medicaid Services; EMB, endomyocardial biopsy; and PYP, ^{99m}technetium pyrophosphate.

CMR when the initial study was negative (strategy 2). In the CMR-based strategies, we included CMR followed by EMB for positive studies (strategy 3), CMR followed by PYP for positive studies (strategy 4), CMR followed by PYP for all studies (strategy 5), and CMR followed by EMB for positive studies and PYP for negative studies (strategy 6). We also included EMB all as a standalone option (strategy 7) (Figure 1). We did not include a "treat none" or "treat all" strategy in the base-case analysis, as these do not reflect current clinical practice. However, they were considered in the supplemental analysis, where contemporary ($225 000 per year) pricing for tafamidis is considered. Invasive EMB carried a 0.03% chance of fatal complications in the base-case analysis.[16] We conducted a sensitivity analysis, varying the diagnostic performance of PYP scans to reflect a more sensitive, but less specific approach. In all strategies, a definite diagnosis of ATTR-CMP required either histological confirmation (by EMB) or a positive PYP study. Those with true positives were assumed to undergo guideline based medical therapy for congestive HF and received tafamidis.

ATTR-CMP Status and Cardiovascular Events

The demographics of the ATTR-ACT study were used to simulate the patient population; specifically, the model population was 91% male with an average age of 74.5 years.[2] The prevalence of ATTR-CMP was set at 13%, reflecting a population of patients hospitalized with HF and preserved ventricular function and increased LV wall thickening.[5] Sensitivity and specificity for detection of ATTR-CMP for PYP was 74% (95% CI, 70%–77%) and 100% (95% CI, 99%–100%) using grade 2 or 3 cardiac uptake on a radionuclide scan in patients in whom a monoclonal process has been excluded, as the definition of a positive study. We chose a high specificity threshold as it forms the basis for the current recommendations of eliminating EMB if the scan is grade 2 or3 positive and a monoclonal process has been excluded.[9] However, in a sensitivity analysis, we used grade 1 or higher cardiac uptake as the definition of a positive study, yielding a sensitivity and specificity of 99% (95% CI, 97%–100%) and 68% (95% CI, 59%–77%).[1] For CMR, we used a sensitivity of 89% (95% CI, 79%–95%) and a specificity of 89% (95% CI, 86%–92%), assuming that in addition to late gadolinium enhancement the latest CMR techniques such as T1 mapping would be available.[17] As the diagnostic gold standard of ATTR-CMP, EMB was assumed to have a sensitivity and specificity of 100%. We conducted the cost-effectiveness analyses using all-cause mortality. Annual risk of mortality and cardiovascular hospitalization for patients with HF with and without ATTR-CMP was derived from population studies and ATTR-ACT.[2,18–20] In patients with amyloidosis undergoing treatment for tafamidis, we applied a hazard rate ratio of 0.70 and 0.68 for all-cause mortality and cardiovascular hospitalization, respectively. In the ATTR-ACT trial, tafamidis was well tolerated and had a similar adverse event rate compared with placebo. Severe side effects were similar between the 2 groups, and permanent discontinuation of the study drug was more common in the placebo arm. For these reasons, we did not model any adverse quality of life effects resulting from taking tafamidis.

Costs and Health-Related Quality-of-Life

We based the costs of cardiovascular hospitalizations on a cost-effectiveness analysis performed by Kazi et al.,[14] who estimated these costs based on 2014 Healthcare Cost and Utilization Project data, adjusted to

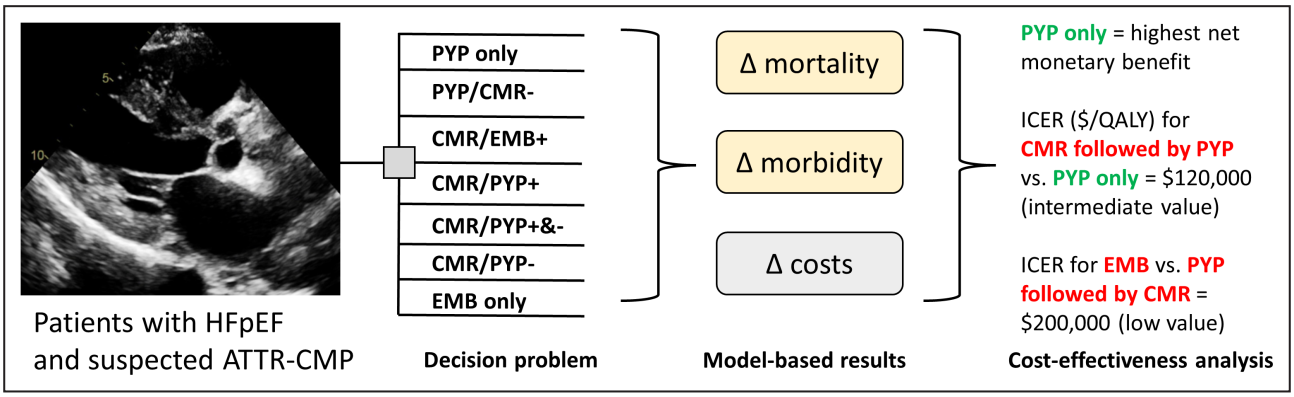

Figure 1. Model structure.
Conceptual diagram of the cost-effectiveness analysis. Individuals enter the simulation model and are assigned a combination of diagnostic strategies. The model estimates the impact of strategy choice on mortality, morbidity, and disease-related cost outcomes. The tradeoffs between quality-adjusted life years (QALYs) and costs are evaluated using incremental cost-effectiveness analysis methods. ATTR-CMP indicates transthyretin cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; HFpEF, heart failure with preserved ejection fraction; ICER, incremental cost-effectiveness ratio; PYP, ^{99m}technetium pyrophosphate; and QALY, quality-adjusted life year.

include physician fees.[21,22] All patients diagnosed with ATTR-CMP were assumed to receive the same drug regimens. Costs of PYP, CMR, and EMB were derived from publicly available 2019 Medicare rates, combining Current Procedural Terminology (CPT) codes to reflect professional costs, as well as Ambulatory Payment Classifications (APC) codes to reflect average technical fee. We used estimated costs as follows: PYP (CPT 78803+APC 5592) cost $509, CMR (CPT 75561+APC 5572) cost $517, EMB (CPT 93505+APC 5182) cost $1324. We incorporated the cost of genetic testing in patients who are diagnosed with ATTR-CMP. Health-related quality of life was assigned to all health states in the model and was represented by utility values between 0 (death) and 1 (perfect health). The utility of HF unrelated to cardiac amyloidosis was assumed to be equivalent to the utility for chronic HF (0.81), which we estimated from an analysis of a nationally representative sample from the Medical Expenditure Panel Survey using the EuroQol-5D instrument.[23] Utility values for correctly treated ATTR-CMP (ie, patients with true positive screening results) and untreated ATTR-CMP (ie, patients with false negative screening results) were based on time-from-baseline utility estimates from the Kazi et al. study,[14] that estimated higher (better) utility values for treated ATTR-CMP based on the Kansas City Cardiomyopathy Questionnaire. For these time-based utility values, we assumed linear interpolation between values, then fixed at final value for remainder of lifetime (Table S1).

Sensitivity Analyses

One-way sensitivity analyses were performed to evaluate the sensitivity of results to plausible variations in parameters for model inputs (Table 1). Given their importance on our cost-effectiveness analysis, we performed a 2-way sensitivity analysis for cost of tafamidis and prevalence of ATTR-CMP. Overall model uncertainty was evaluated in probabilistic sensitivity analysis (PSA) by simultaneously conducting 10 000 random draws from probability distributions (distribution types shown in Table 1) for selected key variables and recalculating the cost-effectiveness of each strategy.

RESULTS

In the base-case analysis, detection of ATTR-CMP (with an overall prevalence of 13.0%) that involved imperfect tests (PYP or CMR) ranged from 9.6% in the PYP-only strategy (strategy 1) to 12.6% in the PYP followed by CMR for negative studies (PYP/CMR-, strategy 2). Rates of true positives, false positives, true negatives, and false negatives are shown in Table S2. PYP only (strategy 1) resulted in the lowest lifetime discounted cost per patient but also the lowest QALYs. An EMB all (strategy 7) had the highest lifetime discounted costs and highest QALYs. Of the 7 strategies examined, PYP only (strategy 1) had the highest net monetary benefit using a willingness-to-pay threshold of $100 000/QALY (Table 2), which is equivalent to stating that PYP only (strategy 1) was the optimal strategy using a cost-effectiveness threshold of $100 000/QALY.

Table 2 shows the cost-effectiveness results for populations using base-case model inputs. The CMR followed by PYP for positive studies (CMR/PYP+, strategy 4) had an ICER of $120 000/QALY compared with strategy 1. PYP/CMR- (strategy 2) had an ICER of $130 000/QALY compared with CMR/PYP+ (strategy 4). EMB all (strategy 7) had an ICER of $200 000/QALY compared with PYP/CMR– (strategy 2). Other strategies were dominated in the algorithm.

When a positive PYP was defined as the presence of grade 1 or higher cardiac uptake, reflecting a higher sensitivity (99%) but lower specificity approach (68%), CMR followed by EMB for positive studies (CMR/EMB+, strategy 3) was the optimal strategy (highest net monetary benefit). Under this scenario, EMB all (strategy 7) had an ICER of $140 000/QALY compared with CMR/EMB+ (strategy 3).

Under an alternate scenario, when considering tafamidis at current pricing, no diagnostic strategies met current cost-effectiveness threshold. In this scenario, the ICER of PYP only, compared with no investigation, was $1 200 000/QALY (Table S3; Figure S2).

Figure 2 shows the 2-way sensitivity analysis results varying the prevalence of ATTR-CMP and cost of tafamidis. Combinations of low disease prevalence and higher cost for tafamidis favored the PYP-only

Table 2. Lifetime Per-Person Usage Outcomes, QALYs, Costs ($), and Incremental Cost-Effectiveness Ratios ($/QALY) for Base-Case Analysis

Strategy	ATTR-CMP diagnosis	QALYs*	Incremental QALY*	Costs*	Incremental cost*	ICER	Net monetary benefit
PYP only (strategy 1)	9.6%	7.19953	…	$209 415	…	Reference	510 537
CMR followed by PYP (strategy 4)	11.6%	7.22930	0.02977	$212 985	$3570	$120 000/QALY	509 944
PYP followed by CMR (strategy 2)	12.6%	7.24560	0.01630	$215 126	$2141	$130 000/QALY	509 434
Endomyocardial biopsy (strategy 7)	13.0%	7.24942	0.00382	$215 881	$755	$200 000/QALY	509 061

ATTR-CMP indicates transthyretin cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; ICER, incremental cost-effectiveness ratio; PYP, ^{99m}technetium pyrophosphate; and QALY, quality-adjusted life year.

*Discounted at 3%. Each strategy is compared with the next best alternative per incremental cost-effectiveness methods.

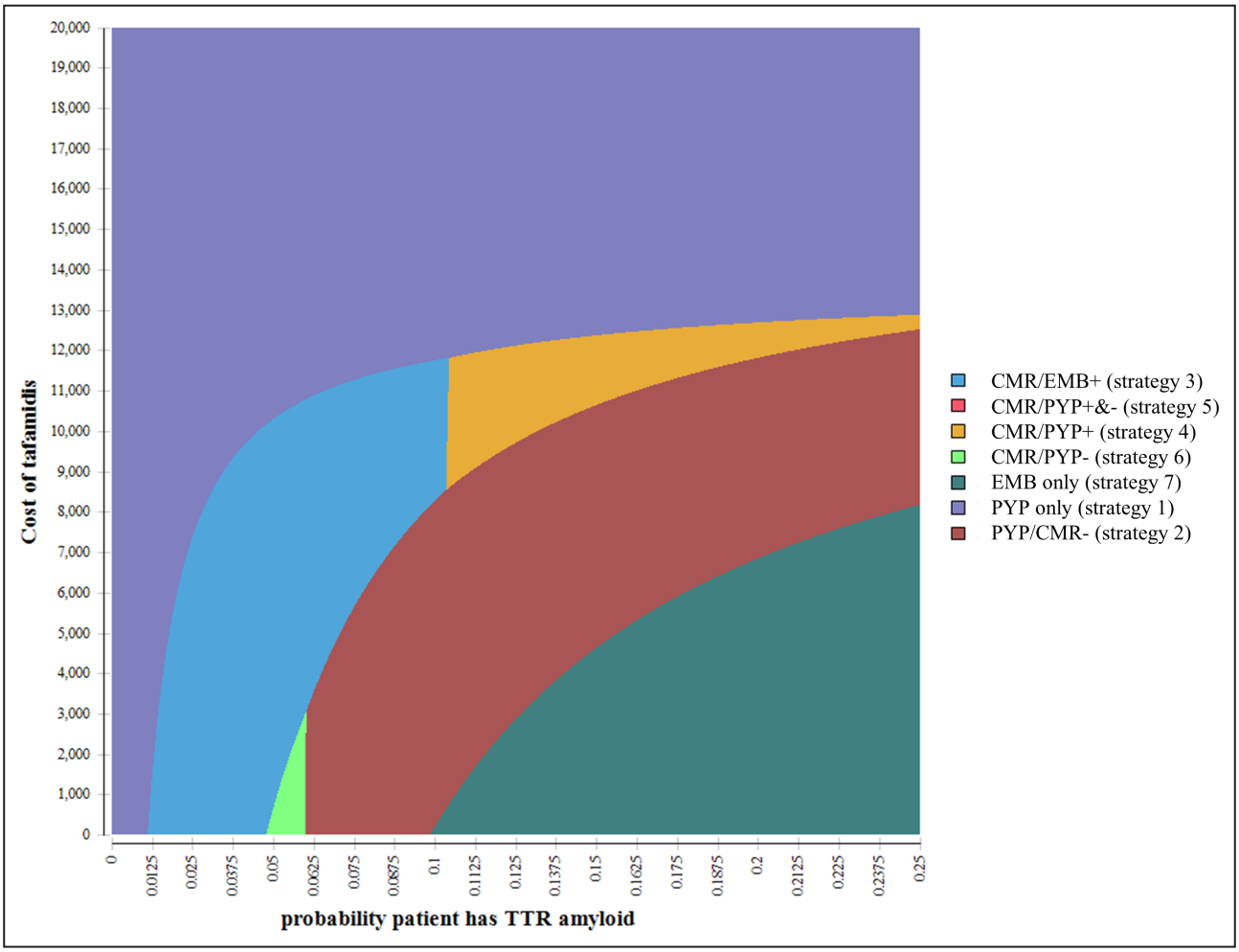

Figure 2. Two-way sensitivity analysis.
Probability of having ATTR-CMP and cost of tafamidis, assuming willingness-to-pay for health of $100 000/QALY. ATTR-CMP indicates transthyretin cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; PYP, ^{99m}technetium pyrophosphate; and QALY, quality-adjusted life year.

strategy; high disease prevalence and lower tafamidis cost favored the EMB strategy. For a cost of tafamidis in excess of $13 000, the PYP-only strategy (strategy 1) was the optimal strategy, up to a disease prevalence of 25%. With our base-case prevalence of 13.0%, other strategies are optimal at much lower costs of tafamidis. CMR/PYP+ (strategy 4) is optimal if the price is between ~$10 000–$12 000, PYP/CMR- (strategy 2) is optimal if the price is between ~$3500–$10 000, and EMB only (strategy 7) if the price is <$3500. The most influential variables from our 1-way sensitivity analyses were test specificity (relevant for any strategies that included PYP or CMR), prevalence of ATTR-CMP (especially using the higher end of willingness to pay of $150 000/QALY), and the cost of tafamidis (with strategies with better specificity more likely to be optimal when cost of tafamidis was high, because the cost of avoiding unnecessary treatment [false positives] is higher when the treatment cost is higher). We conducted a sensitivity analysis by varying the hazard rate ratio for both mortality and cardiovascular hospitalization rate. PYP-only remains the optimal strategy in the majority of ranges considered (Figure S3).

Figure 3 shows the cost-effectiveness acceptability curve results for the PSA. The PYP-only strategy (strategy 1) was most likely to be optimal in the PSA using willingness-to-pay threshold of $50 000/QALY or lower (optimal in 66%–97% of PSA iterations). As the willingness-to-pay threshold increased to $100 000/QALY, the probability that the EMB only strategy (strategy 7) increased to 38% (with strategy 1 being optimal in 55% of iterations at a willingness-to-pay threshold of $100 000/QALY). At willingness-to-pay thresholds greater than $150 000/QALY, the EMB-only strategy (strategy 7) and the PYP-only strategy (strategy 1) have similar percentage chances of being optimal in the PSA (46%–49% for each strategy). No other strategy had a percentage change of being optimal of higher

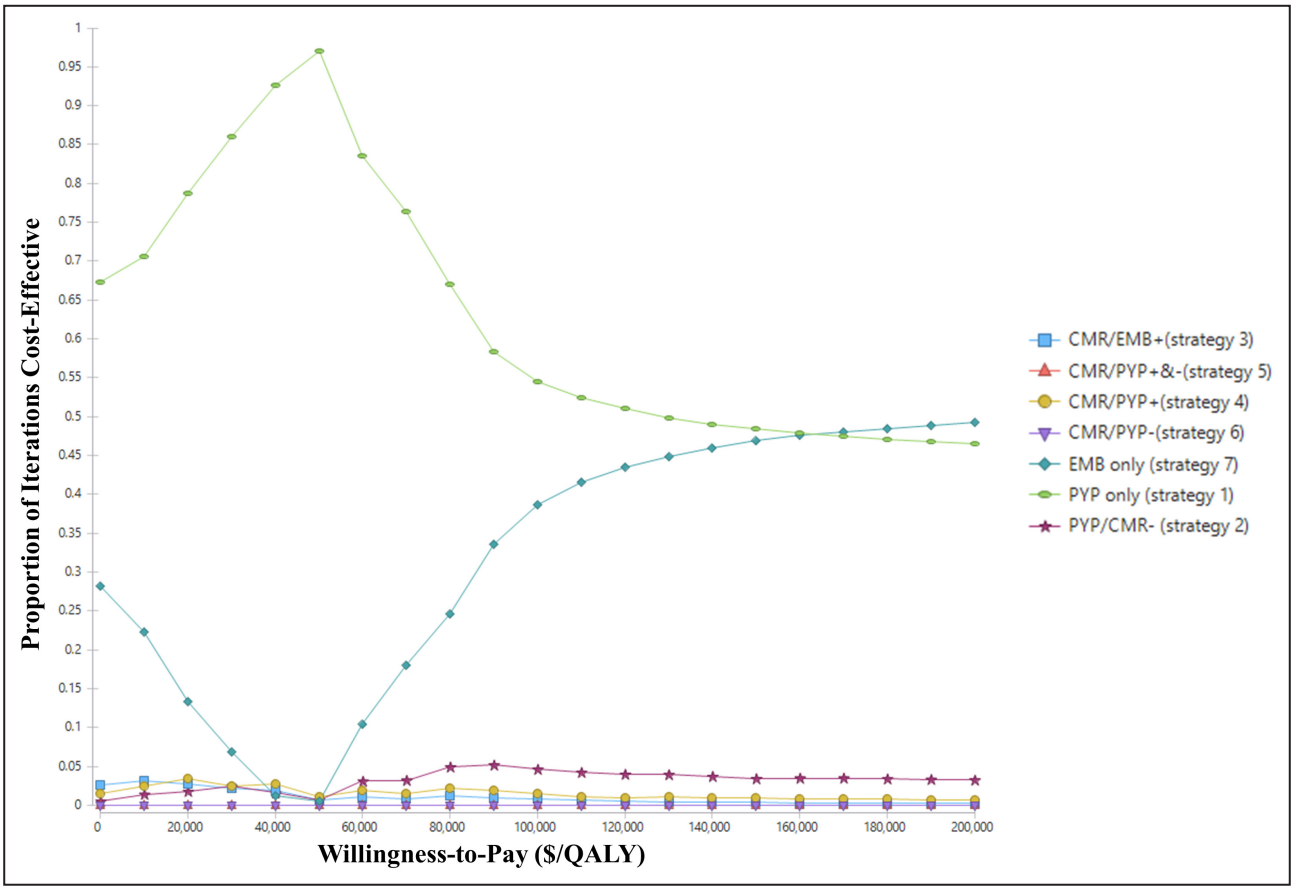

Figure 3. Cost-effectiveness acceptability curve from probabilistic sensitivity analysis.
CMR indicates cardiac magnetic resonance imaging; EMB, endomyocardial biopsy; PYP, ^{99m}technetium pyrophosphate; and QALY, quality-adjusted life year.

than 5% between willingness-to-pay thresholds between $50 000–$150 000/QALY.

DISCUSSION

ATTR-CMP is an increasingly recognized[24] and treatable[2] cause of HFpEF, particularly in older adults. Accurate and early detection of cardiac amyloidosis at a stage where novel therapies are most effective remains a challenge. Multimodality imaging occupies a growing role in the diagnostic algorithm[25] and can diagnose ATTR-CMP without EMB. In patients with symptomatic HF, contemporary expert consensus considers use of imaging including echocardiography, PYP scan, and CMR as "appropriate" for screening ATTR-CMP.[9] Data on the cost-effectiveness of various multimodality imaging algorithms compared with the gold standard, EMB, remain however limited.

Patients with ATTR-CMP diagnosed by bone avid radiotracer cardiac scintigraphy were eligible for participation in clinical trials of novel targeted treatments for transthyretin amyloidosis. Tafamidis, now Food and Drug Administration approved, has been proven to slow the progression of ATTR-CMP[2] but has also been shown to be prohibitively expensive in a prior cost-effectiveness analysis at current listing price of $225 000/year.[14] There are several other agents undergoing phase III trials for the treatment of ATTR-CMP, some of which have been approved for the familial polyneuropathy form of ATTR, at an even higher cost than tafamidis.[26,27]

In the current study, we used estimates from the ATTR-ACT study,[2] a multicenter randomized trial comparing tafamidis versus placebo in patients with ATTR-CMP, and contemporary cohorts with HFpEF,[5] to develop a decision analytic model to evaluate a series of imaging strategies in adults over age of 65 years presenting with HF, increased LV wall thickness, and in whom amyloid light chain amyloidosis has been excluded. We used updated meta-analyses for noninvasive test sensitivity and specificity, with invasive EMB as the gold standard to diagnose cardiac amyloidosis. Because of its dominant impact on treatment cost, we assigned a hypothetical price point of $16 000 for the cost of tafamidis, above which therapy for even known cases of ATTR-CMP has shown not to be cost effective.[14] In this model cohort,

we found that the PYP-only strategy was optimal based on a $100 000/QALY cost-effectiveness threshold for the United States. The PYP-only strategy resulted in the lowest rate of diagnosis of cardiac amyloidosis, lowest lifetime costs, and lowest lifetime QALYs. Strategies that incorporated use of CMR and EMB led to higher QALYs but also higher costs compared with the PYP-only strategy. Although there is no explicit willingness to pay threshold in the United States, an American College of Cardiology/American Heart Association statement has suggested that ICERs of $50 000 to $150 000 may be considered "intermediate value."[28] Therefore, using a higher willingness to pay threshold ($150 000/QALY), strategies involving sequential CMR and PYP could be considered cost effective. Of note, when we defined a positive PYP as the presence of grade 1 or higher cardiac uptake, reflecting a higher sensitivity but lower specificity approach, the PYP-only strategy was no longer the most cost-effective option.

Our findings were robust to plausible variation in PYP and CMR sensitivity and PYP and CMR costs. Our cost-effectiveness results were most sensitive to PYP and CMR specificity and cost of tafamidis. Using base-case model inputs, the PYP-only strategy was optimal when the cost of tafamidis exceeded $13 000. High disease prevalence and low cost of treatment (<$5000–$7000 depending on prevalence) favored EMB, which is clinically intuitive, because the relative value of avoiding false negative results is increased compared with avoiding false positive results in those scenarios. CMR-based strategies are optimal for intermediate disease prevalence and cost of treatment (between $5000 and $10 000). Finally, PYP-based strategies were optimal with high specificity, where a positive study was defined using grade 2 or 3 cardiac uptake on a radionuclide scan. These findings also underscore the need to minimize false positive PYP scan interpretation using single photon emission computed tomography and avoid interpretation of blood pool images as cardiac amyloidosis. This is of particular importance, especially when applying the technique to lower disease prevalence population.[29]

To our knowledge, this is the first study to examine cost-effectiveness of advanced imaging strategies for the diagnosis of ATTR-CMP. Much of the previous discussion around cost-effectiveness has revolved on the listing price of tafamidis, which currently sits at $225 000 per year.[30] Previous work by Kazi et al. has shown that at this price, treatment of patients with confirmed ATTR-CMP is not cost effective, with an ICER of $880 000 per QALY gained.[14] In addition, the authors modeled that nearly all (99%) of the projected increase in annual health care spending was related to the cost of tafamidis. Despite this, initial experience suggests that clinicians are eager to treat, because ATTR-CMP represents one of the few phenotypes of HFpEF with effective targeted therapy.[31] Our results expand on previous studies in important ways. We extrapolated the cost-effectiveness of multiple competing imaging strategies to identify this disease. In a simulated population of older adults with HFpEF and LV thickening, PYP only is the most cost-effective strategy to diagnose ATTR-CMP. Given the economic implication of a false positive finding, our results support the importance of a high specificity strategy, obviating the need for diagnostic confirmation with EMB. Furthermore, EMB as first line investigation is cost effective only at high disease prevalence and low treatment (tafamidis) cost, which is an unlikely scenario given the current listing price.

A few limitations of our study deserve mention. Our study strategy evaluated older patients, with HF and increased LV wall thickness in whom amyloid light chain amyloidosis has been excluded. As such, it does not directly apply as a screening strategy in all patients with HF. Second, because of its reliance on simulation models, we required the combination of inputs from various sources to perform the cost-effectiveness analyses. Despite this, our sensitivity analyses showed that our findings were consistent across plausible changes in most model inputs. Our PSA results are likely an underestimate of model uncertain owing to leaving out certain model inputs because of data availability issues. However, none of the inputs excluded from the PSA (eg, background mortality or costs) were found to be important drivers of model results in one-way sensitivity analyses. Third, the sensitivity and specificity of PYP and CMR were derived from different patient cohort, as there has been limited direct comparative data between CMR and PYP for ATTR-CMP. Fourth, our model was focused on diagnosis of ATTR amyloidosis alone. It did not take into account the possibility of detecting (or treating) alternative causes of HF, which is a unique strength of CMR. It also does not factor in the downstream testing and cost associated with identification of a monoclonal gammopathy, which could prompt further evaluation for AL amyloidosis or myeloma. Finally, our model was designed to compare cost-effectiveness of various diagnostic strategies for ATTR-CMP. It relied on the assumption of a hypothetical price point of $16 000 for the cost of tafamidis, which is well below the current listing price of $225 000. As such, it actually minimizes the negative financial impact of a false positive. At current pricing, a high specificity strategy is therefore even more crucial from a cost-effectiveness perspective.

CONCLUSIONS

In summary, ATTR-CMP is an increasingly recognized and treatable cause of HFpEF. Numerous noninvasive diagnostic techniques are available to enable accurate

diagnosis. At current pricing of tafamidis, no diagnostic strategy can be considered cost effective. When discounting the pricing of tafamidis, our model-based analyses showed that a PYP-only strategy, with a focus on high specificity, is the most cost-effective strategy to diagnose ATTR-CMP, at currently demonstrated cost-effective pricing of drug therapy.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Time-based utility values for ATTR-CMP patients

Year since model start	Utility true positive	Utility false negative
1	0.788	0.788
2	0.773	0.744
6	0.713	0.570
11	0.638	0.439

Table S2. Positive and negative predictive values

	TP	FN	FP	TN
PYP only (strategy 1)	9.6%	3.4%	0.0%	87.0%
PYP/CMR- (strategy 2)	12.6%	0.4%	0.0%	87.0%
CMR/EMB+(strategy 3)	11.6%	1.4%	0.0%	87.0%
CMR/PYP+(strategy 4)	11.6%	1.4%	0.0%	87.0%
CMR/PYP+&-(strategy 5)	12.6%	0.4%	0.0%	87.0%
CMR/PYP-(strategy 6)	9.6%	3.4%	0.0%	87.0%
EMB only (strategy 7)	13.0%	0.0%	0.0%	87.0%

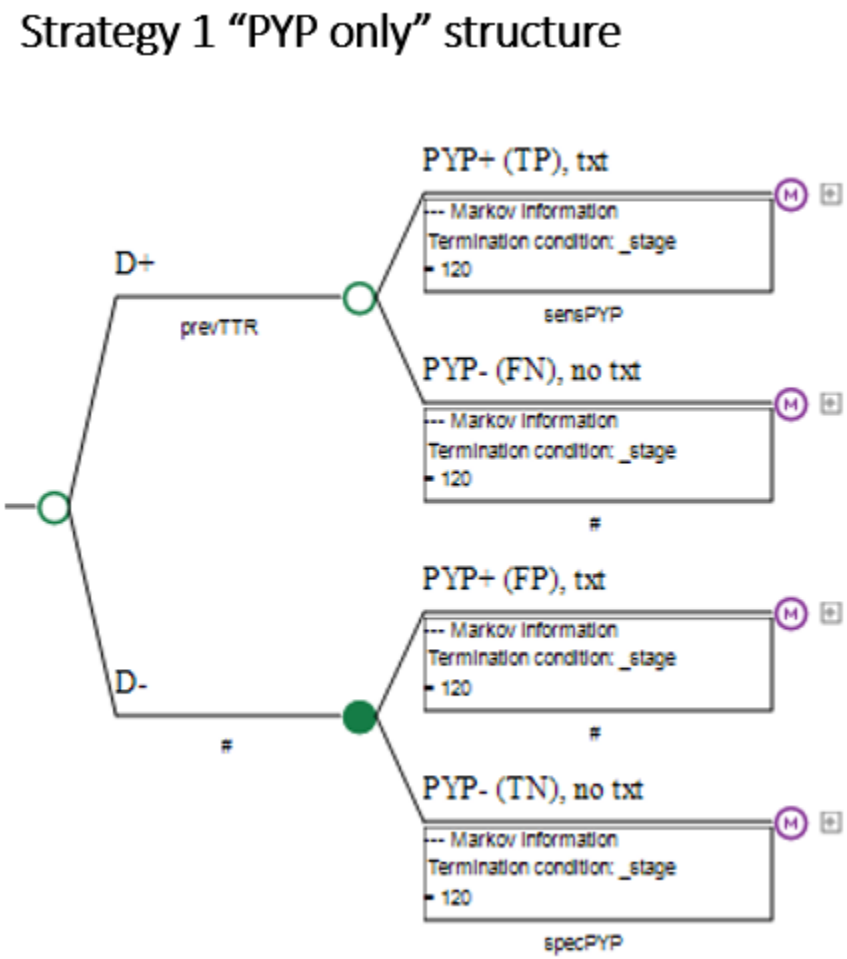
Table S3. Lifetime per-person utilization outcomes, quality-adjusted life years (QALYs), costs ($), and incremental cost-effectiveness ratios ($/QALY) for base-case analysis, using tafamidis pricing $225,000 per year.

Strategy	ATTR-CMP diagnosis	QALYs*	Costs*	ICER	Net monetary benefit
No imaging	0%	7.05133	$192,731	-	512,402
PYP only	9.6%	7.19953	$369,074	$1,200,000/QALY	350,879
PYP followed by CMR	12.6%	7.24357	$422,162	$1,200,000/QALY	302,195
EMB	13.0%	7.24942	$431,540	$1,600,000/QALY	293,402

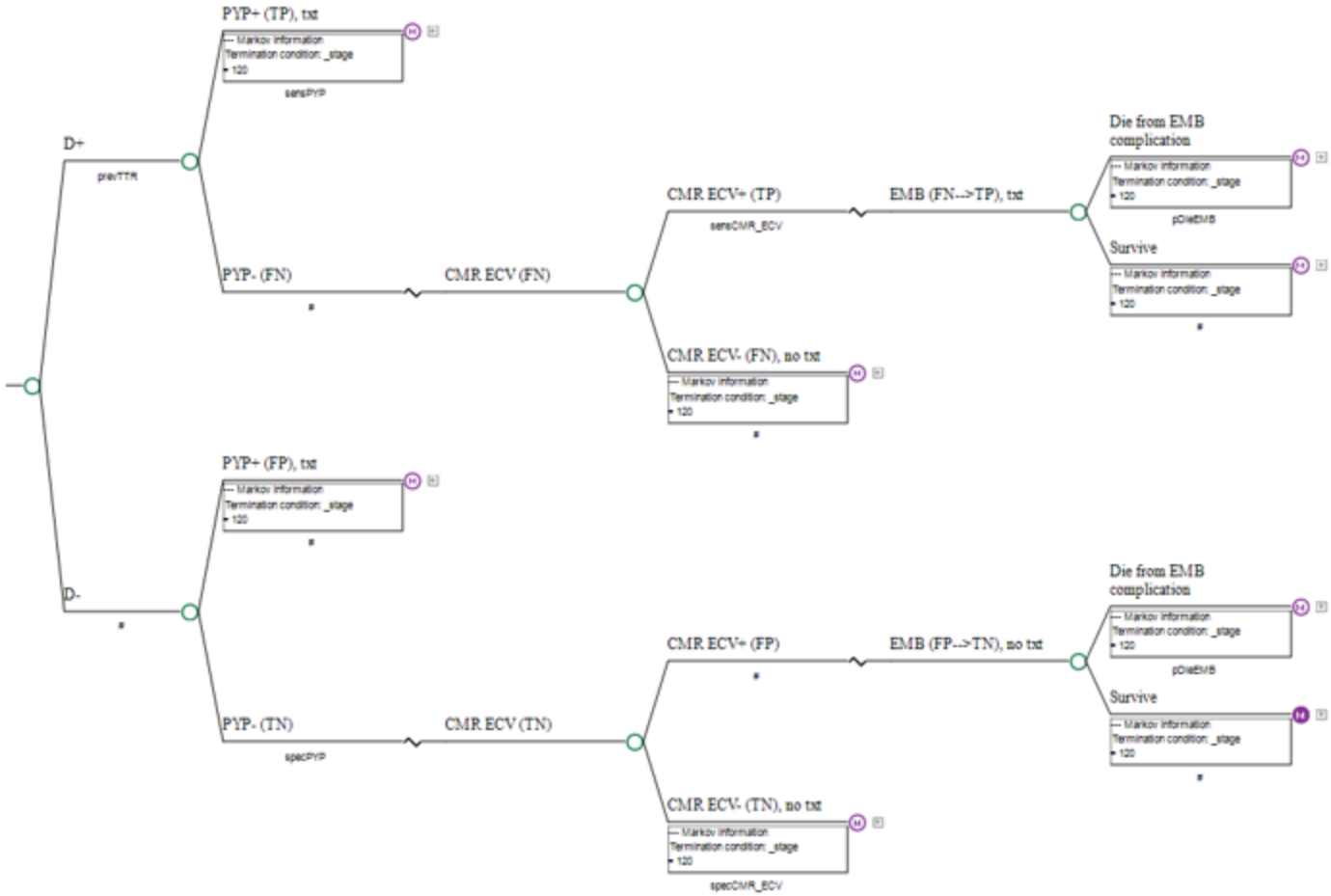
*Discounted at 3%

ATTR-CMP: transthyretin cardiac amyloidosis, PYP: ^{99m}technetium pyrophosphate, CMR: cardiac magnetic resonance imaging, EMB: endomyocardial biopsy, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio.

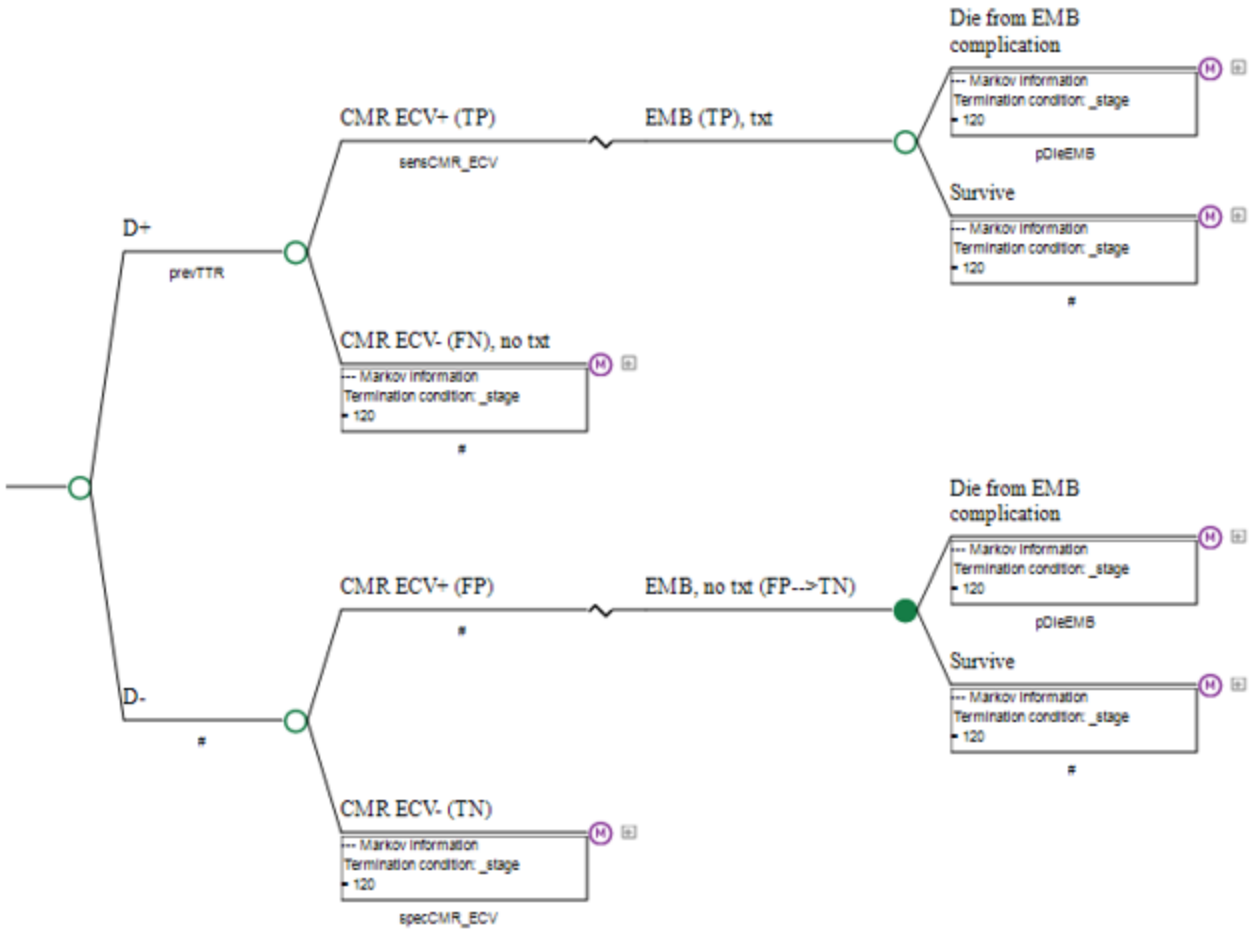
Figure S1. Panels that show model structure details for each strategy evaluated in the model-based cost-effectiveness



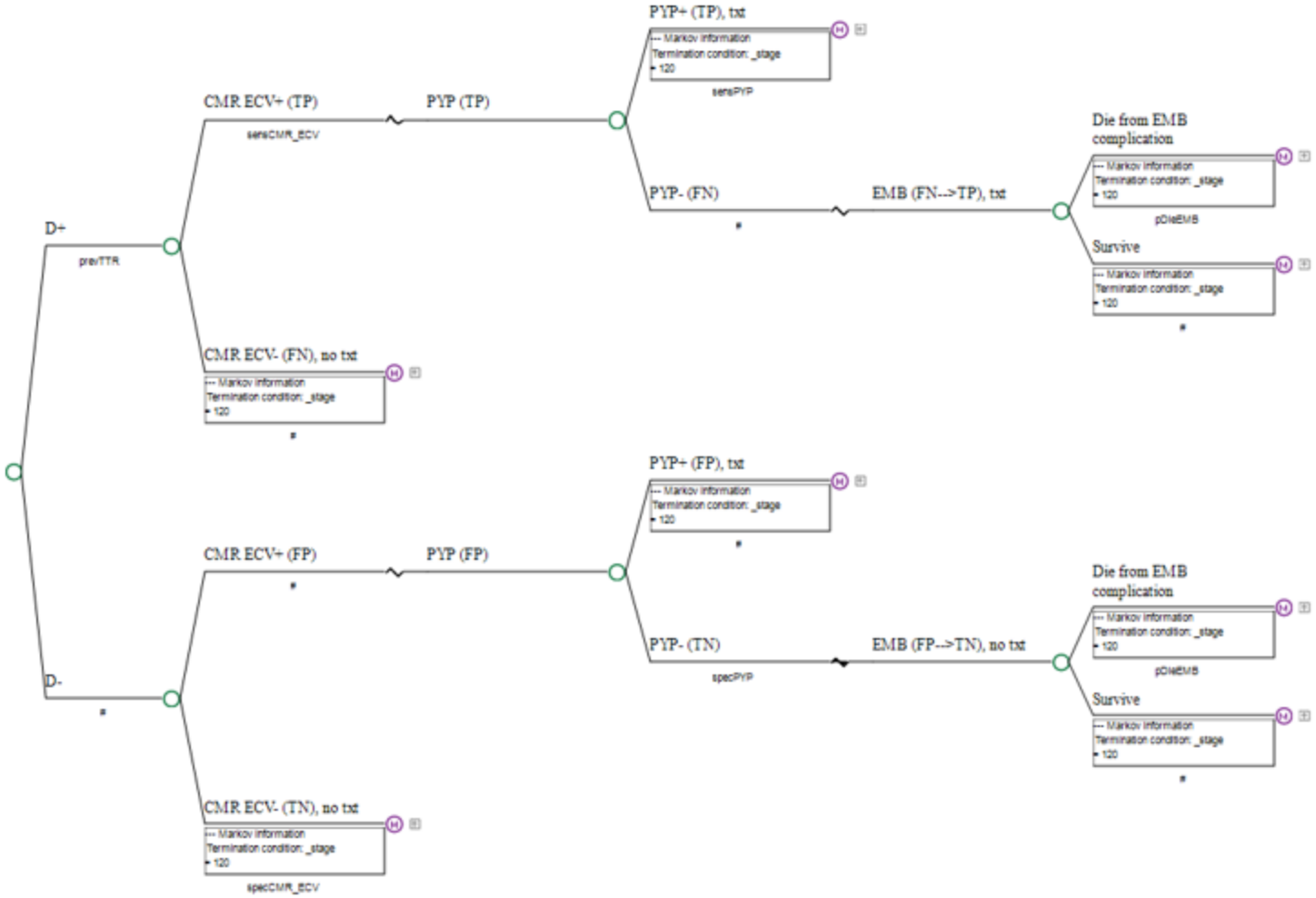
Strategy 2 “PYP/CMR ECV-” structure



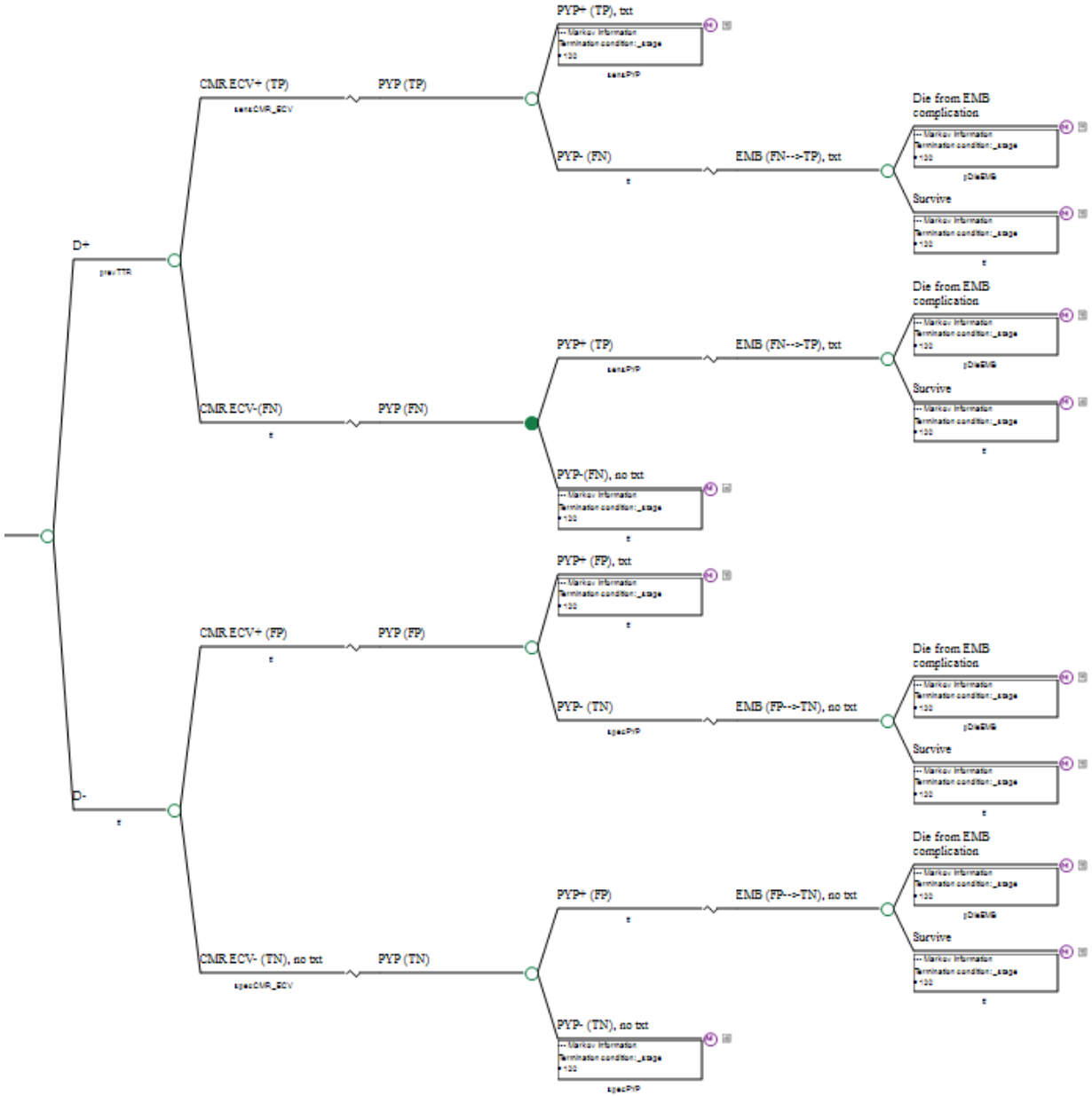
Strategy 3 “CMR ECV/EMB+” structure



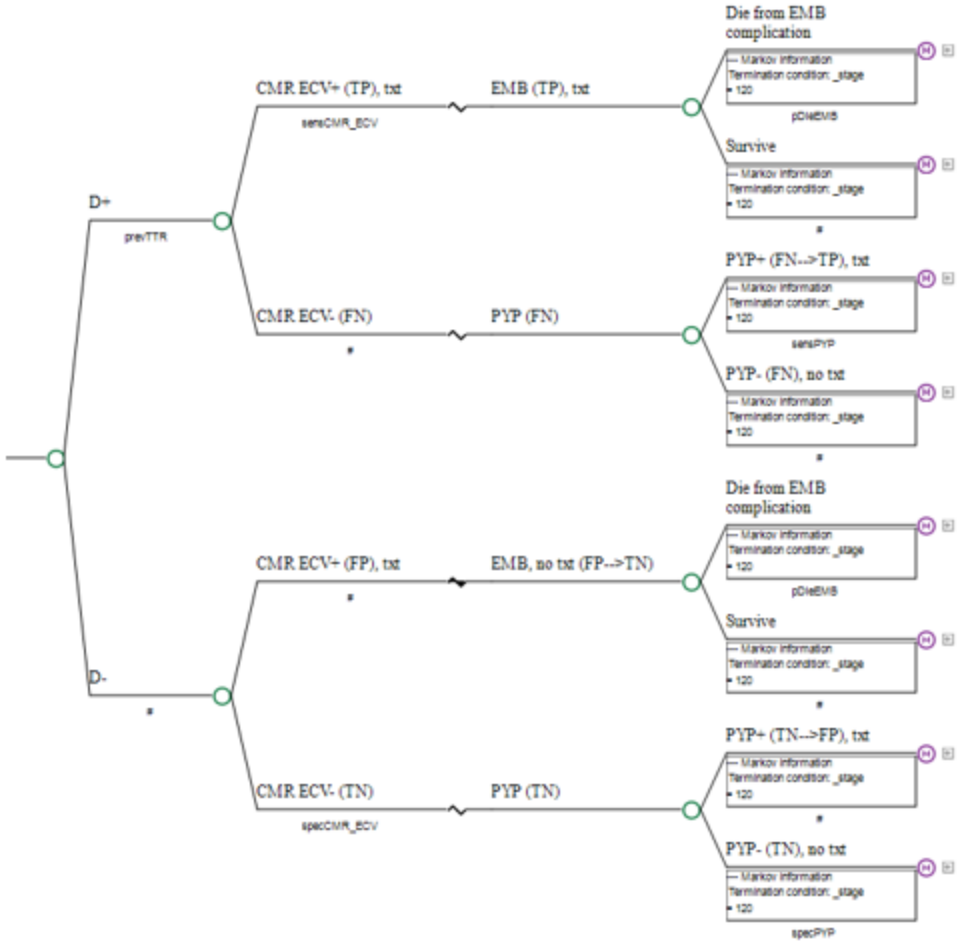
Strategy 4 “CMR ECV/PYP+” structure



Strategy 5 “CMR ECV/PYP-&+” structure



Strategy 6 “CMR ECV/PYP-” structure



Strategy 7 “EMB only” structure

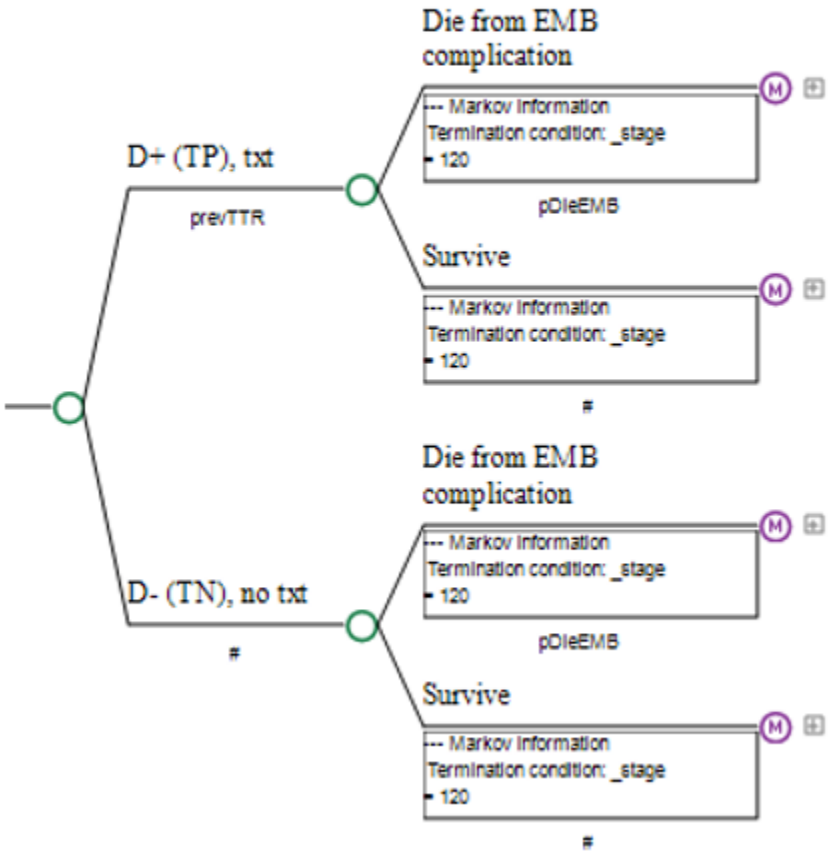


Figure S2. Two-way sensitivity analysis results probability of having ATTR-CMP and cost of tafamidis, assuming willingness-to-pay for health of $100,000/QALY, and tafamidis pricing $225,000 per year.

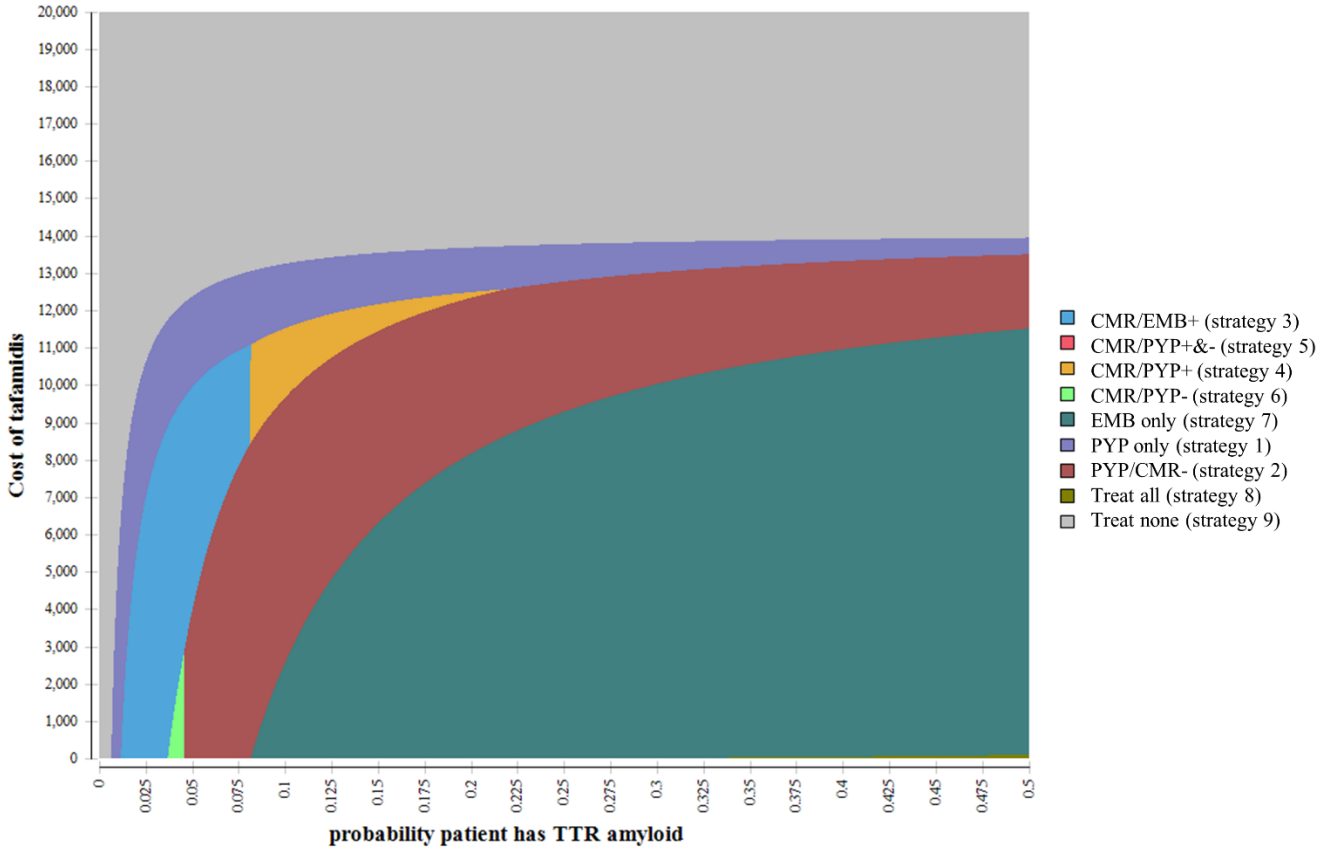


Figure S3. Two-way sensitivity analysis results hazard rate ratio of mortality and cardiovascular hospitalization in patients with ATTR-CMP receiving tafamidis, assuming willingness-to-pay for health of $100,000/QALY.