Disease Modifying Therapies for the Treatment of ATTR-CM: Final Policy Recommendations

October 21, 2024

Policy Recommendations

Introduction

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.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, Special Advisor to ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

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.[1] 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.[2]

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.

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.

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).

References

1. Wardhere A, Bampatsias D, Fine N, et al. Heterogeneous worldwide access and pricing of Tafamidis. *Amyloid*. 2024/01/02 2024;31(1):73-75. doi:10.1080/13506129.2023.2263620
2. Roberts M. NHS offers life-saving drug for still heart condition. BBC News. Updated 13 May 2024. https://www.bbc.com/news/articles/cpwg74zlgl7o

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the September 20th 2024 Public meeting of Disease Modifying Therapies for the Treatment of ATTR-CM.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

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*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).

Appendix Table 2. Midwest CEPAC Panel Member Participants and COI Disclosures

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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
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 3. 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.