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Racial and Ethnic Disparities in Transthyretin Cardiac Amyloidosis

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Abstract

Purpose of Review—Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening disease that disproportionately affects older adults and people of African descent. This review discusses current knowledge regarding racial and ethnic disparities in the diagnosis and management of ATTR-CM.

Recent Findings—Historically, ATTR-CM was thought to be a rare cause of heart failure. Recent evidence has shown that ATTR-CM is more common among older adults, men, and people of African descent. In addition, significant geographic variation exists in the identification of amyloid cardiomyopathy. Despite the high burden of ATTR-CM among Black individuals, most clinical data for ATTR-CM are from North America and Europe. Moreover, only a minority of clinical trial participants thus far have been Black patients. In addition to racial differences, socioeconomic disparities may be further compounded by the potentially prohibitive cost and limited accessibility of disease-modifying ATTR therapies.

Summary—ATTR-CM is an important cause of heart failure that disproportionately affects people of African descent. Efforts to promote earlier identification of ATTR-CM in general practice will likely improve clinical outcomes for all groups. Future trials should strive to enroll a higher proportion of Black patients. Furthermore, enhanced efforts are warranted to improve treatment accessibility among racial and ethnic minority groups that may be more likely to be affected by ATTR-CM.

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Keywords

Amyloidosis; Transthyretin; Cardiomyopathy; Racial disparities; Diagnosis; Treatment; Cardiac scintigraphy

Introduction to Amyloid Cardiomyopathy

Amyloid cardiomyopathy (CM) results when misfolded proteins aggregate to form rigid amyloid fibrils that deposit in the myocardium. [1] The amyloid infiltrates can cause damage to the heart via both direct toxicity and disruption of the normal organ architecture. The subsequent restrictive CM can lead to heart failure, arrhythmias, and sudden death. [1–5] The fibril precursor protein defines the subtype of amyloid CM, which differ in prognosis and treatment. The degree of cardiac involvement in systemic amyloidosis is often the most important predictor of prognosis. The most common types of cardiac amyloidosis are transthyretin amyloid CM (ATTR-CM) and immunoglobulin light chain amyloid CM (AL-CM). Other systemic amyloidoses, such as serum amyloid A (AA) and beta-2 microglobulin (ABeta2M), have rare cardiac involvement. [6, 7] Leukocyte cell-derived chemotaxin 2 (ALECT2) is a more recently identified form of amyloidosis that is much more common in Hispanics/Latinxs, particularly Mexican-Americans. [7] ALECT2 is most commonly associated with renal and hepatic involvement; significant cardiac involvement has not been described. [7]

AL-CM occurs in the setting of a plasma cell dyscrasia with deposition of immunoglobulin light chains in virtually any organ; deposition in the cardiovascular, renal, nervous, integumentary, and gastrointestinal/hepatic organ systems are most common. AL-CM is a rapidly progressive disease with a median survival of only 6 months if left untreated. [8–10] Multiple treatments, including chemotherapy, stem cell transplant, immunotherapy, and monoclonal antibodies, are available for its management. [8, 11] Unlike multiple myeloma which is twice as common and has a higher mortality in Black patients compared to White patients, [12] no clear gender, racial, or ethnic predominance has been reported in AL amyloidosis. However, a recent study by Staron et al. found that non-Hispanic Black patients may have more aggressive disease phenotypes. [13] They also identified lower rates of stem cell transplantation in Hispanic patients, which appeared to be driven by socioeconomic and clinical factors rather than race/ethnicity. [13]

ATTR-CM will be the primary focus of this review. This disease is caused by deposition of transthyretin (TTR), a protein secreted by the liver that transports thyroxine and retinol. The native, homotetramer form dissociates into unstable TTR monomers which misfold, aggregate, and form amyloid fibrils. ATTR-CM carries high morbidity and mortality, although the life expectancy is longer than with AL-CM with a median survival of about 3.5 years. [2] ATTR-CM can result either from a genetic mutation [variant ATTR (ATTR_v)] or from deposition of wild-type TTR (ATTR_{wt}). ATTR_v has an autosomal dominant inheritance pattern with incomplete penetrance; cardiomyopathy and neuropathy are the most common ATTR_v manifestations. Because of its genetic distribution, certain racial and ethnic groups, most notably people of African and Portuguese descent, have higher rates

of ATTR-CM. [14–17] In the USA, an analysis of two biobanks found that participants of African or Latinx descent who carry the V122I TTR variant have twice the risk of incident heart failure compared to non-carriers. [18] ATTRwt, previously known as senile amyloid cardiomyopathy, usually manifests with cardiac, tendon, and ligament involvement in older men. Extracardiac manifestations, such as bilateral carpal tunnel syndrome, [2, 19–21] distal biceps tendon rupture, [22] and lumbar spinal stenosis, [23, 24] are often present years before significant cardiac dysfunction is apparent. [25]

Cardiac biomarkers, including troponin and N-terminal (NT)-pro hormone B-type natriuretic peptide (NT-proBNP), are usually elevated in ATTR-CM but are nonspecific. [2, 25, 26] Echocardiogram findings often raise suspicion for the diagnosis of amyloid CM with concentric left ventricular (LV) wall thickening > 12 mL, bi-atrial enlargement, and reduced LV longitudinal strain with apical sparing. [27–29] The diagnosis was historically confirmed via endomyocardial biopsy. However, ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) cardiac scintigraphy has become the standard for diagnosis for patients in whom the presence of a monoclonal gammopathy has been excluded. [30–35] This has provided a lower-cost, widely available, non-invasive method of diagnosis. [36]

Management of ATTR-CM previously focused on palliation with symptomatic management of progressive heart failure with diuretics to control congestion and antiarrhythmics to control atrial and ventricular arrhythmias. Recently, tafamidis, a TTR stabilizer that reduces the formation and deposition of amyloid fibrils, was approved by the FDA for ATTR-CM. The landmark, randomized ATTR-ACT trial showed improvements in both mortality and cardiovascular hospitalizations at 30 months for tafamidis compared to placebo. [37, 38] Patisiran and inotersen are two TTR silencers that have been recently approved for ATTR polyneuropathy with or without cardiomyopathy. [39, 40] TTR silencers are currently being tested specifically in patients with ATTR-CM. [36, 41, 42]

Disparities in Heart Failure

Overall, Black individuals are 30% more likely to die from heart disease, have higher rates of myocardial infarction, and worse outcomes after acute coronary syndrome events. [43] With regard to heart failure, Black Americans are more likely to develop congestive heart failure and to do so at an earlier age. Black patients have a 2.5-fold increased risk of hospitalization for heart failure compared to White patients and higher mortality (particularly in patient less than 65 years old). [44, 45] Black patients also have higher rates of dilated and peripartum cardiomyopathy with more severe disease profiles when they occur. [46–48] Black patients with hypertrophic cardiomyopathy are less likely to be referred for sudden cardiac death risk stratification and to have implanted cardioverter-defibrillators when indicated, though without noted differences in clinical outcomes and mortality. [49] The etiologies of these disparities in heart failure are thought to be multifactorial with genetic, comorbid, socioeconomic, systemic, and policy contributions that remain to be fully elucidated. [44]

Genetics of ATTR-CM

ATTR-CM is caused by a number of TTR mutations with over 140 known variants associated with clinical amyloidosis. [50] It is becoming increasingly appreciated that specific TTR mutations have distinct demographic predominance. The V122I (valine to isoleucine) mutation is by far the most common variant in the USA and is carried by approximately 4% of Black Americans. [51] Up to 5% of the West African population carries the V122I variant. In a single referral center analysis in the UK, V122I was the most common TTR mutation, comprising 43% of all ATTRv; nearly 50% of this cohort had Afro-Caribbean or African ancestry. [52] The V30M (valine to methionine) mutation is the best described TTR variant. V30M ATTRv is associated with predominant polyneuropathy and is a common variant in Portugal, Japan, Sweden, and Brazil. [53–56]

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is an ongoing multinational registry that collects observational data on the natural history of ATTR. In a publication by the THAOS investigators in 2016, 2530 patients were included, 390 of whom were in the USA and more than 1000 in Portugal. They found that about one in four enrolled patients in the USA were of African descent compared to 0.5% in other regions of the world. While V122I was the most common pathologic mutation in the USA, V30M was the most common in the other included regions of the world. The THAOS data for Hispanic/Latinx patients were sparse with 256 patients from Latin American countries (Brazil, Mexico, and Argentina). The most common pathologic mutation in this group was V30M possibly resulting from Portuguese colonization in South America. [57] Other pathologic TTR variants have been described in different Hispanic subpopulations. For example, S50A (serine to alanine) is the most common TTR variant in certain regions of Mexico. [58] Given the data suggesting worse clinical outcomes for ATTRv compared to ATTRwt, further comprehensive studies in Black and Hispanic/Latinx populations will be critical.[59]

Disparities in the Diagnosis of ATTR-CM

Early diagnosis of ATTR-CM is crucial to slow amyloid deposition and delay disease progression. [37] While diagnoses appear to be increasing over time, [16, 59–61] early recognition and diagnosis remain challenging perhaps in part due to limited physician awareness of the condition and its management. [62, 63] In fact, in the USA, there are large geographic variations in reported mortality due to amyloidosis. The highest mortality rates were reported in counties near amyloid referral centers. Notably, the southern states, despite having the highest proportions of Black individuals, reported the lowest mortality due to amyloidosis, [16] likely reflective the disparities in diagnosis (Fig. 1).

For patients with ATTR-CM that are identified, the median time from onset of cardiac symptoms requiring hospitalization to diagnosis appears to be approximately 2–3 years. [59] The V122I mutation results in almost exclusively cardiac involvement; mortality appears to be higher in patients with V122I ATTRv, with a median survival of 25.6 months versus 43 months in ATTRwt. [64] A multivariable analysis of 1034 patients with ATTR-CM who were referred to an amyloid center in the UK showed that advanced disease and lower ejection fraction at the time of diagnosis and the V122I mutation were factors

associated with a higher mortality. [59] In the case of V122I ATTRv, in a study composed of 96% Black participants, women were, on average, about 7 years older at the time of diagnosis with similar clinical characteristics and mortality despite being older at the time of diagnosis. It is unclear whether this difference in age at the time of diagnosis is attributable to contextual issues like decreased access to care and clinician bias or an intrinsic feature of the disease presentation in women with later development of clinical symptoms.[60]

Several ongoing studies seek to identify the prevalence of ATTR-CM in specific populations. [65, 66] In the ongoing Screening for Cardiac Amyloidosis in Using Nuclear Imaging for Minority Populations (SCAN-MP), investigators are using cardiac scintigraphy to screen and diagnose patients of Black or Hispanic Caribbean origin with heart failure not caused by valvular or ischemic heart disease in an attempt to improve ATTR-CM in these populations. [67] While more asymptomatic carriers are likely to be identified via genotyping, guidelines for screening and management of these patients are not currently available. Some families may choose to forego genetic screening to avoid the influence of pre-existing conditions on acquiring life insurance. [68]

Disparities in ATTR-CM Trials and Treatment

The ATTR clinical trials thus far have studied either patients with predominant polyneuropathy or with primarily cardiac involvement. The phase 3 ATTR-ACT trial tested the efficacy of the TTR stabilizer, tafamidis, compared to placebo in patients with ATTR-CM. [37] The primary endpoint was mortality and cardiovascular hospitalizations. In this multi-center, international study including 441 participants, approximately 14% ($n = 63$) were Black patients. Notably, no site or center from the African continent participated in the trial. Two participants were included from Brazil (the sole South or Central American site). The majority of patients were recruited from the USA ($n = 279$), Germany ($n = 49$), Italy ($n = 29$), France ($n = 28$), and Japan ($n = 17$). [37] The APOLLO trial tested the efficacy of patisiran in 225 patients with ATTRv polyneuropathy. [40] Because this trial recruited patients with ATTR polyneuropathy, only 1% had a V122I mutation. Similarly, NEURO-TTR, which tested the efficacy of inotersen compared to placebo had only 2% of patients with the V122I mutation (Fig. 2). [39] Although there are several ongoing randomized trials focused on patients with ATTR-CM, they do not appear to include African countries as recruitment centers or state explicit goals for recruitment of Black patients or patients with V122I ATTRv (Table 1).

Beyond the need for targeted inclusion of Black patients in trials for ATTR-CM, questions remain regarding the accessibility, affordability, and ethics of the pricing of novel therapeutics. [69] Tafamidis has an estimated yearly cost of \$225,000. [70] Gurwitz and Maurer recently called attention to affordability issues for the uninsured and those with high deductible health plans and/or coverage gaps. They also called into question the drug's designation as an orphan drug given that, thus far, ATTR-CM has likely been grossly underdiagnosed and a true prevalence in the USA of greater than 200,000 people would invalidate the drug's market exclusivity provisions. [69] The multiple deficiencies in identification and accessibility create a leaky pipeline likely to leave many patients undiagnosed and create barriers to accessibility for those who are diagnosed (Fig. 3).

Future Directions

Although there is a growing appreciation and acknowledgement of the prevalence of ATTR-CM and the current underdiagnosis of this condition, there still remains a significant gap in diagnosis of Black and Hispanic/Latinx patients. Current data, though limited, demonstrate that these cohorts may have worse outcomes and prognosis, yet ongoing trials of ATTR-CM overlook these forgotten and likely high-risk groups. To mitigate future disparities, investigators should acknowledge this critical lack in data and be purposeful in recruiting Black and Hispanic/Latinx patients. Studies such as the SCAN-MP trial can serve as an example. This study also highlights that a number of Black patients who carry a diagnosis of heart failure with preserved ejection fraction (HFpEF) have not had thorough evaluation for secondary etiologies and often are assumed to be secondary to hypertensive heart disease. [17] This study will also help answer the question about the utility of using cardiac scintigraphy as a standard evaluation for patients with HFpEF and its utility in screening asymptomatic carriers of clinically significant TTR mutations for early signs of ATTR-CM. In addition to the strong demographic correlation of certain ATTR-CM variants, such as V122I, V30M, and S50A, proteomic and epigenetic evaluations may provide more information to guide diagnosis and treatment among Black and Hispanic/Latinx patients and should be a focus for future research.

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Conflict of Interest

Dr. Spencer-Bonilla, Dr. Pearson, Dr. Njoroge, and Dr. Aras do not have any conflicts of interest to disclose. Dr. Witteles has received consulting fees (modest) from Pfizer, Alnylam, Eidos, and Ionis/Akcea. Dr. Alexander has received an investigator-initiated research grant from Pfizer and has received consulting fees (modest) from Alnylam, Eidos, and Pfizer.

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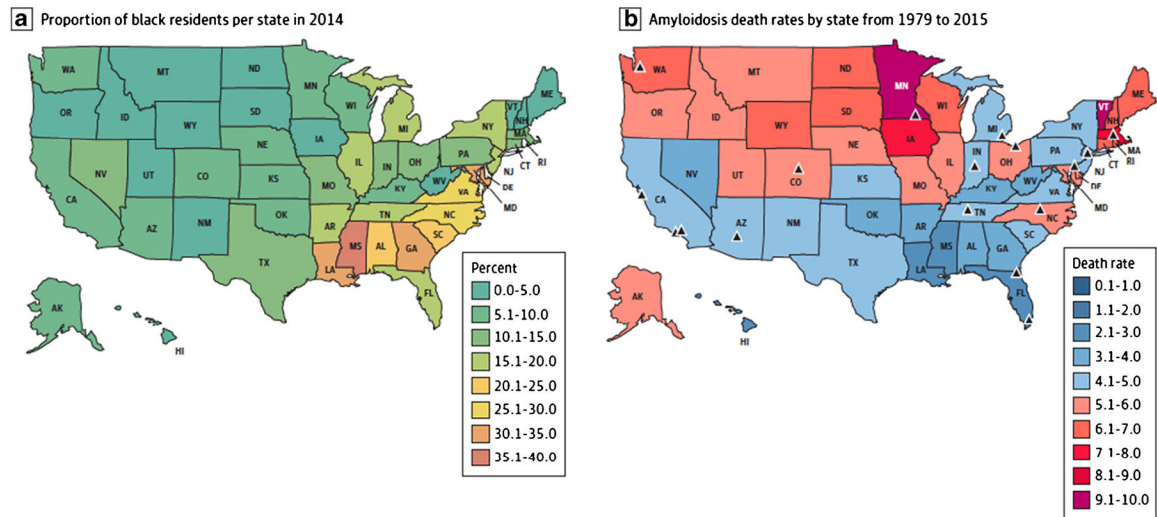


Fig. 1. Geographic disparities in reported age-adjusted death rates for amyloidosis in the USA. The triangles represent the location of established amyloidosis referral centers. Reproduced with permission from Alexander, K.M., et al., *Geographic Disparities in Reported US Amyloidosis Mortality From 1979 to 2015: Potential Underdetection of Cardiac Amyloidosis*. *JAMA Cardiol*, 2018. 3(9): p. 865–870

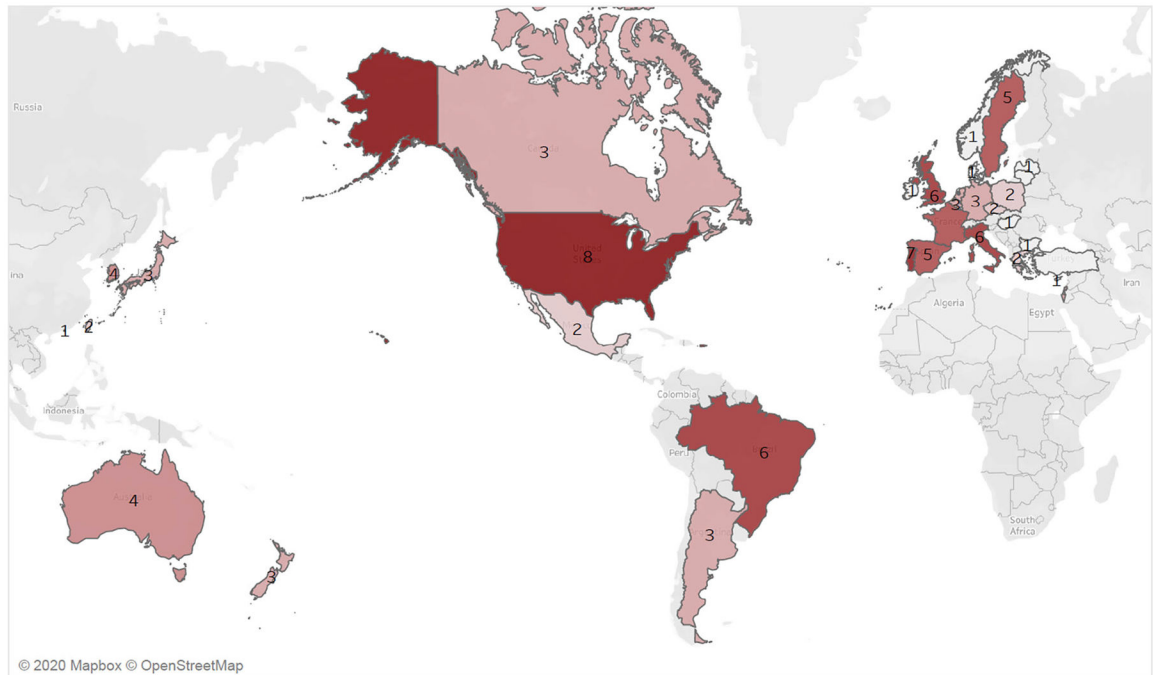


Fig. 2.

Total number of transthyretin amyloidosis (ATTR) clinical trials by country. The heatmap shows the number of ATTR clinical trials, with darker reds reflecting greater numbers of ongoing trials. Eight recent trials for ATTR cardiomyopathy or neuropathy from a total of 33 countries were included. [37, 39–42, 71–73] There were no trial sites on the continent of Africa

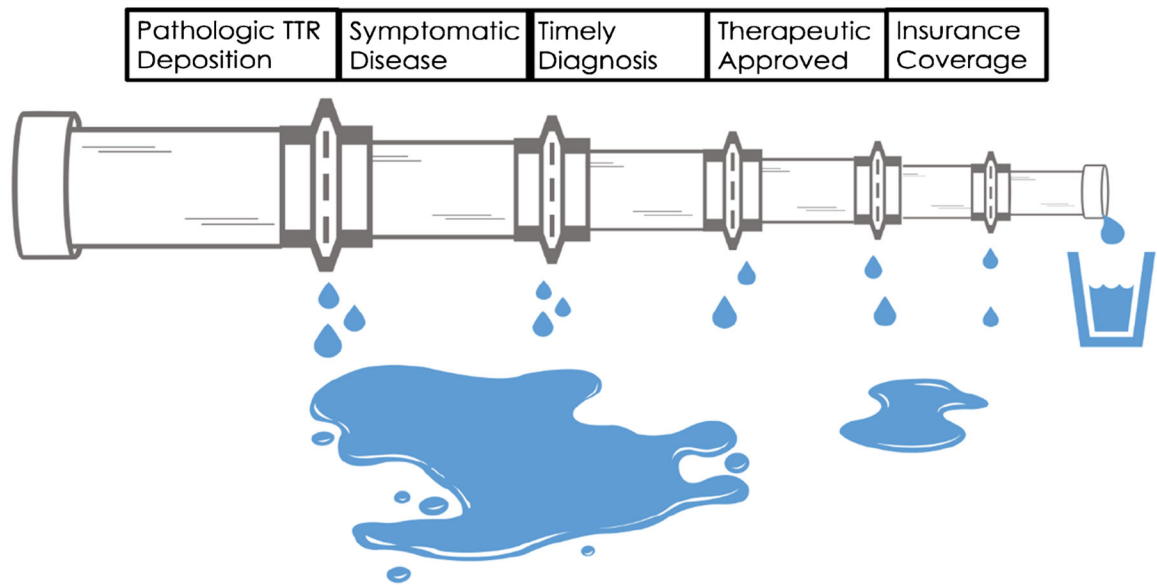


Fig. 3.

The leaky pipeline for transthyretin amyloidosis (ATTR) diagnosis and treatment. Only a fraction of patients with ATTR are treated. Cardiomyopathy does not develop in all patients with pathologic mutations due to incomplete penetrance. ATTR cardiomyopathy is frequently identified post-mortem, an untimely diagnosis. Until May 2019, there were no approved therapeutics specifically approved for ATTR cardiomyopathy. At a cost of over \$200,000, tafamidis remains unaffordable for some patients with high deductibles and coverage gaps

Table 1

Demographics of notable transthyretin amyloidosis (ATTR) clinical trials

Drug name <i>Trial name</i>	Number of patients	Route	Main findings and primary outcomes	Percent women participants	Percent Black participants	Countries included
Transthyretin stabilizers						
Tafamidis <i>ATTR-ACT</i>	441	Oral	Decreased mortality and cardiovascular-related hospitalizations.	10%	14%	Belgium, Brazil, Canada, Czech Republic, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, UK, USA
AG10 <i>ATTRibute-CM</i>	510	Oral	<i>Results pending:</i> Primary outcomes will be change in 6-minute walk test and the composite of all-cause mortality and cardiovascular hospitalizations.	<i>Recruitment ongoing</i>	<i>Recruitment ongoing</i>	Australia, Belgium, Brazil, Canada, Greece, Hungary, Ireland, Israel, Italy, Korea, Netherlands, New Zealand, Poland, Portugal, Spain, USA
Transthyretin silencers						
Patisiran <i>APOLLO</i>	225 (with neuropathy ± cardiomyopathy)	IV	Vastly improved neurological function vs. placebo. Subanalysis showed decreased LV wall thickness, decreased NT-ProBNP, and improved global longitudinal strain.	26%	2%	Argentina, Brazil, Canada, Bulgaria, Cyprus, France, Italy, Japan, Mexico, Netherlands, Portugal, South Korea, Spain, Sweden, Taiwan, Turkey, UK, USA
Inotersen <i>NEURO-TTR</i>	172 (with neuropathy ± cardiomyopathy)	SQ	Greatly improved neurological function vs. placebo. No significant difference in cardiac parameters.	31%	4%	Argentina, Brazil, France, Germany, Italy, New Zealand, Portugal, UK, USA
Patisiran <i>APOLLO-B</i>	300	IV	<i>Recruitment ongoing:</i> primary outcome will be change from baseline at month 12 in Six-Minute Walk Test	<i>Recruitment ongoing</i>	<i>Recruitment ongoing</i>	Argentina, Australia, Brazil, Czechia, Denmark, France, Hong Kong, Italy, Japan, Republic of Korea, Mexico, Poland, Portugal, Sweden, Taiwan, UK, USA
Vutrisiran <i>HELIOS-B</i>	600	SQ	<i>Recruitment ongoing:</i> primary outcome will be the composite of all-cause mortality and cardiovascular-related hospitalizations.	<i>Recruitment ongoing</i>	<i>Recruitment ongoing</i>	Australia, France, Germany, Israel, Republic of Korea, Latvia, Lithuania, Norway, Portugal, Spain, Sweden, UK, USA
AKCEA-TTR-LRx <i>CARDIO-TTRtransferrin</i>	750	SQ	<i>Recruitment ongoing:</i> The primary outcome will be the change in 6-minute walk test and the composite of cardiovascular mortality and clinical cardiovascular events.	<i>Pending</i>	<i>Pending</i>	Australia, Belgium, Brazil, Greece, Israel, Italy, Portugal, Spain, Sweden, USA
Amyloid clearance						
PRX004	36	IV	<i>Results pending:</i> maximum tolerated dose and treatment-emergent adverse events	<i>Pending</i>	Phase I trial	Portugal, Spain, Sweden, USA

ATTR transthyretin amyloidosis, *ATTRv* variant ATTR, *ATTRwt* wild-type ATTR, *IV* intravenous, *SQ* subcutaneous, *TTR* transthyretin