# Disease Modifying Therapies for the Treatment of Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

**Draft Evidence Report**

**July 17, 2024**

**Prepared for**

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Jason H. Wasfy served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section of this report with assistance from Finn Raymond. Aaron N. Winn, Kanya K. Shah, Sodam Kim, and Daniel R. Touchette developed the cost-effectiveness model and authored the corresponding sections of the report with the assistance from Bertha De Los Santos and Michael Kim. Danellys Borroto conducted systematic reviews related to the economic model. Marina Richardson and Woojung Lee conducted analyses for the budget impact model with the assistance of Yasmine Kayali. David M. Rind provided methodologic guidance on the clinical and economic sections. We would also like to thank Madeline Booth, Kelsey Gosselin, Liis Shea, Yamaya Jean, and Emily Nhan for their contributions to this report.

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*In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:*

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*None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of this draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.*

*To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.*

*For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit:* https://icer.org/wp-content/uploads/2024/07/ATTR-CM_Key-Stakeholders-List_For-Publication_07172024.pdf

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## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| % | Percent |
| AE | Adverse event |
| AHRQ | Agency for Healthcare Research and Quality |
| ATTR | Transthyretin Amyloid |
| ATTR-CM | Transthyretin Amyloid Cardiomyopathy |
| ATTRv-CM | Hereditary or variant transthyretin amyloid cardiomyopathy |
| ATTRv-PN | Polyneuropathy in hereditary transthyretin amyloid |
| ATTRwt-CM | Wild-type transthyretin amyloid cardiomyopathy |
| CI | Confidence interval |
| CV | Cardiovascular |
| CMAD | Cardiac mechanical assist device |
| EQ-5D | EuroQol-5-domain questionnaire |
| evLY | Equal value of life year |
| FDA | Food and Drug Administration |
| HF | Heart failure |
| HIDI | Health Improvement Distribution Index |
| HR | Hazard ratio |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| KCCQ-OS | Kansas City Cardiomyopathy Questionnaire-Overall Summary |
| LSM | Least-squares mean |
| LVEF | Left ventricular ejection fraction |
| mg | Milligrams |
| ml | Milliliters |
| n | Number |
| N | Total number |
| NT-proBNP | N-terminal pro B –type natriuretic peptide |
| NYHA | New York Heart Association |
| NE | Not estimated |
| NR | Not reported |
| PDRR | Participant to disease-prevalence representation ratio |
| pg/mL | Picograms per milliliter |
| QALY | Quality-adjusted life year |
| RR | Relative risk |
| SE | Standard error |
| SD | Standard deviation |
| TTR | Transthyretin |
| VAS | Visual analogue scale |
| 6MWT | 6-minute walk test |
| 6MWD | 6-minute walk distance |

# Executive Summary

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of heart muscle disease that occurs when amyloid fibrils – clumps of misfolded proteins – are deposited into heart tissue and cause the heart to stiffen. Eventually, the heart cannot fill properly, leading to shortness of breath, heart failure, arrhythmias, and death. Patients often have complex symptoms, because the shortness of breath can mimic other conditions and because amyloid fibrils can also deposit in other tissues causing other symptoms like pain and numbness. In that context, ATTR-CM patients are often diagnosed late in the disease course, after irreversible damage has been done. Even after diagnosis, patients often struggle with access to knowledgeable subspecialists.

The true prevalence of ATTR-CM in the United States is unclear, given likely systematic underdiagnosis. It is likely at least 50,000 Americans have ATTR-CM, although by some estimates the prevalence could be much higher.

Prior to the approval of the oral TTR stabilizer tafamidis in 2019, patients with ATTR-CM were typically managed like other patients with heart failure, although some young patients would be treated with heart or heart-liver transplants. Another oral stabilizer, acoramidis, is under evaluation by the FDA with a PDUFA date of November 29, 2024. An RNA silencing agent, vutrisiran, recently reported preliminary data. The RNA silencing agents reduce production of TTR proteins and have been approved for nerve damage in people with hereditary ATTR.

The trial that led to the approval of tafamidis demonstrated that tafamidis reduces mortality (HR 0.67) with survival curves diverging after approximately 18 months. Cardiovascular (CV)-related hospitalizations were also reduced, and declines in functional status and quality of life were slowed with minimal side effects.

The availability of tafamidis has led to earlier detection of ATTR-CM, and this has resulted in healthier patients being enrolled in subsequent trials of therapies. In the primary trial of acoramidis, survival was numerically better at 30 months (81% vs. 74%), but this was not statistically significant. CV-related hospitalizations were reduced (RR 0.50) and declines in functional status and quality of life were slowed with minimal side effects. These results affect our judgment of both tafamidis and acoramidis in a contemporary population.

We have high certainty that tafamidis has substantial net health benefits in the population studied in its pivotal trial. While we recognize that, given the evidence base, clinicians and patients would be unwilling to wait for progression of disease before initiating therapy, this uncertainty about the magnitude of benefit is real. Thus, in a contemporary population, we have high certainty that treatment with tafamidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

Similarly, in a contemporary population, we have high certainty that treatment with acoramidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

Top-line results from the HELIOS-B phase 3 trial evaluating vutrisiran were released on June 24, 2024. Vutrisiran reduced a composite outcome of all-cause mortality and recurrent CV events (HR 0.72) over 30 months and, when results from an open-label extension were included, reduced all-cause mortality (HR 0.65) with similar effects in individuals taking or not taking tafamidis. We do not currently have the absolute changes in these outcomes. Given uncertainties from the lack of absolute changes, as well as that results have not yet been published in a peer-reviewed journal, we have high certainty that treatment with vutrisiran, compared with no disease-specific therapy or, apparently, when added to tafamidis, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

Given the different populations studied, and the lack of information at this time about the population and absolute results in HELIOS-B, the evidence is currently insufficient **("I")** to compare the net health benefits of the three agents.

Based on the clinical evidence available, the economic modeling did not assume differences in treatment effects between the TTR stabilizers tafamidis and acoramidis. The modeling also assumed the tafamidis price for acoramidis. With these assumptions, a TTR stabilizer added to best supportive care resulted improved health outcomes and higher costs compared to supportive care alone. Incremental cost-effectiveness ratios, as shown in Table 4.4, suggest that these therapies are unlikely to achieve commonly accepted cost-effectiveness thresholds.

**Table ES1. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained* | Cost per evLY Gained* | Cost per Life Year Gained* | Cost per Time in NYHA Class I and II* |
|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent + Best Supportive Care** | Best Supportive Care alone | $1,883,000 | $735,000 | $717,000 | $844,000 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

# 1. Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of heart muscle disease that occurs when amyloid fibrils – clumps of misfolded proteins – are deposited into heart tissue and cause the heart to stiffen.[1] Eventually, the heart cannot fill properly, leading to shortness of breath, heart failure, arrhythmias, and death. Prior to the availability of disease-specific therapies, care for a patient in the US with ATTR-CM estimated to cost more than $60,000 annually, mostly related to inpatient hospital care.[2]

There are two main types of ATTR-CM that differ with respect to the upstream processes that lead to amyloid protein deposition in the heart. In hereditary ATTR-CM (also referred to as ATTRv-CM for "variant" ATTR-CM), individuals inherit a mutated transthyretin gene that results in protein misfolding, often causing disease at a younger age.[1] In wild-type ATTR-CM (ATTRwt-CM), there is no inherited mutation, but transthyretin still misfolds and deposits in the heart, generally at older ages. ATTRv-CM is more common in people of African descent than other ethnic groups, often caused by the Val122Ile mutation,[3] and is also more common in women than in men.[4] ATTRv-CM tends to have a worse prognosis compared to wild-type.[5] ATTRwt-CM accounts for approximately 90% of cases.[6]

The prevalence of ATTR-CM is extremely difficult to estimate, given likely systematic underdiagnosis and changes in diagnostic modalities over time. Conservative estimates suggest that 50,000 to 150,000 US adults have ATTR-CM.[1,7,8] Autopsy data without any restriction to HFpEF or any specific clinical symptoms suggest that ATTR-CM could affect 25% of all individuals who live past age 85.[9] If true, this would suggest that over 1 million individuals in the United States *might* have ATTR-CM, although the vast majority of these cases would likely be preclinical. These estimates imply the prevalence of ATTR-CM could exceed the FDA's definition of a rare disease.[10]

Historically, a small portion of those with hereditary forms of ATTR-CM would receive cardiac transplantation while most individuals with ATTRwt-CM received no disease-specific treatment as they were above the age where cardiac transplantation would be appropriate.[11] The first treatment specific to ATTR-CM, tafamidis, a stabilizer of transthyretin, was approved by the FDA in 2019.[12] We heard from multiple stakeholders that the availability of a disease-specific treatment for ATTR-CM has resulted in earlier detection since diagnosis now leads to a change in management. As a result, trials of subsequent agents have enrolled patients at much earlier stages of disease.

Acoramidis, also a transthyretin stabilizer, is under evaluation by the FDA with a PDUFA date of November 29, 2024. Another treatment strategy in development is to use RNA silencing to reduce production of transthyretin.[15] Vutrisiran and eplontersen are RNA silencing agents approved for the treatment of nerve pain and dysfunction from ATTR and are being evaluated for treatment of cardiomyopathy. Top-line results from a trial of vutrisiran were released on June 23, 2024 and a

conference presentation is planned at the European Society of Cardiology meeting in August-September 2024.[18]

**Table 1.1. Interventions of Interest**

| Intervention | Mechanism of Action | Delivery Route | Prescribing Information |
|---|---|---|---|
| **Vyndamax®/Vyndagel® (tafamidis)** | TTR stabilizer | Oral | Vyndamax 61 mg once a day (one 61 mg capsule) or Vyndaqel 80 mg once a day (four 20 mg capsules) |
| **acoramidis** | TTR stabilizer | Oral | 800 mg twice daily |
| **Amvuttra® (vutrisiran)** | RNA interference | Subcutaneous injection | 25 mg once every three months |

mg: milligrams, TTR: Transthyretin

# 2. Patient and Caregiver Perspectives

We heard that patients with ATTR-CM face significant challenges in obtaining an accurate, timely diagnosis and accessing appropriate treatment, in part because many clinicians are unfamiliar with this condition, leading to underdiagnosis or delayed diagnosis. Furthermore, there is differential access to advanced imaging modalities and the multi-system nature of amyloidosis can mimic other disorders. Even after the correct diagnosis, the high costs of ATTR-CM medications like tafamidis can be prohibitive, forcing patients to seek financial assistance programs including foundation-based programs. These programs can help substantially but often have strict eligibility criteria and limited funding. In some cases, eligibility for assistance requires patients/families to reduce their incomes. Some patients in similar clinical and financial circumstances reported very different experiences with patient assistance programs. While helpful, receiving cost relief from these programs requires time and effort.

We heard that in addition to the challenges with cost, navigating the health care system requires patients to be highly proactive, persistent self-advocates as they may need to educate their caregivers and seek multiple clinical evaluations. While clinical knowledge exists at amyloidosis centers of excellence, access to such centers can create additional burdens for patients, such as long travel times. This can be particularly problematic for patients in rural areas.

We heard that the multi-organ impact of ATTR necessitates a multidisciplinary treatment approach with patients commonly experiencing multiple symptoms including breathlessness, fatigue, neuropathy, erectile dysfunction, and mobility challenges.

Patients expressed a desire for more research, clinical trials, and development of new, affordable therapies to improve care and access. Patients with ATTR-CM plus other organ involvement seek clearer answers about which treatments are best for these “overlap” situations. The risk and side effect profile of new therapies are important considerations especially for patients who currently have access to effective treatment. We heard concerns from both patients and clinicians about the high prices of therapies and what this suggests about the motivations of those manufacturing and studying such treatments. Patients with hereditary forms of ATTR-CM worry about the risk in family members and desire clarity about screening and prevention strategies for close relatives.

Patients also drew attention to inconsistencies between some formularies and treatment guidelines from the FDA-approved dosage and indication for tafamidis. For example, the U.S. Veterans Administration allows for the 20 mg dose of tafamidis as an option and allows for use of tafamidis for ATTR neuropathy.[19]

Support groups, educational events, social media groups, and patient organizations play a vital role in sharing information and personal experiences within the ATTR-CM community. Despite

significant improvements with current treatments, we heard that the residual quality of life impact from symptoms like fatigue, neuropathy, and mobility limitations is substantial.

**Health Equity Considerations**

Although ATTR-CM is underdiagnosed in both males and females, and more prevalent in men, there is relatively more underdiagnosis of women in actual practice and a smaller proportion of women are enrolled in clinical trials. Both ATTR-ACT and ATTR-CM required patients to have left ventricular wall thickness of 12 mm or greater, but women with amyloidosis tend to have thinner left ventricular walls. Indexing imaging thresholds for body size may reduce this source of underdiagnosis that disproportionally affects women.[20-22] This could reduce underdiagnosis among women in the community and under-enrollment in clinical trials.

ATTR-CM is more prevalent in patients of African descent, largely related to the V142I TTR variant. Among Black Americans, 3.4% carry at least one copy of the V142I allele.[23] Although much about the true prevalence and any differences in race and ethnic groups of ATTR-CM remain unclear, Black individuals are twice as likely to be diagnosed as White individuals and the prevalence of ATTR-CM among Black Americans has increased over time.[24] Despite greater prevalence in Black patients, a smaller proportion of Black patients is enrolled in clinical trials for ATTR-CM.[25] Given that more Black Americans are affected by ATTR-CM, novel, effective therapies could improve health equity. Inclusion in clinical trials needs to better reflect the demographics of patients with ATTR-CM.

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

Procedures for the systematic literature review are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD42024534708).

### Scope of Review

Our review examined the clinical effectiveness and safety of three disease-modifying therapies (acoramidis, tafamidis, vutrisiran) for adults with ATTR-CM, assessing net health benefits versus no treatment and comparing net health benefits among therapies. We sought data on outcomes that patients identify as important such as mortality, hospitalization, functional capacity, and quality of life (see Supplement A1 for definitions). The full scope of this review is detailed in Supplement D1.

### Evidence Base

**Table. 3.1. Overview of Pivotal Study Inclusion Criteria**

| Criteria | tafamidis ATTR-ACT (2013-2018) | acoramidis ATTRibute-CM (2019-2023) | vutrisiran HELIOS-B (2019-2024) |
|---|---|---|---|
| **Age** | 18-90 | 18-90 | 18-85 |
| **Diagnosis Confirmation** | Positive biopsy, immunohistochemical analysis, scintigraphy, or mass spectrometry | Positive biopsy or scintigraphy scan | NR |
| **NYHA Class** | I-III | I-III | I-III, unless class III AND at high risk based on pre-specified criteria |
| **6MWD** | ≥100 m | ≥150 m on at least 2 tests | NR |
| **NT-proBNP Level** | ≥600 pg/mL | 300 - 8499 pg/mL | 600 - 8499 pg/mL |
| **eGFR** | ≥25 mL/min/1.73 $m^2$ | ≥15 mL/min/1.73 $m^2$ | ≥30 mL/min/1.73 $m^2$ |

6MWD: 6-minute walk distance, m: meter, min: minute, NR: not reported, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association, pg/mL: picograms per milliliter

### Tafamidis

ATTR-ACT is a pivotal Phase III study that evaluated the efficacy and safety of oral tafamidis (20 or 80 mg) once daily. Trial participants were randomized in a 2:1:2 ratio to 80 mg of tafamidis, 20 mg of tafamidis, or placebo, with a total of 441 patients. Trial outcomes included survival, rates of

cardiovascular hospitalizations, changes in functional capacity, and quality of life endpoints at 30 months, with additional follow-up via open label extension for 60 months.

The ATTR-ACT trial enrolled patients ages 18 to 90 with ATTR-CM (hereditary or wild-type) confirmed by tissue biopsy. Cardiac involvement criteria included interventricular septal thickness >12 mm, history of heart failure hospitalization or diuretic treatment, NT-proBNP ≥600 pg/mL and 6-minute walk distance >100 m. The trial excluded patients with severe heart failure, organ transplants, certain devices/medications, or poor kidney/liver function (see Supplement Table D2.1 for details). Patients who completed the ATTR-ACT trial could enroll in a long-term extension (LTE) study. Patients previously on placebo were randomized to receive tafamidis 80 mg or 20 mg. In July 2018, the LTE protocol was amended to transition all patients to a new formulation of tafamidis free acid 61 mg, which is bioequivalent to the 80 mg meglumine form.[26]

We also reviewed observational data from the Transthyretin Amyloidosis Outcomes Survey (THAOS), a global observational survey that tracks patients with ATTR-CM, including hereditary and wild-type forms, as well as asymptomatic carriers with TTR gene mutations.[27]

## Acoramidis

Attribute-CM is a pivotal Phase III trial that evaluated the efficacy and safety of oral acoramidis 800 mg twice daily. A total of 632 trial participants were randomized 2:1 to acoramidis or matching placebo and were assessed at 12 and 30 months on functional capacity, cardiovascular-related hospitalization, and all-cause mortality. At end of trial, participants were eligible to continue acoramidis via open-label extension. Concomitant use of tafamidis was allowed in both study arms after 12 months.

Attribute-CM enrolled patients ages 18 to 90 who met 2 separate criteria. First, a diagnosis of ATTR-CM (with exclusion of AL amyloidosis) and clinical heart failure with current NYHA Class I-III heart failure symptoms. Inclusion also required elevated NT-proBNP of 300 pg/mL or greater, left ventricular wall thickness of 12 mm or more, and ability to walk at least 150 meters in 6 minutes. The trial excluded patients with recent major cardiovascular events such as stroke, acute coronary syndrome, or coronary revascularization, or with liver or kidney dysfunction. Individuals with NYHA class IV symptoms or NT-proBNP of 8500 pg/mL or greater were also excluded (Supplement Table D2.1).

An earlier Phase II trial that assessed the safety and tolerability of the drug [acoramidis 400 mg and 800 mg, n=32) vs. (placebo, n=17)] over 28 days was followed by an open-label extension study that extended the follow-up period to 30 months.[28] The open-label extension study was limited by its small sample size and short follow-up time, and therefore did not provide additional insights into the drug's durability beyond what is known from the Phase III ATTRibute-CM trial.

## Vutrisiran

Vutrisiran was evaluated as treatment for ATTR-CM in its pivotal trial, HELIOS-B. The enrolled population included patients on no other disease-modifying therapy and patients on tafamidis. Top-line results from the trial were made publicly available on June 24th, 2024, with further results expected to be presented at the European Society of Cardiology Congress August 30 to September 2, 2024.

The HELIOS-B trial enrolled 655 patients ages 18 to 85 diagnosed with ATTR-CM (hereditary and wild-type).[29-31] Key inclusion criteria included a history of heart failure with at least one prior hospitalization or clinical evidence of heart failure, and NT-proBNP levels between 600-8500 ng/L. Key exclusion criteria included NYHA Class IV, NYHA Class III with high risk as defined by pre-specified criteria (these criteria are not yet available to us) and severe polyneuropathy.[31] Patients were randomized 1:1 to receive either vutrisiran 25 mg subcutaneously or placebo every 3 months for up to 36 months. Approximately 40% of trial participants were on tafamidis.[32] A subsequent open-label extension allowed for vutrisiran use. The primary objective was to evaluate the efficacy of vutrisiran versus placebo in reducing all-cause mortality and cardiovascular hospitalizations in a composite endpoint. Secondary objectives included assessing functional capacity, quality of life, all-cause mortality, and change in NYHA class. On February 15, 2024, the manufacturer revised the primary and secondary endpoints of the HELIOS-B trial to include assessment of vutrisiran in the subset of patients who were not receiving tafamidis.

## Comparisons between Disease Modifying Therapies

In addition to the evidence from the randomized trials, the surrogate outcome of post-treatment TTR serum levels were reviewed.[33-35] We also examined preliminary observational data from a single-center study comparing the long-term outcomes of ATTR-CM patients treated with tafamidis (real-world clinical practice) or acoramidis (former Phase II/III trial participants).[36]

We do not currently have adequate data on the population enrolled in HELIOS-B to know whether comparisons can be made to either of the other agents.

**Table. 3.2. Overview of Key Studies**

| Trial | | ATTR-ACT | | ATTRibute-CM | |
|---|---|---|---|---|---|
| Arms | | Tafamidis 80 mg | Placebo | Acoramidis | Placebo |
| N | | 176 | 177 | 421 | 211 |
| Age, years | Mean (SD) | 75.2 (7.2) | 74.1 (6.7) | 77.4 (6.5) | 77.1 (6.8) |
| Sex, n (%) | Male | 158 (89.8) | 157 (88.7) | 384 (91.2) | 186 (88.2) |
| | Female | 18 (10.2) | 20 (11.3) | 37 (8.8) | 25 (11.8) |
| Race, n (%) | White | 136 (77.3) | 146 (82.5) | 368 (87.4) | 187 (88.6) |
| | Black | 26 (14.8) | 26 (14.7) | 20 (4.8) | 10 (4.7) |
| | Asian | 11 (6.3) | 5 (2.8) | 10 (2.4) | 3 (1.4) |
| | Other | 3 (1.7) | 0 (0) | 23 (5.5) | 11 (5.2) |
| TTR genotype, n (%) | ATTRv (Hereditary/Variant) | 42 (23.9) | 43 (24.3) | 41 (9.7) | 20 (9.5) |
| | ATTRwt (Wild Type) | 134 (76.1) | 134 (75.7) | 380 (90.3) | 191 (90.5) |
| Transthyretin variant, n (%) | V142I | 38 (60.3)* | 23 (53.5) | 24/39 (61.5)† | 12/19 (63.2)† |
| | T60A | 6 (9.5)* | 6 (14) | 3/39 (7.7)† | 2/19 (10.5)† |
| NYHA class, n (%) | Class I | 16 (9.1) | 13 (7.3) | 51 (12.1) | 17 (8.1) |
| | Class II | 105 (59.7) | 101 (57.1) | 293 (69.6) | 162 (76.8) |
| | Class III | 55 (31.3) | 63 (35.6) | 77 (18.3) | 32 (15.2) |
| NT-proBNP, mean pg/mL (IQR) | Median (IQR) | 3122 (1826-4948.5) | 3161 (1864.4-4825) | 2326 (1332-4019) | 2306 (1128-3754) |
| Baseline medications, n (%) | Agents acting on renin-angiotensin system | 69 (26.1)* | 48 (27.1) | NR | NR |
| | Beta blockers | 76 (28.8)* | 53 (29.9) | NR | NR |
| | Diuretics | 175 (66.3)* | 123 (69.5) | NR | NR |
| | Antithrombotic agents | 105 (39.8)* | 72 (40.7) | NR | NR |
| 6MWT distance, mean (SD) | | 344.8 (120.3) | 353.3 (126) | 361.2 (103.7) | 348.4 (93.6) |
| KCCQ, mean (SD) | Overall Summary Score | 67.1 (21.3) | 65.9 (21.7) | 71.5 (19.4) | 70.3 (20.5) |

6MWT: 6-minute walk test, IQR: interquartile range, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire, n: number N: total number, NR: not reported, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association, pg/mL: picograms per milliliter, SD: standard deviation, TTR: transthyretin, %: percent

* Pooled data from the ATTR-ACT trial 20 mg and 80 mg arms

† Of the 58 participants screened for transthyretin variant

See Supplement Tables D2.2-3 for additional details on study baseline characteristics

### *Evaluation of Clinical Trial Diversity*

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool. See Supplement D1 for full details of CDR methods and results.

## 3.2. Results

### Clinical Benefits

### Tafamidis

Key trial results of the ATTR-ACT trial are presented in Table 3.3 and described below.

*Mortality*

The hazard ratio for all-cause mortality with tafamidis (pooled doses) was 0.67 (95% CI: 0.49-0.94). Survival curves appeared to diverge at approximately 18 months after treatment initiation.

*Cardiovascular-related hospitalization*

Cardiovascular-related hospitalization were defined as unplanned admission for at least 24 hours to treat conditions like heart failure, arrhythmias, heart attack, and stroke. Patients taking tafamidis 80 mg experienced fewer cardiovascular-related hospitalizations compared to those on placebo (0.49 vs. 0.70 hospitalizations per year; relative risk [RR] 0.70, 95% confidence interval 0.57 to 0.85).[37]

*Primary Endpoint*

The primary endpoint assessed all-cause mortality along with cardiovascular-related hospitalization using the Finkelstein-Schoenfeld method, which combines different clinical events while placing greater weight on all-cause mortality compared to cardiovascular-related hospitalization. For this analysis, all-cause mortality included death from any cause as well as major events like heart transplant, combined heart and liver transplant, and implantation of a cardiac mechanical assist device. Treatment with tafamidis (pooled doses) demonstrated a significant advantage over placebo in reducing this primary endpoint ($p<0.001$).

*Functional Status*

ATTR-CM is a progressive disorder that diminishes a patient's ability to engage in physical activities. This impairment is often quantified by measuring the distance walked during a 6-minute walk test (6MWT). At baseline, participants could walk about 350 meters in six minutes. Over 30 months, walking distance decreased both in patients who received tafamidis and those who received placebo. The tafamidis 80 mg group declined less than the placebo group (-55 m standard error [SE]: 7.3) vs. -130 m [SE: 9.4]). This 76 m difference favoring tafamidis is of a magnitude that has been considered clinically meaningful for other conditions.[38] At month 30, more patients receiving tafamidis than placebo reported an improvement in 6 MWT distance from baseline (19% vs. 5%).[39]

*Quality of Life*

The quality of life related to health was evaluated by measuring the change from baseline in the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score for both groups. Higher scores in the KCCQ-OS indicate better health status. While both groups showed a decline in their KCCQ-OS scores, the tafamidis group (pooled) demonstrated a significantly slower rate of deterioration compared to the placebo group, with a difference of 13.65 points (95% CI: 9.2, 17.5; P < 0.001), which is considered a clinically meaningful difference.[40] The benefits of tafamidis (pooled) over placebo on this outcome were apparent from as early as 6 months.

*Durability of Treatment Effect*

Across a median follow-up of 51 months in the LTE, there was a significant 41% lower risk of all-cause mortality in patients who received continuous tafamidis treatment. Additionally, both the KCCQ clinical and overall scores remained stable in the group receiving continuous tafamidis treatment over a collective 60 months of follow-up between the ATTR-ACT and LTE studies. For the group that switched from placebo to tafamidis treatment, tafamidis slowed the decline in both KCCQ scores. These results suggest a possible benefit in earlier treatment with tafamidis. See Supplement Table D2.5 for additional LTE results.

**Table 3.3. ATTR-ACT Results**

| Trial | | ATTR-ACT | |
|---|---|---|---|
| **Arms** | | **Tafamidis 80 mg** | **Placebo** |
| **N** | | **176** | **177** |
| **Win Ratio (95% CI)** | **All-cause mortality, CV-related hospitalizations** | 1.70 (1.26, 2.29)* | |
| **CV-related hospitalizations, number per year (95% CI)** | | 0.48 (0.42, 0.54)* | 0.7 (0.62, 0.80) |
| **Frequency of CV-related hospitalizations treatment difference, relative risk ratio (95% CI)** | | 0.70 (0.57–0.85) | |
| **6-Minute Walk, meters** | **Change from baseline, LSM (SE)** | *-54.7 (7.3)* | *-130.3 (9.4)* |
| | **Difference from placebo, LSM (SE)** | *75.6* | |
| **KCCQ-OS** | **Change from baseline, LSM (SE)** | -6.3 (1.5) | -19.6 (1.9) |
| | **Difference from placebo, LSM (SE)** | 13.4 (9.2, 17.5) | |

CI: confidence interval, CV: cardiovascular, EQ-5D: EuroQol-5-domain questionnaire, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, LSM: Least-squares mean, n: number, N: total number, NR: not reported, SE: standard error, VAS: visual analogue scale, %: percent

* Pooled data from the ATTR-ACT trial 20 mg and 80 mg arms.

Note: Italicized data has been digitized or calculated

See Supplement Table D2.4 for additional results from the ATTR-ACT trial

*Contemporary Population*

While the data from ATTR-CM are the highest quality evidence of the effects of tafamidis in the population studied, as noted, there has been a shift in disease severity in patients detected and treated. As such, we also reviewed observational evidence from the THAOS study that described the association of tafamidis with survival in a contemporary patient cohort (2019-2023), comparing rates of survival to those not receiving the treatment.[27] Among THAOS participants enrolled from 2019 onwards, tafamidis-treated patients showed 30- and 42-month survival rates of 87.3% (95% CI 82.6–90.8) and 82.8% (95% CI 75.7–87.9), respectively. In contrast, untreated patients had lower survival rates of 77.2% (95% CI 69.8–83.1) at 30 months and 67.3% (95% CI 56.9–75.8) at 42 months.

## Acoramidis

Key trial results of the ATTRibute-CM trial are presented in Table 3.4 and are described below.

*Mortality*

Survival at 30 months was numerically higher in the acoramidis study arm than in the placebo arm (80.7% vs. 74.3%). The statistical significance of this result in a Cox model relies on the proportional hazards assumption, which requires the ratio of hazards between groups to remain constant throughout the study period.[41] In the early stages of the study, the cumulative incidence curve for death from any cause for acoramidis and placebo crossed multiple times, violating this assumption. Consequently, a post-hoc analysis (restricted mean survival time through 30 months) was conducted, and the effect on survival was not statistically significant.[42]

Further insights into the impact of acoramidis on survival were presented outside of the primary peer-reviewed trial.[43] An intention-to-treat (ITT) analysis was conducted, which included trial participants with stage 4 chronic kidney disease. The results of the Cox model for all-cause mortality in the ITT population showed a hazard ratio of 0.76 (95% CI: 0.54-1.07, p=0.12). Two prespecified sensitivity analyses were also performed, including a stratified log-rank test (p=0.05) and a Cochran-Mantel-Haenszel (CMH) test (p=0.04). These results differ from mortality results published in the main paper, using different statistical methods.

*Cardiovascular Hospitalization*

The risk of CV hospitalization was lower in patients taking acoramidis than placebo (RR 0.50, 95% CI 0.36 to 0.70).

*Primary Endpoint*

The primary endpoint of ATTRibute-CM used a four-step hierarchical analysis including all-cause mortality, the frequency of cardiovascular-related hospitalizations, change in NT-proBNP, and change in 6-minute walk distance using the Finkelstein-Schoenfeld method. For this analysis, all-cause mortality included death from any cause as well as heart transplant or implantation of a cardiac mechanical assist device. The primary hierarchical analysis showed better outcomes in the acoramidis group than the placebo group for the composite outcome (P<0.001).

*Functional Status*

Change from baseline in the 6MWD was assessed at months 12 and 30. At month 12, patients in the acoramidis arm on average experienced a drop in 6MWD that was comparable to placebo arm. At month 30, the average reduction in the 6-minute walk distance from baseline (approximately 357 meters) was smaller in the acoramidis group than the placebo group (-65 vs. -104), with a significant mean difference of 39.6 meters (95% CI: 21.1-58.2) favoring acoramidis. A higher proportion of trial participants in the acoramidis arm than placebo had an improvement in functional capacity (40% vs. 22%), defined as any increase in the 6MWD from baseline to month 30.[44]

*Quality of Life*

Quality of life declined in both arms but, at 30 months, patients receiving acoramidis had a smaller reduction in the KCCQ-OS mean score (difference 9.94, 95% CI, 5.97 to 13.91; P<0.001).

*Durability of Treatment Effect*

Results of the Phase III Attribute-CM open-label extension trial are still pending.

**Table 3.4. Attribute-CM Results**

| Trial | | ATTRibute-CM | |
|---|---|---|---|
| Arms | | Acoramidis | Placebo |
| N | | 421 | 211 |
| Win Ratio (95% CI) | All-cause mortality, CV-related hospitalizations | 1.5 (1.1, 2) | |
| CV-related hospitalizations, number per year (95% CI) | | 0.22 (0.18, 0.28) | 0.45 (0.35, 0.58) |
| Frequency of CV-related hospitalizations treatment difference, relative risk ratio (95% CI) | | 0.50 (0.36, 0.70) | |
| 6-Minute Walk, meters | Change from baseline, LSM (SE) | *-64.6 (10.5)* | *-104.1 (15)* |
| | Difference from placebo, LSM (95% CI) | 39.6 (21.1, 58.2) | |
| KCCQ-OS | Change from baseline, LSM (SE) | *-11.5 (2.3)* | *-21.5 (3.4)* |
| | Difference from placebo, LSM (95% CI) | 9.94 (5.97, 13.91) | |

CI: confidence interval, CV: cardiovascular, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, LSM: Least-squares mean, n: number, N: total number, NR: not reported, SE: standard error, %: percent
Note: Italicized data has been digitized or calculated
See Supplement Table D2.6 for additional results from the ATTRibute-CM trial

## Vutrisiran

Top-line results of the HELIOS-B trial are presented in Table 3.5 and described below.

*Mortality*

Vutrisiran demonstrated a significant reduction in all-cause mortality, with a 36% decrease observed in the overall population, including those using background tafamidis (HR=0.645; p<0.025). This finding came from a pre-specified, intent-to-treat analysis that incorporated up to six months of data from the open-label extension phase, during which eligible participants could receive vutrisiran.

*Primary Endpoint*

The primary endpoint of HELIOS-B was a composite of all-cause mortality and recurrent CV events. Vutrisiran reduced the risk of the primary endpoint (HR= 0.718; p=0.0118).

*Functional Status and Quality of Life*

The manufacturer reported statistically significant benefits for vutrisiran versus placebo on outcomes including 6MWT, New York Heart Association (NYHA) classification, and KCCQ scores.

*Durability of Treatment Effect*

The HELIOS-B trial had the longest double-blind follow-up duration of the three pivotal trials, with primary analysis occurring when the last patient reached month 33.

**Table 3.5. HELIOS-B Results**

| Arm | | Time Point | Overall Population | Vutrisiran Monotherapy |
|---|---|---|---|---|
| N | | | 654 | 395 |
| All-cause mortality and recurrent CV events | HR; p value | Up to 36 months | 0.718; 0.0118 | 0.672; 0.0162 |
| All-cause mortality | HR; p value | Up to 42 months | 0.645; <0.025 | 0.655; <0.05 |
| 6MWT | Change from baseline, p value | 30 months | p<0.025 | p<0.025 |
| KCCQ | Change from baseline, p value | 30 months | p<0.025 | p<0.025 |
| NYHA Class, % stable or improved | | 30 months | p<0.025 | p<0.025 |

6MWT: 6-minute walk test, HR: hazard ratio, KCCQ: Kansas City Cardiomyopathy Questionnaire, N: total number, NYHA: New York Heart Association, RR: relative risk, %: percent

## Comparisons among Disease Modifying Therapies

### *Acoramidis Versus Tafamidis*

At the XIX International Symposium on Amyloidosis in May 2024, BridgeBio, the manufacturer of acoramidis, presented several posters elucidating the relationship between serum TTR levels and cardiovascular (CV)-related mortality and hospitalization. One poster reported that a 1 mg/dL increase in TTR levels at day 28 post-therapeutic intervention was associated with a 5.5% lower risk of CV-related mortality over a 30-month period. In the ATTRibute-CM trial, acoramidis-treated patients saw an increase in serum TTR levels of 9.6 mg/dL at day 28 of treatment, and 7.1 mg/dL at month 30, with little change seen in the placebo arm. A cross-study comparison between the pivotal trials show that acoramidis-treated patients saw a greater increase in serum TTR levels at month 12 than tafamidis 80 mg (39 versus 30%).[44] This comparison may overstate any potential differences due to differences in baseline levels of TTR. A within-trial comparison of serum TTR levels between the acoramidis and placebo to tafamidis crossover arm in ATTRibute-CM showed a ~3 mg/dL difference in favor of acoramidis.[44] This difference may be exaggerated due to the delayed start of tafamidis treatment in the crossover group, which only began at month 12 of the trial. As a result, this group had lower overall exposure to the drug compared to the acoramidis group, which received treatment from the outset.

Bampatsias et al. 2024 is a retrospective cohort study that compared the outcomes of 10 patients receiving acoramidis treatment for a median of 60 months to 137 patients taking tafamidis.[36] The acoramidis group (n=10) was also matched 1:3 to a subset of tafamidis patients (n=30) based on age, gender, race, genotype, and disease severity. Of note, this compared former phase II/III trial participants receiving acoramidis with patients receiving tafamidis in real-world clinical practice.

Survival and a hierarchical endpoint of all-cause mortality followed by cardiovascular-related hospitalization were compared between groups. In the entire cohort, there was numerically better survival with acoramidis that was not statistically significant (p=0.13). In the matched cohort, mortality also did not differ between groups (p=0.19).

### *Vutrisiran Versus Acoramidis or Tafamidis*

There were insufficient data to directly compare the net health benefit of vutrisiran monotherapy for ATTR-CM versus tafamidis or acoramidis.

## Harms

Table 3.6 provides an overview of the safety profiles of the two TTR stabilizers, acoramidis and tafamidis. Vutrisiran's safety profile for ATTR-CM treatment was based on limited HELIOS-B results, supplemented by its established safety profile in treating polyneuropathy in hereditary transthyretin-mediated amyloidosis (ATTRv-PN).

### *Tafamidis*

Tafamidis 80 mg has a favorable safety profile that is comparable to the lower 20 mg dose as well as placebo on the incidence of treatment-emergent adverse events (TEAEs). The majority of events were mild or moderate. The most common adverse events were diarrhea (8%) in the 80 mg group and urinary tract infection (5.7%) in the 20 mg group. Tafamidis 80 mg demonstrated good tolerability, with dose reductions being uncommon, occurring in only 1.1% of patients, compared to a higher rate of 2.3% in the placebo group. See Supplement Table D2.7 for additional safety outcomes from the ATTR-ACT trial.

### *Acoramidis*

The occurrence of adverse events was comparable between the acoramidis group and the placebo group (98.1% and 97.6%, respectively). Acoramidis demonstrated a favorable profile concerning serious adverse events, with a lower incidence (54.6%) compared to the placebo group (64.9%), as well as severe TEAEs (37.3% vs. 45.5%). Fewer trial participants in the acoramidis arm than placebo had events of cardiac failure and atrial fibrillation.

Several AEs occurred more often in patients receiving acoramidis compared to those on placebo. These included COVID-19 (21.1% vs. 14.2%), diarrhea (11.6% vs. 7.6%), upper abdominal pain (5.5% vs. 1.4%), and elevated blood creatinine levels (6.2% vs. 1.9%). See Supplement Table D2.8 for additional safety outcomes from the ATTRibute-CM trial.

***Vutrisiran***

Adverse events were reported in a similar proportion of patients in both groups: 98.8% of those receiving vutrisiran and 98.5% of those on placebo. Serious AEs occurred in 61.7% of vutrisiran-treated patients compared to 67.1% in the placebo group. Treatment discontinuation due to AEs was observed in 3.1% of vutrisiran recipients and 4.0% of placebo recipients. No AEs were found to occur at a rate ≥3% higher in the vutrisiran group relative to the placebo group. See Supplement Table D2.9 for additional safety outcomes from the HELIOS-B trial.

Vutrisiran, when used to treat ATTRv-PN, has been associated with certain AEs, including joint pain, difficulty breathing, and reduced vitamin A levels.[45] To mitigate this risk, the FDA-approved label for vutrisiran recommends supplementation with vitamin A.

**Table 3.6. Key Trial Harms**

| Trial | | ATTR-ACT | | ATTRibute-CM | |
|---|---|---|---|---|---|
| Arms | | Tafamidis 80 mg | Placebo | Acoramidis | Placebo |
| N | | 176 | 177 | 421 | 211 |
| Timepoint | | 30 months | | | |
| TEAE, n (%) | All | 173 (98.3) | 175 (98.9) | 413 (98.1) | 206 (97.6) |
| | Treatment-related | NR | NR | 50 (11.9) | 11 (5.2) |
| | With fatal outcome | NR | NR | 60 (14.3) | 36 (17.1) |
| | Leading to hospitalization | NR | NR | 212 (50.4) | 128 (60.7) |
| | Leading to discontinuation | 40 (22.7) | 51 (28.8) | 39 (9.3) | 18 (8.5) |
| | Leading to dose reduction | 2 (1.1) | 4 (2.3) | 4 (1) | 0 (0) |
| ≥1 severe TEAE, n (%) | | 110 (62.5) | 114 (64.4) | 157 (37.3) | 96 (45.4) |
| Cardiac disorders, n (%) | All | 185 (70.1)* | 124 (70.1) | 230 (54.6) | 144 (68.2) |
| | Cardiac failure | 46 (26.1) | 60 (33.9) | 101 (24) | 83 (39.3) |
| | Atrial fibrillation | 35 (19.9) | 33 (18.6) | 70 (16.6) | 46 (21.8) |

n: number, N: total number, TEAE: Treatment-emergent adverse events, %: percent

* Pooled data from the ATTR-ACT trial 20 mg and 80 mg arms

## Subgroup Analyses and Heterogeneity

We sought evidence on the effectiveness of the three disease modifying therapies in subgroups of interest including ATTR-CM subtype (hereditary versus wild-type), specific transthyretin variants (e.g., V142I, T60A), the New York Heart Association (NYHA) functional class at baseline (class I or II versus class III or IV), race or ethnic group, sex or gender, and age.

The ATTR-ACT trial of tafamidis conducted subgroup analyses for TTR genotype, NYHA class, race (White or Black), gender, and age (<75 or ≥75).[46] There was no clear evidence of subgroup effects for mortality. There was some evidence of increased CV-related hospitalization in patients in NYHA

class III, but this may have been due to longer survival when those patients received tafamidis during a more intensive phase of the disease.[47] See Supplement Table D2.10 for additional subgroup data from the ATTR-ACT trial. The ATTR-ACT trial of tafamidis conducted subgroup analyses for TTR genotype, NYHA class, race (White or Black), gender, and age (<75 or ≥75).[46] There was no clear evidence of subgroup effects for mortality. There was some evidence of increased CV-related hospitalization in patients in NYHA class III, but this may have been due to longer survival when those patients received tafamidis during a more intensive phase of the disease.[47] See Supplement Table D2.10 for additional subgroup data from the ATTR-ACT trial.

The ATTRibute-CM trial of acoramidis conducted subgroup analyses for TTR genotype, age (<78 or >78), and NYHA baseline class. There was no clear evidence of subgroup effects for the multicomponent outcome of mortality, CV-related hospitalization, NT-proBNP, and 6MWD. Patients in the acoramidis trial with a baseline NYHA class III did not have a statistically significant improvement CV-related hospitalization. See Supplement Table D2.10 for additional subgroup data from the ATTRibute-CM trial.

### *Vutrisiran*

In its announcement of HELIOS-B topline results, vutrisiran was reported to have shown positive effects on both the primary composite endpoint and all secondary endpoints across the subgroups of ATTR subtype and measures of disease severity.[48]

## Evaluation of Clinical Trial Diversity

**Table 3.7. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)**

| Trial | Race and Ethnicity | Sex | Age (Older adults) |
|---|---|---|---|
| **ATTR-ACT** | Fair | Fair | Good |
| **ATTRibute-CM** | Poor | Fair | Good |
| **HELIOS-B** | NE | NE | NE |

NE: not estimated, NR: not reported

We evaluated the demographic diversity of the clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[49] Table 3.7. presents clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) on the key trials in our report. Details on each of the demographic categories are provided below. Additional details on the CDR tool, including the scoring and rating of each trial, are provided in Supplement D1. We evaluated the demographic diversity of the clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[49] Table 3.7. presents clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) on the key trials in our report. Details on each of the demographic categories are provided below. Additional details on the CDR tool, including the scoring and rating of each trial, are provided in Supplement D1.

Race and Ethnicity: The ATTR-ACT and ATTribute-CM trial did not sufficiently enroll a diverse population, particularly Black participants, earning a Fair and Poor rating, respectively. See the Health Equity Considerations section above for discussion on potential underdiagnosis of people of color with ATTR-CM.

Sex: Both trials enrolled a high proportion of male trial participants, earning a "Fair" rating. See the Health Equity Considerations section above for discussion on potential underdiagnosis of women with ATTR-CM.

Age: Both trials effectively recruited older adults, consistent with the age profile of ATTR-CM, particularly those with wild-type disease.

## Uncertainty and Controversies

- While tafamidis has demonstrated substantial benefits in the population in which it was originally studied, the current population now being diagnosed with ATTR-CM is earlier in their disease course. The magnitude of benefit of tafamidis in this population is not firmly established, however subgroup analyses of ATTR-ACT suggest greater benefit in less symptomatic patients, which provides some evidence that tafamidis may have important benefits in earlier-stage individuals. The observational study discussed above, while potentially suggesting benefit of tafamidis in a contemporary population, is subject to bias and provides only low quality evidence for the magnitude of benefit.[27]
- For this same reason, it is difficult to compare the stabilizing agents tafamidis and acoramidis as they were studied in very different populations. We did not feel that quantitative indirect comparisons of the randomized trials of these agents could be performed. While a study apparently found that acoramidis raised serum TTR levels more than tafamidis, and found an association between serum TTR levels and clinical outcomes, clinical experts had sharply divergent opinions as to whether TTR level is an adequate surrogate to allow such comparisons across therapies.
- In its pivotal trial, any mortality benefit of acoramidis was small and of questionable statistical significance. This, again, could be due to the spectrum of disease studied in the trial and the difficulty in demonstrating mortality reductions in a healthier population.[50] With fewer deaths, there is less statistical power. Additionally, patients in the trial were allowed to initiate tafamidis after 12 months, which could further blunt differences between the acoramidis and placebo arms. Vutrisiran was able to show a statistically significant reduction in mortality in a contemporary population in the HELIOS-B trial, including many patients (40%) treated with tafamidis, however HELIOS-B was a longer trial; this may have resulted both in greater statistical power and in additional time for disease progression.
- The HELIOS-B trial provided information on relative effects of vutrisiran, but we do not yet have data on the absolute benefits which will be important in making clinical decisions

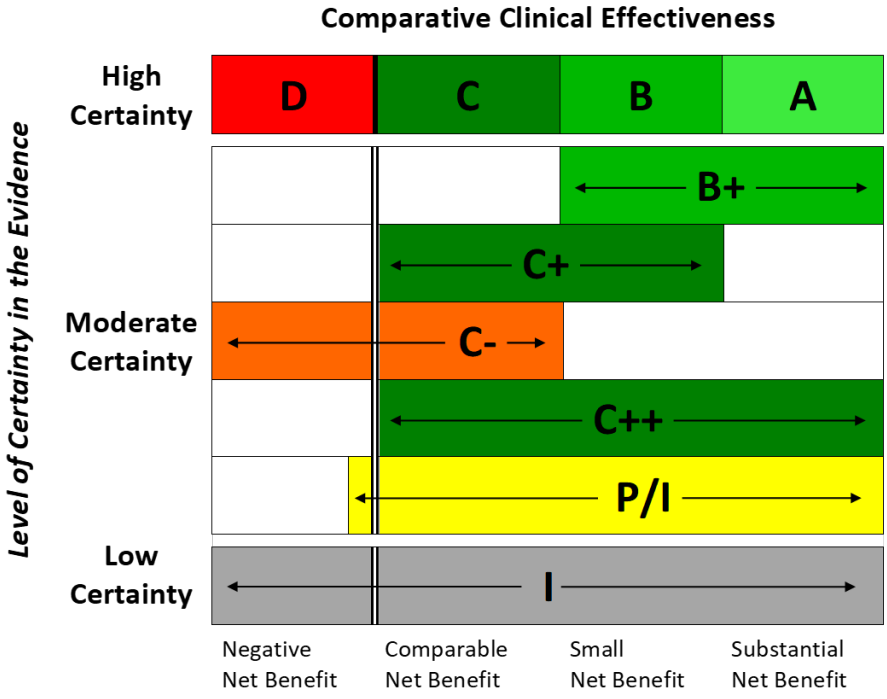
about timing of therapy and about the benefits of adding vutrisiran to a stabilizer versus using monotherapy with a stabilizer or vutrisiran. Additionally, the HELIOS-B trial results have not yet been published in a peer-reviewed journal.

- Patients with NYHA class 4 symptoms were excluded from both the ATTR-ACT and ATTRribute-CM trials and there is no trial-based evidence to support the use of tafamidis in those individuals. However, clinicians will wonder whether treatment is appropriate in such patients.
- Patients with NYHA class 3 symptoms were included in both ATTR-ACT and ATTRibute-CM trials. In ATTR-ACT, individuals with NYHA class 3 symptoms who received tafamidis had more cardiovascular hospitalizations than those who received placebo. Although likely underpowered, mortality results were directionally concordant with the overall trial results. In ATTRibute-CM, individuals with class 3 symptoms who received acoramidis were not statistically distinguishable from other subgroups on either cardiovascular-related hospitalizations or the overall trial results. There is discordance between European and American clinical guidelines – American guidelines recommend tafamidis for patients with NYHA class 3 symptoms but European guidelines do not (see Appendix section C).
- As discussed above, the actual prevalence of ATTR-CM is uncertain. The change in severity of disease reflects greater detection of patients at an earlier stage of disease. There is necessarily a risk for overdiagnosis if screening is performed and asymptomatic patients are found and treated, as some of these patients may never develop clinical manifestations of the condition.
- It is currently uncertain whether combination therapy with an RNA inhibitor to decrease TTR production and a TTR stabilizer to prevent monomer misfolding and dissolution will demonstrate greater benefits than either modality alone.

## 3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

**Figure 3.1. ICER Evidence Rating Matrix**




***A = "Superior" -*** *High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental" -*** *High certainty of a small net health benefit*
***C = "Comparable"-*** *High certainty of a comparable net health benefit*
***D= "Negative"-*** *High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –*** *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -*** *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"*** *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

### *Tafamidis*

In the population studied in the ATTR-ACT trial, tafamidis reduced mortality and CV hospitalization and slowed functional decline and deterioration in quality of life. Additionally, there were minimal side effects or safety concerns. In this population, we have high certainty that tafamidis provides a substantial net health benefit. As noted, the population being detected with ATTR-CM has shifted to

healthier patients. In this population, the magnitude of benefit is less certain, as likely evidenced by the trial of acoramidis.

While we recognize that, given the evidence base, clinicians and patients would be unwilling to wait for progression of disease before initiating therapy, this uncertainty about the magnitude of benefit is real. Thus, in a contemporary population, we have high certainty that treatment with tafamidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

***Acoramidis***

The ATTRibute-CM trial demonstrated that acoramidis generated more "wins" than placebo with respect to a four-component hierarchical clinical outcome of death from any cause, cardiovascular-related hospitalization, change from baseline in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in the 6-minute walk distance. For acoramidis, restricted mean survival time (RMST) did not show a significant difference in mortality alone. Other statistical methods applied to the same data and presented in different settings have suggested mortality reduction. The side effect and safety profile of acoramidis in the ATTRibute-CM trial were excellent. Since 18% of individuals in the ATTRibute-CM trial were also taking tafamidis, the ATTRibute-CM trial may have been biased toward the null.

In a contemporary population, we have high certainty that treatment with acoramidis, compared with no disease-specific therapy, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

***Vutrisiran***

Preliminary results from the HELIOS-B trial show large relative reductions in mortality both in all patients and in those not receiving tafamidis. The specific results suggest that the reduction in mortality was at least as large in patients receiving tafamidis as in those not receiving tafamidis, although we do not have those data yet. Additionally, the mortality benefit was seen during the open-label extension where both arms may have been receiving vutrisiran, and so the relative effects seen in HELIOS-B may underestimate the actual benefits. The primary composite endpoint of all-cause mortality and recurrent CV events was also reduced by vutrisiran.

We have uncertainties both because these results have not yet been published in a peer-reviewed journal and, more importantly, because we do not know the magnitude of the absolute benefits as we only have relative results. As such, we have high certainty that treatment with vutrisiran, compared with no disease-specific therapy or when added to tafamidis, provides at least a small net health benefit, but only moderate certainty that it provides a substantial net health benefit. **("B+")**

### *Comparisons of Therapies*

Given the changing population of patients studied over time, we do not feel we have adequate evidence to compare the net health benefits of tafamidis and acoramidis. **("I")** Without additional data on absolute effects with vutrisiran as well as the characteristics of the population studied in HELIOS-B, we also feel the evidence is insufficient to compare the net health benefits of vutrisiran with either tafamidis or acoramidis. **("I")** Additionally, once more results become available, it may be that the primary clinical question is around combination therapy versus monotherapy.

**Table 3.8. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| **Adults with ATTR-CM** | | |
| **Acoramidis** | No Disease-specific treatment | B+ |
| **Tafamidis** | No Disease-specific treatment | B+ |
| **Acoramidis** | Tafamidis | I |
| **Vutrisiran as add-on to current therapy (e.g., TTR stabilizer)** | Current therapy alone | B+ |
| **Vutrisiran** | No Disease-specific treatment | B+ |
| **Vutrisiran** | Tafamidis | I |
| **Vutrisiran** | Acoramidis | I |

# 4. Long-Term Cost Effectiveness

## 4.1. Methods Overview

We developed a de novo decision analytic model, informed by key clinical trials and prior relevant economic models, to estimate the cost-effectiveness of transthyretin stabilizing agents for ATTR-CM at the class level.[7,51-54] Although the comparative clinical effectiveness analysis reported separate evidence ratings for tafamidis and acoramidis compared to no disease-specific treatment, there was insufficient evidence to compare the net benefits of these therapies, particularly when used in the same patient population. Therefore, we did not estimate cost-effectiveness for a specific product, but instead generally for transthyretin stabilizing agents as a drug class along with best supportive care compared to best supportive care alone. Furthermore, results from vutrisiran were released in June 2024 and the evidence suggests vutrisiran is superior to placebo and has additive effects to tafamidis; however, the granularity of the published results were not sufficient to incorporate vutrisiran in our model at this time. See Supplement E1.3 for additional detail on treatment strategies.

The modeled population was informed by the more recently conducted ATTRibute-CM [acoramidis] clinical trial to reflect the modern characteristics of the ATTR-CM patient population.[53] See Supplement Section E1.4 for a description of the modeled population.

The model structure was based on New York Heart Association (NYHA) Functional Classification, including health states NYHA Class I, NYHA Class II, NYHA Class III, NYHA Class IV, and death as a terminal state (Figure 2) The NYHA Functional Classification is a widely used heart failure severity classification system based on a clinician's assessment of a patient's functional capacity.[55] Given the association of NYHA functional class with health-related quality of life (HRQoL) and survival, and the established use of the NYHA Functional Classification in previous heart failure economic models, we defined health states by NYHA functional class, rather than using a HRQoL measure to define health states (i.e., the Kansas City Cardiomyopathy Questionnaire [KCCQ]).[51,52]

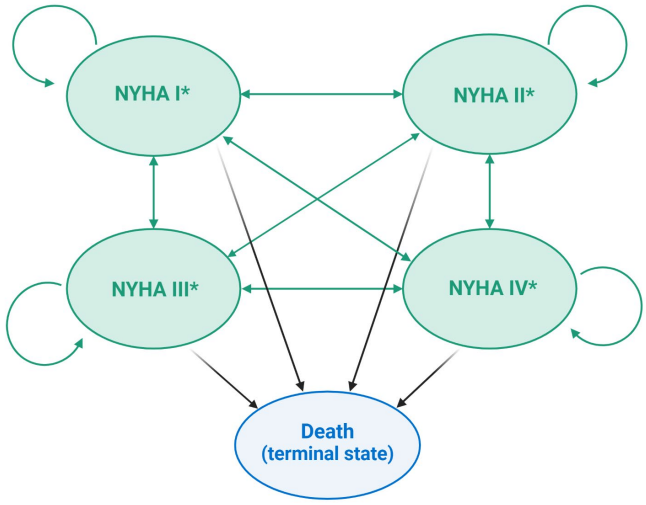
Transition probabilities, indicating differential progression through NYHA functional class, were derived from publicly available ATTR-ACT [tafamidis] trial data, due to lack of publicly available data for acoramidis. We assumed clinical efficacy, in terms of HF progression, was equal across transthyretin stabilizing agents (acoramidis and tafamidis). Improvements in functional class (e.g., from NYHA Class IV to NYHA Class III) and transitions across more than one functional class in one cycle (e.g., from NYHA Class I to NYHA Class III) were plausible. Cardiovascular-related hospitalizations were incorporated as a transient event experienced by a proportion of alive individuals, stratified by NYHA functional class health state, to capture the differential rate, cost, and disutility of cardiovascular-related hospitalizations when ATTR-CM is treated with and without transthyretin stabilizing treatment. Liver or heart transplant events were not modeled due to the

rarity of occurrence and lack of data on the effect size of the ATTR-CM disease modifying therapies on transplant rates.

Individuals could discontinue treatment at rates observed in the ATTRibute-CM [acoramidis] clinical trial, and those discontinuing treatment then followed the (placebo) comparator NYHA class progression and associated transition probabilities. Individuals remained in the model until death. Individuals could transition to the death state due to all-causes or ATTR-CM-specific mortality from any of the living health states. ATTR-CM-specific mortality was calibrated to the survival rates observed in the ATTRibute-CM [acoramidis] clinical trial.

The outcomes of total life years (LY) gained, total quality-adjusted life years (QALYs) gained, total equal value life years (evLY) gained, total costs, and cumulative time spent in NYHA Class I and II were calculated over a lifetime horizon, with costs and health outcomes discounted at 3% per year, and costs inflated to the 2024 Q1 US dollar. The model cycle length was 6 months, to align with clinical data and previously published economic models.[52,56]

**Figure 4.1. Model Schematic**




NYHA: New York Heart Association
* Each NYHA functional class health state includes a potential for a hospitalization event, with different probabilities of hospitalization for each NYHA functional class.

## 4.2. Key Model Assumptions and Inputs

Given the lack of direct comparative evidence and to address the differences in patient populations between the ATTRibute-CM [acoramidis], and ATTR-ACT [tafamidis] clinical trials, a 'transthyretin

stabilizing agent' class effect strategy was adopted, and associated model assumptions are detailed below.

## Model Assumptions

The key model assumptions used to evaluate transthyretin stabilizing agents in treating ATTR-CM are presented in Table 4.1. These assumptions were based on clinical trial data, expert opinion, and prior modeling studies.

**Table 4.1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| **Clinical Efficacy Data** | |
| **The transthyretin stabilizing agent class, comprised of tafamidis and acoramidis (which are assumed equivalent), is the modeled intervention.** | Due to the sparseness of granular acoramidis clinical efficacy data and insufficient evidence to assess within-class differences, the two treatment strategies were grouped into a "transthyretin stabilizing agent" class. With this approach, acoramidis and tafamidis were assumed equivalent in clinical effectiveness, hospitalization rates, discontinuation rates, costs, and mortality. |
| **Treatment efficacy was defined by observed progression through the NYHA functional class health states and was assumed equivalent for acoramidis and tafamidis.** | Based on clinical expert opinion and lack of evidence suggesting otherwise, the effect of transthyretin stabilizing treatment on progression through NYHA functional class health states was assumed equal for acoramidis and tafamidis. Transition probabilities are publicly available and were utilized to model transthyretin stabilizing agent class plus best supportive care compared to best supportive care alone.[57] |
| **Tafamidis efficacy data (NYHA functional class progression) was based on pooled results from the 20 mg and 80 mg once daily tafamidis arm of the trial.** | The ATTR-ACT [tafamidis] trial was sufficiently powered to detect a difference between pooled intervention (20 mg and 80 mg daily doses) and placebo populations.[54] It is worth acknowledging that in follow-on studies, after randomization was broken, there is suggestive evidence that the 80 mg dose was more effective. However, since randomization was broken, this evidence is not as strong as that seen within the trial period.[37] Therefore, this population, with a larger combined sample size and randomization preserved, provides the most appropriate evidence. The current recommended dose of tafamidis is 61 mg free acid once daily, which is bioequivalent to 80 mg once daily. |
| **Cardiovascular-related hospitalizations were extracted from tafamidis data and assumed equivalent for acoramidis and tafamidis** | Based on clinical expert opinion and lack of evidence on NYHA-specific hospitalization probabilities for acoramidis, we based the transthyretin stabilizing agent class cardiovascular-related hospitalization probabilities on tafamidis data.[57] |
| **Utility** | |
| **Health state utilities for each NYHA functional class were assumed equal for the transthyretin stabilizing agent class and best supportive care comparator arms.** | There was no statistically significant difference in utility values, stratified by NYHA functional class, between the treatment and placebo group, based on non-overlapping confidence intervals.[54] However, the reported clinical trial utility values for NYHA Class I were higher than the estimated national average utility at age 70 (0.82); therefore, we subtracted an |

| | |
|---|---|
| | adjustment factor to deflate the observed utility values to reflect national estimates while preserving the interval difference between NYHA classes.[54,58] |
| **Costs and Resource Use** | |
| **Transthyretin stabilizing treatments were added-on to best supportive care.** | Best supportive care included management of symptomatic heart failure and encompassed all therapies patients may receive until death, such as diuretics, treatment of arrhythmias (e.g., atrial fibrillation), and palliative care. |
| **Model Structure** | |
| **Patients discontinued transthyretin stabilizing treatment when they progress to NYHA Class IV.** | Individuals with NYHA Class IV were excluded from clinical trials (ATTR-ACT [tafamidis] and ATTRibute-CM [acoramidis]), and thus efficacy and safety data is lacking. Clinical experts suggest discontinuing transthyretin stabilizing treatment in the most symptomatic disease stages (i.e., NYHA Class IV). Therefore, we assumed patients transitioning to NYHA Class IV discontinued treatment and incurred no treatment-related costs. |
| **The effect of adverse events was incorporated only as treatment discontinuation, with no effect on costs or utilities.** | Adverse events were mild and generally similar between treatment and comparator groups in clinical trials. Furthermore, cardiac-related adverse reactions are assumed to be reflected in ATTR-CM disease progression. Therefore, applying additional costs and disutilities for adverse events could lead to double counting. We incorporated discontinuation of treatment due to adverse events, but did not include costs and disutilities associated with adverse events. |

## Model Inputs

The analytic base-case model was conducted from the health care sector perspective, focusing on direct medical costs only. Key model inputs are presented in Table 4.2. While data from the more recent ATTRibute-CM [acoramidis] clinical trial was preferred, clinical inputs based on the ATTR-ACT [tafamidis] in published literature were used where ATTRibute-CM [acoramidis] data was not available to reflect the transthyretin stabilizing agent class. For additional details on model inputs, please refer to the Supplement Section E2.

**Table 4.2. Key Model Inputs**

| Input | Transthyretin Stabilizing Agent Class + Best Supportive Care Value | Best Supportive Care Alone Value | Source |
|---|---|---|---|
| **Clinical Inputs** | | | |
| **Progression through NYHA functional class** | **[Please see Supplementary Tables E1 and E2]** | | |
| **Discontinuation Rates** | 1.9% | n/a | ATTRibute-CM [acoramidis][53] |
| **Hospitalization Rates** | | | |
| **NYHA Class I** | 10% | 31% | French National Authority for Health (HAS)[57] |
| **NYHA Class II** | 27% | 36% | |
| **NYHA Class III** | 77% | 81% | |
| **NYHA Class IV** | 149% | 33% | |
| **Mortality Hazard Ratio** | | | |
| **NYHA Class II v. NYHA Class I Mortality (HR)** | 1.78 | 1.78 | JMO Arnold 2013[59,60] |
| **NYHA Class III v. NYHA Class I Mortality (HR)** | 3.51 | 3.51 | |
| **NYHA Class IV v. NYHA Class I Mortality (HR)** | 5.74 | 5.74 | |
| **ATTR-CM Specific Mortality (HR)** | 1.18 | 1.18 | Calculated from ATTR-ACT [tafamidis] clinical trial[54] |
| **Calibrated Treatment Mortality Effect (HR for treatment compared to standard care alone)** | 0.58 | 1 | |
| **Cost Inputs** | | | |
| **Drug Cost Inputs (annual)** | $194,291 | $0 | RED BOOK Federal Supply Schedule |
| **Annual Background Costs (including supportive care)** | | | |
| **NYHA Class I** | $5,822 | $5,822 | Wang 2023[61] |
| **NYHA Class II** | $8,259 | $8,259 | |
| **NYHA Class III** | $12,388 | $12,388 | |
| **NYHA Class IV** | $20,417 | $20,417 | |
| **Hospitalization Costs (per admission)** | | | |
| **NYHA Class I** | $15,292 | $15,292 | Wang 2023[61] |
| **NYHA Class II** | $8,700 | $8,700 | |
| **NYHA Class III** | $8,847 | $8,847 | |
| **NYHA Class IV** | $10,521 | $10,521 | |
| **Health State Utility Inputs** | | | |
| **NYHA Class I** | 0.82 | 0.82 | Adjusted from ATTR-ACT [tafamidis]<br><br>Maurer 2018, Shaw 2005, Jiang 2021[54,58,62] |
| **NYHA Class II** | 0.729 | 0.729 | |
| **NYHA Class III** | 0.633 | 0.633 | |
| **NYHA Class IV** | 0.333 | 0.333 | |

| Disutility per Hospitalizations (per ~4-day hospitalization) | | | |
|---|---|---|---|
| **NYHA Class I** | -0.04 | -0.04 | Griffiths 2014[117] |
| **NYHA Class II** | -0.07 | -0.07 | |
| **NYHA Class III** | -0.1 | -0.1 | |
| **NYHA Class IV** | -0.29 | -0.29 | |

### *Clinical Inputs*

The key clinical inputs for this model included NYHA functional class progression (represented by health state transitions probabilities), cardiovascular hospitalization rates, discontinuation due to adverse event, and all-cause/ATTR-CM HF mortality. We incorporated no additional impact for adverse events beyond discontinuation. Additional details on the clinical inputs are present in the supplement.

Mortality was modeled as all-cause and disease-specific mortality. Disease-specific mortality was obtained by applying NYHA functional class-specific and ATTR-CM-specific mortality hazard ratios, and an additional treatment effect was incorporated based on the survival benefit observed in the ATTR-ACT [tafamidis] clinical trial treatment arm.[54] Additional details on mortality are presented in the supplement.

### *Economic Inputs*

The key economic inputs for this model included medication costs, background best supportive care costs, and hospitalizations cost. The transthyretin stabilizing agent price was based on the tafamidis list price, calculated from the average RED BOOK reported wholesale acquisition cost (WAC) across all applicable formulations. Patient and caregiver costs (presented in the supplement) were considered in the societal perspective analysis only. Additional details on the economic inputs are presented in the supplement.

### *Health State Utility Inputs*

Utility values for each NYHA functional class health state were derived from a targeted systematic review of publicly available literature, manufacturer submitted data, and estimates from prior heart failure treatment models.[51-54] The health state utility values for each NYHA functional class were equal for the treatment and comparator arms of the model. Additionally, we applied a disutility for individuals experiencing cardiovascular-related hospitalization per cycle. Additional details on the utility inputs are presented in the supplement.

## 4.3. Results

### Base-Case Results

The discounted total costs, life years, quality-adjusted life years (QALYs), equal-value life years (evLYs), and cumulative time spent in NYHA Class I and II for transthyretin stabilizing agent plus best supportive care treatment compared to best supportive care alone are presented in Table 4.3. Transthyretin stabilizing agent plus best supportive care resulted in more costs, driven by drug costs, and improved health outcomes compared to supportive care alone. Undiscounted base-case results are presented in the supplement.

Total number of hospitalizations was found to be higher with transthyretin stabilizing agent plus best supportive care versus the best supportive care alone (0.45 vs. 0.42 average hospitalizations per life-year). This is due to being in NYHA class IV for longer durations with the invention versus the comparator since the intervention has higher rates of hospitalizations in NYHA class IV.

**Table 4.3. Discounted Results for the Base-Case for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs | Years In NYHA Class I and II |
|---|---|---|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent + Best Supportive Care** | $634,000 | $32,000 | $38,000 | $703,000 | 3.7 | 1.6 | 2.2 | 2.4 |
| **Best Supportive Care Alone** | $0 | $22,000 | $30,000 | $52,000 | 2.9 | 1.3 | 1.3 | 1.7 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

Table 4.4 presents the discounted incremental cost-effectiveness ratios, in cost-per-QALY gained, cost-per-LY gained, and cost-per-evLY gained, for transthyretin stabilizing agent plus best supportive care treatment compared to best supportive care alone.

**Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case**

| Treatment | Comparator | Cost per QALY Gained* | Cost per evLY Gained* | Cost per Life Year Gained* | Cost per Year in NYHA Class I and II* |
|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent + Best Supportive Care** | Best Supportive Care alone | $1,896,000 | $740,000 | $720,000 | $844,000 |

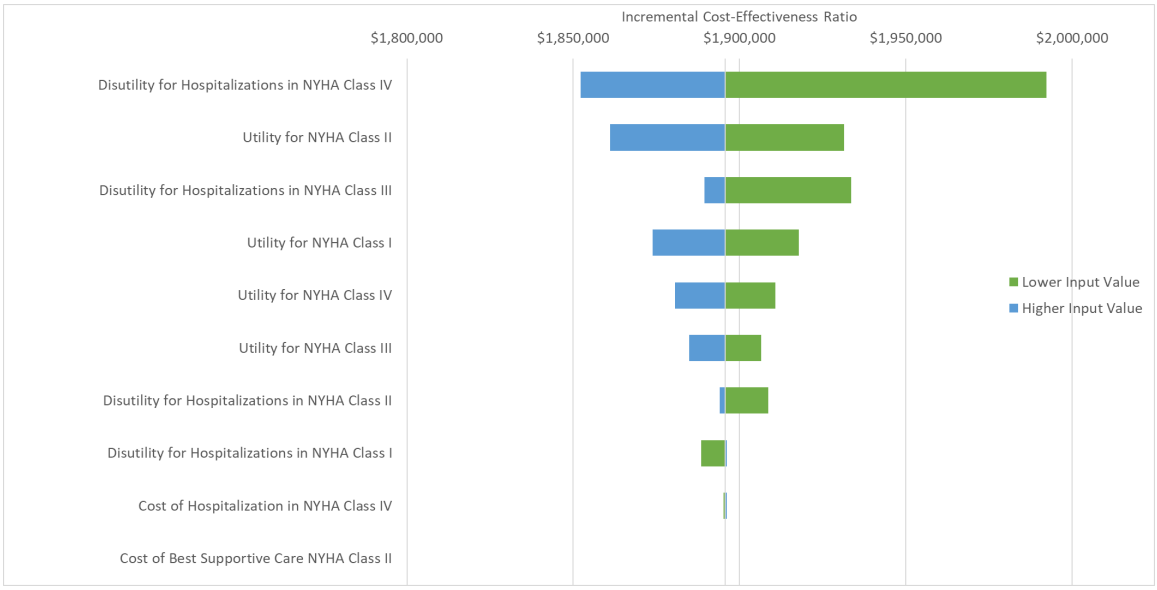
evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

## Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in findings. The model results were most sensitive to utility and inputs for the NYHA functional class health states, and disutility inputs for hospitalizations. Figure 4.2 shows the tornado diagram, additional details are in the supplement.

**Figure 4.2. Tornado Diagram**




NYHA: New York Heart Association, WAC: Wholesale Acquisition Costs

* Based on tafamidis pricing

Tables 4.5 present the probability of transthyretin stabilizing agents being cost-effective at common thresholds of $50,000, $100,000, and $150,000 per QALY and evLY gained, respectively. At the input price for the interventions, none of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios beneath these commonly used thresholds. The cost-effectiveness plane and acceptability curve are presented in the supplement.

**Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**

| | Cost Effective at $50,000 per QALY Gained* | Cost Effective at $100,000 per QALY Gained* | Cost Effective at $150,000 per QALY Gained* | Cost Effective at $200,000 per QALY Gained* |
|---|---|---|---|---|
| **Transthyretin Stabilizing Agent** | 0% | 0% | 0% | 0% |

QALY: quality-adjusted life year

* Based on tafamidis pricing

## Scenario Analyses

We conducted numerous scenario analyses to examine uncertainty and potential variation in the findings. In our modified societal perspective scenario analysis (#1), we included patient and caregiver productivity costs in the analysis. In the tafamidis trial population scenario analysis (#2), the population characteristics (age, gender, and baseline NYHA functional class proportions) emulated the ATTR-ACT [tafamidis] clinical trial. In the mortality calibrated to ATTRibute-CM [acoramidis] clinical trial scenario analysis (#3), we calibrated survival in our mode to match the ATTRibute-CM [acoramidis] clinical trial data. In the unadjusted utility values scenario analysis (#4), we used the utility values as reported in the ATTR-ACT [tafamidis] clinical trial, without adjusting to the population averages. We also conducted scenario analyses (#5-7) where we systematically excluded hospital and/or supportive care costs, to observe the impact of non-drug costs in the results.

Incremental cost-effectiveness ratio results for transthyretin stabilizing agent plus best supportive care treatment compared to best supportive care alone are presented in Table 4.7, and additional details are in the supplement.

**Table 4.7. Scenario Analysis Results**

| Treatment | Cost per QALY Gained* | Cost per evLY Gained* | Cost per Life Year Gained* |
|---|---|---|---|
| **Base-Case Results** | $1,896,000 | $740,000 | $720,000 |
| **Scenario Analysis 1: Modified Societal Perspective** | $2,108,000 | $823,000 | $801,000 |
| **Scenario Analysis 2: Mortality Calibrated to ATTRibute-CM [acoramidis] Clinical Trial** | $2,724,000 | $1,158,000 | $1,079,000 |
| **Scenario Analysis 3: Tafamidis Trial Population** | $1,846,000 | $710,000 | $692,000 |
| **Scenario Analysis 4: Unadjusted Utility Values** | $1,697,000 | $740,000 | $708,000 |
| **Scenario Analysis 5: Exclude Non-Drug Costs** | $1,845,000 | $720,000 | $701,000 |
| **Scenario Analysis 6: Exclude Hospital Costs** | $1,868,000 | $729,000 | $710,000 |
| **Scenario Analysis 7: Exclude Supportive Care Costs** | $1,873,000 | $731,000 | $712,000 |

*Based on tafamidis pricing

## Threshold Analyses

Threshold analyses were conducted to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds for QALY gained (Table 4.8) and evLY gained (Table 4.9).

**Table 4.8. QALY-Based Threshold Analysis Results**

| | Annual WAC | Annual Net Price | Annual Price to Achieve $50,000 per QALY Gained | Annual Price to Achieve $100,000 per QALY Gained | Annual Price to Achieve $150,000 per QALY Gained | Annual Price to Achieve $200,000 per QALY Gained |
|---|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent** | $267,987 | $194,291 | $0 | $5,200 | $10,400 | $16,000 |

QALY: quality-adjusted life year , WAC: wholesale acquisition cost

**Table 4.9. evLY-Based Threshold Analysis Results**

| | Annual WAC | Annual Net Price | Annual Price to Achieve $50,000 per evLY Gained | Annual Price to Achieve $100,000 per evLY Gained | Annual Price to Achieve $150,000 per evLY Gained | Annual Price to Achieve $200,000 per evLY Gained |
|---|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent** | $267,987 | $194,291 | $8,500 | $22,400 | $36,000 | $50,000 |

evLYs: equal value of life years gained, WAC: wholesale acquisition cost

## Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate the face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also offered to share the model with the relevant manufacturers for external verification around the time of publishing this draft report. Finally, we compared results to other cost-effectiveness models in this therapy area, noting that the incremental life years gained for the intervention were smaller compared to other studies. Additionally, to check the validity of our model in terms of mortality, we ensured our calculated treatment effect hazard ratio (0.58) was within the published confidence interval from the ATTR-ACT [tafamidis] clinical trial (0.51-0.96).

## Uncertainty and Controversies

The uncertainties and controverses in this analysis include incorporating a class-effect for transthyretin stabilizing agents, limited ATTR-CM-specific mortality, disease progression, and cost data, and the inclusion of vutrisiran.

Given the limited amount of publicly available data on acoramidis to inform a differentiated effect compared to tafamidis, we estimated the impact of transthyretin stabilizing agents as a class rather than as individual medications. This decision was also driven by the availability of stage-specific clinical data from the older ATTR-ACT [tafamidis] clinical trial, which was not available for the ATTRibute [acoramidis] study population; we note that the ATTR-ACT [tafamidis] clinical trial was more advanced in their stage of disease, and clinical experts voiced this may not reflect the current ATTR-CM population as screening has improved. Therefore, in an attempt to model the effects of treatment in a current ATTR-CM population given available data, we melded the clinical efficacy data from ATTR-ACT [tafamidis] and population characteristics from the ATTRibute [acoramidis] trial. To make comparisons at the medication-level rather than class-level, studies with granular NYHA functional class specific disease progression, hospitalization rates, costs, and survival data would be necessary to inform the model parameters and ascertain a difference between transthyretin stabilizing medications.

Given the limited availability of contemporary, real-world, population-level data relating to ATTR-CM disease progression, identifying ATTR-CM specific mortality, disease progression, and cost data was challenging. For mortality estimation, reported mortality rates in the ATTRribute [acoramidis] clinical trial were significantly better than all-cause average population mortality (we estimated a standardized mortality ratio [SMR] of 0.8), and was inconsistent with prior findings and discussions with clinical experts. Therefore, we estimated mortality using the older ATTR-ACT [tafamidis] clinical

trial, and found a SMR of ~1.18 for ATTR-CM and a relative risk of 0.58 for the treatment group, which aligns better with prior research. To test how our mortality assumption impacts the value of the transthyretin stabilizing agent class, we conducted a scenario analysis modeling the ATTRibute trial [acoramidis] clinical trial population and mortality estimates to test the uncertainty. We find baseline survival changes, but the incremental life years and QALYs gained are similar between approaches. However, the overall health care costs decline and incremental change in costs is smaller which improves the estimated value of treatments.

Furthermore, uncertainty around our disease progression and cost inputs exists. We assumed the disease progression data (transition probabilities), publicly available based on the ATTR-ACT [tafamidis] clinical trial, from the placebo arm represented the general NYHA functional class progression of ATTR-CM over time, and the treatment arm incorporated the treatment effect in NYHA functional class progression of ATTR-CM over time; it is known that disease progression can be more rapid in more advanced disease and these transition probabilities should help capture this effect. Given the lack of publicly available transition probabilities indicating ATTR-CM disease progression with and without treatment for acoramidis, we assume the ATTR-ACT [tafamidis] clinical trial represented the transthyretin stabilizing agent class. With additional data on acoramidis, we may have been able to conduct a drug-level, rather than class-level analysis. Furthermore, ATTR-CM specific health care costs by NYHA functional class were not available in the published literature, and we instead used estimates for obstructive hypertrophic cardiomyopathy (OCH). Non-ATTR-CM specific data may increase uncertainty in our results.

Based on recent findings from the HELIOS-B phase 3 trial, vutrisiran is likely an effective treatment. Given the limited amount of data that is available (primary composite outcome of all-cause mortality and recurrent cardiovascular [CV] events [HR 0.718, p-value 0.0118] from the primary trial and all-cause mortality [HR 0.645, p<0.025] in an open-label extension study), we have not been able to incorporate this new treatment into our results. Additionally, as vutrisiran is not the same class of treatments as acoramidis and tafamidis, and we are not able to fold in these results to the current model.

## 4.4 Summary and Comment

Our analyses suggest that transthyretin stabilizing agents generate greater length of life and quality of life with much greater costs. At a net price of $194,291 per year, the incremental cost-effectiveness ratios far exceed commonly used thresholds.

# 5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

**Table 5.1. Benefits Beyond Health and Special Ethical Priorities**

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **There is substantial unmet need despite currently available treatments.** | There is systematic, widespread underdiagnosis of ATTR-CM. In addition, although there is one approved therapy currently, cost and access are tremendous barriers for many patients with ATTR-CM.<br><br>To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below:<br>evLY shortfalls:<br>• Absolute evLY shortfall: 6.29<br>• Proportional evLY shortfall: 72.89%<br>QALY shortfalls:<br>• Absolute QALY shortfall: 6.54<br>• Proportional QALY shortfall: 79.52%<br>The absolute and proportional shortfalls represent the total and proportional health units of remaining quality-adjusted life expectancy, respectively, that would be lost due to untreated illness. For this analysis, untreated illness represented no additional treatment beyond a stabilizing agent (i.e., patients were assumed to be receiving a stabilizing agent). Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews. |
| **This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.** | Much about the epidemiology of ATTR-CM remains unclear, given the problems with underdiagnosis, preventing us from calculating the health improvement distribution index (HIDI). However, in the United States, a lower proportion of Black than White patients enroll in clinical trials. |

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.** | The improvement in health status observed with new ATTR-CM therapies could reduce burden on caregivers. |
| **The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.** | The mechanism of acoramidis is similar to tafamidis, and both are taken orally. Vutrisiran is subcutaneous. There are no specific reasons to believe that the differences in mechanism or method of delivery of tafamidis/acoramidis versus vutrisiran would improve access to treatment. |

ICER did not calculate the HIDI in this review due to uncertainty surrounding the prevalence of ATTR-CM in specific racial subpopulations and the overall United States population. While an estimated 3 to 4% of Black Americans are carriers of the TTR variant, V142I it's crucial to note that this does not guarantee disease development.[63-65] Likewise, the actual prevalence of ATTR-CM within the US population remains unclear, with estimates ranging from 50,000-200,000 and potentially much higher.

Despite our inability to calculate the HIDI, we recognize the disproportionate burden of the disease in Black Americans.[66] Carriers of the V142I variant have worse clinicals outcomes (increased heart failure hospitalization and mortality) and earlier manifestation of disease. A recent study projected that for a cohort of Black Americans aged 50 to 95 who carry the V142I variant, the cumulative loss of life years associated with this variant is close to 1 million years. Thus, efforts such as genomic testing, increased clinical trial recruitment of underrepresented groups, and earlier treatment with disease modifying treatments are crucial.[67]

# 6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

# 7. Potential Budget Impact

A potential budget impact analysis was not conducted for transthyretin stabilizing agents. Our model analysis plan expected to compare acoramidis to the management of ATTR-CM without treatment. We noted in our analysis plan that if the relative effectiveness and price of acoramidis compared to tafamidis is similar, the budget impact of acoramidis replacing tafamidis is likely to be minimal. There was insufficient data to differentiate between acoramidis and tafamidis in the cost-effectiveness analysis, and as such, the treatment efficacy and cost of both agents were assumed to be the same. It is expected that acoramidis will compete with tafamidis for market share among the same eligible patient population, so under conditions of the same efficacy and cost, there would be no impact on payer budgets. Should evidence emerge before the Final Evidence Report is published to differentiate between the two agents, we will follow the methods described in our Model Analysis Plan to conduct our analysis. As stated in Section 4, there was also insufficient data to model the long-term cost-effectiveness of vutrisiran in addition to a stabilizing agent compared to a stabilizing agent alone, and as such, the potential budgetary impact of vutrisiran was not evaluated.

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# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

**6 Minute Walk Distance:** The 6-minute walk distance (6MWD) is a measure of cardiopulmonary function, in which patients walk as far as possible for six minutes on flat ground. The 6MWD is used to assess response to exercise in individuals with chronic pulmonary and/or cardiac disease.[68]

**Kansas City Cardiomyopathy Questionnaire (KCCQ):** This is a disease-specific patient-reported outcome specific for patients with heart failure. The instrument is based on a self-administered 23-item questionnaire that quantified patient-reported physical limitations, symptoms, self-efficacy, social interference, and quality of life.

**NT-proBNP:** N-terminal pro B-type natriuretic peptide (NT-proBNP) is a prohormone produced by the heart, found usually at small levels in the bloodstream. NT-proBNP tests draw a blood sample to assess for raised levels of the protein, which may signal left ventricular dysfunction or heart failure in a patient.[69]

**EQ-5D:** A patient-completed health status instrument consisting of 2 parts. In the first, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain, or discomfort, and anxiety or depression). These scores are used to calculate a single EQ-5D-3L Index Score. In the second, patients rate their current health state on the EQ visual analog scale (EQ VAS), with end points labeled "best imaginable health state" and "worst imaginable health state".[70]

**New York Heart Association (NYHA) Functional Classification:** The NYHA classification is a clinician-assessed measure of functional status broadly applicable to patients with cardiac disease.[71]

| | |
|---|---|
| **Class 1** | Patients with cardiac disease but without limitations of physical activity |
| **Class 2** | Patients with cardiac disease resulting in slight limitation of physical activity |
| **Class 3** | Patients with cardiac disease resulting in marked limitation of physical activity |
| **Class 4** | Patients with cardiac disease resulting in inability to exert physically at all and/or the presence of symptoms at rest |

**Win-ratio:** A win ratio is a statistic used in comparative effectiveness research. To generate a win-ratio, patients in control and treatment groups are matched based on risk profile. For each matched

pair, patients are labelled a 'winner' or a 'loser' depending on who reaches the outcome first. The proportion of comparisons for which active treatment wins over placebo divided by the proportion of comparisons for which placebo wins, equals the win-ratio.[72] An advantage of reporting a win ratio is that it can integrate information about multiple clinical endpoints in one summary statistic.

**Wild-type transthyretin cardiac amyloidosis:** Wild-type transthyretin amyloidosis (ATTRwt), results from the buildup of misfolded wild-type (normal) transthyretin. However, the exact process by which normal transthyretin causes the formation of harmful deposits is unclear.[73]

**Variant transthyretin cardiac amyloidosis:** Hereditary transthyretin amyloidosis (ATTRv/ATTRm) is caused due to genetic mutations within the transthyretin gene (TTR), that predispose the tetrameric structure of transthyretin to instability, misfolding, and deposition.[73]

*Other Relevant Definitions*

**Absolute and Proportional Shortfalls:** Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[74] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[75,76] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

**Health Improvement Distribution Index (HIDI)**: The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by

achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

## A2. Potential Cost-Saving Measures in ATTR-CM

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for ATTR-CM (e.g. hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of ATTR-CM beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with ATTR-CM that could be reduced, eliminated, or made more efficient.

Although underdiagnosis of ATTR-CM is well established, clinical experts also raised concerns about some overdiagnosis related to heterogenous protocols for bone scintigraphy in community practice. Addressing overdiagnosis is challenging, given that underdiagnosis is a difficult and consequential problem as well. Risk-stratification of "red flags" on echocardiography and using higher-specificity bone scintigraphy protocols could potentially improve both sensitivity and specificity of the diagnosis of ATTR-CM.[77]

Clinical guidelines support the assessment of serum light chains before bone scintigraphy testing. However, many patients undergo bone scintigraphy testing without prior serum light chain testing or despite positive serum monoclonal protein test results. Increased awareness and education among physicians regarding paraprotein evaluation prior to PYP scanning is still needed to prevent misdiagnosis, delayed diagnosis, and unnecessary health care costs.[78] In some cases, patients with AL amyloidosis or no cardiac amyloidosis at all are misdiagnosed as having ATTR-CM and receive tafamidis.[79] Treating AL amyloidosis with tafamidis can cause harm by delaying therapies that are

effective for AL amyloidosis (such as stem cell transplant). Furthermore, the use of tafamidis in individuals who do not have amyloid cardiomyopathy at all or AL amyloidosis will increase costs without health benefits.

## A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive any feedback on this specific inquiry.

# B. Patient Perspectives: Supplemental Information

## B1. Methods

The research team conducted two patient focus groups. Between these two focus groups, eight patients participated. These eight patient participants represented a combination of three different patient groups (Amyloidosis Research Consortium, Mackenzie's Mission, and Amyloidosis Support Groups) and an individual patient. The research team also received one patient story through ICER's Share Your Story Form from a patient who was also one of the participants in a focus group.

The patient feedback was directly informative to this report by adding critically important qualitative context relevant to access to care and treatments in ATTR-CM. Nearly all patients reported frustration with delays in the initial diagnosis, given that many caregivers are not familiar with the syndrome. After diagnosis, patients nearly all reported difficulties affording tafamidis and reported huge differences in experience with patient assistance programs. Many patients not close to academic referral centers also reported difficulties with access to their specialists after diagnosis.

# C. Clinical Guidelines

Clinical guidelines, consensus statements, and expert consensus decision pathways on cardiac amyloidosis have been published by a variety of professional societies.

## 2023 World Heart Federation Consensus on Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM)[80]

This consensus document from the World Heart Foundation provides detailed recommendations on definitions in cardiac amyloidosis and interpretation of cardiac imaging when cardiac amyloidosis is suspected. The document reviews the role of traditional heart failure and antiarrhythmic medications in cardiac amyloidosis. For example, the document specifies:

Diuretics: loop diuretics and mineralocorticoid receptor antagonists can reduce congestion and edema

Beta blockers and calcium channel blockers: these agents often worsen conduction disturbances and low cardiac output and are generally avoided

Digoxin: since digoxin binds to amyloid fibrils, digoxin has traditionally been considered contraindicated in amyloidosis although in some cases can be used cautiously

Sodium-glucose cotransporter type 2 inhibitors: role in amyloidosis needs to be better defined

Angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blocker and angiotensin-receptor neprilysin inhibitors: no evidence to support use and can cause hypotension

Amiodarone, dofetilide, and sotalol: can be used for rhythm control in atrial fibrillation in cardiac amyloidosis

Anticoagulation: generally recommended when atrial fibrillation coexists with cardiac amyloidosis

The document notes strong evidence from the ATTR-ACT trial supporting use of tafamidis and notes the importance of accessibility for clinical decision making with tafamidis. "Eligibility for treatment can vary between different countries and even between different institutions in the same country, leading to unfair access inequalities. The high price of tafamidis is another limiting factor making it the most expensive cardiovascular medication listed." The document also discusses acoramidis in the context of the ATTRibute-CM trial (which was ongoing at the time) and discusses the potential benefit of diflunisal. Finally, the document also summarizes the state of evidence for transthyretin

silencers including patisiran, vutrisiran, inotersen, eplontersen, and reviews the potential for gene editing through CRISPR/Cas9 to reduce TTR levels.

The consensus document also discusses patient perspectives including the consequences of delayed diagnosis including emotional distress as well as clinical deterioration in the pre-diagnosis phase. In the diagnosis phase, patients report high amounts of stress and value the amount of time health professionals spend with patients. In the treatment phase, the document notes substantial heterogeneity in access to tafamidis in different countries. The document also notes substantial distress after diagnosis related to the potential that family members may also be at risk for developing cardiac amyloidosis.

## 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee[81]

This expert consensus decision pathway notes the effectiveness of tafamidis as demonstrated in the ATTR-ACT trial and also discussed the favorable side effect profile. The document notes cost of tafamidis as the primary barrier and notes that challenges with navigating copayment assistance programs pose barriers to use the use of tafamidis by general cardiologists. The document notes that diflunisal has a similar chemical structure but is generally not as well tolerated and has a weaker evidence base for clinical efficacy. However, diflunisal is noted as a potential alternative to tafamidis for example for patients who cannot afford tafamidis.

## 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure[82]

The US multi-society clinical guidelines provide recommendations for both the evaluation and treatment of cardiac amyloidosis. In terms of evaluation, the guidelines recommend that patients for whom there is a clinical suspicion for cardiac amyloidosis should have screening for serum and urine monoclonal light chains with serum and urine immunofixation electrophoresis and serum free light chains (class 1, level of evidence B). For patients for whom there is a high level of clinical suspicion for cardiac amyloidosis without evidence of serum or urine monoclonal light chains, the guidelines recommend bone scintigraphy (class 1, level of evidence B). In patients for whom a diagnosis of ATTR-CM is made, the guidelines recommend genetic testing for TTR to distinguish hereditary ATTR-CM from wild-type ATTR-CM (class 1, level of evidence B).

In terms of treatment, the guidelines recommend that select patients with wild-type or hereditary ATTR-CM and NYHA class 1-3 symptoms should receive tafamidis to reduce cardiovascular morbidity and mortality (class 1, level of evidence B). For patients with cardiac amyloidosis and

atrial fibrillation, the guidelines recommend consideration of anticoagulation to reduce the risk of stroke regardless of traditional risk scores for cardioembolic stroke in atrial fibrillation (class 2a, level of evidence C). The guidelines note that although tafamidis is recommended with a class 1 guideline, tafamidis provides "low economic value" based on an estimate of >$180,000 per QALY gained.

## 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[83]

The guidelines recommend tafamidis for both hereditary and wild-type ATTR-CM when patient symptoms are NYHA class 1-2 (class 1, level of evidence B).

## 2021 Diagnosis and Treatment of Cardiac Amyloidosis: A Position Statement of the ESC Working Group on Myocardial and Pericardial Diseases

This statement proposes a therapeutic framework for ATTR-CM based on wild type or hereditary and presence or absence of polyneuropathy. In wild-type ATTR-CM, the statement proposes generally using tafamidis. In hereditary ATTR-CM, the statement also proposes generally using tafamidis when cardiomyopathy is dominant but considering patisiran as an alternative when polyneuropathy is also present.

## 2020 Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement of the Evaluation and Management of Patients with Cardiac Amyloidosis[84]

This joint position statement notes the efficacy of tafamidis in the ATTR-ACT trial, and the potential role of TTR silencing agents. The statement also notes that in individuals who have a mixed phenotype (cardiac and neurological involvement) the decision to use tafamidis or a TTR stabilizer should be individualized and is best made with interdisciplinary teams. The document also discusses a lack of evidence for different imaging strategies in cardiac amyloidosis and suggests imaging follow up intervals between 6-48 months.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS

#### *Population*

The population of focus for the review is adults with transthyretin amyloid cardiomyopathy (ATTR-CM).

Data permitting, we will evaluate the evidence for subpopulations defined by:

- ATTR-CM subtype (hereditary versus wild-type)
- Transthyretin variant (e.g., V142I, T60A)
- NYHA functional class at baseline (class I or II, class III or IV)
- Race or ethnic group
- Sex or gender
- Age

#### *Interventions*

The full list of interventions is as follows:

- (acoramidis) (BridgeBio Pharma)
- Vyndamax®/Vyndaqel® (tafamidis) (Pfizer Inc.)
- Amvuttra® (vutrisiran) (Alnylam Pharmaceuticals, Inc.)

### *Comparators*

Data permitting, we aim to compare interventions to each other and to no disease-specific treatment; this will be represented by the placebo arms of clinical trials in some circumstances, but we are aware that more recent trials have allowed some patients to receive open-label tafamidis.

### *Outcomes*

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality (e.g., all-cause, CV and non-CV related)
    - Cardiovascular-related hospitalization
    - Need for liver or heart-liver transplant
    - Change in exercise capacity (e.g., Six Minute Walk Distance)
    - Health related quality of life (e.g., Transthyretin Amyloidosis – Quality of Life Questionnaire [ATTR-QOL], Kansas City Cardiomyopathy Questionnaire [KCCQ])
        - Reduction in cardiac (e.g., fatigue, shortness of breath), neuropathic (e.g., muscle weakness, sexual dysfunction), and gastrointestinal symptoms
    - Adverse events including:
        - Treatment-related mortality
        - Serious adverse events
        - Treatment-related discontinuation
- Other Outcomes
    - Changes in cardiac related biomarkers (e.g., NT-proBNP)
    - Changes in serum transthyretin levels
    - Changes in echocardiographic parameters (e.g., tissue Doppler imaging)
    - Changes in amyloid burden (e.g., extracellular volume measurement)

### *Timing*

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

### *Settings*

All relevant settings will be considered, with a focus on outpatient settings in the United States.

**Table D1.1 PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review. |
| **ABSTRACT** | | |
| **Abstract** | 2 | See the PRISMA 2020 for Abstracts checklist. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of existing knowledge. |
| **Objectives** | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| **METHODS** | | |
| **Eligibility Criteria** | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
| **Information Sources** | 6 | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. |
| **Search Strategy** | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. |
| **Selection Process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Data Collection Process** | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. |
| **Data Items** | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. |
| **Study Risk of Bias Assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Effect Measures** | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **Synthesis Methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| **Reporting Bias Assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| **Certainty Assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| **RESULTS** | | |
| **Study Selection** | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. |
| **Study Characteristics** | 17 | Cite each included study and present its characteristics. |
| **Risk of Bias in Studies** | 18 | Present assessments of risk of bias for each included study. |
| **Results of Individual Studies** | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. |
| **Results of Syntheses** | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| **Reporting Biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **Certainty of Evidence** | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |
| **DISCUSSION** | | |
| **Discussion** | 23a | Provide a general interpretation of the results in the context of other evidence. |
| | 23b | Discuss any limitations of the evidence included in the review. |
| | 23c | Discuss any limitations of the review processes used. |
| | 23d | Discuss implications of the results for practice, policy, and future research. |
| **OTHER INFORMATION** | | |
| **Registration and Protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. |
| **Competing Interests** | 26 | Declare any competing interests of review authors. |
| **Availability of Data, Code, and Other Materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. |

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for ATTR-CM followed established best research methods.[85,86] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[87] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

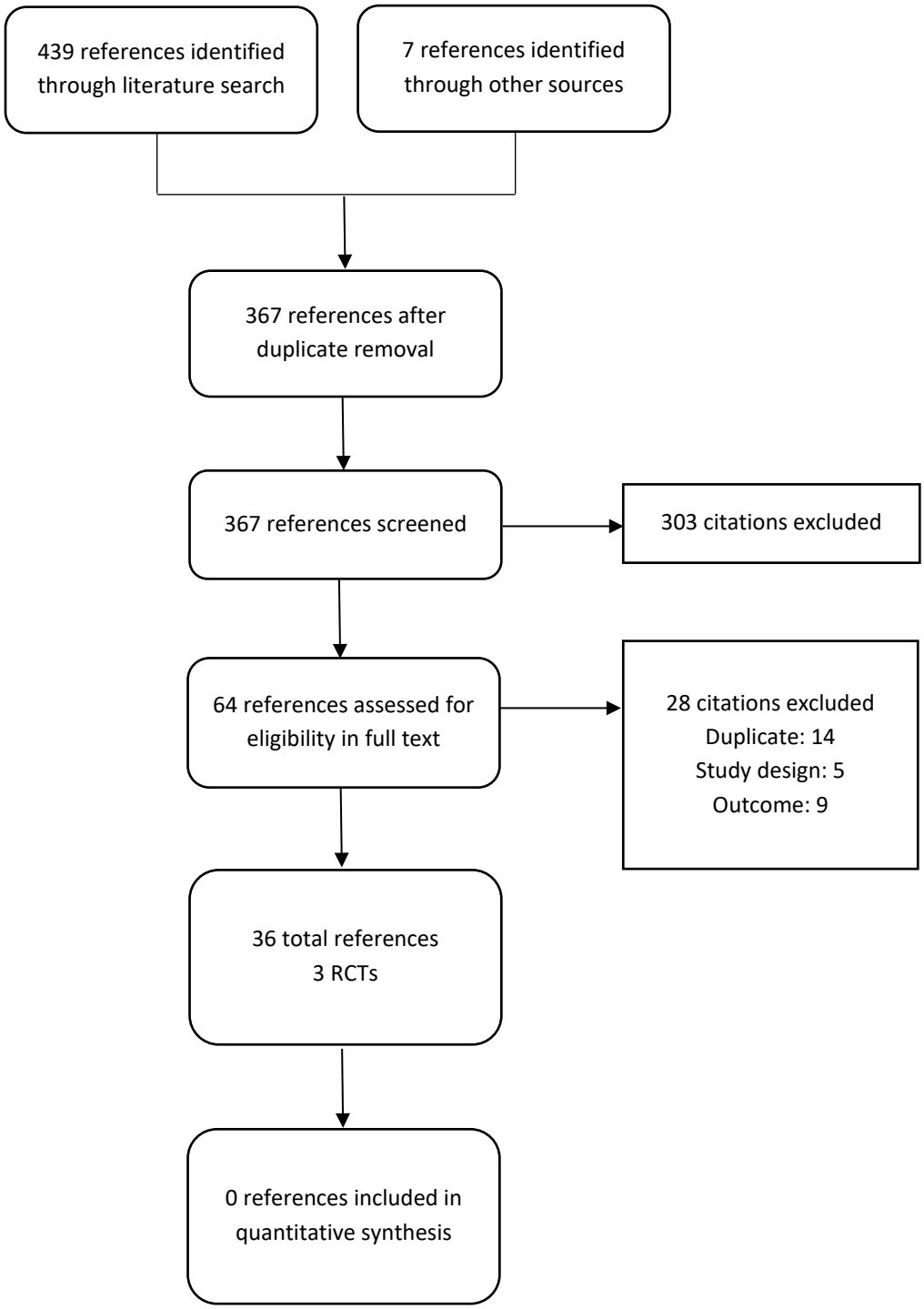
**Table D1.2 Search Strategy of EMBASE SEARCH**

| | |
|---|---|
| **1** | 'familial amyloid cardiomyopathy'/exp OR 'familial amyloid cardiomyopathy' |
| **2** | (‘cardiac amyloidosis’ OR ‘ATTR-CM’ OR ‘transthyretin amyloid cardiomyopathy’ OR ‘ATTR cardiomyopathy’ OR ‘hATTR-CM’ OR ‘TTR amyloid cardiomyopathy’ OR ‘ATTR amyloidosis with cardiomyopathy’ OR ‘hATTR amyloidosis with cardiomyopathy’ OR ATTRv OR ATTRwt):ti,ab |
| **3** | #1 OR #2 |
| **4** | tafamidis/exp OR tafamidis |
| **5** | (vyndamax OR vyndaqel OR ‘FX 1006A’):ti,ab |
| **6** | acoramidis/exp OR acoramidis |
| **7** | (AG10 OR ‘AG 10’):ti,ab |
| **8** | vutrisiran/exp OR vutrisiran |
| **9** | (amvuttra OR alnttrsc02):ti,ab |
| **10** | #4 OR #5 OR #6 OR #7 OR #8 OR #9 |
| **11** | #3 AND #10 |
| **12** | ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| **13** | #11 NOT #12 |
| **14** | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| **15** | #13 NOT #14 |
| **16** | #15 AND [English]/lim |

**Table D1.3 Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials**

| | |
|---|---|
| **1** | (“ATTR-CM” or “Cardiac amyloidosis” or “Transthyretin Amyloid Cardiomyopathy” or “ATTR cardiomyopathy” or ATTRv or ATTRwt or ATTRh or “TTR amyloid cardiomyopathy”).ti,ab |
| **2** | (Tafamidis or Vyndamax or Vyndaqel or “FX 1006A”).ti,ab |
| **3** | (Acoramidis or AG10 or “AG 10”).ti,ab |
| **4** | (Vutrisiran or Amvuttra or “ALN TTRsc02”).ti,ab |
| **5** | 2 or 3 or 4 |
| **6** | 1 and 5 |
| **7** | ("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt. |
| **8** | 6 not 7 |
| **9** | (animals not (humans and animals)).sh. |
| **10** | 8 not 9 |
| **11** | Limit 10 to English language |
| **12** | Remove duplicates from 11 |

**Figure D1.1 PRISMA flow Chart Showing Results of Literature Search for Tafamidis, Acoramidis, and Vutrisiran for ATTR-CM**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to tafamidis. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

## Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

## Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[86,88] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any

disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias****: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns****: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias****: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcome of all-cause mortality. See Table D1.3.

**Table D1.4. Risk of Bias Assessment**

| Studies | Randomization Process | Deviation from the Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Result | Overall Risk of Bias | Comment |
|---|---|---|---|---|---|---|---|
| **Acoramidis** | | | | | | | |
| **ATTRibute-CM** | Some risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk: The randomization process was slightly compromised due to unblinding of 6MWD outcomes at Month 12 for some staff. Additionally, the increased use of tafamidis from Month 12 onwards was likely driven by the lack of efficacy in the placebo arm, resulting in a higher percentage use compared to ACO. |
| **Tafamidis** | | | | | | | |
| **ATTR-ACT** | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | Low Risk | |

## Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[89] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5 below. Representation for each demographic category was evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

**Table D1.5. Demographic Characteristics and Categories**

| Demographic Characteristics | Categories |
|---|---|
| **1. Race and Ethnicity** | Racial categories:<br>• White<br>• Black or African American<br>• Asian<br>• American Indian and Alaskan Native<br>• Native Hawaiian and Other Pacific Islanders<br>Ethnic Category:<br>• Hispanic or Latino |
| **2. Sex** | • Female<br>• Male |
| **3. Age** | • Older adults (≥65 years) |

**Table D1.6. Representation Score**

| PDRR | Score |
|---|---|
| **0** | 0 |
| **>0 and Less Than 0.5** | 1 |
| **0.5 to 0.8** | 2 |
| **≥0.8** | 3 |

PDRR: Participant to Disease-prevalence Representation Ratio

**Table D1.7. Rating Categories**

| Demographic Characteristics | Demographic Categories | Maximum Score | Rating Categories (Total Score) |
|---|---|---|---|
| **Race and Ethnicity*** | Asian, Black or African American, White, and Hispanic or Latino | 12 | Good (11-12)<br>Fair (7-10)<br>Poor (≤6) |
| **Sex** | Male and Female | 6 | Good (6)<br>Fair (5)<br>Poor (≤4) |
| **Age** | Older adults (≥65 years) | 3 | Good (3)<br>Fair (2)<br>Poor (≤1) |

* American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity. For this review, all trials were multinational (i.e., enrolled patients from the US and other countries). We were unable to obtain US subgroup data on any of these trials, thus, these trials were rated on race/ethnicity using the full sample (including both US and non-US participants). When possible, prevalence data on ATTR-CM sub grouped by race/ethnicity, sex, and age, was derived from the THAOS registry of US patients.[90] In instances of unknown race/ethnicity subgroups in ATTR-CM, we derived values from the general US population using the US Census (July 1, 2023).

***Results***

**Table D1.8. Race and Ethnicity [20,21,90]**

| | White | Black/ African American | Asian | Hispanic/ Latino | Total Score | Diversity Rating | AIAN | NHPI |
|---|---|---|---|---|---|---|---|---|
| **Prevalence** | 75.5% | 25.4%* | 6.3% | 19.1% | - | - | 1.3% | 0.3% |
| **ATTR-ACT** | 81% | 14.3% | 4.1% | 3.2% | - | - | 0% | 0% |
| **PDRR** | 1.07 | 0.56 | 0.65 | 0.17 | - | - | 0 | 0 |
| **Score** | 3 | 2 | 2 | 1 | 8 | Fair | NC | NC |
| **ATTRibute-CM** | 87.8% | 4.7% | 2.1% | 1.9 | - | - | 0.2% | 0.2% |
| **PDRR** | 1.16 | 0.19 | 0.33 | 0.10 | - | - | 0.15 | 0.67 |
| **Score** | 3 | 1 | 1 | 1 | 6 | Poor | NC | NC |
| **HELIOS-B** | NR | NR | NR | NR | - | - | NR | NR |
| **PDRR** | NC | NC | NC | NC | - | - | NC | NC |
| **Score** | NC | NC | NC | NC | NC | NC | NC | NC |

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

* THAOS US registry data

**Table D1.9. Sex and Age[20,21,91,92]**

| | Sex | | | | Age | | |
|---|---|---|---|---|---|---|---|
| | Male | Female | Score | Rating | Older Adults (≥65 years) | Score | Rating |
| **Prevalence** | 85.4%* | 14.6%* | - | - | 67%* | - | - |
| **ATTR-ACT** | 90.2% | 9.8% | - | - | 90.5% | - | - |
| **PDRR** | 1.06 | 0.67 | - | - | 1.35 | - | - |
| **Score** | 3 | 2 | 5 | Fair | 3 | 3 | Good |
| **ATTRibute-CM** | 90.2% | 9.8% | - | - | 96.7% | - | - |
| **PDRR** | 1.06 | 0.67 | - | - | 1.44 | - | - |
| **Score** | 3 | 2 | 5 | Fair | 3 | 3 | Good |
| **HELIOS-B** | NR | NR | - | - | NR | - | - |
| **PDRR** | NC | NC | - | - | NC | - | - |
| **Score** | NC | NC | NC | NC | NC | NC | NC |

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio *THAOS US registry data

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[93,94]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: tafamidis, vyndamax, vyndaqel, acoramidis, AG10, vutrisiran, amvuttra, transthyretin amyloid cardiomyopathy, and ATTR-CM. We selected studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

## Data Synthesis and Statistical Analyses

Evidence Tables in Section D2 provide a summary of the key outcomes from the three therapies, which are further synthesized qualitatively in the report. Due to the variations in trial designs and populations, a quantitative comparison of the results was not possible.

# D2. Evidence Tables

**Table D2.1. Study Design of Key Trials[31,53,54]**

| Trial (NCT) | Study Design | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Primary Outcomes [Timepoint] |
|---|---|---|---|---|
| **ATTR-ACT NCT01994889** | Phase III, randomized, double-blind, placebo-controlled<br><br>Follow-up: 30 months | 20 mg tafamidis once daily (n=88)<br><br>80 mg tafamidis (4 20mg capsules) once daily (n=176)<br><br>Placebo once daily (n=177) | **Inclusion Criteria**:<br>-Age 18 to 90 years<br>-Diagnosed with transthyretin amyloid cardiomyopathy (ATTRwt or ATTRm)<br>-Medical history of heart failure (HF) with at least 1 prior hospitalization for HF<br>-Clinical evidence of HF (without hospitalization) -Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm<br>-Presence of amyloid deposits in biopsy tissue and presence of a variant TTR genotype and/or TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry<br>**Exclusion Criteria:**<br>-NYHA IV classification<br>-Presence of primary (light chain) amyloidosis<br>-Prior liver or heart transplantation or implanted cardiac mechanical assist device<br>-<25 mL/min/1.73 $m^2$ | Hierarchically assessed composite of all-cause mortality and CV-related hospitalizations)<br><br>[30 months] |

| Trial (NCT) | Study Design | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Primary Outcomes [Timepoint] |
|---|---|---|---|---|
| **ATTRibute-CM NCT03860935** | Phase III, randomized, double-blind, placebo-controlled<br><br>Follow-up: 30 months | 800 mg acoramidis twice daily (n=421)<br><br>Placebo twice daily (n=211) | **Inclusion Criteria:**<br>-Age 18 to 90 years<br>-Established diagnosis of ATTR-CM (wild-type or variant)<br>-History of HF (at least one prior hospitalization for heart failure)<br>-Clinical evidence of heart failure without prior HF hospitalization<br>-NYHA Class I-III symptoms due to ATTR cardiomyopathy<br>-On stable doses of cardiovascular medical therapy<br>-Completed ≥150 m on the 6MWT on 2 tests that are within 15% of total distance walked<br>-NT-proBNP level ≥300 pg/mL<br>-Have left ventricular wall thickness ≥12 mm<br>**Exclusion Criteria:**<br>-Had acute myocardial infarction, acute coronary syndrome coronary revascularization, stroke or transient ischemic attack within 90 days<br>-Has hemodynamic instability<br>-Likely to undergo heart transplantation within a year of screening<br>-Confirmed diagnosis of primary (light chain) amyloidosis<br>-NT-proBNP level ≥8500 pg/mL<br>-eGFR by MDRD formula <15 mL/min/1.73 m2<br>-Current treatment with calcium channel blockers with conduction system effects | 6-Minute Walk Test [12 months]<br><br>Hierarchically assessed composite of all-cause mortality, CV-related hospitalizations, NT-proBNP, 6MWT)<br><br>[30 months] |

| Trial (NCT) | Study Design | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Primary Outcomes [Timepoint] |
|---|---|---|---|---|
| **HELIOS-B NCT04153149** | Phase III, randomized, double-blind, placebo-controlled<br><br>Follow-up: 30-36 month | 25 mg vutrisiran subcutaneously once every 3 months<br><br>Placebo<br><br>N=655 | **Inclusion Criteria:**<br>-Age 18 to 85 years<br>-Diagnosis of transthyretin ATTR amyloidosis with cardiomyopathy, classified as either ATTRm or ATTRwt amyloidosis<br>-Has medical history of heart failure (HF) with at least 1 prior hospitalization for HF OR clinical evidence of HF<br><br>**Exclusion Criteria:**<br>-Has known primary amyloidosis or leptomeningeal amyloidosis<br>-Has NYHA Class IV heart failure<br>-Has NYHA Class III heart failure AND is at high risk<br>-Has a polyneuropathy disability Score IIIa, IIIb, or IV<br>-Has eGFR <30 mL/min/1.73 m^2<br>-Has received prior TTR-lowering treatment | Composite endpoint of all-cause mortality and recurrent cardiovascular events (30-36 months] |

6MWT: 6-minute walk test, ATTRm: hereditary ATTR, ATTRwt: wild-type ATTR, CV: cardiovascular, eGFR: estimated glomerular filtration rate, HF: heart failure, m: meter, MDRD: modification of diet in renal disease, mg: milligram, min: minute, mL: milliliter, mm: millimeter, ng/mL: nanograms per milliliter, NT-proBNP: N-terminal pro b-type natriuretic peptide, NYHA: New York Heart Association, TTR: transthyretin

**Table D2.2. Tafamidis Baseline Characteristics[37,54,95-99]**

| Trial | | | ATTR-ACT | | | |
|---|---|---|---|---|---|---|
| Arms | | | Tafamidis 20 mg | Tafamidis 80 mg | Tafamidis (pooled) | Placebo |
| N | | | 88 | 176 | 264 | 177 |
| Age, years | Mean (SD) | | 73.3 (7.1) | 75.2 (7.2) | 74.5 (7.2) | 74.1 (6.7) |
| | Median (range) | | 73.5 (51-86) | 76 (46-88) | 75 (46-88) | 74 (51-89) |
| Sex, n (%) | Male | | 83 (94.3) | 158 (89.8) | 241 (91.3) | 157 (88.7) |
| | Female | | 5 (5.7) | 18 (10.2) | 23 (8.7) | 20 (11.3) |
| Race, n (%) | White | | 75 (85.2) | 136 (77.3) | 211 (79.9) | 146 (82.5) |
| | Black | | 11 (12.5) | 26 (14.8) | 37 (14) | 26 (14.7) |
| | Asian | | 2 (2.3) | 11 (6.3) | 13 (4.9) | 5 (2.8) |
| | Other | | 0 (0) | 3 (1.7) | 3 (1.1) | 0 (0) |
| TTR genotype, n (%) | ATTRv (Hereditary/Variant) | | 21 (23.9) | 42 (23.9) | 63 (23.9) | 43 (24.3) |
| | ATTRwt (Wild Type) | | 67 (76.1) | 134 (76.1) | 201 (76.1) | 134 (75.7) |
| Transthyretin variant, n/N (%) | V142I | | NR | NR | 38 (60.3) | 23 (53.5) |
| | T60A | | NR | NR | 6 (9.5) | 6 (14) |
| Country, n (%) | US | | 63 (72) | 108 (61) | 171 (65) | 108 (61) |
| | Non-US | | 25 (28) | 68 (39) | 93 (35) | 69 (39) |
| Blood pressure, mmHg (SD) | Supine | Systolic | NR | NR | 115.4 (15.4) | 115.1 (15.7) |
| | | Diastolic | NR | NR | 70.4 (10.3) | 70.2 (9.5) |
| | Standing | Systolic | NR | NR | 115.5 (15.5) | 115.9 (15.9) |
| | | Diastolic | NR | NR | 70.6 (9.9) | 71 (10.3) |
| Heart rate, mean bpm (SD) | Supine | | NR | NR | 70.7 (12.3) | 69.9 (11.7) |
| | Standing | | NR | NR | 72.9 (12.9) | 73.8 (12.2) |
| NYHA class, n (%) | Class I | | 8 (9.1) | 16 (9.1) | 24 (9.1) | 13 (7.3) |
| | Class II | | 57 (64.8) | 105 (59.7) | 162 (61.4) | 101 (57.1) |
| | Class III | | 23 (26.1) | 55 (31.3) | 78 (29.5) | 63 (35.6) |
| Modified BMI, mean (SD) | | | 1047.5 (176.7) | 1064.5 (172.5) | 1058.8 (173.8) | 1066.4 (194.4) |

| Trial | | ATTR-ACT | | | |
|---|---|---|---|---|---|
| **Arms** | | **Tafamidis 20 mg** | **Tafamidis 80 mg** | **Tafamidis (pooled)** | **Placebo** |
| **N** | | **88** | **176** | **264** | **177** |
| **NT-proBNP, mean pg/mL (IQR)** | **Mean (SD)** | NR | NR | NR | NR |
| | **Median (IQR)** | NR | 3122 (1826-4948.5) | 2995.9 (1751.5-4861.5) | 3161 (1864.4-4825) |
| **Serum TTR, mean mg/dL (SD)** | | *22.13* | *21.74* | NR | *21.19* |
| **Baseline medications, n (%)** | **Agents acting on renin-angiotensin system** | NR | NR | 69 (26.1) | 48 (27.1) |
| | **Beta blockers** | NR | NR | 76 (28.8) | 53 (29.9) |
| | **Diuretics** | NR | NR | 175 (66.3) | 123 (69.5) |
| | **Antithrombotic agents** | NR | NR | 105 (39.8) | 72 (40.7) |
| **Coexisting conditions, n (%)** | **Hypertension** | NR | 90 (51.1) | 145 (54.9) | 84 (47.5) |
| | **Diabetes** | NR | 14 (8) | 20 (7.6) | 13 (7.3) |
| | **Atrial fibrillation** | NR | 93 (52.8) | NR | 89 (50.3) |
| | **Coronary artery disease** | NR | 35 (19.9) | NR | 40 (22.6) |
| | **Chronic kidney disease** | NR | 31 (17.6) | NR | 41 (32.2) |
| **6MWT distance, mean (SD)** | | 375 (24-680)* | 344.8 (120.3) | 350.6 (121.3) | 353.3 (126) |
| **KCCQ, mean (SD)** | **Overall Summary Score** | NR | 67.1 (21.3) | 67.3 (21.4) | 65.9 (21.7) |
| | **Clinical Summary Score** | NR | 71.1 (20.1) | 71.3 (20.0) | 70.2 (20.5) |
| **EQ-5D, mean (SD)** | **EQ-5D-3L Index Score** | NR | NR | 0.8 (0.2) | 0.8 (0.2) |
| | **EQ VAS** | NR | NR | 68.3 (18.6) | 66.5 (17.8) |
| **LVEF, mean % (SD)** | | NR | 48 (10.5)† | 48.4 (10.3) | 48.6 (9.5)‡ |

6MWT: 6-minute walk test, BMI: body mass index, EQ-5D: EuroQol-5-Domain Questionnaire, IQR: interquartile range, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire, LVEF: left ventricular ejection fraction, mg: milligram, n: number N: total number, NR: not reported, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association, pg/mL: picograms per milliliter, SD: standard deviation, TTR: transthyretin, VAS: visual analogue scale, %: percent.

* 6MWT distance, median (range)

† N=173

‡ N=175

**Table D2.3. Acoramidis Baseline Characteristics[53,100,101]**

| Trial | | ATTRibute-CM | |
|---|---|---|---|
| Arms | | Acoramidis | Placebo |
| N | | 421 | 211 |
| Age, years | Mean (SD) | 77.4 (6.5) | 77.1 (6.8) |
| Sex, n (%) | Male | 384 (91.2) | 186 (88.2) |
| | Female | 37 (8.8) | 25 (11.8) |
| Race, n (%) | White | 368 (87.4) | 187 (88.6) |
| | Black | 20 (4.8) | 10 (4.7) |
| | Asian | 10 (2.4) | 3 (1.4) |
| | Other | 23 (5.5) | 11 (5.2) |
| TTR genotype, n (%) | ATTRv (Hereditary/Variant) | 41 (9.7) | 20 (9.5) |
| | ATTRwt (Wild Type) | 380 (90.3) | 191 (90.5) |
| TTR variant, n/N (%) | V30M | 1/39 (2.6) | 0 (0) |
| | V142I | 24/39 (61.5) | 12/19 (63.2) |
| | T60A | 3/39 (7.7) | 2/19 (10.5) |
| | E89Q | 0 (0) | 1/19 (5.3) |
| | Other | 11/39 (28.2) | 4/19 (21.1) |
| NYHA class, n (%) | Class I | 51 (12.1) | 17 (8.1) |
| | Class II | 293 (69.6) | 162 (76.8) |
| | Class III | 77 (18.3) | 32 (15.2) |

| Trial | | ATTRibute-CM | |
|---|---|---|---|
| Arms | | Acoramidis | Placebo |
| N | | 421 | 211 |
| NT-proBNP, mean pg/mL (IQR) | Mean (SD) | 2946 (2226) | 2725 (1971) |
| | Median (IQR) | 2326 (1332-4019) | 2306 (1128-3754) |
| eGFR, mean mL/min/1.73m2 | | 61 (18) | 61 (19) |
| NAC stage, n (%) | I | 241 (57.2) | 120 (56.9) |
| | II | 134 (31.8) | 69 (32.7) |
| | III | 46 (10.9) | 22 (10.4) |
| Serum transthyretin, mean mg/dL (SD) | | 23 (6) | 24 (6) |
| 6MWT distance, mean (SD) | | 361.2 (103.7) | 348.4 (93.6) |
| KCCQ, mean (SD) | Overall Summary Score | 71.5 (19.4) | 70.3 (20.5) |
| EQ-5D, mean (SD) | EQ-5D-3L Index Score | 0.8 (0.2)* | 0.8 (0.2)† |
| | EQ VAS | 72.3 (16.4)* | 72 (16.9)† |

6MWT: 6-minute walk test, eGFR: estimated glomerular filtration rate, EQ-5D: EuroQol-5-Domain Questionnaire, IQR: interquartile range, KCCQ: Kansas City Cardiomyopathy Questionnaire, n: number N: total number, NAC: National Amyloidosis Centre, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association, pg/mL: picograms per milliliter, SD: standard deviation, TTR: transthyretin, VAS: visual analogue scale, %: percent

* N=405

† N=202

**Table D2.4. Tafamidis Efficacy Outcomes[37,54,70,96,98,102,103]**

| Trial | | ATTR-ACT | | | |
|---|---|---|---|---|---|
| Arms | | Tafamidis 20 mg | Tafamidis 80 mg | Tafamidis (Pooled) | Placebo |
| N | | 88 | 176 | 264 | 177 |
| Timepoint | | 30 Months | | | |
| Win Ratio (95% CI) | All-cause mortality, CV-related hospitalizations | NR | NR | 1.70 (1.26-2.29) | |
| Patients alive, n (%) | | 64 (72.7) | 122 (69.3) | 186 (70.5) | 101 (57.1) |
| All-cause mortality, n (%) | All | 24 (27.3) | 54 (30.7) | 78 (29.5) | 76 (42.9) |
| | Deaths | 23 (26.1) | 46 (26.1) | 69 (26.1) | 72 (40.7) |
| | Heart transplants | 1 (1.1) | 6 (3.4) | 7 (2.7) | 4 (2.3) |
| | Implantation of a CMAD | 0 (0) | 2 (1.1) | 2 (0.8) | 0 (0) |
| Probability of survival, hazard ratio (95% CI) | | 0.72 (0.45–1.14) | 0.69 (0.49–0.98) | 0.70 (0.51-0.96) | |
| CV-related hospitalizations, n (%) | | 42 (47.7) | 96 (54.5) | 138 (52.3) | 107 (60.5) |
| CV-related hospitalizations, number per year (95% CI) | | 0.46 | 0.49 | 0.48 (0.42-0.54) | 0.7 (0.62-0.80) |
| Frequency of CV-related hospitalizations treatment difference, relative risk ratio (95% CI) | | 0.66 (0.51–0.86) | 0.70 (0.57–0.85) | 0.68 (0.56-0.81) | |
| Time to first CV-related hospitalization, hazard ratio (95% CI) | | NR | NR | 0.80 (0.62-1.03) | |
| CV-related hospitalizations, average number per patient per year | | 0.22 | 0.34 | 0.3 | 0.46 |
| CV-related hospitalization length of stay, mean days (95% CI) | | NR | NR | 8.63 (7.57-9.68) | 9.56 (8.38-10.74) |
| CV-related events, n (%) | All | 19 (21.6) | 45 (25.6) | 64 (24.2) | 63 (35.6) |
| | Deaths | 18 (20.5) | 37 (21) | 55 (20.8) | 59 (33.3) |
| | Heart transplants | 1 (1.1) | 6 (3.4) | 7 (2.6) | 4 (2.3) |
| | Implantation of a CMAD | 0 (0) | 2 (1.1) | 2 (0.8) | 0 (0) |
| CV-related mortality, % | | 37 (21) | 18 (20.5) | NR | 59 (33.3) |
| CV-related mortality, treatment vs. placebo, hazard ratio (95% CI) | | 0.68 (0.40–1.14) | 0.69 (0.47–1.01) | 0.69 (0.49-0.98) | |

| Trial | | ATTR-ACT | | | |
|---|---|---|---|---|---|
| Arms | | Tafamidis 20 mg | Tafamidis 80 mg | Tafamidis (Pooled) | Placebo |
| N | | 88 | 176 | 264 | 177 |
| Timepoint | | 30 Months | | | |
| Heart failure, hazard ratio (95% CI) | | NR | NR | 0.70 (0.45-1.08) | |
| 6-Minute Walk | Change from baseline, LSM m (SE) | *-55 (10.1)* | *-54.7 (7.3)* | *-55 (5.4)* | *-130.3 (9.4)* |
| | Difference from placebo, LSM m (SE) | NR | NR | 75.68 (9.24) | |
| KCCQ-OS | Change from baseline, LSM (SE) | NR | -6.3 (1.5) | NR | -19.6 (1.9) |
| | Difference from placebo, LSM (SE) | NR | 13.4 (9.2-17.5) | NR | |
| KCCQ-CS | Change from baseline, LSM (SE) | NR | -7.5 (1.4) | NR | -19.9 (2.0) |
| | Difference from placebo, LSM (SE) | NR | 12.4 (8.2-16.5) | NR | |
| EQ-5D | EQ-5D-3L, change from baseline, LSM (SE) | NR | NR | *-0.05 (0.01)* | *-0.14 (0.02)* |
| | EQ VAS, change from baseline, LSM (SE) | NR | NR | *-3.8 (1.2)* | *-12.9 (1.6)* |
| NT-proBNP | Change from baseline, LSM (SE) | 2542.2 (577.8) | 1371.7 (296.3) | NR | NR |
| | Difference from placebo, LSM (SE) | -1417.02 (743.38) | -2587.54 (570.25) | -2180.54 (95% CI: -3326.14, -1034.95) | |
| LVEF | Change from baseline, LSM % (SE) | NR | *-1.92 (1.1)* | -2.82 (0.85) | -4.34 (1.10) |
| | Difference from placebo, LSM % (SE) | NR | 2.09 (95% CI: -0.62 to 4.79); 0.13 | 1.51 (1.06) | |
| Serum TTR level | Change from baseline, LSM mg/dL (SE) | *5.16* | *8.14* | NR | *0.49* |

Note: Italicized data has been digitized or calculated

CI: confidence interval, CMAD: cardiac mechanical assist device, CV: cardiovascular, EQ-5D: EuroQol-5-domain questionnaire, EQ-5D-3L: 3-level version of EQ-5D, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, LSM: Least-squares mean, mg: milligram, n: number, N: total number, NR: not reported, NT-proBNP: N-terminal pro–B-type natriuretic peptide, SE: standard error, TTR: transthyretin, VAS: visual analogue scale, %: percent

**Table D2.5. Tafamidis Long-term Follow-up[104]**

| Arms | | Tafamidis continued (80 mg) | Switched placebo |
|---|---|---|---|
| **N** | | **176** | **177** |
| **Timepoint** | | **Median: 58.5 months** | |
| **All-cause mortality, n (%)** | **All** | 79 (44.9) | 111 (62.7) |
| | **Deaths** | 70 (39.8) | 105 (59.3) |
| | **Heart transplant** | 7 (4) | 6 (3.4) |
| | **Implantation of CMAD** | 2 (1.1) | 0 (0) |
| **Kaplan-Meier estimates of time to event, median months (95% CI)** | | 67 (47-NE) | 35.8 (29.7-41.1) |
| **Kaplan-Meier preliminary estimates of 5-year survival** | | 0.532 | 0.324 |
| **All-cause mortality, vs. placebo, hazard ratio (95% CI)** | | 0.59 (0.44-0.79); <0.001 | |

CI: confidence interval, CMAD: cardiac mechanical assist device, mg: milligram, n: number, N: total number, NE: not estimable, %: percent

**Table D2.6. Acoramidis Efficacy Outcomes[33-35,53,100,101]**

| Trial | | ATTRibute-CM | |
|---|---|---|---|
| Arms | | Acoramidis | Placebo |
| N | | 421 | 211 |
| Timepoint | | 30 months | |
| Win Ratio (95% CI) | All-cause mortality, CV-related hospitalizations, NT-proBNP, 6MWD | 1.8 (1.4-2.2) | |
| | All-cause mortality, CV-related hospitalizations, 6MWD | 1.4 (1.1-1.8) | |
| | All-cause mortality, CV-related hospitalizations | 1.5 (1.1-2) | |
| Time to first event of All-cause mortality or CV-related hospitalization, hazard ratio (95% CI) | | 0.65 (0.50-0.83) | |
| Time to first event of CV-mortality or CV-related hospitalization, hazard ratio (95% CI) | | 0.62 (0.48, 0.8) | |
| All-cause mortality, n (%) | All | NR | 25.70% |
| CV-related hospitalizations, n (%) | | 109 (26.7) | 86 (42.6) |
| CV-related hospitalizations, number per year (95% CI) | | 0.22 (0.18-0.28) | 0.45 (0.35-0.58) |
| Frequency of CV-related hospitalizations treatment difference, relative risk ratio (95% CI) | | 0.50 (0.36-0.70) | |
| Time to first CV-related hospitalization, hazard ratio (95% CI) | | 0.60 (0.45, 0.8) | |
| CV-related mortality, % | | 14.90% | 21.30% |
| CV-related mortality, treatment vs. placebo, hazard ratio (95% CI) | | 0.71 (0.48, 1.05) | |
| 6-Minute Walk | Change from baseline, LSM m (SE) | *-64.6 (10.5)* | *-104.1 (15)* |
| | Difference from placebo, LSM m (95% CI) | 39.6 (21.1, 58.2) | |
| KCCQ-OS | Change from baseline, LSM (SE) | *-11.5 (2.3)* | *-21.5 (3.4)* |
| | Difference from placebo, LSM (95% CI) | 9.94 (5.97, 13.91) | |
| EQ-5D | EQ-5D-3L, change from baseline, LSM (95% CI) | -0.17 ( -0.2, -0.14)* | -0.3 (-0.34, -0.25)† |
| | EQ VAS, change from baseline, LSM (95% CI) | -10.12 ( -12.49, -7.74)* | -19.66 (-22.95, -16.37)† |
| NT-proBNP | Ratio of adjusted geometric mean factor change (95% CI) | 0.529 (0.463-0.604) | |
| Serum TTR level | Change from baseline, LSM mg/dL | *6.5* | *-0.78* |
| | Difference from placebo, LSM mg/dL (95% CI) | 7.1 (5.79-8.40) | |

Note: Italicized data has been digitized or calculated

6MWD: 6-minute walk distance, CI: confidence interval, CV: cardiovascular, EQ-5D: EuroQol-5-domain questionnaire, EQ-5D-3L: 3-level version of EQ-5D, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, LSM: Least-squares mean, n: number, N: total number, NR: not reported, NT-proBNP: N-terminal pro–B-type natriuretic peptide, SE: standard error, TTR: transthyretin, VAS: visual analogue scale, %: percent

* N=401

† N=201

### Table D2.7. Tafamidis Safety Outcomes[37,54,96]

| Trial | | ATTR-ACT | | | |
|---|---|---|---|---|---|
| Arms | | Tafamidis 20 mg | Tafamidis 80 mg | Tafamidis (pooled) | Placebo |
| N | | 88 | 176 | 264 | 177 |
| Timepoint | | 30 months | | | |
| TEAE, n (%) | All | 87 (98.9) | 173 (98.3) | 260 (98.5) | 175 (98.9) |
| | Leading to discontinuation | 16 (18.2) | 40 (22.7) | 56 (21.2) | 51 (28.8) |
| | Leading to dose reduction | 0 (0) | 2 (1.1) | 2 (0.8) | 4 (2.3) |
| | Leading to temporary discontinuation | 20 (22.7) | 33 (18.8) | 53 (20.1) | 46 (26) |
| Treatment-emergent SAE, n (%) | | 66 (75) | 133 (75.6) | 199 (75.4) | 140 (79.1) |
| ≥1 severe TEAE, n (%) | | 54 (61.4) | 110 (62.5) | 164 (62.1) | 114 (64.4) |
| Cardiac disorders, n (%) | All | NR | NR | 185 (70.1) | 124 (70.1) |
| | Cardiac failure | 30 (34.1) | 46 (26.1) | 76 (28.8) | 60 (33.9) |
| | Atrial fibrillation | 16 (18.2) | 35 (19.9) | 51 (19.3) | 33 (18.6) |
| | Cardiac failure congestive | 17 (19.3) | 22 (12.5) | 39 (14.8) | 33 (18.6) |
| Fall-related SAEs | n (%) | 10 (11.4) | 20 (11.4) | 30 (11.4) | 9 (5.1) |
| | Incidence rate ratio (95% CI) | 2.1 (0.9-5.2) | 2.1 (1-4.7) | 2.1 (1-4.5) | NA |
| Lens disorder SAEs | n (%) | 7 (8) | 18 (10.2) | 25 (9.5) | 6 (3.4) |
| | Incidence rate ratio (95% CI) | 2.2 (0.7-6.5) | 2.9 (1.1-7.3) | 2.6 (1.1-6.4) | NA |
| Treatment adherence ≥80%, n (%) | | 80 (95.2)* | 164 (98.2)* | 97.20% | 97% |

CI: confidence interval, mg: milligram, n: number, N: total number, SAE: serious adverse event, TEAE: treatment-emergent adverse event, %: percent.

* Total number of participants assessed for this outcome not reported

**Table D2.8. Acoramidis Safety Outcomes[53]**

| Trial | | ATTRibute-CM | |
|---|---|---|---|
| Arms | | Acoramidis | Placebo |
| N | | 421 | 211 |
| Timepoint | | 30 months | |
| TEAE, n (%) | All | 413 (98.1) | 206 (97.6) |
| | Treatment-related | 50 (11.9) | 11 (5.2) |
| | With fatal outcome | 60 (14.3) | 36 (17.1) |
| | Leading to hospitalization | 212 (50.4) | 128 (60.7) |
| | Leading to discontinuation | 39 (9.3) | 18 (8.5) |
| | Leading to dose reduction | 4 (1) | 0 (0) |
| Treatment-emergent SAE, n (%) | All | 230 (54.6) | 137 (64.9) |
| | Treatment-related | 2 (0.5) | 0 (0) |
| | Leading to discontinuation | 21 (5.0) | 15 (7.1) |
| | Leading to dose reduction | 2 (0.5) | 0 (0) |
| ≥1 severe TEAE, n (%) | | 157 (37.3) | 96 (45.5) |
| Cardiac disorders, n (%) | All | 230 (54.6) | 144 (68.2) |
| | Cardiac failure | 101 (24) | 83 (39.3) |
| | Atrial fibrillation | 70 (16.6) | 46 (21.8) |
| | Cardiac failure acute | 27 (6.4) | 17 (8.1) |
| | Bradycardia | 23 (5.5) | 9 (4.3) |
| | Ventricular tachycardia | 17 (4) | 14 (6.6) |
| | Atrial flutter | 22 (5.2) | 9 (4.3) |
| | Cardiac failure chronic | 17 (4) | 11 (5.2) |

n: number, N: total number, SAE: serious adverse event, TEAE: treatment-emergent adverse event, %: percent

**Table D2.9. Vutrisiran Safety Outcomes[32]**

| Trial | HELIOS-B | |
|---|---|---|
| **Arm** | **Vutrisiran** | **Placebo** |
| **N** | **326** | **328** |
| **Adverse events, %** | 98.8 | 98.5 |
| **Serious adverse events, %** | 61.7 | 67.1 |
| **AEs leading to study drug discontinuation, %** | 3.1 | 4 |

AE: adverse event, N: total number

* No AEs were seen ≥3% more frequently with vutrisiran compared with placebo

**Table D2.10. Subgroup Data: Genotype and Baseline NYHA Class[53,54]**

| Subgroup Category | Subgroup | Trial | CV-related Hospitalizations Relative Risk Ratio (95% CI) |
|---|---|---|---|
| **Genotype** | **ATTRv** | ATTR-ACT | *0.92 (0.66, 1.40)* |
| | | ATTRibute-CM | 0.38 (0.14-1.03) |
| | **ATTRwt** | ATTR-ACT | *0.62 (0.46, 0.77)* |
| | | ATTRibute-CM | 0.51 (0.36-0.73) |
| **Baseline NYHA Class** | **NYHA Class I/II** | ATTR-ACT | *0.46 (0.38, 0.61)* |
| | | ATTRibute-CM | 0.45 (0.31-0.65) |
| | **NYHA Class III** | ATTR-ACT | *1.48 (1.07, 1.91)* |
| | | ATTRibute-CM | 0.72 (0.31-1.66) |

ATTRv: hereditary ATTR, ATTRwt: wild-type ATTR, NYHA: New York Heart Association

Note: Italicized data has been digitized

## D4. Previous Systematic Reviews and Technology Assessments

We identified several previously conducted systematic literature reviews and report the summary of one with a meta-analysis below. We also identified two recommendations from health technology assessment organizations, both of which are summarized below.

### Wang J, Chen H, Tang Z, et al. Tafamidis treatment in patients with transthyretin amyloid cardiomyopathy: a systematic review and meta-analysis. EClinicalMedicine.2023; 63:102172.[105]

This systematic review and meta-analysis aimed to assess the effectiveness of tafamidis treatment in people living with ATTR-CM, versus those on no treatment. The primary focus of this review was to assess the risk of adverse endpoints including all-cause death, heart transplantation, cardiac-assist device implantation, heart failure exacerbations, and hospitalization between the two arms. Five databases were searched for observational cohort studies (retrospective and prospective) or randomized controlled trials with a mean/median follow-up time greater than 6 months that examined the impact of tafamidis on the prognosis of patients with ATTR-CM. The researchers included 15 studies involving 2765 patients in total. For the primary outcome of all-cause death heart transplantation patients who received tafamidis treatment were associated with a significantly lower than those who did not. Treatment with tafamidis was also associated with a significantly lower risk for the composite endpoint of all-cause death, heart transplant, heart assist device implantation, heart failure exacerbations and hospitalizations. Additional analyses found a significant decrease in left ventricular ejection fraction for patients with ATTRm but not those with ATTRwt, and no significant differences in intraventricular septum thickness or global longitudinal strain after tafamidis treatment. Overall, tafamidis treatment was associated with a low risk of all-cause death, adverse cardiovascular events, and no significant deterioration in LVEF in the patients with wild-type ATTR. The study acknowledges limitations, such as few RCTs included in the analysis, a relatively small sample size of ATTRm, and a mean follow-up duration of 20 months, further research is needed to determine the long-term efficacy of tafamidis.

### 2021 National Institute for Heath and Care Excellence (NICE) Report on Tafamidis for Treating Transthyretin Amyloidosis with Cardiomyopathy[106]

This report notes the evidence for clinical efficacy of tafamidis but notes heterogeneous effects and limitations in the use of NYHA classification in assessing eligibility for treatment. The report also notes the unfavorable cost effectiveness of tafamidis and had recommended against its use in the

UK National Health Service. This recommendation was reversed in June 2024, based on a commercial patient access scheme.

### 2020 Clinical Review Report: Tafamidis from the Canadian Agency for Drugs and Technologies in Health (CADTH)[107]

This report notes strong evidence for efficacy of tafamidis and recommends coverage of tafamidis for ATTR-CM in Canada provided a reduction in price of 92%. The report also notes no comparative effectiveness evidence of tafamidis versus diflunisal.

# E. Long-Term Cost-Effectiveness: Supplemental Information

## E1. Detailed Methods

### E1.1 Impact Inventory

**Table E1.1. Impact Inventory**

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Treatment effects | X | X | Gillmore et al.[53] Maurer et al.[54] |
| | Longevity effects | X | X | JMO Arnold[59] 2021 US Life Table[108] |
| | Health-related quality of life effects | X | X | Maurer et al.[54] Kansal et al.[109] |
| | Adverse events | X | X | Mauer et al.[54] Gillmore et al.[53] |
| **Medical Costs** | Paid by third-party payers | X | X | IPD Analytics[110] Wang et al.[61] |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | X | X | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | ☐ | |
| | Unpaid caregiver-time costs | NA | ☐ | |
| | Transportation costs | NA | ☐ | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | ☐ | |
| | Cost of unpaid lost productivity due to illness | NA | X | Patient indirect cost estimates: Çavuşoğlu et al.[111] Caregiver indirect cost estimate: Lahoz et al.[112] |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al[113]

## E1.2 Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[114]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

## E1.3 Treatment Strategies

Interventions of interest were identified with input from patient organizations, clinicians, and manufacturers. Transthyretin stabilizing agents were modeled as a class instead of individual stabilizing agents, and were considered an add-on to best supportive care. The full list of included transthyretin stabilizing agents were (Table E1.2):

- acoramidis (BridgeBio Pharma)
- tafamidis (Vyndamax®/ Vyndaqel®, Pfizer Inc.)

The comparator was best supportive care for ATTR-CM without a transthyretin stabilizing agent. Best supportive care may include diuretics, treatment of arrhythmias (e.g., atrial fibrillation), and palliative care.

**Table E1.2. Treatment regimen recommended dosage**

| Generic Name | Tafamidis | Acoramidis |
|---|---|---|
| **Brand Name** | Vyndamax/ Vyndaqel | AG10* |
| **Manufacturer** | Pfizer | BridgeBio |
| **Route of Administration** | Oral | Oral |
| **Dosing** | 80 mg once daily (bioequivalent to 61 mg free acid once daily) | 800 mg twice daily |
| **Duration** | Chronic medication | Chronic medication |

## E1.4. Target Population

The base-case population for the economic model emulated the ATTRibute-CM [acoramidis] clinical trial population, with an average age of 77 years and 9.8% female.[53] The proportions of individuals starting in each NYHA functional class was also reflective of the ATTRibute-CM [acoramidis] clinical trial. Compared to the ATTR-ACT [tafamidis] clinical trial population, the ATTRibute-CM [acoramidis] clinical trial population more accurately reflects the characteristics of patients presently treated in practice (e.g., treatment initiation earlier in disease progression); the tafamidis clinical trial cohort tended to have more advanced disease. However, in a scenario analysis, we modeled the ATTR-ACT [tafamidis] clinical trial population to examine how the economic outcomes are impacted.[54] Baseline characteristics of the acoramidis and tafamidis trials are shown in Table E1.2.

**Table E1.3. Base-Case Model Cohort Characteristics**

| Characteristic | ATTRibute-CM* (Acoramidis) N=632 | ATTR-ACT† (Tafamidis) N=441 |
|---|---|---|
| | Base Case Population | Scenario Analysis Population |
| **Age (mean, SD)** | 77.3 ± 6.6 | 74.3 ± 6.7 |
| **Gender (n, %)** | | |
| **Male** | 570 (90.2%) | 398 (90.2%) |
| **Female** | 62 (9.8%) | 43 (9.8%) |
| **Race/Ethnicity (n, %)** | | |
| **Asian** | 13 (2.1%) | 18 (4.1%) |
| **Black** | 30 (4.7%) | 63 (14.3%) |
| **White** | 555 (87.8%) | 357 (80.9%) |
| **Other racial or ethnic group (n, %)** | 34 (5.4%) | 3 (0.6%) |
| **Transthyretin genotype (n, %)** | | |
| **ATTR-CM Wild type** | 571 (90.3%) | 335 (75.9%) |
| **ATTR-CM Variant** | 61 (9.7%) | 106 (24%) |
| **NYHA Functional Class (n, %)** | | |
| **Class I** | 68 (10.8%) | 37 (8.4%) |
| **Class II** | 455 (72.0%) | 263 (59.6%) |
| **Class III** | 109 (17.2%) | 141 (31.9%) |
| **Class IV** | 0 (0%) | 0 (0%) |

ATTR-CM: transthyretin amyloid cardiomyopathy, NYHA: New York Heart Association

* Gillmore et al.[53]

† Mauer et al. (weighted average)[54]

# E2. Model Inputs and Assumptions

## Model Inputs

### *Clinical Inputs*

*NYHA Heart Failure Functional Class Progression - Transition Probabilities*

Treatment efficacy was modeled by differential progression through NYHA functional classes, represented by transition probabilities related to heart failure progression (changes in NYHA functional class over time) between the treatment and comparator arms. The transition probability matrix was identified from clinical trial data as reported from the French Health Technology assessment.[57] Movement between NYHA functional classes were conditional on a member of the modeled cohort not dying within the cycle.

The transition probabilities were assumed equal across all treatments in the transthyretin stabilizing agent class. This decision was based on limited available data for acoramidis and was confirmed with clinical experts for face validity. The transition probabilities between NYHA functional classes are listed in Table E2.1.1 and E2.1.2 for the transthyretin stabilizing treatment and best-supportive care arms, respectively.[57] These transition probability matrices present time-varying probabilities of moving between NYHA functional classes in 6-month increments up to 30 months (the end of the tafamidis clinical trial). For the transthyretin stabilizing treatment arms, we carried the 30-month values forward through the modeled lifetime horizon; for the best supportive care (placebo) arms, we carried the 24-month values forward, because individuals in the placebo arm of ATTR-ACT (tafamidis clinical trial) were given tafamidis at 30 months.

**Table E2.1. NYHA Functional Class Transition Probabilities for Transthyretin Stabilizing Agent plus Best Supportive Care***

| To: | NYHA I | | | | NYHA II | | | | NYHA III | | | | NYHA IV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **From:** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** |
| **6 Months** | 56.5% | 7.2% | 0.0% | 0.0% | 39.2% | 75.1% | 29.0% | 0.0% | 4.3% | 17.0% | 67.8% | 0.0% | 0.0% | 0.7% | 3.2% | 100.0% |
| **12 Months** | 52.2% | 6.9% | 1.9% | 0.0% | 47.8% | 75.8% | 39.6% | 0.0% | 0.0% | 16.6% | 56.6% | 0.0% | 0.0% | 0.7% | 1.9% | 100.0% |
| **18 Months** | 38.1% | 9.6% | 2.3% | 0.0% | 47.6% | 69.7% | 27.3% | 0.0% | 14.3% | 20.7% | 68.1% | 0.0% | 0.0% | 0.0% | 2.3% | 100.0% |
| **24 Months** | 50.0% | 10.3% | 0.0% | 0.0% | 30.0% | 67.5% | 27.0% | 0.0% | 15.0% | 21.4% | 62.2% | 0.0% | 5.0% | 0.8% | 10.8% | 100.0% |
| **≥ 30 Months** | 36.8% | 11.5% | 0.0% | 0.0% | 36.8% | 59.8% | 30.0% | 0.0% | 21.1% | 28.7% | 63.3% | 0.0% | 5.3% | 0.0% | 6.7% | 100.0% |

* Haute Autorité de Santé [57]

**Table E2.2. NYHA Functional Class Transition Probabilities for Best Supportive Care Alone***

| To: | NYHA I | | | | NYHA II | | | | NYHA III | | | | NYHA IV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **From:** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** | **NYHA I** | **NYHA II** | **NYHA III** | **NYHA IV** |
| **6 Months** | 53.8% | 6.2% | 3.9% | 0.0% | 46.2% | 76.3% | 21.6% | 0.0% | 0.0% | 17.5% | 70.6% | 0.0% | 0.0% | 0.0% | 3.9% | 100.0% |
| **12 Months** | 27.3% | 7.0% | 0.0% | 0.0% | 54.5% | 65.1% | 23.9% | 0.0% | 18.2% | 26.7% | 69.6% | 0.0% | 0.0% | 1.2% | 6.5% | 100.0% |
| **18 Months** | 22.2% | 3.9% | 5.4% | 0.0% | 55.6% | 64.9% | 24.3% | 0.0% | 11.1% | 29.9% | 67.6% | 0.0% | 11.1% | 1.3% | 2.7% | 100.0% |
| **24 Months** | 12.5% | 1.6% | 0.0% | 0.0% | 75.0% | 50.0% | 28.0% | 0.0% | 12.5% | 45.2% | 60.0% | 0.0% | 0.0% | 3.2% | 12.0% | 100.0% |
| **≥ 30 Months** | 16.7% | 5.3% | 0.0% | 0.0% | 66.6% | 49.1% | 26.3% | 0.0% | 16.7% | 38.6% | 63.2% | 0.0% | 0.0% | 7.0% | 10.5% | 100.0% |

* Haute Autorité de Santé [57]

*Cardiovascular-Related Hospitalizations*

The risk of cardiovascular-related hospitalizations was incorporated as a transient event in the model. The probability of experiencing a cardiovascular-related hospitalization was NYHA functional class specific as determined from a systematic review of the literature. Rates of NYHA state specific cardiovascular hospitalization were identified from ATTR-ACT [tafamidis] trial data as reported by the French HTA and applied to respective treatment and placebo arms. Probabilities are presented in Table E2.1.3.[57]

**Table E2.3 Cardiovascular-Related Hospitalization Probabilities (per 6-month cycle)**

| Health State | Treatment Arms | Comparator (Placebo) Arm* |
|---|---|---|
| **NYHA Class I** | 10.3% | 30.7% |
| **NYHA Class II** | 27.5% | 36.4% |
| **NYHA Class III** | 76.7% | 80.8% |
| **NYHA Class IV** | 148.9% | 32.5% |

* Source: ATTR-ACT

*Adverse Events*

Adverse events of transthyretin stabilizing treatments were generally mild and not different from the placebo groups in clinical trials. Observed cardiovascular-related adverse event rates are assumed to be related to the treatment's effectiveness in slowing disease progression, which is captured by NYHA functional class progression. Therefore, no additional impact of adverse events was modeled beyond those already described here and in the discontinuation section.

*Discontinuation*

In the base-case, individuals received transthyretin stabilizing treatment until progression to NYHA Class IV or discontinuation due to adverse events. All individuals received best supportive care until death regardless of NYHA functional class or treatment status. Individuals transitioning into NYHA Class IV did not accumulate costs associated with transthyretin stabilizing treatment but accumulated costs associated with best supportive care.

Individuals discontinued treatment at a rate of 1.9% per 6-month cycle, after which they followed transition probabilities indicating lack of treatment effect (the comparator/placebo arm probabilities) and did not accumulate transthyretin stabilizing treatments costs. We applied the discontinuation rates for each 6-month cycle up to 30 months (to align with the end of the clinical trial). After 30 months, individuals on treatment remained on treatment, and individuals who

discontinued treatment remained off treatment and could not transition back to receiving treatment.

*Mortality*

Individuals transitioned to the death state due to all-cause mortality and/or ATTR-CM/HF mortality . All-cause mortality was sourced from sex- and age-adjusted actuarial life tables. [108] HF-specific mortality was calculated from published hazard ratios of HF mortality stratified by NYHA functional class (Table E2.3), sourced from a systematic review of published literature. We assumed NYHA Class I mortality rates are equivalent to all-cause mortality when applying the identified hazard ratios for differential mortality by NYHA functional class. Given the lack of published ATTR-CM-specific mortality data, we calibrated our simulated mortality to the placebo survival plot observed in the ATTR-ACT [tafamidis] clinical trial to obtain ATTR-CM-specific mortality. Calibration was achieved by applying a single adjustment factor to the HF-specific morality rates.

Finally, an additional single treatment effect was applied to the transthyretin stabilizing agent arm, across all four NYHA functional classes. This treatment effect was calculated by calibrating our simulated treatment arm mortality to the treatment survival plot observed in the ATTR-ACT [tafamidis] clinical trial. Mortality was calibrated to the ATTR-ACT [tafamidis] clinical trial, as the ATTRibute-CM [acoramidis] clinical trial's mortality rates were lower than those observed by the general population, and we believe calibration to the ATTRibute-CM [acoramidis] clinical trial would artificially inflate survival.

**Table E2.4. Mortality Inputs**

| Parameter | Value | Source |
|---|---|---|
| **Background Mortality** | Refer to the source | 2019 US Life Table[108] |
| **NYHA Class II v. NYHA Class I Mortality (HR, 95% CI)** | 1.78 (1.54, 2.06) | JMO Arnold 2013[59,60] |
| **NYHA Class III v. NYHA Class I Mortality (HR)** | 3.51 (3.05, 4.04) | |
| **NYHA Class IV v. NYHA Class I Mortality (HR)** | 5.74 (4.81, 6.85) | |
| **ATTR-CM Specific Mortality (HR)** | 1.18 | Calculated from ATTR-ACT [tafamidis] clinical trial[54] |
| **Calibrated Treatment Mortality Effect (HR for treatment compared to standard care alone)** | 0.58 | |

HR: Hazard Ratio, NYHA: New York Heart Association

### *Economic Inputs*

All costs used in the model were updated to first-quarter 2024 US dollars using the consumer price index for health care using Bureau of Economic Analysis data.[115]

*Drug Acquisition Costs*

Medication list prices were calculated as 6-month values based on FDA-approved dosing regimens to align with the model cycle length. The transthyretin stabilizing agent price was based on the tafamidis list price, calculated from the average RED BOOK reported wholesale acquisition cost (WAC) across all applicable formulations. When gross-to-net discounts are not available in SSR health, the Federal Supply Schedule (FSS) pricing is recommended to be used be used to calculate the discount from the WAC in ICER's Reference Case. This methodology yielded a discount from WAC that was believed to substantially underestimate the discount observed in practice. An alternative source from IPD Analytics' Rebate Monitor tool was used to represent the anticipated discount from WAC for tafamidis.[110] The mid-point of the IPD estimate (25%-30%) was applied to calculate a Net Annual Cost.

**Table E2.5. Drug Cost Inputs**

| Drug | Annual WAC | Discount from WAC | Annual Net Price |
|---|---|---|---|
| **Transthyretin Stabilizing Agents*** | $267,987.48 annual supply | 27.5% † | $194,290.92 |

WAC: wholesale acquisition cost

* Based on tafamidis pricing

† Sourced from IPD Analytics

*Background & Best Supportive Care Cost*

Given the lack of identified literature for NYHA class specific costs for a population of patents with ATTR-CM, data from a 2022 study including patients with obstructive hypertrophic cardiomyopathy (OCH) was used. Best supportive care costs were inclusive of costs for outpatient visits, emergency room visits, other visits and pharmacy costs. These costs were in addition to the transthyretin stabilizing agent costs in the treatment arms. The estimates utilized are presented in Table E2.7.[61]

**Table E2.6. Annual Cost of ATTR-CM best supportive care**

| NYHA Class | Annual Costs*† |
|---|---|
| **NYHA Class I** | $5,821 |
| **NYHA Class II** | $8,259 |
| **NYHA Class III** | $12,387 |
| **NYHA Class IV** | $20,416 |

* Wang et al.[61]

† Including outpatient, emergency, other visits and pharmacy costs

*Cardiovascular-Related Hospitalization Costs*

As previously detailed, given the lack of available literature on NYHA class specific ATTR-CM costs, a 2022 study on OCH was identified and utilized for cardiovascular-related hospitalization cost inputs. These estimates were deemed acceptable after consultations with clinical experts. Inputs are presented in Table E2.9.[61]

**Table E2.7. Annual Cardiovascular-Related Hospitalizations Costs by NYHA Functional Class [61]**

| NYHA Class | Annual Cardiovascular-Related Hospitalization Cost |
|---|---|
| **NYHA Class I** | $29,317 |
| **NYHA Class II** | $16,679 |
| **NYHA Class III** | $16,961 |
| **NYHA Class IV** | $20,170 |

NYHA: New York Heart Association

*Productivity Costs*

***Patient Productivity Cost***

Indirect cost values were identified from a systematic review of HF patient productivity costs. Annual costs for productivity loss per patient were identified for both non-working and working patients.[111] For working patients, productivity loss included absenteeism and presenteeism. Annual percentages for absenteeism, presenteeism, and overall work impairment were utilized and multiplied by the average January 2024 salary in the US, as reported by the Bureau of Labor Statistics.[116] Calculated inputs are shown below. From the payer's perspective, the analysis incorporated productivity losses stemming from work impairment, including both presenteeism and absenteeism. The modified societal perspective expanded this scope to encompass work productivity for all patients, regardless of employment status. Given that the study was conducted in Turkey, it is important to consider potential income, work habits, and lifestyle differences.

**Table E2.8. Annual Cost of Productivity Loss per patient[111]**

| NYHA Class | Annual Productivity Loss % | Average Salary (Jan 2024) | Value |
|---|---|---|---|
| **Loss of Work Productivity Caused by Nonworking Patients** | | | |
| **NYHA Class I** | 34.3% | $59,384 | $20,369 |
| **NYHA Class II** | 41.7% | $59,384 | $24,585 |

| | | | |
|---|---|---|---|
| **NYHA Class III** | 70.0% | $59,384 | $41,569 |
| **NYHA Class IV** | 95.8% | $59,384 | $56,890 |
| **Loss of Work Productivity Due to Overall Work Impairment** | | | |
| **NYHA Class I** | 20.8% | $59,384 | $12,352 |
| **NYHA Class II** | 36.4% | $59,384 | $21,616 |
| **NYHA Class III** | 66.1% | $59,384 | $39,253 |
| **NYHA Class IV** | 91.6% | $59,384 | $54,396 |

### *Caregiver productivity cost*

Costs associated with the caregiver burden were identified through a comprehensive review of existing literature. A cross-sectional survey, conducted among patients with HF and their caregivers in multiple European countries, provided data on time spent on caregiving, categorized by NYHA class.[112] Based on the literature, which indicates that HF caregivers are typically family members of the patient, the average annual US labor market price was selected, instead of the cost associated with hiring a formal caregiver.[112] The US average hourly wage was sourced from the quarterly report, "Usual Weekly Earnings of Wage and Salary Workers, First Quarter 2024".[116] Weekly caregiver productivity costs were then calculated by multiplying the weekly hours spent on caregiving by the average hourly wage, and these costs were subsequently annualized.

**Table E2.9. Annual Cost of Productivity Loss per patient**

| NYHA Class | Hours / Week* | 2024 Hourly Wage | Annual Value† |
|---|---|---|---|
| **NYHA Class I** | 11.8 | $28.49 | $17,481 |
| **NYHA Class II** | 18.1 | $28.49 | $26,815 |
| **NYHA Class III** | 25.9 | $28.49 | $38,370 |
| **NYHA Class IV** | 25.9 | $28.49 | $38,370 |

∗ [112]

† Calculated by multiplying time spent on caregiving by 2024 US average hourly wage

### *Utility Inputs*

Utility values for each NYHA functional class health state were derived from a targeted systematic review of publicly available literature, manufacturer submitted data, and estimates from prior heart failure treatment models.[51-54] The health state utility values for each NYHA functional class were equal for the treatment and comparator arms of the model.

Utility values reported in the ATTR-ACT [tafamidis] clinical trial are presented in Table E2.4; these values were obtained by crosswalking EQ-5D-3L results with the US value set.[54,58] Noting that the NYHA Class I utility value was higher than the average utility at age 70 for the US general population (0.82), we adjusted the reported clinical trial utilities to match the general population average values, preserving the observed margins between NYHA functional class utilities reported from the clinical trial.[62]

Additionally, we applied a disutility for individuals experiencing cardiovascular-related hospitalization per cycle. The disutility value was identified through a systematic literature review, and the values are presented in table E2.5. The source publication was an economic model that calculated disutilities based on an average hospital length of stay of 4 days.[117]

**Table E2.10. Health State Utilities**

| Parameter | Reported Utility Values [95% CI]* | Adjusted Utility Based on General Population Averages† |
|---|---|---|
| **NYHA Class I** | 0.893 [0.854–0.932] | 0.82 |
| **NYHA Class II** | 0.802 [0.782–0.822] | 0.729 |
| **NYHA Class III** | 0.706 [0.686–0.726] | 0.633 |
| **NYHA Class IV** | 0.406 [0.289–0.524] | 0.333 |

* ATTR-ACT and US value set [54,58]

† Calculated from the US population norms [62]

**Table E2.11. Hospitalization Disutility (for an ~4-day length of stay, on average)**

| Parameter | Reported Utility Values * |
|---|---|
| **NYHA Class I** | -0.04 |
| **NYHA Class II** | -0.07 |
| **NYHA Class III** | -0.1 |
| **NYHA Class IV** | -0.29 |

* Griffiths 2014

# E3. Results

The undiscounted total costs, life years, quality-adjusted life years (QALYs), equal-value life years (evLYs), and time (years) spent in NYHA Class I and II for transthyretin stabilizing agent plus best supportive care treatment compared to best supportive care alone are presented in Table E3.1.

**Table E3.1 Undiscounted Results for the Base-Case for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs | Time (years) in NYHA Class I and II |
|---|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $677,000 | $35,000 | $41,000 | $753,000 | 4.0 | 1.7 | 2.3 | 2.5 |
| **Best Supportive Care Alone** | $0 | $23,000 | $32,000 | $55,000 | 3.0 | 1.3 | 1.3 | 1.7 |

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

Table 4.5 presents the undiscounted time the simulated cohort spent (in years) in each NYHA functional class in the base-case over the lifetime horizon. Transthyretin stabilizing agent plus best

supportive care results in a higher percentage of time spent in NYHA Class I and II compared to best supportive care alone. Alternatively, best supportive care alone had a higher percentage of time in NYHA Class III and IV compared to transthyretin stabilizing agent plus best supportive care.

**Table E3.2 Time Spent (in years) in NYHA Functional Class (Undiscounted)**

| | NYHA I | NYHA II | NYHA III | NYHA IV | Total LYs |
|---|---|---|---|---|---|
| **Transthyretin Stabilizing Agent + Best Supportive Care (% of total LY)** | 0.39 (9%) | 2.12 (45%) | 1.16 (30%) | 0.35 (16%) | 4.02 |
| **Best Supportive Care Alone (% of total LY)** | 0.19 (4%) | 1.55 (39%) | 0.96 (32%) | 0.3 (25%) | 3.00 |

# E4. Sensitivity Analyses

## One-Way Sensitivity Analysis

**Table E4.1. Tornado Diagram Inputs and Results for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**

| | Lower Input CE Ratio† (Cost/QALY Gained) | Upper Input CE Ratio† (Cost/QALY Gained) | Lower Input | Upper Input |
|---|---|---|---|---|
| **Utilities** | | | | |
| **Utility for NYHA Class I** | $1,918,000 | $1,874,000 | 0.78 | 0.86 |
| **Utility for NYHA Class II** | $1,931,000 | $1,861,000 | 0.71 | 0.75 |
| **Utility for NYHA Class III** | $1,906,000 | $1,885,000 | 0.61 | 0.65 |
| **Utility for NYHA Class IV** | $1,911,000 | $1,881,000 | 0.22 | 0.45 |
| **Disutility for Hospitalizations in NYHA Class I** | $1,888,000 | $1,896,000 | -0.16 | -0.03 |
| **Disutility for Hospitalizations in NYHA Class II** | $1,909,000 | $1,894,000 | -0.19 | -0.06 |

| | | | | |
|---|---|---|---|---|
| **Disutility for Hospitalizations in NYHA Class III** | $1,934,000 | $1,889,000 | -0.22 | -0.08 |
| **Disutility for Hospitalizations in NYHA Class IV** | $1,992,000 | $1,852,000 | -0.41 | -0.23 |
| **Costs** | | | | |
| **Cost of Best Supportive Care NYHA Class I** | $1,896,000 | $1,896,000 | $2,876 | $2,946 |
| **Cost of Best Supportive Care NYHA Class II** | $1,896,000 | $1,896,000 | $4,096 | $4,163 |
| **Cost of Best Supportive Care NYHA Class III** | $1,896,000 | $1,896,000 | $6,133 | $6,255 |
| **Cost of Best Supportive Care NYHA Class IV** | $1,896,000 | $1,896,000 | $9,982 | $10,435 |
| **Cost of Hospitalization in NYHA Class I** | $1,896,000 | $1,896,000 | $15,107 | $15,477 |
| **Cost of Hospitalization in NYHA Class II** | $1,896,000 | $1,896,000 | $8,629 | $8,771 |
| **Cost of Hospitalization in NYHA Class III** | $1,896,000 | $1,896,000 | $8,760 | $8,935 |
| **Cost of Hospitalization in NYHA Class IV** | $1,895,000 | $1,896,000 | $10,287 | $10,754 |

CE: cost-effectiveness

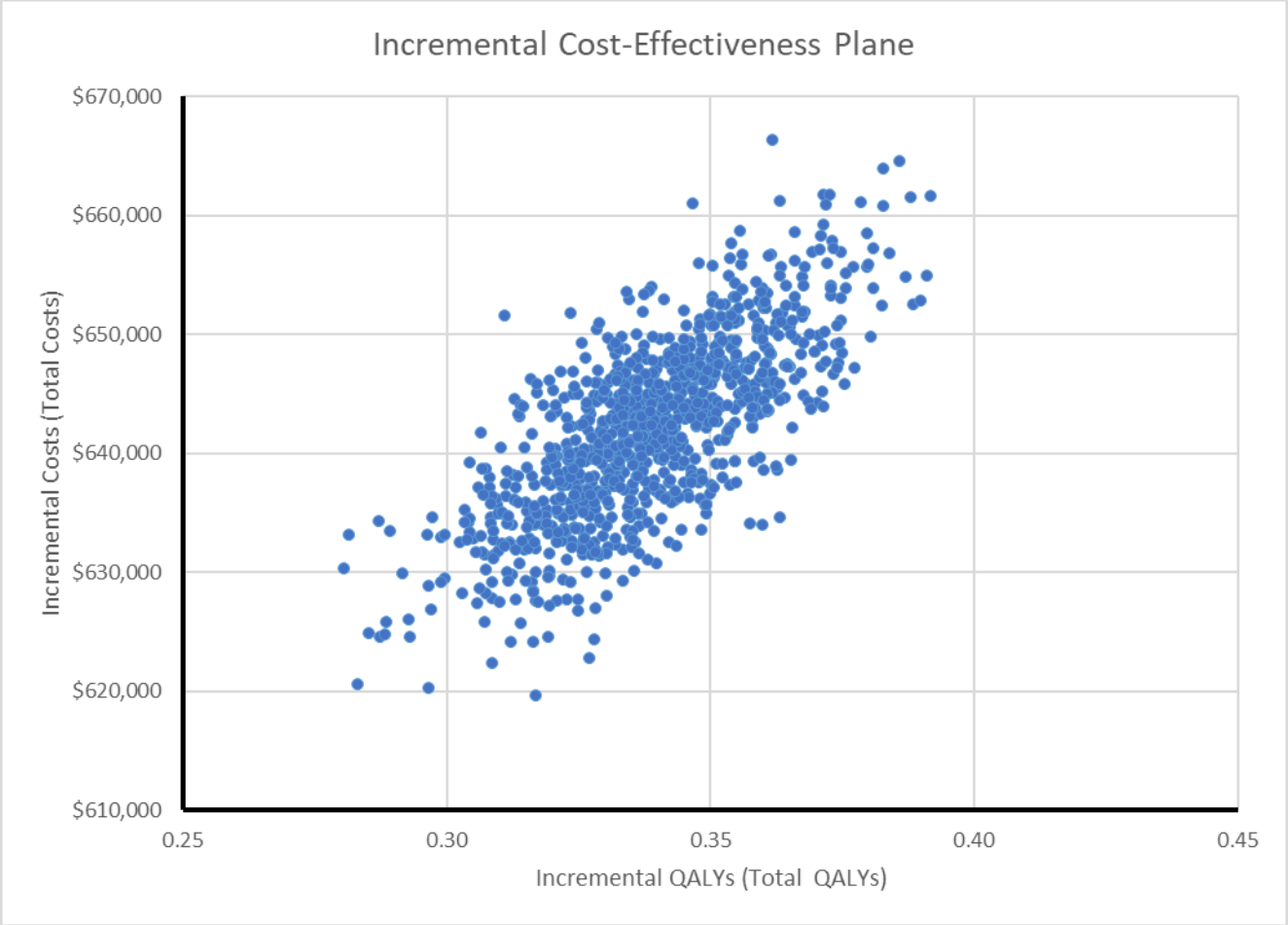
* Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

† Based on tafamidis pricing

## Probabilistic Sensitivity Analysis

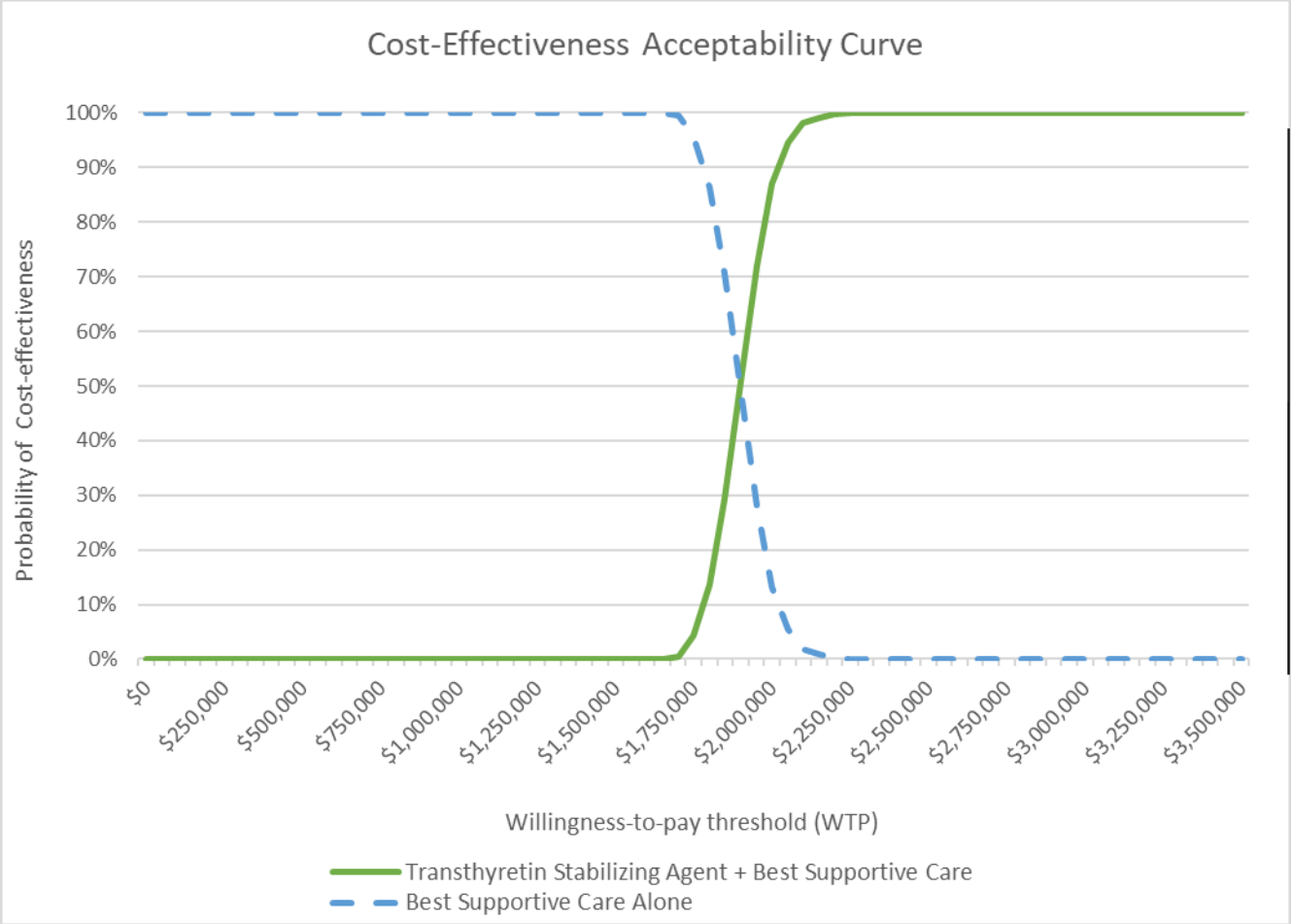
The cost-effectiveness plane and acceptability curves for the probabilistic sensitivity analysis are presented in Figures E4.1 and E4.2.

**Figure E4.1: Cost-Effectiveness Plane for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**




* Based on tafamidis pricing

**Figure E4.2: Acceptability Curve for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone**




# E5. Scenario Analyses

## Scenario Analysis 1: Modified Societal Perspective

In the modified societal perspective scenario, patient productivity gains and caregiver time spent caregiving were included as non-intervention costs. Results are presented in Table E5.1.

**Table E5.1. Discounted Results for Modified Societal Perspective**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $634,000 | $32,000 | $390,000 | $1,055,000 | 3.7 | 1.6 | 2.2 |
| **Best Supportive Care Alone** | $0 | $22,000 | $309,000 | $331,000 | 2.9 | 1.3 | 1.3 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 2: Mortality Calibrated to ATTRibute-CM [acoramidis] Clinical Trial

In the mortality calibrated to ATTRibute-CM [acoramidis] clinical trial, we followed recalibrated the survival observed in our model to match the ATTRibute-CM [acoramidis] clinical trial data. Results are presented in Table E5.2.

**Table E5.2. Discounted Results for Mortality Calibrated to ATTRibute-CM [acoramidis] Clinical Trial**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $1,312,000 | $66,000 | $68,000 | $1,446,000 | 6.2 | 2.6 | 3.3 |
| **Best Supportive Care Alone** | $0 | $42,000 | $62,000 | $103,000 | 5.0 | 2.1 | 2.1 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 3: Tafamidis Trial Population

In the tafamidis trial population scenario, population characteristics (age, gender, and baseline NYHA functional class proportions) reflected the ATTR-ACT [tafamidis] clinical trial population. Results are presented in Table E5.3.

**Table E5.3. Discounted Results for Tafamidis Trial Population**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $724,000 | $42,000 | $47,000 | $813,000 | 4.4 | 1.8 | 2.5 |
| **Best Supportive Care Alone** | $0 | $27,000 | $38,000 | $65,000 | 3.3 | 1.4 | 1.4 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 4: Unadjusted Utility Values

In the unadjusted utility values scenario, the utility values reported in ATTR the-ACT [tafamidis] clinical trial were used without adjustment to population average values. Results are presented in Table E5.4.

**Table E5.4. Discounted Results for Unadjusted Utility Values**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $634,000 | $32,000 | $38,000 | $703,000 | 3.7 | 1.8 | 2.3 |
| **Best Supportive Care Alone** | $0 | $22,000 | $30,000 | $52,000 | 2.9 | 1.4 | 1.4 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 5: Exclude Non-Drug Costs

In the exclude non-drug costs scenario, all hospitalization and non-drug costs were excluded from the analysis. Results are presented in Table E5.5.

**Table E5.5. Discounted Results for Exclude Non-Drug Costs**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $634,000 | $0 | $0 | $634,000 | 3.7 | 1.6 | 2.2 |
| **Best Supportive Care Alone** | $0 | $0 | $0 | $0 | 2.9 | 1.3 | 1.3 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 6: Exclude Hospital Costs

In the exclude hospital costs scenario, all hospitalization costs were excluded from the analysis. Results are presented in Table E5.6.

**Table E5.6. Discounted Results for Exclude Hospital Costs**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $634,000 | $0 | $38,000 | $672,000 | 3.7 | 1.6 | 2.2 |
| **Best Supportive Care Alone** | $0 | $0 | $30,000 | $30,000 | 2.9 | 1.3 | 1.3 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

## Scenario Analysis 7: Exclude Supportive Care Costs

In the exclude supportive care costs scenario, all costs related to supportive care were excluded from the analysis. Results are presented in Table E5.7.

**Table E5.7. Discounted Results for Exclude Supportive Care Costs**

| Treatment | Drug Cost* | Hospital Cost | Non-Drug Cost† | Total Cost* | Life Years | QALYs | evLYs |
|---|---|---|---|---|---|---|---|
| **Stabilizing Agent + Best Supportive Care** | $634,000 | $32,000 | $0 | $665,000 | 3.7 | 1.6 | 2.2 |
| **Best Supportive Care Alone** | $0 | $22,000 | $0 | $22,000 | 2.9 | 1.3 | 1.3 |

evLYs: equal value of life years gained, QALY: quality-adjusted life year

* Based on tafamidis pricing

† Including supportive card and non-stabilizing therapies costs

# E6. Heterogeneity and Subgroups

ATTR-CM genotype (wild type vs. variant) may influence disease progression and treatment effectiveness. However, due to insufficient accessible data, we did not consider the impact of ATTR-CM genotype in the base-case analysis or scenario analysis.

# E7. Model Validation

## Prior Economic Models

Our systematic literature review did not yield any cost-effectiveness analyses of acoramidis. However, we identified three reports assessing the cost-effectiveness and/or modeling long term health impact of tafamidis (with or without incorporating various ATTR-CM screening strategies).[7,51,52] Additionally the health technology assessments of tafamidis were identified from multiple countries.[57] Our model used NYHA functional class health states and allowed for improvements in functional class and transitions across more than one function class in one cycle, which aligns with the structural assumptions taken by other modelers.[51,52,56] The assumptions made in our analysis were similar to other published cost-effectiveness models in ATTR-CM and heart failure.

One published model examined the long-term impact of tafamidis on morbidity and mortality based on the ATTR-ACT [tafamidis] clinical trials data.[51] This model used treatment efficacy inputs from both the original ATTR-ACT 30-month trial as well as from the 49-month open-label extension study, and applied parametric mortality methods to extrapolate the clinical findings from tafamidis over a 30-year time horizon. However, the published study did not incorporate costs or any other economic inputs. The ATTR-ACT model made two optimistic assumptions that our model did not: 1) predicted survival was based on NYHA class at baseline and 2) that tafamidis has an independent effect on mortality. Based on clinical expert review, we determined a patient's current NYHA class is a more reasonable predictor for these clinical events than a patient's NYHA class at baseline. Additionally, extrapolation of overall survival from the trial with no adjustment for background mortality may be inappropriate as the population of interest is elderly and clinical trial data is unlikely to capture the increasing disease unrelated hazards associated with increasing age.[52,56]