Current and emerging treatment options for transthyretin amyloid cardiomyopathy

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Abstract

Transthyretin (ATTR) amyloidosis is a condition caused by TTR protein misfolding and amyloid deposition, particularly in the heart and nervous system, leading to organ dysfunction. Advances in therapeutic strategies have revolutionized the management of ATTR amyloidosis. Treatments available in clinical practice include TTR stabilizers (tafamidis and acoramidis), which prevent the dissociation of TTR tetramer into monomers and oligomers that subsequently form amyloid fibrils; and gene-silencing therapies (patisiran, inotersen and vutrisiran) which suppress the hepatic synthesis TTR, which is the amyloid precursor protein. Novel treatment strategies that are at various stages of development include CRISPR-Cas9 gene-editing technology (nexiguran ziclumeran), which if successful offers the prospect of a single-dose treatment, and monoclonal (cormitug and ALXN220) and pan-amyloid antibodies (AT-02) that seek to target and remove amyloid fibrils that have deposited in the myocardium. Amyloid removal remains a significant unmet clinical need and hence, the ability to promote amyloid degradation and clearance through use of anti-amyloid therapies would represent a ground-breaking advancement in the treatment of ATTR amyloidosis. The success of ATTR-specific disease modifying therapies has already altered the treatment landscape and changed the perception of ATTR amyloidosis from a progressive and fatal disease to one that is treatable through availability of highly effective disease modifying therapies. However, important questions remain including the long-term safety of these drugs, whether combining therapies with different mechanisms of action has an additive prognostic benefit and how best to monitor the treatment response.

1. Introduction

Transthyretin cardiomyopathy (ATTR-CM) is the exemplar infiltrative cardiomyopathy and is caused by the deposition of misfolded transthyretin (TTR) in the form of amyloid fibrils within the myocardium. The sporadic, non-inherited, wild-type form (ATTRwt-CM), is a condition of older, predominantly male individuals; while the variant form (ATTRv-CM) occurs secondary to a single-point mutation in TTR-gene and presents with a varying clinical phenotype, often comprising both CM and polyneuropathy (PN).[1]

Before the development of disease-modifying therapies, successful treatment of ATTR-PN had been achieved through liver transplantation, which suppresses the hepatic production of variant TTR, and prevents ATTRv-fibril deposition within the nerves. However, due to the risks associated with liver transplantation, this treatment option was reserved for select cases.[2]

The advent of highly specific disease-modifying therapies that target different stages of the amyloidogenic cascade has changed the perception of ATTR amyloidosis from a progressive and fatal disease to one that is treatable through the availability of highly effective pharmacotherapies [2,3](**Figures 1-2** and **Table 1**). Despite these advances, significant challenges remain regarding the translation of clinical trial findings into real-world practice. This narrative review aims to bridge this gap by providing a comprehensive overview of the evolving therapeutic landscape of ATTR-CM. It will explore the rationale behind the development of treatment options, including supportive measures, ATTR-specific disease-modifying therapies that are already available in clinical practice, and experimental therapies that are at various stages of development. By contextualizing recent advancements within the broader clinical framework, this review seeks to offer insights that are relevant to both researchers and clinicians striving to optimize patient outcomes.

2. Current treatment approaches

2.1 Support therapy

In the past, the mainstay of management of patients with ATTR-CM was meticulous volume control through loop diuretics. Two recent studies have shown that low-dose beta-blockers in patients with a reduced ejection fraction and both mineralocorticoid receptor antagonists and sodium-glucose co-transporter-2 inhibitors across the spectrum of disease were associated with improved survival.[3,4] Patients with ATTR-CM have a similar and possibly greater neurohormonal activation than is observed in heart failure different aetiologias and it is therefore plausible that prognostic benefit could be derived from neurohormonal modulation.[5] Treatment of cardiac complications is also of paramount importance. Atrial fibrillation is extremely common in ATTR-CM and anticoagulation as stroke prophylaxis is recommended. Atrial electromechanical dissociation is also a common phenomenon.[6] Atrial thrombi can form in the absence of atrial fibrillation and hence, anticoagulation can be considered even with sinus rhythm.[8] Conduction abnormalities are also prevalent, often necessitating pacemaker implantation, but there is no evidence that prophylactic pacing improves patient outcomes. [7] Finally, heart transplantation represents a viable option for highly selected patients with advanced ATTR-CM. [8]

However, none of these therapies specifically target the pathways responsible for ATTR amyloid fibril formation. A deeper understanding of the underlying pathophysiology has resulted in the discovery of multiple disease specific pharmacotherapies that are either approved for clinical use or at different stages of development.

2.3 Transthyretin stabilisers

Tafamidis

Tafamidis is a benzoxazole derivative that binds with a high affinity to the thyroxine-binding regions of TTR to stabilize the tetramer and prevent dissociation into amyloidogenic monomers

and oligomers. The phase 3 Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) demonstrated that treatment with tafamidis reduced all-cause mortality and cardiovascular-related hospitalizations as compared with placebo, and also slowed the decline in functional capacity and quality of life (QoL) [9]. Tafamidis showed long-term efficacy in the open-label extension with a median follow-up duration of 58 months.[10] Consequently, tafamidis became the first drug approved by the Food and Drug Administration (FDA) for the treatment of ATTR-CM in 2019 [11] (**Table 2**).

Acoramidis

Acoramidis is a novel TTR stabilizer designed to mimic the action of the Thr119Met variant to achieve near-complete TTR stabilization. The phase 3 ATTRIBUTE-CM trial demonstrated that acoramidis was associated with a favorable win ratio in a 4-component hierarchical analysis that included all-cause mortality, the cumulative frequency of cardiovascular-related hospitalization, change in N-terminal pro-b-type natriuretic peptide (NT-proBNP), and change in 6 minute walking test (6MWT) distance.[12]

The compelling efficacy and safety data from clinical trials led to FDA approval of acoramidis for both ATTRwt-CM and ATTRv-CM in November 2024, followed by a recommendation for approval by the European Medicines Agency in December 2024.

3.1 Gene silencing approaches

The circulating ATTR amyloid precursor protein is synthesized mainly by the liver and coded for by a single gene, making ATTR amyloidosis the prototypic model disease for targeted gene interference therapies[13] (Figure 3).

Patisiran

Patisiran is a first-generation small interfering RNA (siRNA) that induces degradation of the mRNA coding for TTR and hence inhibits the hepatic synthesis of TTR.[14] The phase 3 APOLLO trial, recruited patients with ATTRv-PN and demonstrated significant neurological improvement in those treated with patisiran.[15] A post-hoc analysis on a subset of 126 patients with cardiac involvement (defined as left ventricular [LV] wall thickness >13 mm in the absence of known hypertension or significant aortic valve disease) demonstrated that patisiran was associated with a reduced mean left ventricular (LV) wall thickness and relative wall thickness, and improved global longitudinal strain compared with placebo. However, the definition of cardiac involvement is nonspecific and could have resulted in the inclusion of patients who do not fulfill the guideline-mandated diagnostic criteria for ATTR-CM.[16], Subsequently, patisiran was evaluated specifically in ATTR-CM in the APOLLO-B trial, which demonstrated that treatment with patisiran resulted in a slower decline in 6MWT distance.[17] However, the FDA declined the application to approve patisiran for the treatment of ATTR-CM, expressing concerns about the small effect size. [19]

Inotersen

Inotersen is a first-generation antisense oligonucleotide (ASO) that selectively targets the mRNA responsible for coding TTR, promoting its degradation and thus lowering circulating TTR levels. [21] The phase 3 NEURO-TTR trial, demonstrated the efficacy of inotersen in treating patients with ATTRv-PN,[18] however, the assessment of inotersen in patients with cardiac involvement is limited to small single-centre studies. A study involving 15 patients with ATTR-CM demonstrated that treatment with inotersen over 12 months resulted in disease stabilisation with stable measurements of LV wall thickness, LV mass, 6MWT, and global systolic strain reflected disease stabilization.[19] The efficacy of inotersen in ATTR-CM is yet to

be assessed in a large trial, and therefore, it has only been approved for the treatment of ATTRv-PN.

Vutrisiran

Vutrisiran is a second-generation siRNA, which demonstrated efficacy in treating ATTRv-PN in the phase 3 HELIOS-A trial. A post-hoc analysis assessed the impact of vutrisiran on cardiac parameters. In the overall population, and in those considered to have cardiac involvement (based on the definition used in the post-hoc APOLLO analysis), treatment with vutrisiran was associated with favourable NT-proBNP changes and a nominally significant beneficial change in stroke volume compared with placebo. This study utilized a historical placebo group from the APOLLO trial and there were significant differences in baseline characteristics between the two groups. Furthermore, the definition of cardiac involvement is nonspecific and fraught with the same limitations as the post-hoc analysis of the APOLLO trial.[20]

The phase 3 HELIOS-B trial demonstrated that treatment with vutrisiran in patients with ATTR-CM resulted in a reduction in the composite primary endpoint of all-cause mortality and cardiovascular events in both the overall population and the monotherapy population (patients not treated with tafamidis at enrollment).[21]

The HELIOS-B results represent the first evidence of clinical benefits in cardiovascular endpoints for a gene-silencing therapy in ATTR-CM, and vutrisiran has recently become the first FDA-approved therapy for both ATTR-CM and ATTR-PN.

Eplontersen

Eplontersen is a second-generation ASO, with a similar design to inotersen but is 50-fold more potent, translating to a 15-fold greater reduction in plasma TTR levels. [22] The phase 3 NEURO-TTRansform trial demonstrated the efficacy of eplontersen in treating patients with ATTRv-

PN.[23] Switching from inotersen to eplontersen further reduced serum TTR levels, established neuropathic disease, and improved tolerability, supporting a favorable benefit-risk profile for eplontersen.[24] A post-hoc analysis of the change in echocardiographic parameters in patients treated with eplontersen compared to the historical placebo group from NEURO-TTR showed that, in the overall population, eplontersen was associated with improvements in LV end-diastolic volume, stroke volume, E/e′, and left atrial volume. In a subgroup of patients considered to have cardiac involvement (based on the prespecified definition used in the post-hoc APOLLO analysis), treatment with eplontersen was associated with an improvement in LV stroke volume and ejection fraction. However, the study design and use of a historical cohort has the same limitations as the post-hoc analyses of the APOLLO and HELIOS-A trial populations.[25]

The ongoing phase 3 CARDIO-TTRansform trial (NCT04136171), the largest ATTR-CM study to date, has enrolled over 1,400 patients to investigate the impact of eplontersen on a composite endpoint of cardiovascular mortality and recurrent cardiovascular clinical events at 120 weeks, with additional assessments of functional capacity, QoL, and biomarkers.

Nexiguran ziclumeran (nex-z)

Nex-z, formerly NTLA-2001, is a Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9-based therapy developed to remove the *TTR* gene from the genome with potential long-lasting benefits. [26,27] Nex-z employs Cas9 endonuclease and a single guide RNA to induce targeted DNA cleavage, effectively halting TTR liver production. [22] In a phase 1 trial, nex-z demonstrated profound and sustained efficacy with an 89% reduction in serum TTR levels. [28] Biomarkers, functional assessment, and imaging studies confirmed halted amyloid deposition and stability in cardiac structure and extracellular volume. [28]

The ongoing phase 3 MAGNITUDE trial (NCT06128629) is evaluating the long-term safety and efficacy of nex-z, enrolling approximately 765 participants, randomized in a 2:1 ratio to receive nex-z or placebo, with an event-driven study design.

3.2 Anti-amyloid immunotherapies

TTR stabilisers and gene silencers/gene editing therapies all seek to reduce amyloid production, but amyloid removal remains an important unmet clinical need, especially for patients with advanced cardiac disease.[29] Monoclonal antibody (mAb)-mediated removal was recently described in 3 patients who spontaneously developed anti-amyloid antibodies. This was associated with reversion to near-normal cardiac structure and function and provided proof of concept that antibody-based therapies can accelerate amyloid removal and disease regression.[30]

Coramitug

Coramitug (NNC6019-0001, formerly PRX004) is a humanized IgG1 mAb specifically targeting misfolded monomeric and aggregated forms of TTR, without affecting its native tetrameric configuration.[31] Coramitug binds an epitope exposed only on non-native TTR, triggering the clearance of amyloid fibrils via macrophage-mediated phagocytosis.

A phase 1 study (NCT03336580) evaluated the safety of Coramitug in 21 ATTRv patients and demonstrated a mean reduction in neuropathy impairment score and improved cardiac global longitudinal strain.[32] An ongoing phase 2 trial aims to evaluate the efficacy of Coramitug in ATTR-CM (NCT05442047) assessing the change in 6MWT distance and NT-proBNP.[33]

ALXN2220

ALXN2220 (formerly NI006) is another IgG1 mAb, which becomes accessible on misfolded TTR and amyloid deposits.[31] In a phase 1 trial (NCT04360434), 40 patients with ATTR-CM

serial cardiac imaging investigations revealed dose-dependent reductions in cardiac amyloid burden, as indicated by decreased extracellular volume on cardiac magnetic resonance.[34] Following these promising findings, FDA granted a Fast Track designation to ALXN2220 which is currently being evaluated in the phase 3 DepleTTR-CM trial (NCT06183931).

Pan-amyloid antibodies

Pan-amyloid removal (PAR) therapies represent an innovative approach to amyloid removal by inducing Fc-receptor mediated phagocytosis of all forms of amyloid fibrils. Miridesap, a molecule promoting serum amyloid P (SAP) clearance from circulation, in combination with the fully humanized IgG1 anti-SAP mAb dezamizumab, was capable of binding amyloid deposits and inducing an immune-mediated response from giant multinucleate.[35] In a phase 1 study involving 15 patients with systemic amyloidosis, the combined therapy improved liver function and reduced amyloid load.[36] However, further research on anti-SAP antibodies has been held back by the onset of vasculitis in some of the trial patients.[37]

AT-02 is a next-generation PAR therapy that consists of a humanized mAb with an amyloid-binding peptide genetically fused to the light chain. This peptide binds to multiple different amyloid fibrils and induces macrophage-mediated degradation and is being tested in ongoing phase 1 (NCT05521022) and phase 2 (NCT05951049) trials. [35]

3.3 Seeding inhibitors

Amyloid seeding, the self-propagating process of amyloid fibril formation and deposition, driven by fibrillary fragments, may accelerate the aggregation of TTR monomers even in the presence of stabilizing therapies.[38] The TabFH2 peptide binds and caps the F and H β-strands of TTR fibrils, preventing the growth and nucleation of new amyloid seeds. Preclinical studies demonstrated its efficacy in completely halting TTR aggregation, even in the presence of *ex*

vivo seeds from ATTR fibrils.[39] These inhibitors may be most effective when used early to prevent rapid amyloid deposition or combined with fibril-clearing agents in advanced cases to address both new and existing deposits.

4. Monitoring cardiac disease progression

The treatment landscape for ATTR amyloidosis is constantly evolving and hence, there is an increasing need to identify markers of disease progression that might indicate a need to intensify treatment. A large multicenter study recently showed that NT-proBNP progression (an increase >700 ng/L and >30%) and outpatient diuretic intensification were independently associated with mortality.[40] A decline in glomerular filtration rate >20% is also associated with mortality. All 3 markers can be applied in combination and remain independently associated with mortality, indicating that each marker captures different aspects of the underlying disease process.[41] The change in 6MWT can also be leveraged as a marker of disease burden, with an absolute reduction >35 m or relative reduction >5% being independently associated with mortality.[42] These markers are universally applicable across the different genotypes, widely available and easy to measure and, hence, could be easily applied to clinical practice with significant implications in terms of guiding optimization of treatment strategies.

The search for novel markers of disease progression and treatment response has resulted in multiple clinical trials leveraging imaging-based parameters as end-points that are reflective of the change in cardiac amyloid burden.[43] Cardiac magnetic resonance with multiparametric mapping has already demonstrated utility in tracking the treatment response in cardiac light-chain amyloidosis, with extracellular volume mapping acting as a surrogate marker of the amyloid burden.[44,45] These techniques have already been utilized in the context of clinical trials to assess changes in amyloid burden in response to treatment, however, further studies are

needed to define the prognostic importance of changes in the myocardial extracellular volume in ATTR-CM.

5. Future perspectives

5.1 Combination therapy

The ever-expanding landscape of treatments for ATTR-CM means that the amyloid cascade can be targeted at multiple different points. It is possible that the combination of a TTR stabiliser and gene silencer could have a synergistic and reduce amyloid formation more than a single agent and hence, result in improved patient outcomes. Alternatively pairing stabilizers or silencers with anti-amyloid therapies could synergistically halt new deposition while clearing existing amyloid. Further large-scale studies are required to determine whether combination therapy provides additional clinical benefit in ATTR-CM.

5.2 Earlier diagnosis

Advances in cardiac imaging, alongside an increased awareness amongst clinicians and the changing perception of ATTR-CM from a progressive and fatal disease to one that is treatable through the availability of highly specific and effective disease-modifying therapies have resulted in a significant increase in diagnoses in recent years.[46] Alongside the upsurge in diagnoses, patients are now being diagnosed earlier in the disease course, as evidenced by a shorter duration of symptoms before diagnosis, better functional capacity, and milder disease stage at the time of diagnosis, all of which have translated to improved survival. Changes in the clinical phenotype of patients will influence the design of future clinical trials evaluating the efficacy of novel agents and will likely result in a requirement for greater patient numbers and a longer duration of follow-up to ensure adequate power.[47]

As a result of these changes many patients are being diagnosed before the development of heart failure symptoms, and some are even being diagnosed with early amyloid deposits, before the development of overt cardiomyopathy. Further research is needed to define the role of ATTR-specific disease modifying therapies in patients with early amyloid deposits.[48]

Greater awareness has also resulted in a greater number of asymptomatic carriers of TTR-gene variants being identified, but due to the varying penetrance of the disease and lack of clinical research it is currently unclear whether these patients should be monitored or actively treated with prophylactic ATTR-specific disease-modifying therapies. The ACT-EARLY trial has been designed to address these questions and is actively recruiting carriers of TTR variants who remain asymptomatic but are at risk of disease progression and randomizing them to treatment with acoramidis or placebo.[49] This shift in focus is essential to optimising treatment across the full spectrum of disease.

5.3 Access barriers

The elevated cost of these drugs represents a substantial barrier. The cost-effectiveness of therapeutic strategies needs to be evaluated in the context of their long-term benefits. Tafamidis is one of the most expensive cardiovascular drugs on the market. [50]

Future efforts must prioritize these goals while overcoming economic and logistical barriers, paving the way for more accessible and inclusive treatments, and making research advancements translate into meaningful clinical improvements.

Conclusions

Advances in the understanding of the underlying pathogenesis responsible for ATTR-amyloid fibril formation and the subsequent accumulation in the myocardium have resulted in the emergence of multiple novel treatments that target different elements of the amyloid formation

cascade. TTR stabilisers have demonstrated efficacy in the context of clinical trials and have been approved for the treatment of ATTR-CM, yet a significant gap remains between clinical trial outcomes and real-world patients, as many patients still experience disease progression whilst on treatment. The potential expansion of treatment options shortly will provide an alternative for those who do not achieve an adequate response to TTR stabilization. With the results of large-scale clinical trials expected over the next few years, anti-amyloid therapies may also enter the treatment arena and offer a treatment option for patients with advanced cardiac disease in need of disease reversal. Aiming to bridge the gap between research and clinical practice, future studies are needed to assess whether combination therapies have an additive prognostic benefit over single agents and considering that patients are being diagnosed earlier in the course of their disease, further research is needed to inform when treatment should be initiated, and which treatments should be initiated at each disease stage.

Figure Legends

Figure 1. Overview of possible therapeutic strategies in transthyretin amyloidosis. Therapeutic approaches target different phases of the pathogenic cascade. ATTR-CM, transthyretin cardiac amyloidosis; ATTR-PN, transthyretin amyloid polyneuropathy; nex-z, nexiguran ziclumeran; PAR, pan-amyloid removal therapies; TTR, transthyretin.

Figure 2. Clinical indications for proposed therapeutic alternatives in transthyretin amyloidosis patients. ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CM, cardiomyopathy; PN, polyneuropathy.

Figure 3. Transthyretin (TTR) synthesis. Small interfering RNA (siRNA) leads to the degradation of TTR mRNA through RNA-induced silencing complex (RISC), while antisense oligonucleotide (ASO) through RNAse H1; CRISPR-Cas9 directly suppresses the TTR protein synthesis inducing frameshift mutation.

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Statements

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Prof Fontana reported receiving consultant fees from and/or service on advisory boards for Alnylam Pharmaceuticals, Alexion/Caelum Biosciences, AstraZeneca, Eidos/BridgeBio Pharma, Prothena, Attralus, Intellia Therapeutics, Ionis, Cardior, Lexeo Therapeutics, Janssen Pharmaceuticals, Prothena, Pfizer, Novo Nordisk, Bayer, and Mycardium; research grants from Alnylam Pharmaceuticals, BridgeBio Pharma, AstraZeneca, and Pfizer; intermediate fellowship salary from the British Heart Foundation; share options in Lexeo Therapeutics; and shares in Mycardium outside the submitted work.

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All the Authors of the manuscript:
• Provided substantial contributions to the conception and design of the work;
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• Final approval of the version to be published;
• Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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Table 1. Treatment currently approved or under investigation for transthyretin cardiac amyloidosis.

Drug	Drug Type	Study Name (Year)	Study Design	Study Population	Main Efficacy Results	Safety Outcomes	Regulatory Approval
Tafamidis	TTR Stabilizer	ATTR-ACT (2018)	Phase III, multicenter, randomized, double-blind, placebo-controlled trial; 2:1:2 randomization to 80 mg tafamidis, 20 mg tafamidis, or placebo for 30 months	441 patients with ATTR-CM	Significative reduction in all-cause mortality, CV hospitalizations. slower decline in 6MWT and KCCQ-OS score	Well-tolerated, mild AEs	EMA: approved for ATTR-PN (2011). FDA and EMA: approved for ATTR-CM and (2019)
Acoramidis	TTR Stabilizer (mimicking the stabilizing T119M variant)	ATTRIBUTE-CM (2024)	Phase III, multicentre, randomized, double-blind, placebo-controlled; 2:1 randomization to oral acoramidis (800 mg BID) or placebo for 30 months	632 patients with ATTR-CM	Significant improvement in NT-proBNP, 6MWT, KCCQ, and survival; superior serum TTR stabilization	Mild gastrointestinal symptoms	FDA: approved for wt- and hATTR-CM (2024) EMA: recommendation for approval (2024)
Patisiran		APOLLO (2018)	Phase III, multicentre, randomized, double-blind, placebo-controlled; 2:1 randomization to IV patisiran (0.3 mg/kg) or placebo once every 3 weeks for 18 months	225 patients with hATTR-PN; 126 patients (56%) had hATTR-CM	Improved neuropathy scores, QoL, walking parameters, nutritional status and gait speed.	Most AEs were mild or moderate. Infusion-related reactions, flushing, and abdominal discomfort were the most common.	FDA: approved for adults with hATTR-PN (2018) EMA: approved for adults with stage 1–2 hATTR-PN (2018)
		APOLLO-B (2023)	Phase 3, multicentre, randomized, double-blind, placebo-controlled, 1:1 randomization to IV patisiran (0.3 mg/kg) or placebo once every 3 weeks for 12 months	360 patients with wt- or hATTR-CM	Improved 6MWT and QoL but no significant differences in a composite of mortality, hospitalizations, and cardiovascular events		
Vutrisiran	GalNAc-siRNA	HELIOS-A (2023)	Phase III, multicenter, randomized, open-label, 3:1 randomization to SC vutrisiran 25 mg every 3 months or IV patisiran 0.3 mg/kg every 3 weeks for 18 months.	164 patients with hATTR-PN	Significant improvement in neuropathy scores, QoL, and gait speed	No serious AEs, mostly mild and transient injection site reactions	FDA: approved for hATTR-PN (2022), and for ATTR-CM (2025) EMA: approved for stage 1–2 hATTR-PN (2022)
		HELIOS-B (2024)	Phase III, multicenter, randomized, double-blind, placebo-controlled, 1:1 randomization to SC vutrisiran (25 mg) every 3 months or placebo for up to 36 months	655 patients with wt- or hATTR-CM	A 28% reduction in the composite primary endpoint of all-cause mortality and cardiovascular events; significant improvements in 6MWT and KCCQ scores		
Inotersen	2′-MOE-modified ASO	NEURO-TTR (2018)	Phase III, international, randomized, double-blind, placebo-controlled; 2:1 randomization to weekly SC	172 adults with stage 1–2 hATTR-PN	Improved neuropathy and QoL scores.	Increased risk of thrombocytopenia and glomerulonephritis;	FDA and EMA: approved for adults

			inotersen (300 mg) or placebo for 15 months		No significant echocardiographic improvements noted	enhanced monitoring required	with stage 1–2 hATTR-PN (2018)
Eplontersen	2′-MOE-modified, GalNAc3-conjugated ASO	NEURO-TTRansform (2023)	Phase III, international, open-label, single-group trial; 144 patients received SC eplontersen (45 mg every 4 weeks); historical placebo (n=60) from NEURO-TTR trial served as a comparator	168 patients with stage 1–2 hATTR-PN	Mean TTR serum reduction of 81.7%, improved neuropathy and QoL scores	Well-tolerated, mild AEs	FDA: approved for hATTR-PN (2023) EMA: approved for stage 1-2 hATTR-PN (2024)
		CARDIO-TTRansform (NCT04136171) *ongoing*	Phase III, international, randomized, double-blind, placebo-controlled; 1:1 randomization to SC eplontersen or placebo after 120 weeks	Over 1400 patients with ATTR-CM	Primary endpoint: composite of CV mortality and recurrent CV events Secondary endpoint: changes in 6MWT, KCCQ and clinical events at week 140		
Nexiguran ziclumeran (formerly NTLA-2001)	Gene editing (CRISPR-Cas9)	NCT04601051 (2024)	Phase I, multicenter, randomized, open-label, single IV infusion of nex-z	36 patients with ATTR-CM	Sustained reductions in TTR protein concentration (>90%)	Mild transient infusion-related reactions	NA
		MAGNITUDE (NCT06128629) *ongoing*	Phase III, multicenter, randomized, double-blind, placebo-controlled; 2:1 randomization to a single IV infusion of nex-z (55 mg) or placebo	Patients with ATTR-CM	Primary endpoint: composite of CV mortality and events Secondary endpoint: changes in serum TTR and KCCQ score		
NNC6019-0001 (formerly PRX004)	Humanized mAb IgG1	NCT03336580 (2024)	Phase I, multicenter, open-label, dose-escalation IV infusions across six escalating dose cohorts (0.1–30 mg/kg) every 28 days for 3 months	21 patients with either ATTR-CM or ATTR-PN	Stable/improved neuropathy and cardiac function; reduced serum TTR	Generally well-tolerated; mild AEs such as anemia and back pain	NA
		NCT05442047 *ongoing*	Phase II, multicenter, randomized, double-blind, placebo-controlled; 2:1 randomization to IV NNC6019-0001 or placebo every 4 weeks for 64 weeks	Patients with ATTR-CM	Primary endpoint: changes in 6MWD and NT-proBNP Seconday endpoint: changes in ECV, GLS, clinical events and QoL scores		
ALXN2220 (formerly NI006)	Human-derived mAb IgG1	NCT04360434 (2023)	Phase I, multicenter, double-blind, randomized, placebo-controlled; 2:1 randomization to IV ALXN2220 (0.30-60 mg/kg) or placebo every 4 weeks for 4 months	40 patients with wt- or hATTR-CM and chronic HF	At doses of ≥10 mg/kg, reductions in CA burden (scintigraphy and CMR) and biomarkers (NT-proBNP, troponin T) were observed over 12 months	Transient musculoskeletal symptoms, mild cytokine release syndrome	NA
		DepleTTR-CM trial (NCT06183931)	Phase III, multicenter, randomized, double-blind, placebo-controlled; 2:1	~1000 patients expected			

		ongoing	randomization to ALXN2220 or placebo				
AT-02	Pan-amyloid antibodies	NCT05521022 *ongoing* OLE (NCT05951049) *ongoing*	Phase I, multicenter, three-part, randomized, double-blind, placebo-controlled; randomization to IV infusion of AT-02 or placebo	Patients with systemic amyloidosis (e.g., AL, ATTR)	Safety and tolerability outcomes	Preclinical and early-stages; safety not yet established	NA
AT-03 **AT-04**		Preclinical studies (2024)					
TabFH2	Peptide-based seeding inhibitor	Preclinical studies (2023)				NA	NA

6MWT, 6-minute walk test; AEs, adverse events; AL, light-chain amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTR-PN, transthyretin amyloid polyneuropathy; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BID, twice daily; CM, amyloid cardiomyopathy; CMR, cardiac magnetic resonance imaging; CV, cardiovascular; ECV, extracellular volume; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GLS, global longitudinal strain; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LNP, lipid nanoparticle; NA, not available/applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OLE, open-label extension; QoL, quality of life; SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin.

Table 2. Summary of clinical and pharmacological properties of ATTR amyloidosis treatments approved by the FDA and EMA

	Dosage and administration	Dose adjustments	Food interactions	Drug-drug interactions	Lab test anomalies	Contraindications	Pregnancy	Side effects
Tafamidis	80 mg PO QD (Tafamidis meglumine) 61 mg PO QD (Tafamidis)	Not required, limited data in severe hepatic and kidney dysfunction	None	In vitro BCRP inhibition; potential interactions with substrates (e.g., methotrexate, rosuvastatin, imatinib)	Possible decrease in T4 levels without affecting free T4 or TSH	Hypersensitivity to the active ingredient or any of the excipients	Effective contraception is required during treatment and for one month after discontinuation.	Very common: urinary tract infections, vaginal infections, diarrhea, upper abdominal pain
Acoramidis*	712 mg PO BID	Not required	None	Avoid concomitant use with UGT inducers and strong CYP3A inducers. Consider more frequent monitoring when co administered with sensitive CYP2C9 substrates.	Possible increase in serum creatinine generally occurs within 4 weeks of starting therapy and stabilizes	None	Insufficient data	Diarrhea and upper abdominal pain
Patisiran	0.3 mg/kg IV every 3 weeks if weight <100 kg (maximum dose 30 mg) *Premedication required*	Not required. It has not been studied in severe hepatic and kidney dysfunction	None	None	Decrease in serum vitamin A levels	None	No available data	Upper respiratory tract infections and infusion-related reactions
Vutrisiran	25 mg SC once every 3 months	Not required. It has not been studied in moderate/severe hepatic and severe kidney dysfunction	None	None	Decrease in serum vitamin A levels	None	No available data	Pain in extremity, arthralgia, dyspnea
Inotersen	284 mg SC once weekly	Not required. It has not been studied in moderate/severe hepatic and	None	Because of the risk of thrombocytopenia and renal toxicity, caution should be used when using	Possible decrease in platelet count and increase in creatinine, AST, and ALT	- Platelet count <100 x 10^9/L - UPCR ≥1000 mg/g - History of acute glomerulonephritis	No available data	Warnings: thrombocytopenia, glomerulonephritis, renal toxicity, stroke and cervicocephalic arterial dissection,

		severe kidney dysfunction		antiplatelet/ anticoagulants and nephrotoxic drugs, respectively		caused by inotersen - Hypersensitivity to inotersen		liver injury, inflammatory and immune effects
Eplontersen	45 mg SC once monthly	Not required. It has not been studied in moderate/severe hepatic and severe kidney dysfunction	None		Decrease in serum vitamin A levels	None	No available data	Vomiting, injection site reactions

*Approved only by the FDA (November 2024) for the treatment of ATTR-CM.

ALT, alanine transaminase; AST, aspartate transaminase; ATTR, amyloid transthyretin; BCRP, breast cancer resistance protein; CYP, cytochrome P450; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; PO, orally; QD, once daily; SC, subcutaneous; T4, thyroxine; TSH, thyroid-stimulating hormone; UGT, uridine 5'-diphospho-glucuronosyltransferase; UPCR, urine protein-to-creatinine ratio.