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

Final Evidence Report

October 21, 2024

Prepared for

December 8, 2025: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 12 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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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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No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous 36 months from health care manufacturers or insurers.

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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 the 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/2024/09/ICER_ATTR-CM_Key-Stakeholders-List_For-Publication_090524.pdf

Table of Contents

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
HFpEF	Heart failure with preserved ejection fraction
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
NT-proBNP	N-terminal pro B –type natriuretic peptide
NA	Not applicable
NYHA	New York Heart Association
n	Number
N	Total number
NE	Not estimated
NR	Not reported
PDRR	Participant to disease-prevalence representation ratio
pg/AEmL	Picograms per milliliter
QALY	Quality-adjusted life year
RR	Relative risk
SE	Standard error
SD	Standard deviation
TTR	Transthyretin
VAS	Visual analogue scale
WAC	Wholesale acquisition cost
6MWD	6-minute walk distance
6MWT	6-minute walk test

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 occurred. Even after diagnosis, patients often struggle with access to treatments and 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 transthyretin (TTR) stabilizer tafamidis in 2019, patients with ATTR-CM were typically managed like other patients with heart failure with preserved ejection fraction, although some young patients would be treated with heart or heart-liver transplants. Another oral stabilizer, acoramidis, is under evaluation by the Food and Drug Administration (FDA) with a Prescription Drug User Fee Act (PDUFA) date of November 29, 2024. Efficacy data for treating ATTR-CM for an RNA silencing agent, vutrisiran, has recently been reported and the manufacturer has submitted a supplemental new drug application (sNDA). Vutrisiran and other 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. The lack of a statistically significant mortality benefit with acoramidis affects our judgment of both acoramidis and tafamidis 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+")**

In the HELIOS-B phase 3 trial, with full results published on August 30, 2024, vutrisiran reduced all-cause mortality at 33 to 36 months (16% vs. 21%; HR 0.69), achieved similar though statistically non-significant reductions in mortality in subgroups receiving or not receiving tafamidis. HELIOS-B recruited a contemporary population where 40% of participants were receiving tafamidis at baseline. Vutrisiran was well tolerated. As such, we have high certainty that treatment with vutrisiran, compared with no disease-specific therapy or when added to tafamidis, provides a substantial net health benefit. **("A")**

Given the different populations studied, and the lack of additional data and analyses comparing the population in the HELIOS-B trial of vutrisiran with the population in the ATTRibute-CM trial of acoramidis or the ATTR-ACT trial of tafamidis, 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 in 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 LY Gained	Cost per evLY Gained	Cost per Additional Year in NYHA Class I and II*
Transthyretin Stabilizing Agent + Best Supportive Care	Best Supportive Care alone	$873,000	$566,000	$627,000	$871,000

evLYs: equal value of life years gained, NYHA: New York Heart Association, QALY: quality-adjusted life year
*Based on tafamidis pricing

The Health Benefit Price Benchmark (HBPB) for transthyretin stabilizing agents ranges from $13,600 to $39,000 annually. This would require discounts of 85% to 95% from the wholesale acquisition cost (WAC) for tafamidis. Because of the timing of new information on vutrisiran and lack of data needed for modeling, we did not perform economic modeling of this agent.

ICER did not undertake a budget impact analysis for transthyretin stabilizing agents or vutrisiran, and as such, is not issuing an access and affordability alert for these agents. 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 anticipated material impact on payer budgets from introduction of acoramidis. A cost-effectiveness analysis for vutrisiran was not conducted, so we are unable to comment on the potential budget impact and affordability considerations associated with this agent.

Key policy recommendations include:

- Federal and state policymakers should remove barriers to the use of telemedicine, including across state lines, so that individuals with ATTR-CM can access the most knowledgeable centers of excellence, regardless of geographic location.
- Clinical specialty societies should establish diagnostic cutoffs normalized for gender and/or body size both for screening for ATTR-CM in clinical practice and enrollment in clinical trials, to reduce failure to accurately diagnosis the condition in women and smaller patients.
- Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- Researchers and funding agencies should focus future research on efforts to establish the comparative effectiveness of tafamidis, acoramidis, and vutrisiran in similar populations.

Appraisal committee votes on questions of comparative effectiveness, benefits beyond health, and long term value of money are found at the end of their corresponding sections. Key policy recommendations regarding pricing, access, and future research are included in Chapter 8 and Supplement F.

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, and is also more common in women than in men.[3,4] 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 heart failure with preserved ejection fraction (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 Prescription Drug User Fee Act (PDUFA) date of November 29, 2024.[13,14] Another treatment strategy in development is to use RNA silencing to reduce production of transthyretin.[15] Eplontersen is an RNA silencing agent approved for the treatment of nerve pain and dysfunction from ATTR and is being evaluated

for treatment of cardiomyopathy.[16,17] The manufacturer for another RNA silencing agent previously approved for ATTR neuropathy, vutrisiran, has submitted a supplementary new drug application to expand the indications to ATTR-CM based on recent data from the HELIOS B trial.

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. Patients highlighted data showing mean delays to correct diagnosis of around six years.[18] 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 overall is 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.[20-20] 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.[21] 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.[22] Despite greater prevalence in Black patients, a smaller proportion of Black patients is enrolled in clinical trials for ATTR-CM.[23] 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	Positive biopsy or scintigraphy scan
NYHA Class	I-III	I-III	I-III*
6MWD	≥100 m	≥150 m on at least 2 tests	≥150 m
NT-proBNP Level	≥600 pg/mL	300 - 8499 pg/mL	300 - 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, eGFR: estimated glomerular filtration rate, 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

*Excludes NYHA class III with a National Amyloidosis Centre ATTR stage of 3 (defined as an NT-proBNP level of >3000 pg per milliliter and an eGFR of <45 ml per minute per 1.73 m2 of body-surface area)

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 2:1 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.[24]

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.[25]

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.[26] 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.[27] The enrolled population included both patients on no other disease-modifying therapy and patients on tafamidis.

The HELIOS-B trial enrolled 655 patients ages 18 to 85 diagnosed with ATTR-CM (hereditary and wild-type).[28-30] 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 a National Amyloidosis Centre ATTR stage of 3 (defined as an NT-proBNP level of >3000 pg per milliliter and an eGFR of <45 ml per minute per 1.73 m2 of body-surface area).[27] 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 at baseline.[31] 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

We conducted a qualitative indirect comparison between the two TTR stabilizers, reviewing the surrogate outcome of post-treatment TTR serum levels between the agents.[32-34] 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).[35]

We were unable to make any indirect comparisons between vutrisiran and the TTR stabilizers due to differing mechanisms of action and data availability.

Table 3.2. Overview of Key Studies

Trial		ATTR-ACT tafamidis 80 mg n=176 Placebo n=177	ATTRibute-CM acoramidis n=421 Placebo n=211	HELIOS-B vutrisiran n=326 Placebo n=328
N		353	632	654
Age, Years	**Mean**	74.3	77	77*
Sex, %	**Male**	90.2	90.2	92.5
	Female	9.8	9.8	7.5
Race, %	**White**	80.9	87.8	84.4
	Black	14.3	4.7	7.2
	Asian	3.9	2.1	5.7
	Other	0.4	5.4	2.8
TTR Type, %	**ATTRv**	24	9.7	11.6
	ATTRwt	75.9	90.3	88.4
Transthyretin Variant, %	**V122I**	56.9	62.1†	64.5
	T60A	11.8	8.6†	10
NYHA Class, %	**Class I**	8.4	10.8	12.8
	Class II	59.6	72	77.7
	Class III	31.9	17.2	9.5
NT-proBNP, pg/mL	**Median**	2995.9‡	2326	1801#
Baseline Medications, %	**Agents acting on renin-angiotensin system**	26.5	NR	NR
	Beta Blockers	29.3	NR	NR
	Diuretics	67.6	NR	79.5
	Antithrombotic Agents	40.1	NR	NR
6MWT Distance, mean		351.9	354.8	374.5‡
KCCQ, mean	**Overall Summary Score**	66.6	70.9	72.65

6MWT: 6-minute walk test, ATTRv: hereditary/variant type, ATTRwt: wild type, 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

*Age was reported as a median in the HELIOS-B trial

†Of the 58 participants screened for transthyretin variant

‡Median of tafamidis arm only

#Median of vutrisiran arm only

See Supplement Tables D2.2-4 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

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. 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.

There was no statistically significant difference in all-cause mortality reduction versus placebo between the 20 mg and 80 mg dose of tafamidis during the randomized portion of the ATTR-ACT trial (30-month median follow-up). A longer follow-up analysis that included ATTR-ACT as well as its long-term extension study (median 51 months) found a significant difference in survival in favor of the 80 mg dose compared with the 20 mg dose.[36]

Cardiovascular-related hospitalization

Cardiovascular-related hospitalizations 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).[36]

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. 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.[37] At month 30, more patients receiving tafamidis than placebo reported an improvement in 6 MWT distance from baseline (19% vs. 5%).[38]

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.[39] 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 D2.6 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 D2.5 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.[25] 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.[40] 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.[41]

Further insights into the impact of acoramidis on survival were presented outside of the primary peer-reviewed trial.[42] 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.[43]

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 D2.7 for additional results from the ATTRibute-CM trial

Vutrisiran

Results of the HELIOS-B trial are presented in Table 3.5 and described below.[27]

Mortality

In the primary population, after 33 to 36 months of follow-up, vutrisiran reduced all-cause mortality (16% vs. 21%; HR 0.69, 95% CI 0.49-0.98). Receipt of a heart transplant or left ventricular assist device were counted as deaths in this analysis. Statistically non-significant reductions in mortality were seen in the subgroup of patients not receiving tafamidis at baseline (18% vs 23%; HR 0.71; 95% CI 0.47-1.06) and in those receiving tafamidis at baseline (11.5% vs. 17.8%; HR based on 42 months of follow-up 0.59; 95% CI 0.32-1.08). Mortality through 42 months was reduced in the overall population (HR 0.65) and in those not receiving tafamidis (HR 0.66).

Recurrent Cardiovascular Events

In the HELIOS-B trial, recurrent cardiovascular events were defined as CV-related hospitalizations and urgent heart failure visits. Vutrisiran was superior to placebo on this outcome in both the monotherapy (HR: 0.68, 95% CI: 0.53 to 0.86) and overall (HR: 0.73, 95% CI: 0.61 to 0.88) study populations.

Primary Endpoint

The primary endpoint of HELIOS-B was a composite of all-cause mortality and recurrent CV events. It was analyzed using a modified Andersen-Gill model with a robust variance estimator, with deaths and recurrent cardiovascular events weighed equally, and the model was stratified by tafamidis use at baseline. Vutrisiran reduced the risk of the primary endpoint in the overall population (HR=0.72; 95% CI 0.56-0.93, p=0.0118).

Functional Status and Quality of Life

More patients receiving vutrisiran had stable or improved NYHA class at 30 months (68% vs. 61% in the overall population and 66% vs. 56% in those not receiving tafamidis). Loss of walking distance on the 6MWT at 30 months was less with vutrisiran (-45 m vs. -72 m in the overall population and -60 m vs. -92 m in those not receiving tafamidis). Decline in KCCQ-OS at 30 months was less with vutrisiran (-9.7 vs. -15.5 in the overall population and -10.8 vs. -19.5 in those not receiving tafamidis).

Durability of Treatment Effect

Patients in the HELIOS-B trial were eligible to continue treatment with vutrisiran for an additional 24 months after an initial randomized follow-up period of 33 to 36 months.

Table 3.5. HELIOS-B Results

Trial	HELIOS-B			
Arms	Overall Population		Monotherapy Population	
	Vutrisiran	Placebo	Vutrisiran	Placebo
N	326	328	196	199
Death from any cause and recurrent cardiovascular events, HR (95% CI; p value)	0.72 (0.56, 0.93; 0.01)		0.67 (0.49, 0.93; 0.02)	
Time to first event (death from any cause and recurrent cardiovascular events), months HR (95% CI; p value)	0.72 (0.57, 0.91; 0.006)		0.64 (0.48, 0.87; 0.004)	
Death from any cause, HR (95% CI; p value)	0.69 (0.49, 0.98; 0.04)		0.71 (0.47, 1.06; 0.12)	
Recurrent cardiovascular events, HR (95% CI; p value)	0.73 (0.61, 0.88; 0.001)		0.68 (0.53, 0.86; 0.001)	
Patients with at least one event, n (%)	125 (38)	159 (48)	76 (39)	105 (53)
Death from any cause, n (%)	51 (16)	69 (21)	36 (18)	46 (23)
Recurrent CV Events, n (%)	112 (34)	133 (41)	66 (34)	87 (44)
Death from any cause through 42 months, HR (95% CI; p value)	0.65 (0.46, 0.90; 0.01)		0.66 (0.44, 0.97; 0.045)	
Death from any cause, n (%)	60 (18)	85 (26)	43 (22)	58 (29)
Least-squares mean change from baseline at 30 months 6MWD, meters (95% CI)	26.5 (13.4, 39.6; <0.001)		32.1 (14.0, 50.2; <0.001)	
Least-squares mean change from baseline in KCCQ-OS score at 30 months, points	5.8 (2.4, 9.2; <0.001)		8.7 (4, 13.4; <0.001)	
Adjusted difference in percentage points of improved or stable NYHA class at 30 months (95%CI; p value)	8.7 (1.3, 16.1; 0.02)		12.5 (2.7, 22.2; 0.01)	

6MWD: 6-minute walk distance, CI: confidence interval, CV: cardiovascular, HR: hazard ratio, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, N: total number, NYHA: New York Heart Association, %: percent
Note: For the analyses that included death from any cause, heart transplantation and implantation of a left ventricular assist device were treated as deaths
See Supplement Table D2.8 for additional results from the HELIOS-B trial

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%).[43] 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.[43] 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.[35] 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.

Tafamidis 80 mg Versus Tafamidis 20 mg

The LTE analysis comparing the two doses of tafamidis was not a direct randomized comparison. Bias could result if there were differential enrollment of patients with different severities of disease in the LTE; we lack the data to assess this. Following a protocol amendment, all patients in the LTE were transitioned to tafamidis 61 mg free acid, which is bioequivalent to tafamidis 80 mg. As such, differential amounts of time exposed to the tafamidis 80 mg and 20 mg doses before the protocol amendment could also introduce bias into the comparison. Finally, while mortality is reported in the LTE dose comparison, we lack data on other patient-important outcomes.

Harms

Table 3.6 provides an overview of the safety profiles of the three therapies.

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 D2.9 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 D2.10 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. The three most common adverse events seen in patients treated with vutrisiran were cardiac failure, COVID-19, and atrial fibrillation. 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 D2.11 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.[44] 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		HELIOS-B	
Arms		Tafamidis 80 mg	Placebo	Acoramidis	Placebo	Vutrisiran	Placebo
N		176	177	421	211	326	328
Timepoint		30 months		30 months		33-36 months	
TEAE, n (%)	All	173 (98.3)	175 (98.9)	413 (98.1)	206 (97.6)	322 (99)	323 (98)
	Treatment-related	NR	NR	50 (11.9)	11 (5.2)	NR	NR
	With fatal outcome	NR	NR	60 (14.3)	36 (17.1)	49 (15)	63 (19)
	Leading to hospitalization	NR	NR	212 (50.4)	128 (60.7)	NR	NR
	Leading to discontinuation	40 (22.7)	51 (28.8)	39 (9.3)	18 (8.5)	10 (3)	13 (4)
	Leading to dose reduction	2 (1.1)	4 (2.3)	4 (1)	0 (0)	NR	NR
Severe TEAE, n (%)		110 (62.5)	114 (64.4)	157 (37.3)	96 (45.4)	158 (48)	194 (59)
Cardiac Disorders, n (%)	All	185 (70.1)*	124 (70.1)	230 (54.6)	144 (68.2)	227 (70)	242 (74)
	Cardiac failure	46 (26.1)	60 (33.9)	101 (24)	83 (39.3)	38 (12)	57 (17)
	Atrial fibrillation	35 (19.9)	33 (18.6)	70 (16.6)	46 (21.8)	26 (8)	20 (6)

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.

Tafamidis

Among our subgroups of interest , the ATTR-ACT trial conducted subgroup analyses for TTR genotype, NYHA class, race (White or Black), gender, and age (<75 or ≥75).[45] 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.[46] See Supplement Table D2.10 for additional subgroup data from the ATTR-ACT trial.

Acoramidis

Among our subgroups of interest, the ATTRibute-CM trial 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 D2.12 for additional subgroup data from the ATTRibute-CM trial.

Vutrisiran

Among our subgroups of interest, the HELIOS-B trial conducted subgroup analyses of TTR genotype, age (<75 or ≥75), and NYHA baseline class on the primary composite endpoint of death from any cause and recurrent CV events, as well death from any cause as an individual component. Subgroup effects in HELIOS-B were mostly inconsistent across outcomes and analyses, suggesting that most of these were due to random variation. Of note, it appeared that patients with lower levels of NT-proBNP consistently had larger improvements with vutrisiran than patients with higher levels of NT-proBNP, patients younger than age 75 had somewhat larger improvements than those ages 75 and older, and there may have been smaller effects of vutrisiran in patients with variant ATTR-CM who were already receiving tafamidis than in other groups. See Supplement Table D2.13 for additional subgroup data from the HELIOS-B trial.

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	Fair	Fair	Not reported

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.[47] 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.[47] 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: None of the three trials sufficiently enrolled a diverse population, particularly Black participants, earning two Fair and one Poor ratings. See the Health Equity Considerations section above for discussion on potential underdiagnosis of people of color with ATTR-CM.

Sex: All 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: The ATTR-ACT and ATTribute-CM trials effectively recruited older adults, consistent with the age profile of ATTR-CM, particularly those with wild-type disease. The HELIOS-B trial did not report on the proportion of trial participants that were ≥65 years old.

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.[25]
- 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.[48] 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.
- Additional data and analyses are needed to understand similarities and differences between the populations studied in the ATTRibute-CM trial of acoramidis and the HELIOS-B trial of

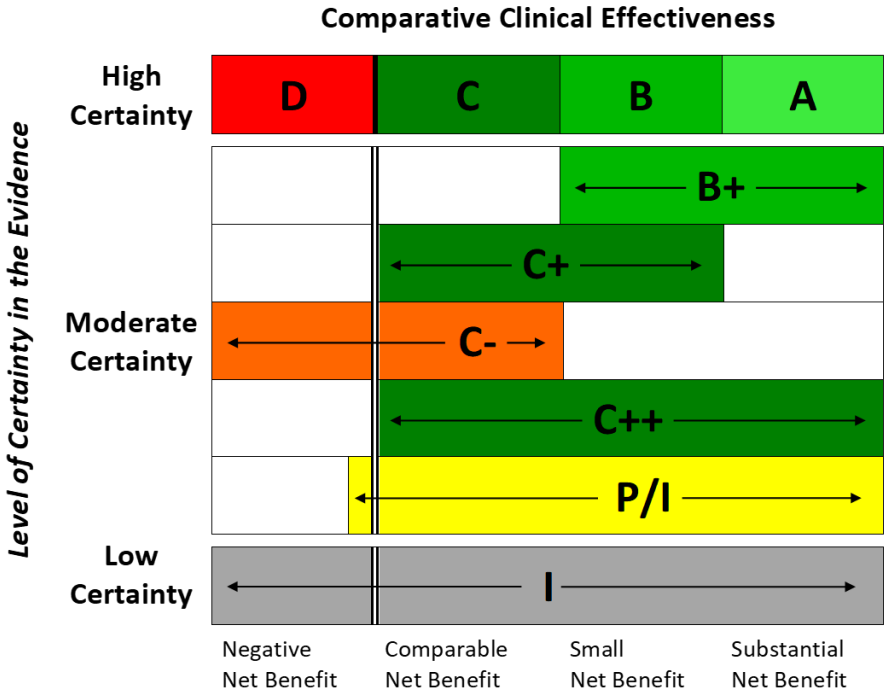
vutrisiran. Both these populations differed from those in the earlier ATTR-ACT trial of tafamidis.

- Patients with NYHA class 4 symptoms were excluded from all three pivotal 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.
- The FDA-approved dose of tafamidis is 80 mg daily, based on potentially suggestive evidence of greater efficacy than 20 mg daily in the LTE phase of ATTR-ACT.[36] This evidence from the LTE suggested an association between improved mortality and the higher 80 mg dose but included individuals previously receiving placebo who then switched to 20 mg or 80 mg. This comparison does not preserve the original trial randomization. However, the FDA decision was influenced by the fact that these data are concordant with *ex vivo* evidence for greater TTR stabilization for 80 mg rather than 20 mg.[49] In the FDA review, concern was raised that the evidence for superiority of 80 mg in the LTE was entirely driven by a subset of patients who received placebo in the phase 3 study and then switched to tafamidis 20 mg or 80 mg in the LTE phase. Some formularies have preferred the 20 mg dose for treatment of ATTR-CM, even those that is not the FDA-approved dose for this condition. The WAC price for 20 mg is one-fourth that of 80 mg (1 pill versus 4 pills). Thus, it is important for real-world policy decisions whether the 80 mg dose is superior to the 20 mg dose.

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

Results from the HELIOS-B trial show large relative reductions in mortality in all patients and similar (but statistically non-significant) reductions in those receiving or not receiving tafamidis. The population studied was a contemporary population where 40% of patients were receiving tafamidis. Mortality benefit was seen during the open-label extension where both arms may have been receiving vutrisiran, and so those 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. The absolute reductions in all-cause mortality in HELIOS-B were clinically important. There were no concerns about safety or side effects.

As such, we have high certainty that treatment with vutrisiran, compared with no disease-specific therapy or when added to tafamidis, provides a substantial net health benefit. **("A")**

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 and analyses comparing the characteristics of the populations studied in HELIOS-B and ATTRibute-CM, we also feel the evidence is insufficient to compare the net health benefits of vutrisiran with either tafamidis or acoramidis. **("I")** Additionally, given the findings in HELIOS-B, it may be that a primary issue will be whether combination therapy is superior to 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 Tafamidis	Current therapy alone	A
Vutrisiran	No Disease-specific treatment	A
Vutrisiran	tafamidis	I
Vutrisiran	acoramidis	I

Midwest CEPAC Votes

Table 3.9. Midwest CEPAC Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
***Patient Population for all questions**: Adults with transthyretin amyloid cardiomyopathy (ATTR-CM).*		
For adults with ATTR-CM is the current evidence adequate to demonstrate that the net health benefit of tafamidis is greater than that of no disease-specific treatment?	14*	0
For adults with ATTR-CM is the current evidence adequate to demonstrate that the net health benefit of acoramidis is greater than that of no disease-specific treatment?	15	0
For adults with ATTR-CM is the current evidence adequate to demonstrate that the net health benefit of vutrisiran is greater than that of no disease-specific treatment?	14†	0
For adults with ATTR-CM is the current evidence adequate to demonstrate that the net health benefit of vutrisiran added to tafamidis is greater than that of tafamidis alone?	0	15
Is the currently available evidence adequate to distinguish the net health benefit among the interventions when used as monotherapy (tafamidis, acoramidis, vutrisiran)?	0	15

*One council member was unable to vote, resulting in 14 total votes.

†One council member was unable to vote, resulting in 14 total votes.

The council unanimously voted that the current evidence is adequate to demonstrate that the net health benefit of tafamidis is greater than that of no disease-specific treatment. One council member was unable to vote.

The council unanimously voted that the current evidence is adequate to demonstrate that the net health benefit of acoramidis is greater than that of no disease-specific treatment.

The council unanimously voted that the current evidence is adequate to demonstrate that the net health benefit of vutrisiran is greater than that of no disease-specific treatment after reflecting on the results from the HELIOS-B trial where vutrisiran showed a large reduction in mortality. One council member was unable to vote.

Despite the A rating from the ICER research team, the council members unanimously voted that the current evidence is not adequate to demonstrate that the net health benefit of vutrisiran added to tafamidis is greater than that of tafamidis alone. The clinical experts shared their uncertainty of vutrisiran's added effect and spoke about how the combination therapy arm of the HELIOS B trial may not be adequate to determine clinical beneficial effects. The clinical experts stated the apparent absence of heterogenous treatment effects between the combination and monotherapy arms in HELIOS B does not lead to a conclusion of proof of efficacy of the combination (vutrisiran plus a stabilizer).

The council members unanimously voted that the currently available evidence is not adequate to distinguish the net health benefit among the interventions when used as monotherapy. The council heard from the evidence author and clinical expert that the different populations in trials causes real uncertainty about the comparative effectiveness of the three key medications. In addition to the concerns about different trial populations, one of the clinical experts also pointed out that the confidence intervals of the effects in the different trials are overlapping. All of this argues against any ability to compare the treatment effects of the 3 agents against one another.

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.[7,50-53] Although the comparative clinical effectiveness analysis reported separate evidence ratings for acoramidis and tafamidis 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 added to best supportive care compared to best supportive care alone. Furthermore, results from the vutrisiran clinical trial were released in June 2024 and evidence suggested that vutrisiran was superior to placebo and had 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.[52] See Supplement Section E1.4 for a description of the modeled population.

The model structure was based on the 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.[54] 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]).[50,51]

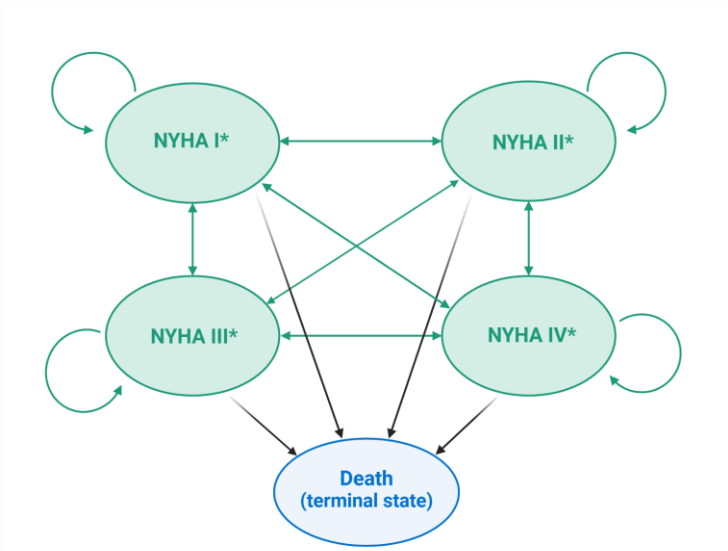
Transition probabilities, indicating differential progression through NYHA functional class with and without a transthyretin stabilizing agent, were derived from publicly available ATTR-ACT [tafamidis] trial data. There were no similar data available for acoramidis. We assumed clinical efficacy, in terms of heart failure progression, was equal across transthyretin stabilizing agents (i.e., 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 was treated with and without a transthyretin stabilizing agent. 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 ATTR-ACT [tafamidis] 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. Costs and health outcomes were discounted at 3% per year, and costs were inflated to the 2024 Q1 US dollar. The model cycle length was 6 months, to align with clinical data and previously published economic models.[51,55]

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.

Changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- Updated Mortality Estimation: To better represent the mortality observed in the clinical trial, we updated our approach to modeling mortality. In the first 18 months of the ATTR-ACT [tafamidis] trial, survival in both arms were very similar, but the survival curves diverged after 18 months. Therefore, we updated our mortality calibration to align with the two-part survival curve for better approximation of observed survival. Additionally, we found an error in how the transition probabilities accounted for mortality, which has been fixed.

- Corrected Utility Calculation: There was an error in our calculation of utilities, which has been fixed.

- Updated Hospital Related Disutility: The initial publication used for hospital disutility was not clear in the calculation and duration of hospitalization related disutility. We updated our source for the corresponding disutilities, as well as the time for which they were applied.

- Updated Hospitalization Rates: We updated our hospitalization rates to use a pooled rate, across arms, from the ATTR-ACT [tafamidis] clinical trial. Previously, we used a different rate of hospitalization for each arm, however, it appeared that differences in hospitalization rates for each NYHA class were inconsistent across trial arms and were more likely due to random differences with small samples.

- Added Scenario Analyses: We added two additional scenario analysis: 1) where the price of the transthyretin stabilizing agent is 25% of the base case price, and 2) no disutility from hospitalization. The scenario that used a 25% reduction in price reflects what we heard from patients regarding the variation in coverage across formularies. For example, the U.S. Veterans Administration allows for the 20 mg dose of tafamidis as an option, which costs one quarter of the price of the FDA approved 80 mg dose (1 pill versus 4 pills). The second scenario analysis was performed based on manufacturer comments that hospital related disutility may already be captured by the utilities from the ATTR-ACT [tafamidis] clinical trial.

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 were assumed equivalent), was 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, utility, 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.[56]
Transthyretin stabilizing agent 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.[53] It is worth acknowledging that in follow-on studies, there is some evidence that the 80 mg dose was more effective. However, as discussed in the clinical sections, this evidence is not definitive.[36] 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.[56]

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.[53] 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.[53,57]
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 (ATTRibute-CM [acoramidis] and ATTR-ACT [tafamidis]), 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.

NYHA: New York Heart Association

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 + 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][52]
Hospitalization Rates			
NYHA Class I	16.8%	16.8%	French National Authority for Health (HAS)[56]
NYHA Class II	31.1%	31.1%	
NYHA Class III	69.8%	69.8%	
NYHA Class IV	86.3%	86.3%	
Mortality Hazard Ratio			
NYHA Class II v. NYHA Class I Mortality (HR)	1.78	1.78	JMO Arnold 2013[58,59]
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) 0-18 Months	2.25	2.25	Calculated from ATTR-ACT [tafamidis] clinical trial[53]
ATTR-CM Specific Mortality (HR) 18+ Months	2.75	2.75	
Calibrated Treatment Mortality Effect Month 18+ (HR for treatment compared to standard care alone)	0.44	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[60]
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	$30,584	$30,584	Wang 2023[60]
NYHA Class II	$17,400	$17,400	
NYHA Class III	$17,695	$17,695	
NYHA Class IV	$21,042	$21,042	

Health State Utility Inputs			
NYHA Class I	0.82	0.82	Adjusted from ATTR-ACT [tafamidis] Maurer 2018, Shaw 2005, Jiang 2021[53,57,61]
NYHA Class II	0.729	0.729	
NYHA Class III	0.633	0.633	
NYHA Class IV	0.333	0.333	
Disutility per Hospitalizations (for an ~2 month length of stay, on average)			
NYHA Class I	-0.023	-0.023	Griffiths 2017 [62]
NYHA Class II	-0.01	-0.01	
NYHA Class III	-0.027	-0.027	
NYHA Class IV	-0.07	-0.07	

NYHA: New York Heart Association, HR: Hazard Ratio

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 hazards to the general population. We then estimated ATTR-CM-specific and treatment-effect specific mortality by calibrating the disease specific mortality estimates to the survival benefit observed in the ATTR-ACT [tafamidis] clinical trial treatment arm.[53] 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.[50-53] 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. Compared with supportive care alone, transthyretin stabilizing agent plus best supportive care resulted in improved health outcomes and higher drug and non-drug costs, attributable to patients living longer. Undiscounted base-case results are presented in the supplement.

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	$744,000	$69,000	$45,000	$858,000	4.4	2.9	3.2	2.7
Best Supportive Care Alone	$0	$45,000	$31,000	$76,000	3.0	2.0	2.0	1.8

evLYs: equal value of life years gained, QALY: quality-adjusted life year, NYHA: New York Heart Association

*Based on tafamidis pricing

†Including supportive care and non-stabilizing therapy costs

Table 4.4 presents the discounted incremental cost-effectiveness ratios 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 LY Gained*	Cost per evLY Gained	Cost per Additional Year in NYHA Class I and II*
Transthyretin Stabilizing Agent + Best Supportive Care	Best Supportive Care alone	$873,000	$566,000	$627,000	$871,000

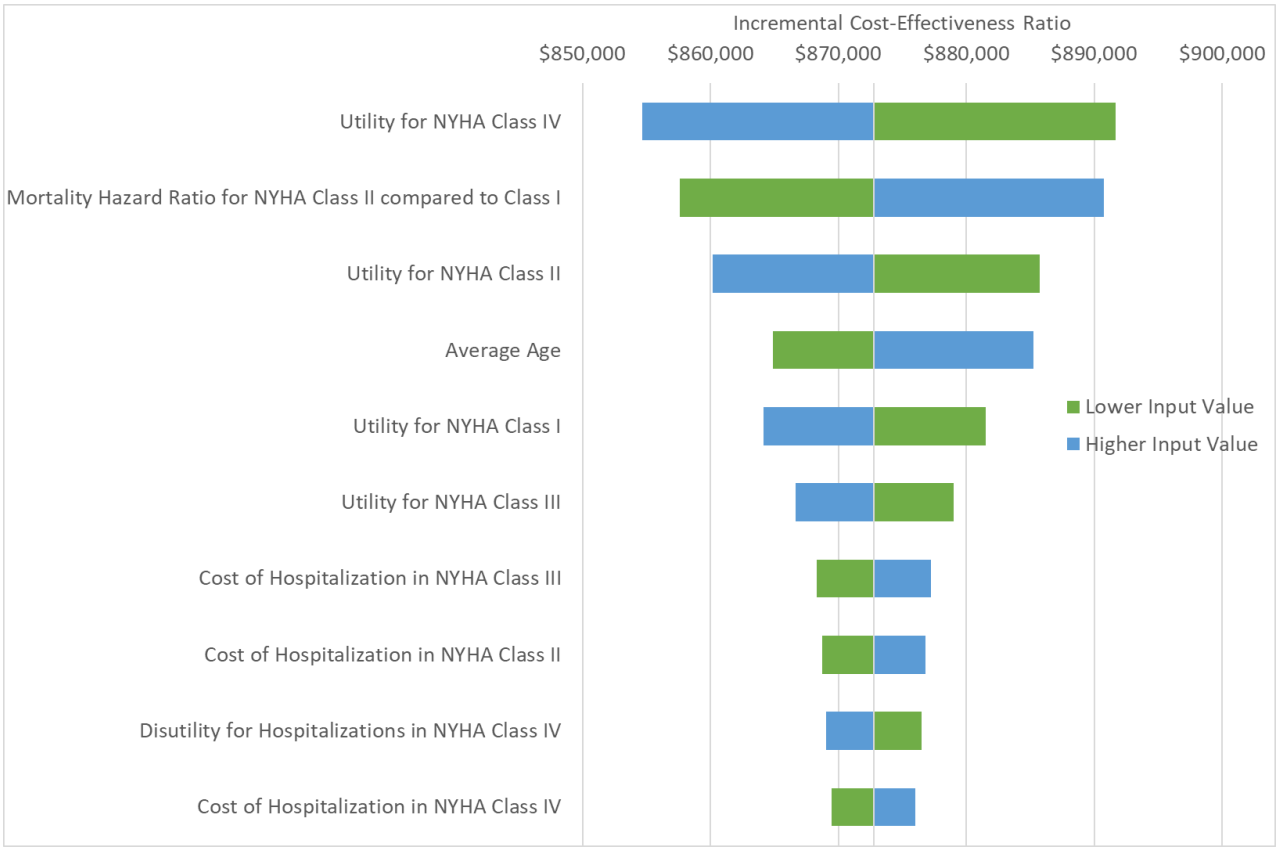
evLYs: equal value of life years gained, LY: life year, QALY: quality-adjusted life year, NYHA: New York Heart Association

*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 health state utilities, mortality hazard ratios, age of the cohort, costs of hospitalizations, and disutility for hospitalizations in NYHA Class IV. 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. Using tafamidis pricing, none of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios at or below 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 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 health state utility values as reported in the ATTR-ACT [tafamidis] clinical trial, without adjusting to the population averages. In the exclude disutility due to hospitalization scenario analysis (#5), we assumed disutility due to hospitalization was captured in the in the health state utilities from the ATTR-ACT [tafamidis] clinical trial, and thus did not incorporate a disutility for those experiencing a hospitalization. In the cost of reduced dose (20 mg) scenario analysis (#6), the drug cost input was lowered 25% of the base case cost, to reflect that some payers provide coverage for the 20 mg dosage of tafamidis. We also conducted scenario analyses (#7-9) 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 4.6. Scenario Analysis Results

Scenario	Cost per QALY Gained*	Cost per LY Gained*	Cost per evLY Gained*
Base-Case Results	$873,000	$566,000	$627,000
Scenario Analysis 1: Modified Societal Perspective	$1,016,000	$659,000	$731,000
Scenario Analysis 2: Mortality Calibrated to ATTRibute-CM [acoramidis] Clinical Trial	$1,155,000	$862,000	$859,000
Scenario Analysis 3: Tafamidis Trial Population	$826,000	$527,000	$579,000
Scenario Analysis 4: Unadjusted Utility Values	$784,000	$566,000	$627,000
Scenario Analysis 5: Exclude Disutility due to Hospitalization	$838,000	$566,000	$634,000
Scenario Analysis 6: Cost of Reduced Dose (20 mg)	$250,000	$162,000	$179,000
Scenario Analysis 7: Exclude Non-Drug Costs (Both Hospital and Supportive Care Costs)	$831,000	$538,000	$597,000
Scenario Analysis 8: Exclude Hospital Costs Only	$847,000	$549,000	$609,000
Scenario Analysis 9: Exclude Supportive Care Costs Only	$857,000	$555,000	$616,000

*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 4.7. 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	$1,900	$13,600	$25,300	$37,000

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

*Based on tafamidis pricing

Table 4.8. 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	$6,500	$22,700	$39,000	$55,200

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

*Based on tafamidis pricing

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.

Uncertainty and Controversies

The uncertainties and controversies in this analysis include incorporating a class-effect for transthyretin stabilizing agents, limited ATTR-CM-specific data on mortality, disease progression, and cost, as well as 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, to model the effects of treatment in a current ATTR-CM population given available data, we combined 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, identifying ATTR-CM specific mortality, disease progression, and cost data was challenging. 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.

Furthermore, uncertainty around our disease progression and cost inputs exists. We assumed the disease progression data (transition probabilities) from the placebo arm, which are publicly available based on the ATTR-ACT [tafamidis] clinical trial, represented the general NYHA functional class progression of ATTR-CM over time. Further, we assumed 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 available data (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 agent (plus best supportive care) generate greater length of life and quality of life with much greater costs compared to best supportive care alone. Assuming the same treatment effects for acoramidis and tafamidis, and using tafamidis pricing, the cost-effectiveness of transthyretin stabilizing agents (plus best supportive care) exceeded commonly used cost-effectiveness thresholds in the US. Because of the timing of new information on vutrisiran and lack of data needed for modeling, we did not perform economic modeling of this agent.

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 interventions 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. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below: evLY shortfalls: • Absolute evLY shortfall: 5.5 • Proportional evLY shortfall: 63.9% QALY shortfalls: • Absolute QALY shortfall: 5.1 • Proportional QALY shortfall: 62.1% 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 transthyretin stabilizing agent (i.e., patients were assumed to be receiving a transthyretin 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.[21,63,64] 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.[23] 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.[65]

Midwest CEPAC Votes

At the public meeting, the Midwest CEPAC deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.2. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Condition

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
There is substantial unmet need despite currently available treatments.	0	0	4	5	6
This condition is of substantial relevance for people from a health/ethnic group that have not been equitably served by the healthcare system.	0	0	0	7	8*

*One council member had technical difficulties when voting and submitted a vote manually.

Six council members voted that they "strongly agree," five council members voted that they "agree," and four council members voted "neutral" for whether there is substantial unmet need despite currently available treatments. Both patient and clinical experts spoke about the large unmet need among patients. Patient experts spoke about the need for higher rates of diagnosis and how the lack of accessible and effective medicine led to receiving a transplant. Clinical experts spoke about the residual risks and how the quality of life and functional capacity decreases even when receiving treatment. The council members discussed the progressive clinical deterioration seen in untreated ATTR-CM and how there is a large unmet need for heart failure treatments in general.

Eight council members voted that they "strongly agree," while seven council members voted that they "agree" this condition is of substantial relevance for people from a health/ethnic group that have not been equitably served by the healthcare system. The council members heard from both patient experts and clinical experts who expressed their concern for those with West African ancestry, as they are a highly impacted community from ATTRv-CM. They spoke about the lack of diagnostic tools, access to care, and genetic testing. Although ATTR-CM is not uncommon, there are huge unmet needs and disparities due to underdiagnosis and inaccessibility of both care and treatments.

To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:

Table 5.3. Midwest CEPAC Votes on Benefits Beyond Health and Special Ethical Priorities - Treatment

Benefits Beyond Health and Special Ethical Priorities	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
The TTR stabilizers are likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	0	0	1	12	2
Acoramidis offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	0	9	6	0	0

A great majority of the council members voted that they "agree" that TTR stabilizers are likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life. Two council members voted "strongly agree" while one remained neutral. The patient experts spoke about the difficulties they experienced with a rapidly progressing disease with being undiagnosed for years. They spoke about the immense burden on their family and other caregivers due to the lack of knowledge about the disease and the poor condition patients experience. One patient expert spoke about how after treatment, his wife did not have to provide as much hands-on care, which had significantly helped the caregiver burden. Clinical experts expressed how the caregiver burden is high among his patients, and they may experience financial toxicity, making it difficult for patients to continue receiving proper diagnoses and treatment year-to-year.

Nine council members voted that they "disagree" that acoramidis offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery, while six council members remained "neutral." While council members raised concerns about the increase in daily intake of oral medication for acoramidis versus other treatments, clinical experts expressed the significantly high adherence to treatments for this condition. Clinical experts also spoke about how acoramidis seems to be a better stabilizer through experimental results but remains uncertain until more data is to be shown.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the intervention(s) are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. The HBPB for transthyretin stabilizing agents ranges from $13,600 to $39,000 annually. This would require discounts of 85% to 95% from the WAC for tafamidis.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Transthyretin Stabilizing Agents

Annual Prices Using…	Annual WAC*	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Transthyretin Stabilizing Agent + Best Supportive Care				
QALYs Gained	$267,987	$13,600	$25,300	90.6% - 94.9%
evLYs Gained		$22,700	$39,000	85.4% - 91.5%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost
*Based on tafamidis pricing without any discounting

Midwest CEPAC Votes

Table 6.2. Midwest CEPAC Votes on Long-Term Value for Money at Current Prices

Question	High long-term value for money at current pricing	Intermediate long-term value for money at current pricing	Low long-term value for money at current pricing
Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering benefits beyond health and special ethical priorities, what is the long-term value for money of tafamidis compared to no disease-specific treatment at current pricing?	0	2	13

A large majority of the council members voted that tafamidis compared to no disease-specific treatment at current pricing has “low long-term value for money at current pricing,” while two council members voted “intermediate long-term value for money at current pricing.” The council members reflected on the clinical and economic data and considered how, despite the large treatment benefits with tafamidis, its price is excessive.

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. As stated in Section 4, because of the timing of new information on vutrisiran and the lack of data needed for modeling, we did not 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.

Access and Affordability Alert

The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

ICER did not undertake a budget impact analysis for transthyretin stabilizing agents or vutrisiran, and as such, is not issuing an access and affordability alert for these agents. As stated above, 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 anticipated material impact on payer budgets. A cost-effectiveness analysis for vutrisiran was not conducted, so we are unable to comment on the potential budget impact and affordability considerations associated with this agent.

8. Policy Recommendations

Following the Midwest CEPAC's deliberation on the evidence, a policy roundtable discussion was moderated by Dr. Steve Pearson around how best to apply the evidence on the use of disease modifying therapies for ATTR-CM. The policy roundtable members included two patient advocates, two clinical experts, and two payers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The topline policy implications are presented below, and additional information can be found here.

Health Equity

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that diagnosis and access to effective new treatment options for patients with ATTR-CM are implemented in a way that will help reduce health inequities.

As new treatments for ATTR-CM become available, all stakeholders should take stock of existing problems with diagnosis and access to effective treatment that helps drive disparities in outcomes while undermining the potential benefits of new treatments for all patients. Several factors contribute to this gap in care. First, patients with ATTR-CM routinely face misdiagnosis and delays in diagnosis. Second, even after accurate diagnosis, ATTR-CM is often managed by subspecialty clinicians who are sometimes not easily accessible for patients with ATTR-CM. Third, in the setting of a paucity of evidence, clinical guidelines are inadequate for patients with overlap syndromes, such as ATTR-CM coexisting with neuropathy. Fourth, because of high prices, even after appropriate diagnosis and access to knowledgeable specialists, patients face additional barriers to access from cost-sharing.

To address these concerns:

Federal and state policymakers should take the following actions:

- Remove barriers to the use of telemedicine, including across state lines, so that individuals with ATTR-CM can access the most knowledgeable centers of excellence, regardless of geographic location.
- Remove barriers to intra-professional consultation, such as electronic consults, including across state lines, so that knowledgeable ATTR-CM specialists can collaborate with general neurologists and cardiologists to expand access to ATTR-CM care.

Clinical specialty societies should take the following actions:

- Increase efforts to promote awareness of amyloidosis generally and ATTR-CM specifically, to reduce misdiagnosis and delays to diagnosis for ATTR-CM.

- Establish diagnostic cutoffs normalized for gender and/or body size both for screening for ATTR-CM in clinical practice and enrollment in clinical trials, to reduce failure to accurately diagnosis the condition in women and smaller patients.

- Engage primary care and other generalists in awareness of ATTR-CM, since they can play an important role in suspecting a diagnosis by noting a pattern of symptoms that are often non-specific and involve other organ systems, including orthopedic and peripheral neurologic problems.

- Validate screening strategies, including clinical and imaging criteria that should prompt screening as well as appropriate protocols for screening. Since many patients have wild type ATTR-CM, widespread genetic screening is not likely to substantially solve the problem of underdiagnosis.

Provider organizations such as hospitals and clinics should take the following actions:

- Make transparent how funds from the 340B program, a provision of the Public Health Service Act, helps support lower cost sharing and improved access to expensive medications for patients with lower incomes.

Payer organizations should take the following actions:

- Medicare should pay for genetic testing in appropriate clinical circumstances, given that ATTR-CM is common among older Americans.
- Private insurers and Medicare Advantage plans should take steps to assure that patients can access an adequate network of specialists in the care of ATTR-CM. Experts in ATTR-CM should be identified, and in geographic areas where there are few experts, payers should provide robust coverage of telehealth options.

Manufacturers

Recommendation 1

Manufacturers should set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. Progress in therapeutics for ATTR-CM has been remarkable. Despite that progress, patients have limited access to tafamidis and the price is substantially higher than a cost-effective price. As new options become

available soon, there needs to be more attention to the deleterious effect of high prices on patient access.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes individuals and families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

In this case, substantial evidence suggests that tafamidis, acoramidis, and vutrisiran are effective at improving important clinical outcomes for patients with ATTR-CM. Tafamidis' very high price has led payers to enforce tight limits on utilization. Given newly available data, we anticipate that the FDA will approve acoramidis for ATTR-CM and expand the indication of vutrisiran to include ATTR-CM. As these new options evolve, lower prices would improve access. In the United States, the price of tafamidis is $234,900 per year. By contrast, the price of tafamidis in Japan is $93,600 and the price of tafamidis in Colombia is $120,000.[66] In the United Kingdom, the price is roughly £10,000 for 30 pills (equivalent to roughly $160,000 per year) and a new commercial use agreement between Pfizer and the National Health Service will reportedly reduce the price even further.[67]

Recommendation 2

Given that the incidence of ATTR-CM is unclear, and underdiagnosis is common, it is not clear that ATTR-CM meets the FDA's definition of a rare disease. The prevalence of ATTR-CM might exceed 200,000 patients. Pricing should not be based on the assumption that ATTR-CM is a rare disease.

In setting prices for existing and emerging therapies for ATTR-CM, manufacturers should not assume that ATTR-CM is a rare disease. The prevalence is unclear, and misdiagnosis and underdiagnosis are common. However, advances in imaging and awareness have resulted in some more patients with ATTR-CM being detected. The aggregate burden on the medical system of these high prices will be higher as more individuals continue to be recognized as affected by ATTR-CM.

Recommendation 3

Manufacturers should not rely on patient assistance programs alone to reduce financial toxicity to patients. Although patient assistance programs can be helpful to some patients, patient assistance programs do not offset the harmful effects of high prices.

Patient assistance programs can be difficult to navigate. They can cause distress for patients who are already facing a difficult diagnosis. Furthermore, patients from more disadvantaged backgrounds may also have more trouble navigating these complex programs. That difference likely creates inequitable access to effective treatment. Even if patient assistance programs were more predictable and less burdensome, these programs do not resolve the challenge of high drug costs for several reasons. First, in some cases the full cost is paid by either payers or patients,

contributing to increased cost of health care for all insured individuals as well as direct financial toxicity to individual patients. Furthermore, when these funds are paid by foundations, that financial support could be repurposed to other mechanisms of supporting patients with ATTR-CM. Manufacturers should not rely on patient assistance programs to offset the challenges created by high prices.

Payers

Recommendation 1

Payers should use trial inclusion criteria to develop coverage policy and engage clinical experts and patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given some evidence of inaccurate diagnoses of ATTR-CM, the consequences of missing the diagnosis of light-chain cardiac amyloidosis, and the high prices of treatments for ATTR-CM, it will be reasonable for payers to use prior authorization as a component of coverage policy. Prior authorization criteria should be based on the FDA labels and specific clinical criteria in pivotal trials that are deemed important for targeting therapy to patients for whom the clinical benefit has been demonstrated. At present, there is not adequate evidence to evaluate the effectiveness of these medications for very early-stage disease. Trials are ongoing to assess effectiveness in individuals with pathogenic transthyretin variants but no clinical pathology (see section on Clinical Investigators and Grant Funding Organizations). Given drug cost, payers are likely to restrict coverage to the trial populations. However, clinical experts noted that for conceptual and mechanistic reasons, these medications are likely to work even in patients with clinical pathology but low levels of N-terminal pro-B-type natriuretic peptide (NT pro-BNP). Some of these patients were excluded from trials. For example, patients with NT pro-BNP below 600 pg/mL were excluded from the ATTR-ACT trial and individuals with NT pro-BNP below 300 pg/mL were excluded from the other trials. Clinical experts said such patients with low NT pro-BNP are likely to have similar benefits from these medications as patients who met trial enrollment criteria.

Patient Organizations

Recommendation 1

Patient groups should continue to demonstrate leadership in advocating for awareness and describing differences in coverage policies.

The Amyloidosis Research Consortium and Amyloidosis Support Groups have a tremendous legacy of advocating for more prompt and accurate diagnosis for patients with ATTR-CM. Patient groups have also shared helpful information about differences and inconsistencies in coverage policies.

Clinical Investigators and Grant Funding Organizations

Recommendation 1

Researchers and funding agencies should focus future research on efforts to establish the comparative effectiveness of tafamidis, acoramidis, and vutrisiran in similar populations.

The trial populations in the three pivotal trials establishing efficacy versus no disease-specific therapy of tafamidis, acoramidis, and vutrisiran are very different. Those population differences include different clinical characteristics and severity of disease. In addition to those population differences, since the FDA approval of tafamidis in 2019, the trials evaluating acoramidis and vutrisiran have included individuals in both treatment and placebo arms who are receiving tafamidis.

As such, there are gaps of evidence that are clinically consequential. Caregivers and patients will want to know which medication is most effective. Ideally, tafamidis, acoramidis, and vutrisiran should be compared against each other in head-to-head randomized trials. However, there are several likely barriers to these trials. High drug costs in addition to other trial costs will limit the likelihood that these trials will be performed. Changes in US law requiring pharmaceutical companies to provide medications at marginal production cost for trials would likely improve this problem. The statistical power needed to detect treatment effects that are different between effective therapies (as opposed to versus placebo) is higher. As such, these trials will need to be larger, further increasing costs. Finally, companies are not likely to fund trials that at least could show that a medication they produce might be less effective than one of the alternatives.

If head-to-head trials are not performed, as new options enter clinical practice, observational data may provide important insights. Although trials are a gold standard in comparative effectiveness research, clinical and coverage decisions still need to be made, even when evidence from trials is not available. Comparative effectiveness research comparing tafamidis, acoramidis, and vutrisiran in observational datasets should apply the most rigorous causal inference methods to adjust for confounding as well as address other common threats to validity in observational comparative effectiveness research.

Recommendation 2

Researchers and funding agencies should also address five critically important unanswered questions important to clinicians and patients with ATTR-CM.

Experienced clinician-investigators as well as patients also identified important gaps in evidence. Addressing these gaps with funding decisions and new research would be very impactful and significant. Leading questions include:

1. If a patient with ATTR-CM is worsening clinically despite treatment with any of tafamidis, acoramidis, and vutrisiran, does switching to another medication improve clinical outcomes versus continuing with the first medication?
2. Is combination therapy with either stabilizer (tafamidis or acoramidis) plus vutrisiran, which acts via a different mechanism, better than monotherapy? In the HELIOS B trial, there was not any signal for different efficacy of vutrisiran in individuals receiving tafamidis or not, suggesting potential synergistic effects. However, clinical experts and the Midwest CEPAC panel did not think this represented adequate evidence to support combination therapy.
3. Are these three newer agents superior to diflunisal, a generic non-steroidal anti-inflammatory (NSAID) with some ability to stabilize transthyretin?
4. How effective and cost-effective will these medications be for patients with very early-stage disease? For example, evaluation of acoramidis for asymptomatic carriers of pathogenic transthyretin variants without clinical pathology is planned (NCT06563895). Initial enrollment is estimated in October 2024 and planned study completion is December 2032.
5. The amyloid-specific Transthyretin Amyloidosis – Quality of Life Questionnaire (ATTR-QoL) needs to have a cross-walk to more common patient-reported outcomes measures such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol-5-domain questionnaire (EQ-5D).

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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]

Table A1.1. New York Heart Association Functional Classification

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[54]109

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[6,82]

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[83]

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.[84,85] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[86] 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.

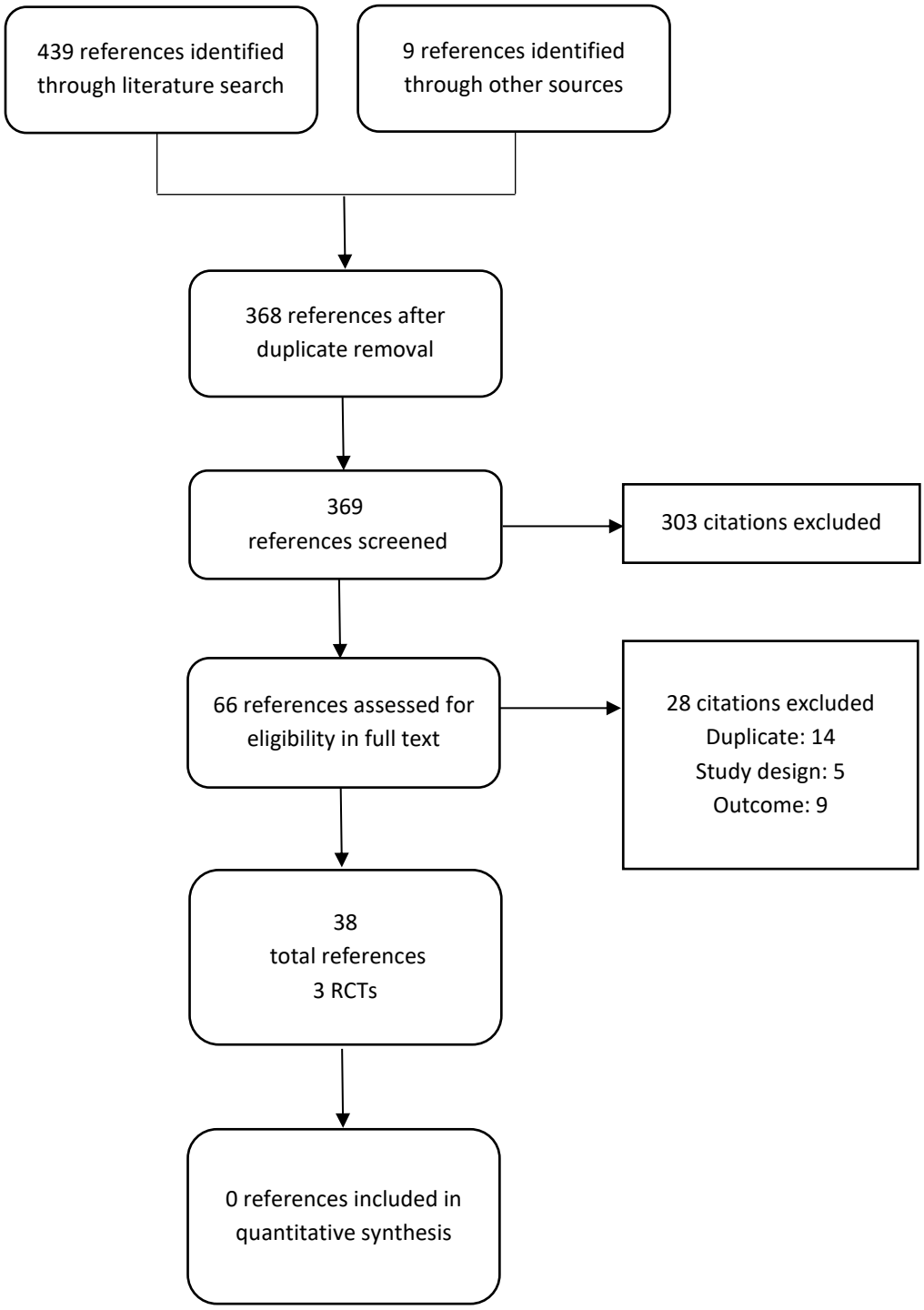
Table D1.2 Search Strategy of EMBASE SEARCH

#	Search Terms
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

#	Search Terms
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.[85,87] 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 D1.4.

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	
Vutrisiran							
HELIOS-B	Low Risk	Low Risk	Low Risk	Low Risk	Some Risk	Low Risk	The study protocol was amended to extend the minimum follow-up from 30 months to 33 months, with revisions to the all-cause mortality outcome evaluated at the 42-month mark.

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[88] 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
Race and Ethnicity	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
Sex	• Female • Male
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) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) 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.[89] 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 [27,52,53,89]

	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	84.5%	7%	6%	6%	-	-	NR	NR
PDRR	1.12	0.28	0.95	0.31	-	-	NC	NC
Score	3	1	3	1	8	Fair	NC	NC

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

*THAOS US registry data

Table D1.9. Sex and Age[27,52,53,90,91]

	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	92.5%	7.5%	-	-	NR	-	-
PDRR	1.08	0.51	-	-	NC	-	-
Score	3	2	5	Fair	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).[92,93]

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 did not identify any studies that would have met our inclusion criteria, and for which no findings have been published.

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[27,30,52,53]

Trial (NCT)	Study Design	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Primary Outcomes [Timepoint]
ATTR-ACT NCT01994889	Phase III, randomized, double-blind, placebo-controlled Follow-up: 30 months	20 mg tafamidis once daily (n=88) 80 mg tafamidis (4 20mg capsules) once daily (n=176) Placebo once daily (n=177)	**Inclusion Criteria**: -Age 18 to 90 years -Diagnosed with transthyretin amyloid cardiomyopathy (ATTRwt or ATTRm) -Medical history of heart failure (HF) with at least 1 prior hospitalization for HF -Clinical evidence of HF (without hospitalization) -Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm -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 **Exclusion Criteria:** -NYHA IV classification -Presence of primary (light chain) amyloidosis -Prior liver or heart transplantation or implanted cardiac mechanical assist device -<25 mL/min/1.73 m^2	Hierarchically assessed composite of all-cause mortality and CV-related hospitalizations) [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 Follow-up: 30 months	800 mg acoramidis twice daily (n=421) Placebo twice daily (n=211)	**Inclusion Criteria:** -Age 18 to 90 years -Established diagnosis of ATTR-CM (wild-type or variant) -History of HF (at least one prior hospitalization for heart failure) -Clinical evidence of heart failure without prior HF hospitalization -NYHA Class I-III symptoms due to ATTR cardiomyopathy -On stable doses of cardiovascular medical therapy -Completed ≥150 m on the 6MWT on 2 tests that are within 15% of total distance walked -NT-proBNP level ≥300 pg/mL -Have left ventricular wall thickness ≥12 mm **Exclusion Criteria:** -Had acute myocardial infarction, acute coronary syndrome coronary revascularization, stroke or transient ischemic attack within 90 days -Has hemodynamic instability -Likely to undergo heart transplantation within a year of screening -Confirmed diagnosis of primary (light chain) amyloidosis -NT-proBNP level ≥8500 pg/mL -eGFR by MDRD formula <15 mL/min/1.73 m2 -Current treatment with calcium channel blockers with conduction system effects	6-Minute Walk Test [12 months] Hierarchically assessed composite of all-cause mortality, CV-related hospitalizations, NT-proBNP, 6MWT [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 Follow-up: 30-36 month	25 mg vutrisiran subcutaneously once every 3 months Placebo N=655	**Inclusion Criteria:** -Age 18 to 85 years -Diagnosis of transthyretin ATTR amyloidosis with cardiomyopathy, classified as either ATTRm or ATTRwt amyloidosis -Has medical history of heart failure with at least 1 prior hospitalization for HF OR clinical evidence of HF **Exclusion Criteria:** -Has known primary amyloidosis or leptomeningeal amyloidosis -Has NYHA Class IV heart failure -Has NYHA Class III heart failure with a National Amyloidosis Centre ATTR stage of 3 (defined as an NT-proBNP level of >3000 pg per milliliter and an eGFR of <45 ml per minute per 1.73 m2 of body-surface area) -Has a polyneuropathy disability Score IIIa, IIIb, or IV -Has eGFR <30 mL/min/1.73 m^2 -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[36,53,94-98]

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[52,99,100]

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)
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)

Trial		ATTRibute-CM	
Arms		Acoramidis	Placebo
N		421	211
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. Vutrisiran Baseline Characteristics[27]

Trial		HELIOS-B			
Arms		Overall Population		Monotherapy Population	
		Vutrisiran	Placebo	Vutrisiran	Placebo
N		326	328	196	199
Median age at randomization, years (range)		77.0 (45–85)	76.0 (46–85)	77.5 (46–85)	76.0 (53–85)
Male, n (%)		299 (92)	306 (93)	178 (91)	183 (92)
Race, n (%)†	White	277 (85)	275 (84)	169 (86)	169 (85)
	Asian	18 (6)	19 (6)	12 (6)	15 (8)
	Black	23 (7)	24 (7)	10 (5)	11 (6)
	Other or not reported	8 (2)	10 (3)	5 (3)	4 (2)
Wild-type ATTR, n (%)		289 (89)	289 (88)	173 (88)	174 (87)
Median time since diagnosis of ATTR, years (range)		0.86 (0–11.1)	1.03 (0–10.8)	0.50 (0–8.3)	0.63 (0–6.2)
Tafamidis use at baseline, n (%)		130 (40)	129 (39)	NA	NA
Median duration of tafamidis use before start of trial, months (range)		9.2 (1.1–65.3)	11.3 (1.1–65.5)	NA	NA
Initiated Tafamidis after randomization, n (%)		NA	NA	44 (22)	41 (21)
NYHA class, n (%)	I	49 (15)	35 (11)	15 (8)	12 (6)
	II	250 (77)	258 (79)	172 (88)	169 (85)
	III	27 (8)	35 (11)	9 (5)	18 (9)
NAC stage, n (%)‡	1	208 (64)	229 (70)	113 (58)	138 (69)
	2	100 (31)	87 (27)	68 (35)	55 (28)
	3	18 (6)	12 (4)	15 (8)	6 (3)
Laboratory values	Median NT-proBNP level, pg/ml (IQR)	2021 (1138–3312)	1801 (1042–3082)	2402 (1322–3868)	1865 (1067–3099)
	Median high-sensitivity troponin I level. pg/ml (IQR)	71.9 (44.9–115.9)	65.2 (41.1–105.5)	76.3 (48.4–138.8)	62.2 (39.2–105.6)

ATTR: transthyretin amyloidosis, IQR: interquartile range, NAC: National Amyloidosis Centre, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association

Table D2.5. Tafamidis Efficacy Outcomes[36,53,70,95,97,101,102]

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 D2.6. Tafamidis Long-term Follow-up[103]

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 D2.7. Acoramidis Efficacy Outcomes[32-34,52,99,100]

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)†

Trial		ATTRibute-CM	
Arms		Acoramidis	Placebo
N		421	211
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 D2.8. Vutrisiran Efficacy Outcomes[27]

Trial	HELIOS-B			
Arms	Overall Population		Monotherapy Population	
	Vutrisiran	Placebo	Vutrisiran	Placebo
N	326	328	196	199
Death from any cause and recurrent cardiovascular events, HR (95% CI; p value)*	0.72 (0.56, 0.93; 0.01)		0.67 (0.49, 0.93; 0.02)	
Time to first event (death from any cause and recurrent cardiovascular events), months HR (95% CI; p value)*	0.72 (0.57, 0.91; 0.006)		0.64 (0.48, 0.87; 0.004)	
Death from any cause, HR (95% CI; p value)*	0.69 (0.49, 0.98; 0.04)		0.71 (0.47, 1.06; 0.12)	
Recurrent cardiovascular events, HR (95% CI; p value)	0.73 (0.61, 0.88; 0.001)		0.68 (0.53, 0.86; 0.001)	
Patients with at least one event, n (%)	125 (38)	159 (48)	76 (39)	105 (53)
Death from any cause, n (%)*	51 (16)	69 (21)	36 (18)	46 (23)
Recurrent CV events, n (%)	112 (34)	133 (41)	66 (34)	87 (44)
Death from any cause through 42 months, HR (95% CI; p value)*	0.65 (0.46, 0.90; 0.01)		0.66 (0.44, 0.97; 0.045)	
Death from any cause, n (%)	60 (18)	85 (26)	43 (22)	58 (29)
Least-squares mean change from baseline at 30 months 6MWD, meters (95%CI; p value)	-45.4 (-54.5, -36.3)	−71.9 (-81.3, -62.4)	-59.7 (-72.7, -46.7)	91.8 (-104, -79.2)
	26.5 (13.4, 39.6; <0.001)†		32.1 (14.0, 50.2; <0.001)†	
Least-squares mean change from baseline in KCCQ-OS score at month 30 (95%CI; p value)	-9.7 (-12, -7.4)	-15.5 (-18, -13)	-10.8 (-14.1, -7.5)	-19.5 (-22.9, -16.1)
	5.8 (2.4, 9.2; <0.001)†		8.7 (4, 13.4; <0.001)†	
Least-squares mean change from baseline percent with improved or stable NYHA class at month 30 (95%CI; p value)	68	61	66	56
	8.7 (1.3, 16.1; 0.02)‡		12.5 (2.7, 22.2; 0.01)‡	

6MWD: 6-minute walk distance, CI: confidence interval, CV: cardiovascular, HR: hazard ratio, KCCQ-OS: KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary, N: number, NYHA: New York Heart Association

*For the analyses that included death from any cause, heart transplantation and implantation of a left ventricular assist device were treated as deaths.

†The difference is the least-squares mean difference

‡The difference is the adjusted difference in percentage points

Table D2.9. Tafamidis Safety Outcomes[36,53,95]

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 D2.10. Acoramidis Safety Outcomes[52]

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 D2.11. Vutrisiran Safety Outcomes[27]

Trial	HELIOS-B	
Arm	**Vutrisiran**	**Placebo**
N	326	328
Adverse Events, n (%)*	322 (99)	323 (98)
Serious Adverse Events, n (%)	201 (62)	220 (67)
AEs leading to study drug discontinuation, n (%)	10 (3)	13 (4)

AE: adverse event, N: total number

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

Table D2.12. Tafamidis and Acoramidis Subgroup Data: Genotype and Baseline NYHA Class[52,53]

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

Table D2.13. Vutrisiran Subgroup Data[27]

Population	Subgroup Category	Subgroup	N	Time to First Event (composite of death from any cause and recurrent cardiovascular events), hazard ratio (95% CI)	Death From Any Cause, Hazard Ratio (95% CI)
Overall	Age	<75	257	0.55 (0.35, 0.85)	0.55 (0.29, 1.04)
		≥75	397	0.81 (0.58, 1.11)	0.69 (0.46, 1.01)
	Tafamidis use at baseline	No	395	0.67 (0.49, 0.93)	0.66 (0.44, 0.97)
		Yes	259	0.79 (0.51, 1.21)	0.59 (0.32, 1.08)
	ATTR disease type	Variant	76	0.92 (0.49, 1.72)	0.89 (0.39, 2.03)
		Wild type	578	0.67 (0.51, 0.90)	0.61 (0.42, 0.88)
	NYHA class	I or II	592	0.73 (0.55, 0.96)	0.66 (0.47, 0.94)
		III	62	0.68 (0.33, 1.41)	0.58 (0.20, 1.69)
	Baseline NT-proBNP level	≤2000 pg/ml	342	0.53 (0.35, 0.79)	0.35 (0.18, 0.66)
		>2000 pg/ml	312	0.80 (0.56, 1.13)	0.83 (0.55, 1.24)
Monotherapy	Age	<75	153	0.53 (0.32, 0.88)	0.58 (0.28, 1.20)
		≥75	242	0.72 (0.47, 1.10)	0.68 (0.42, 1.09)
	ATTR disease type	Variant	48	0.67 (0.31, 1.44)	0.67 (0.25, 1.78)
		Wild type	347	0.66 (0.45, 0.95)	0.65 (0.42, 1.00)
	NYHA class	I or II	368	0.73 (0.53, 1.02)	0.70 (0.47, 1.06)
		III	27	0.31 (0.09, 1.02)	0.19 (0.02, 1.63)
	Baseline NT-proBNP level	≤2000 pg/ml	188	0.50 (0.28, 0.92)	0.43 (0.18, 1.01)
		>2000 pg/ml	207	0.71 (0.47, 1.07)	0.75 (0.48, 1.18)

ATTR: transthyretin amyloidosis, CI: confidence interval, NT-proBNP: N-terminal pro–B-type natriuretic peptide, NYHA: New York Heart Association

D3. 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.[104]

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[55]

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)[105]

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.[52] Maurer et al.[53]
	Longevity effects	X	X	JMO Arnold[58] 2019 US Life Table[106]
	Health-related quality of life effects	X	X	Maurer et al.[53] Kansal et al.[107]
	Adverse events	X	X	Mauer et al.[53] Gillmore et al.[52]
Medical Costs	Paid by third-party payers	X	X	IPD Analytics[108] Wang et al.[60]
	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	X	Patient indirect cost estimates: Çavuşoğlu et al.[109] Caregiver indirect cost estimate: Lahoz et al.[110]
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	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	
Consumption	Future consumption unrelated to health	NA	☐	
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[111]

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.[112]
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.[52] 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.[53] 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.[52]

†Mauer et al. (weighted average)[53]

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.[56] 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.[56] 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%

NYHA: New York Heart Association

*Haute Autorité de Santé [56]

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%

NYHA: New York Heart Association

*Haute Autorité de Santé [56]

Cardiovascular-Related Hospitalizations

The risk of cardiovascular-related hospitalizations was incorporated as a transient event in the model. The rate 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] clinical trial data as reported by the French HTA (Table 21, Scenario 5b).[56] Table E2.3 below presents the cardiovascular-related hospitalization rates.

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

Health State	Treatment Arms	Comparator (Placebo) Arm*
NYHA Class I	16.8%	16.8%
NYHA Class II	31.1%	31.1%
NYHA Class III	69.8%	69.8%
NYHA Class IV	86.3%	86.3%

NYHA: New York Heart Association

*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 a transthyretin stabilizing agent 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.[106] HF-specific mortality was calculated from published hazard ratios of HF mortality stratified by NYHA functional class (Table E2.4), 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 an adjustment factor from months 0-18 and a different factor after 18 months to the HF-specific morality rates.

Finally, an additional single treatment effect was applied to the transthyretin stabilizing agent arm after 18 months (when arm survival separates in the ATTR-ACT [tafamidis] clinical trial), 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.

Table E2.4. Mortality Inputs

Parameter	Value	Source
Background Mortality	Refer to the source	2019 US Life Table[106]
NYHA Class II v. NYHA Class I Mortality (HR, 95% CI)	1.78 (1.54, 2.06)	JMO Arnold 2013[58,59]
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) Months 0-18	2.25	Calculated from ATTR-ACT [tafamidis] clinical trial[53]
ATTR-CM Specific Mortality (HR) Months 18+	2.75	
Calibrated Treatment Mortality Effect Month 18+ (HR for treatment compared to standard care alone)	0.44	

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.[113]

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.[108] 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 of 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 E2.6.[60]

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

NYHA Class	Annual Costs*†
NYHA Class I	$5,822
NYHA Class II	$8,259
NYHA Class III	$12,388
NYHA Class IV	$20,417

NYHA: New York Heart Association

*Wang et al.[60]

†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 E2.7.[60]

Table E2.7. Cardiovascular-Related Hospitalizations Costs by NYHA Functional Class [60]*

NYHA Class	Cardiovascular-Related Hospitalization Cost
NYHA Class I	$30,584
NYHA Class II	$17,400
NYHA Class III	$17,695
NYHA Class IV	$21,042

NYHA: New York Heart Association

*Inflated to Q1 2024 US Dollar

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.[109] 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 in Table E2.8. 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[109]*

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	$21,760
NYHA Class II	41.7%	$59,384	$29,880
NYHA Class III	70.0%	$59,384	$44,408
NYHA Class IV	95.8%	$59,384	$60,775
Loss of Work Productivity Due to Overall Work Impairment			
NYHA Class I	20.8%	$59,384	$13,195
NYHA Class II	36.4%	$59,384	$23,092
NYHA Class III	66.1%	$59,384	$41,934
NYHA Class IV	91.6%	$59,384	$58,111

NYHA: New York Heart Association
*Inflated to Q1 2024 US Dollar

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.[110] 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.[110] The US average hourly wage was sourced from the quarterly report, "Usual Weekly Earnings of Wage and Salary Workers, First Quarter 2024".[114] 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).

Table E2.9. Annual Caregiver Productivity Loss

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

NYHA: New York Heart Association

*Lahoz, 2021[110]

†Calculated by multiplying time spent on caregiving by 2024 US average hourly wage and inflated to Q1 2024 US Dollar

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.[50-53] 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 E2.10; these values were obtained by crosswalking EQ-5D-3L results with the US value set.[53,57] 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.[61]

Additionally, we applied a disutility for individuals experiencing a cardiovascular-related hospitalization per cycle. The disutility value was identified through a systematic literature review, and the values are presented in table E2.11.[62]

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

NYHA: New York Heart Association, CI: Confidence Interval

*ATTR-ACT and US value set[53,57]

†Calculated from the US population norms[61]

Table E2.11. Hospitalization Disutility (for an ~2 month length of stay, on average)

Parameter	Reported Utility Values*
NYHA Class I	-0.023
NYHA Class II	-0.010
NYHA Class III	-0.027
NYHA Class IV	-0.070

NYHA: New York Heart Association

*Griffiths, 2017

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	$812,000	$77,000	$50,000	$940,000	4.8	3.1	3.5	2.9
Best Supportive Care Alone	$0	$48,000	$33,000	$81,000	3.2	2.1	2.1	1.9

NYHA: New York Heart Association, QALYs: Quality-Adjusted Life-Years, evLYs: Equal Value Life-Years

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy 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 IV compared to best supportive care alone. Alternatively, best supportive care alone had a higher percentage of time in NYHA Class II and III 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)	0.46 (9%)	2.44 (51%)	1.48 (31%)	0.44 (9%)	4.82
Best Supportive Care Alone (% of total LY)	0.2 (6%)	1.66 (52%)	1.07 (34%)	0.24 (7%)	3.17

NYHA: New York Heart Association, LY: Life Year

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
Average Age	$865,000	$885,000	76.7	77.9
Mortality				
Mortality Hazard Ratio for NYHA Class II compared to Class I	$858,000	$891,000	1.54	2.06
Mortality Hazard Ratio for NYHA Class III compared to Class I	$870,000	$876,000	3.05	4.04
Mortality Hazard Ratio for NYHA Class IV compared to Class I	$870,000	$875,000	4.81	6.85
Utilities				
Utility for NYHA Class I	$882,000	$864,000	0.78	0.86
Utility for NYHA Class II	$886,000	$860,000	0.71	0.75

	Lower Input CE Ratio† (Cost/QALY Gained)	Upper Input CE Ratio† (Cost/QALY Gained)	Lower Input	Upper Input
Utility for NYHA Class III	$879,000	$867,000	0.61	0.65
Utility for NYHA Class IV	$892,000	$855,000	0.22	0.45
Disutility for Hospitalizations in NYHA Class I	$873,000	$872,000	-0.03	-0.02
Disutility for Hospitalizations in NYHA Class II	$874,000	$872,000	-0.01	-0.01
Disutility for Hospitalizations in NYHA Class III	$875,000	$870,000	-0.03	-0.02
Disutility for Hospitalizations in NYHA Class IV	$877,000	$869,000	-0.08	-0.06
Costs				
Cost of Best Supportive Care NYHA Class I (for 6-month cycle)	$872,000	$874,000	$1,455	$4,366
Cost of Best Supportive Care NYHA Class II (for 6-month cycle)	$870,000	$876,000	$2,065	$6,194
Cost of Best Supportive Care NYHA Class III (for 6-month cycle)	$871,000	$875,000	$3,097	$9,291
Cost of Best Supportive Care NYHA Class IV (for 6-month cycle)	$871,000	$875,000	$5,104	$15,312
Cost of Hospitalization in NYHA Class I	$871,000	$874,000	$15,292	$45,876
Cost of Hospitalization in NYHA Class II	$869,000	$877,000	$8,700	$26,100

	Lower Input CE Ratio† (Cost/QALY Gained)	Upper Input CE Ratio† (Cost/QALY Gained)	Lower Input	Upper Input
Cost of Hospitalization in NYHA Class III	$868,000	$877,000	$8,847	$26,542
Cost of Hospitalization in NYHA Class IV	$870,000	$876,000	$10,521	$31,562

CE: cost-effectiveness, NYHA: New York Heart Association, QALY: Quality-Adjusted Life Years

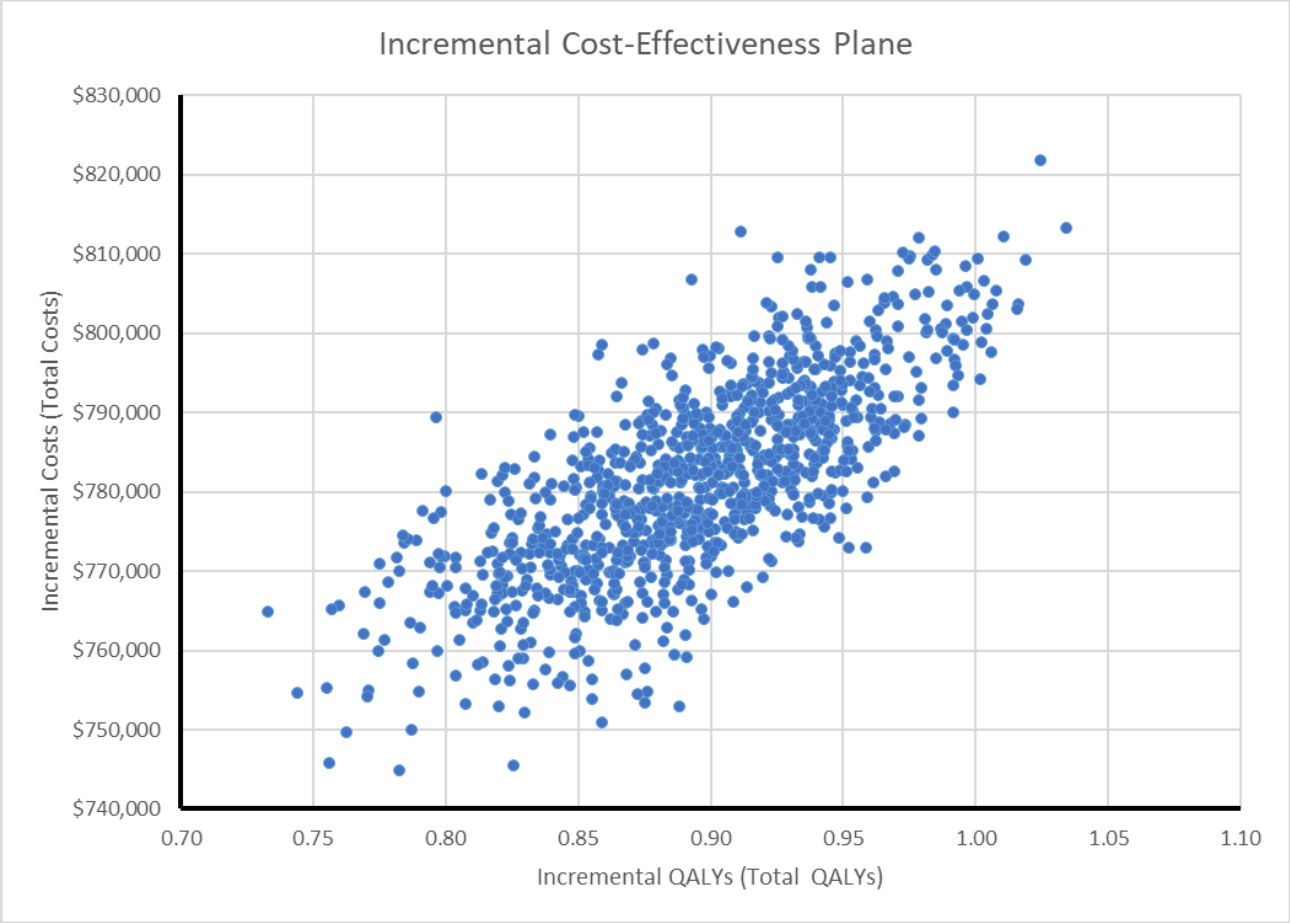
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output

†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.

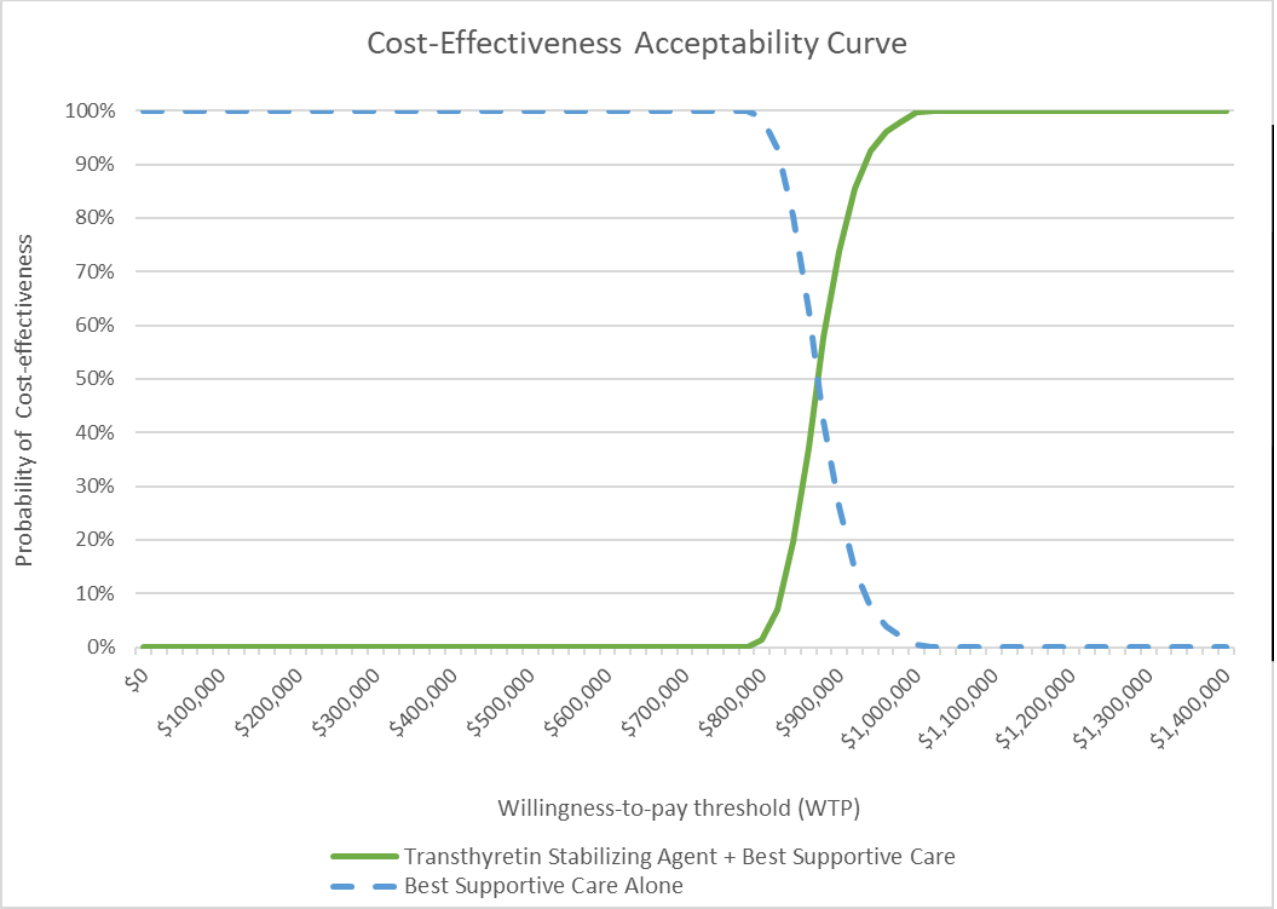
Figure E4.1: Cost-Effectiveness Plane for Transthyretin Stabilizing Agent Plus Best Supportive Care Treatment Compared to Best Supportive Care Alone



QALY: Quality Adjusted Life Years

*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 Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$69,000	$464,000	$1,277,000	4.4	2.9	3.2
Best Supportive Care Alone	$0	$45,000	$321,000	$366,000	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

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

In the mortality calibrated to ATTRibute-CM [acoramidis] clinical trial, we 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 Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$851,000	$81,000	$53,000	$985,000	5.1	3.3	3.5
Best Supportive Care Alone	$0	$69,000	$45,000	$114,000	4.0	2.5	2.5

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy 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 Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$844,000	$87,000	$56,000	$986,000	5.1	3.2	3.7
Best Supportive Care Alone	$0	$57,000	$38,000	$95,000	3.4	2.2	2.2

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy 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 Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$69,000	$45,000	$858,000	4.4	3.2	3.4
Best Supportive Care Alone	$0	$45,000	$31,000	$76,000	3.0	2.2	2.2

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

Scenario Analysis 5: Exclude Disutility due to Hospitalization

In the exclude disutility due to hospitalization scenario, disutility due to hospitalization was not included in the model and was instead assumed to be captured in the health state utilities from the ATTR-ACT [tafamidis] clinical trial. Results are presented in Table E5.5.

Table E5.5. Discounted Results for Exclude Disutility due to Hospitalization Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$69,000	$45,000	$858,000	4.4	3.0	3.3
Best Supportive Care Alone	$0	$45,000	$31,000	$76,000	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

Scenario Analysis 6: Cost of Reduced Dose (20 mg)

In the cost of reduce dose (20 mg) scenario, the drug cost input was lowered 25% of the base case cost, to reflect that some payers provide coverage for the 20 mg dosage of tafamidis. This dose represents one quarter of the cost of the 80 mg dose (1 pill versus 4 pills). Results are presented in Table E5.6.

Table E5.6. Discounted Results for Cost of Reduced Dose (20 mg) Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$186,000	$69,000	$45,000	$300,000	4.4	2.9	3.2
Best Supportive Care Alone	$0	$45,000	$31,000	$76,000	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

Scenario Analysis 7: 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 E5.7.

Table E5.7. Discounted Results for Exclude Non-Drug Costs Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$0	$0	$744,000	4.4	2.9	3.2
Best Supportive Care Alone	$0	$0	$0	$0	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

Scenario Analysis 8: Exclude Hospital Costs

In the exclude hospital costs scenario, all hospitalization costs were excluded from the analysis. Results are presented in Table E5.8.

Table E5.8. Discounted Results for Exclude Hospital Costs Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$0	$45,000	$789,000	4.4	2.9	3.2
Best Supportive Care Alone	$0	$0	$31,000	$31,000	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy costs

Scenario Analysis 9: 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 E5.9.

Table E5.9. Discounted Results for Exclude Supportive Care Costs Scenario

Treatment	Drug Cost*	Hospital Cost	Non-Drug Cost†	Total Cost*	Life Years	QALYs	evLYs
Stabilizing Agent + Best Supportive Care	$744,000	$69,000	$0	$813,000	4.4	2.9	3.2
Best Supportive Care Alone	$0	$45,000	$0	$45,000	3.0	2.0	2.0

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

*Based on tafamidis pricing

†Including supportive care and non-stabilizing agent therapy 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).[7,50,51] Additionally the health technology assessments of tafamidis were identified from multiple countries.[55,56,115] 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.[50,51,55,115] 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.[50] This model used treatment efficacy inputs from both the original ATTR-ACT [tafamidis] 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 [tafamidis] 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 input, we determined a patient's current NYHA class was 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 older adults and clinical trial data is unlikely to capture the increasing disease unrelated hazards associated with increasing age.[51,55] To allow for easy comparison between our model and other models, we performed scenario analysis 3 which models the tafamidis population. Specifically, when comparing the ICER model (scenario 3) to results presented in the French HTA report, we found that the life years were similar (5.1 discounted LY for the tafamidis population and 3.4 in the best supportive care population in the ICER model vs 4.98 discounted LY for the tafamidis population and 3.41 in the best supportive care population in the French HTA report) and the QALYs are also similar (3.2 discounted QALYs for the tafamidis population and 2.2 in the best supportive care population in the ICER model vs 3.28 discounted QALYs for the tafamidis population and 1.83 in the best supportive care population in the French HTA report). Despite having nearly identical estimates of discounted life years for the best supportive care arm, we observed modest difference between the QALYs in the best supportive care population between models. We believe this is due to having consistent health utilities between arms in the ICER model, whereas the French HTA report allowed for differential utilities within each arm.

F. Supplemental Policy Recommendations

Payers

Clinical Coverage Criteria

Diagnosis

Payers should include confirmation of the diagnosis of ATTR-CM as part of coverage policy to avoid futile health spending as well as to avoid adverse clinical events.

There is evidence that patients in clinical practice can be misdiagnosed with ATTR-CM. Given the price of the medications, authorizing use of tafamidis, acoramidis, and vutrisiran for individuals who do not have ATTR-CM will lead to wasteful spending that does not benefit patients. Furthermore, authorizing use of tafamidis, acoramidis, and vutrisiran for patients who have light chain amyloidosis (primary amyloidosis) can lead to potentially fatal delays in diagnosis and treatment for that separate syndrome, for which different treatment is appropriate. Although there is widespread under recognition of ATTR-CM in real-world practice, erroneous diagnosis is also a problem. Awareness of the appropriate testing protocols, including best practices with bone scintigraphy as well as ruling out light-chain amyloidosis, are critical. Prior authorization may be an effective tactic to improve proper diagnostic protocols.

Clinical Eligibility

Clinical experts at the Policy Roundtable felt that it was not unreasonable for payers to use specific inclusion/exclusion criteria from the pivotal trials as the basis for insurance coverage.

Combination Therapy

It is not unreasonable for payers to consider coverage of dual therapy with a stabilizer medication and vutrisiran, but concerns about the evidence and the obvious cost implications are likely to lead most payers to withhold coverage until further evidence is generated.

The Midwest CEPAC voted unanimously that evidence was not adequate to demonstrate superiority for dual therapy, and clinical experts at the ICER meeting emphasized that the pivotal trial for vutrisiran was not designed specifically to evaluate dual therapy, leading them to feel that it was

not unreasonable for payers to withhold coverage pending research on this issue that should be completed in the next few years.

On the other hand, the ICER research team, looking at existing evidence from HELIOS B, assigned an "A" rating to the evidence on the added clinical benefit of vutrisiran added to background tafamidis. This rating was based largely on findings in the HELIOS B trial that did not suggest heterogeneity in treatment effects of vutrisiran versus placebo in individuals who were or were not receiving tafamidis.

It should be noted that several health systems are favoring use of a 20 mg dose of tafamidis, which would make combination therapy much less costly. However, there are no data at the present time to support this practice. Payers can examine the evidence and consider coverage for dual therapy, which will likely be very expensive.

Step Therapy

Given the high costs and uncertainty about the relative effectiveness of different medications, and the lack of evidence to help clinicians identify patients for whom one drug is more likely to be effective than another, it is not unreasonable for payers to consider preferring specific agents based on cost as part of a broader evidence-based approach to negotiating lower prices.

After the approval of acoramidis and likely expansion of the FDA-approved indication for vutrisiran, competition might diminish any differences in costs between these three medications. If differences in cost are low, the rationale for any type of "economic step therapy" is diminished. However, if formal step therapy will induce lower prices through negotiation, it is reasonable for payers to implement it as long as all criteria for ethical step therapy are met. ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Given their common mechanism of action, step therapy is most likely between the transthyretin stabilizers, tafamidis and acoramidis. Clinical experts agreed that it is not unreasonable to exclude one or the other from a formulary if that exclusion allows for substantially lower price for the covered medication.

More convincing evidence eventually may emerge that one of the two stabilizers is more effective than the other, particularly in specific patient subgroups. If that occurs, formularies should allow use of that medication in any relevant subpopulation.

Although lack of clinical differentiation makes it reasonable to consider step therapy between vutrisiran and either of the stabilizers, payers should be sensitive to the difference in delivery mechanism that may make oral stabilizers easier for some patients to take compared to subcutaneous vutrisiran. However, in part, this distinction is driven by the fact that vutrisiran has been administered in clinician offices and not self-administered by patients at home. Payers may wish to explore home administration as a way to facilitate access for patients with travel barriers, and this approach may also reduce markups that can drive up total costs.

A final but important consideration relates to patients who have ATTR-CM and amyloid-related neuropathy. For these patients, clinical experts expressed preference for vutrisiran since vutrisiran is the only agent with a current FDA label for neuropathy. Any step therapy policies favoring first use of stabilizers should therefore have a clear clinical exception for patients with neuropathy.

G. Public Comments

This section includes a summary of a public comment prepared for the Midwest CEPAC Public Meeting on September 20, 2024. This summary was prepared by one speaker who delivered a public comment at the meeting.

A video recording of all comments can be found here, beginning at minute 00:18. A conflict of interest disclosure is included at the bottom of the statement.

Marianna Bruno, PharmD, MPH, MBA
US Rare Cardiology Medical Team Lead, Pfizer

Good afternoon, my name is Marianna Bruno. I am the US Medical Affairs Lead for the Pfizer cardiac amyloidosis team.

I'm here today to talk to you about how the totality of our data and the clinical effectiveness of tafamidis merits an A rating. At Pfizer, we are proud to have pioneered treatment with tafamidis in this space. The breadth of our clinical data, coupled with real-world experience is unparalleled.

To start, it's helpful to ground the audience in the unprecedented results from the Phase 3 ATTR-ACT study which significantly reduced the combination of All-cause mortality and CV related hospitalizations vs placebo over 30-months, with a p-value that was highly statistically significant. This trial led to the breakthrough therapy designation and FDA approval of tafamidis as the only treatment for both hereditary and wild-type ATTR-CM to reduce CV mortality and CV-related hospitalizations with a safety profile similar to placebo, as reflected in the US label.[1,2]

With more than a decade of research and six years of real-world experience, we have generated the most robust and consistent clinical evidence to-date across NYHA stages I to III, which we believe supports an A rating.[1,3,4,5]

ATTR-ACT and its long-term extension study demonstrated a statistically significant reduction in all-cause mortality and CV-related hospitalization out to five years. To put this into context, for every eight people treated with tafamidis, one death is prevented, and treatment of four people prevents one CV hospitalization within 30-months.[1] I hope we can all agree that this profound impact on patient outcomes is not commonly seen in CV outcomes trials.[6]

During the "ICER Early Insights Webinar Series," ICER acknowledged an "A" rating for tafamidis if evaluated in the original trial population,[7] but expressed less certainty for its effectiveness in the contemporary population, resulting in a B+ rating in the absence of a clear definition. We strongly disagree with this assessment. There is no basis to suggest uncertainty in the benefit of tafamidis in contemporary ATTR-CM patients.

On the contrary, in a pre-specified analysis of ATTR-ACT in NYHA class I and II subgroup, a less sick population, and a reflection of patients diagnosed today, there was a significant 43% reduction in mortality in the primary analysis[1] and a 44% reduction with nearly five years of follow up.[3] As a reminder to our audience, NYHA class I and II patients accounted for ~70% of the original ATTR-ACT population, and those Class I and II patients performed consistently better than the overall population[1,3]

Further to this, most recently, a post-hoc analysis from ATTR-ACT and its long-term extension study showed a separation of survival curves in the first few months of tafamidis treatment in patients with NAC stage I disease, emphasizing the importance of early diagnosis and treatment with tafamidis.[5]

These robust, consistent clinical data are also supported by a recent real-world survival analysis from the THAOS disease registry, which looked at patients treated and untreated with tafamidis.

A sensitivity analysis reflecting a contemporary cohort comprising healthier patients in earlier stages of the disease showed a 42-month survival rate of 86.3% in tafamidis-treated patients. Importantly, no new safety signals were identified.[4]

With this totality, depth and breadth of experience, there is no scientific basis to conclude tafamidis would not have similar efficacy and safety in patients diagnosed today. Furthermore, based on the data I've described, tafamidis has been recognized with a Class 1 recommendation in NYHA stages I through III, the highest evidence rating, in the AHA/ACC/HFSA heart failure guidelines.[8]

In closing, tafamidis is the only FDA-approved disease modifying therapy for both hereditary and wild type ATTR-CM to reduce mortality and CV-hospitalization.[2] Robust clinical and real-world evidence consistently demonstrate the net health benefit of tafamidis across NYHA stages I to III, including in healthier contemporary patients, along with a safety profile comparable to placebo.[1,3,4,5]

Tafamidis has redefined the treatment of ATTR-CM, dramatically improving patient outcomes and leading to earlier diagnosis.

We absolutely welcome advancements and innovation in this disease area, and as leaders in this space, we look forward to continuing to empower efforts with stakeholders to advance suspicion and early diagnosis for patients with this serious and progressive disease. Thank you for your attention.

References

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Dr. Bruno is a full-time employee at Pfizer.

H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the September 20th, 2024 Public meeting of Disease Modifying Therapies for the Treatment of Transthyretin Amyloid Cardiomyopathy.

Table H1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
Madeline Booth, BA, Program Manager, ICER	**Sarah K. Emond, MPP**, President and Chief Executive Officer, ICER
Grace Ham, MSc, Senior Program and Events Coordinator, ICER	**Jasmeen Kaur, PhD Candidate**, Economic Modeler, University of Illinois at Chicago
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David Rind, MD, MSc, Chief Medical Officer, ICER	**Kanya Shah, PharmD, MS, MBA, PhD Candidate**, Economic Modeler, University of Illinois at Chicago
Daniel Touchette, PharmD, MA, Professor, University of Illinois at Chicago	**Jason Wasfy, MD, MPhil**, Associate Professor, Harvard Medical School; Director of Outcomes Research and Cardiologist, Massachusetts General Hospital Heart Center
Aaron Winn, MPP, PhD, Associate Professor, University of Illinois at Chicago	

*No conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report including comparators during the previous year from health care manufacturers or insurers (including anyone in the member's household).

Table H2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC*	
Eric Armbrecht, PhD, Professor, Saint Louis University	**Alan J. Balch, PhD,** CEO, Patient Advocate Foundation | National Patient Advocate Foundation
Bijan J. Borah, PhD, Professor of Health Services Research, Mayo Clinic College of Medicine and Science	**Aaron Carroll, MD, MS**, President and CEO, AcademyHealth
Gregory Curfman, MD, Executive Editor, JAMA	**Yngve Falck-Ytter, MD, AGAF**, Case Western Reserve University
Heather Guidone, BCPA, Program Director, Center for Endometriosis Care	**Jayani Jayawardhana, PhD**, Associate Professor, University of Kentucky
Jill Johnson, PharmD, Professor, Pharmacy Practice, UAMS	**David Kim, PhD,** Assistant Professor, University of Chicago
Bradley Martin, PharmD, PhD, Professor, University of Arkansas for Medical Sciences	**Timothy McBride, PhD**, Professor, Washington University in St. Louis
Rachel Sachs, JD, MPH, Professor of Law, Washington University in St. Louis	**Kurt Vanden Bosch, PharmD**, System Formulary Lead, St. Luke's Health System
Stuart Winston, DO, Patient Experience Consultant, Trinity Health IHA Medical Group	

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Alyssa Guest, PharmD, Associate Director, Clinical Pharmacy, IPD Analytics	Alyssa is a full-time employee at IPD Analytics.
Michelle Kittleson, MD, PhD, Professor of Medicine, Smidt Heart Institute at Cedars-Sinai	No conflicts to disclose.
Mathew S. Maurer, MD, Professor of Cardiology, Columbia University Irving Medical Center	Dr. Maurer has received funds in excess of $5,000 from Novo-Nordisk and has received research support and consulting from Alnylam, Pfizer, Ionis, Intellia, and Attralus.
Milton Mitchell, Patient Advocate, Donate Life Ambassador and Active Amyloidosis Support Group Member	No conflicts to disclose.
Sean Riley, Patient Advocate/Speaker, Mackenzie's Mission – Amyloidosis Speakers Bureau	Sean had equity interests in excess of $10,000 from Alnylam and BridgeBio.
John Watkins, PharmD, MPH, BCPS, Senior Clinical Pharmacist, Premera Blue Cross	John is a full-time employee at Premera Blue Cross.