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Therapy of amyloidosis: stabilizers and silencers

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Transthyretin amyloidosis (ATTR) is a systemic disease characterized by the deposition of misfolded transthyretin (TTR) fibrils. It most commonly presents as cardiomyopathy (ATTR-CM), particularly in elderly patients with the wild-type form, whereas hereditary variants may manifest with polyneuropathy (ATTRv-PN) and/or cardiac involvement. The widespread adoption of non-invasive diagnostic pathways has increased disease recognition and facilitated the early initiation of disease-modifying therapies. Stabilizers limit dissociation of the TTR tetramer and the formation of new amyloid fibrils. Tafamidis demonstrated a benefit on mortality and cardiovascular hospitalizations in the ATTR-ACT trial and remains the treatment supported by the most robust evidence, with greater efficacy when initiated at earlier disease stages. Acoramidis, a next-generation stabilizer, improved a hierarchical composite end-point in the ATTRibute-CM trial and has been approved for ATTR-CM treatment, too. Gene-silencing therapies (small interfering RNA and antisense oligonucleotides) reduce hepatic TTR synthesis and circulating protein levels. Patisiran is approved for ATTRv-PN and, in the APOLLO-B trial, showed a functional benefit in ATTR-CM, although it has not been approved for this indication in the United States. Vutrisiran, a subcutaneously administered siRNA given every 12 weeks, reduced mortality and recurrent cardiovascular events in the HELIOS-B trial and has been approved for ATTR-CM treatment. This review summarizes the rationale and principal clinical evidence supporting tetramer stabilizers and gene-silencing therapies, which are now central to the management of ATTR-CM.

Systemic amyloidosis encompasses a heterogeneous group of diseases characterized by the extracellular deposition, in one or more organs, of misfolded proteins organized into amyloid fibrils. These fibrils share a highly ordered β-sheet conformation and marked insolubility, features that promote their accumulation and the progressive disruption of tissue architecture. To date, 42 proteins have been identified as capable of forming amyloid fibrils; precise identification of the fibril-forming protein represents a crucial step in the evaluation of any suspected systemic amyloidosis.

Transthyretin amyloidosis (ATTR) results from the progressive deposition of transthyretin (TTR) in fibrillar form. TTR is a transport protein that binds thyroxine and conveys retinol (vitamin A) through interaction with retinol-binding protein. ATTR may present as a wild-type form (ATTRwt), typically affecting older individuals, or as a hereditary form (ATTRv), caused by

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pathogenic variants of the TTR gene that reduce tetramer stability and increase its propensity for dissociation and amyloidogenesis. Clinically, ATTRwt most commonly manifests as transthyretin amyloid cardiomyopathy (ATTR-CM), whereas ATTRv may present with polyneuropathy (ATTRv-PN) and/or cardiac involvement.

In ATTR-CM, amyloid deposition leads to expansion of the extracellular matrix and disruption of myocardial architecture, resulting in early diastolic dysfunction and potential systolic impairment in advanced stages. Increased myocardial mass is accompanied by reduced ventricular cavity size and a relatively preserved end-diastolic volume, promoting over time the development of heart failure, atrial fibrillation, and conduction disturbances. Prognosis depends on the extent of cardiac involvement and on factors such as age at onset, diagnostic delay, and, in genetic forms, the specific TTR variant.[1]

Although it is still frequently classified as a rare disease, ATTR-CM is likely underdiagnosed. In recent years, increased awareness of the condition and the adoption of non-invasive diagnostic criteria have allowed a substantial proportion of patients to be diagnosed without biopsy, contributing to a rise in recognized cases and enabling earlier therapeutic intervention.

Growing insight into the amyloidogenic cascade has driven the development of disease-modifying therapies aimed at reducing the formation of new amyloid and at rebalancing, at least in part, the relationship between deposition and clearance. These include TTR tetramer stabilizers, therapies that reduce TTR synthesis (gene silencers), and, currently under development, immunotherapeutic strategies using antibodies directed against TTR amyloid to accelerate removal of deposits. Specialist management of cardiac involvement remains essential, although it lies beyond the scope of the present review. This article focuses on TTR stabilizers and gene-silencing therapies, given their prognostic and therapeutic relevance.

TTR tetramer stabilizers

Transthyretin (TTR) stabilizing agents represent the first established therapeutic strategy to reduce the formation of new amyloid, acting on the rate-limiting step of amyloidogenesis: dissociation of the tetramer into monomers, which are more prone to misfolding and aggregation (*Figure 1*).

Tafamidis is the first-in-class oral stabilizer. It binds to the thyroxine-binding sites of the TTR tetramer and reduces its dissociation. In the Phase 3 ATTR-ACT trial, conducted in patients with ATTRwt and ATTRv cardiomyopathy, tafamidis reduced all-cause mortality (hazard ratio 0.70) and the rate of cardiovascular hospitalizations (rate ratio 0.68) over 30 months, and slowed the decline in 6-minute walk distance and quality of life (KCCQ-OS) compared with placebo.[2] Survival curves began to diverge mainly after approximately 18 months; patients in NYHA Class IV were not included in the trial.[2] In the NYHA Class III subgroup, a numerically higher unadjusted rate of cardiovascular hospitalizations was observed with tafamidis compared with placebo[2]; this signal was interpreted as potentially influenced by survival bias, as patients who live longer have a longer 'time at risk' for hospitalization. In the long-term extension of ATTR-ACT, among patients in NYHA Class III at baseline, continuous treatment with tafamidis was associated with a 36% lower mortality compared with delayed switching from placebo,[3] reinforcing the importance of early treatment; however, hospitalization data were not reported in that analysis.[3]

In routine clinical practice, consistent findings have been reported in observational studies. In the THAOS registry, survival at 30 and 42 months was higher in treated than in untreated patients.[4] A large US cohort showed a probability of survival greater than 50% at 65 months.[5] Data specifically addressing very elderly patients indicate a benefit also in octogenarians, albeit attenuated in more advanced stages.[6] A recent meta-analysis further described more favourable trends in remodelling parameters and amyloid burden during tafamidis therapy.[7]

Acoramidis is a next-generation stabilizer designed to mimic the protective effect of the Thr119Met variant and to achieve near-complete TTR stabilization (≥90%).[8] In the Phase 3 ATTRibute-CM trial, acoramidis improved the primary hierarchical endpoint (integrating mortality, cardiovascular hospitalizations, NT-proBNP and 6-min walk distance), with a win ratio of 1.8 (95% confidence interval, percentile method, 1.4–2.2; $P < 0.001$). Subgroup analyses did not show an increase in hospitalizations among NYHA Class III patients.[9] Acoramidis has been approved for ATTR-CM in the United States and Europe.

From a pharmacodynamic perspective, acoramidis leads to an increase in circulating TTR levels, interpreted as a marker of stabilization and maintained over time. Post hoc analyses have reported an association between an early rise in TTR levels and a more favourable prognosis[8]; however, the use of this parameter to define therapeutic response or to guide treatment decisions requires confirmation in prospective studies.

The ACT-EARLY trial (NCT06563895) is evaluating a primary prevention approach in asymptomatic carriers of pathogenic TTR gene variants, with the clinical endpoint of time to development of ATTR-CM and/or ATTR-PN.

Gene-silencing therapies

Circulating TTR is a key determinant of amyloidogenesis in ATTR. The protein is encoded by a single gene and is produced predominantly by the liver, with a residual fraction synthesized by the choroid plexus and the retinal pigment epithelium. Consequently, suppression of hepatic production leads to a marked reduction in plasma TTR but does not abolish synthesis within the central nervous system and the eye. Because the physiological functions of TTR (thyroxine transport and stabilization of the retinol–retinol-binding protein complex) are partially redundant with other systems, reduction of serum TTR is generally considered feasible; however, gene-silencing therapies lower

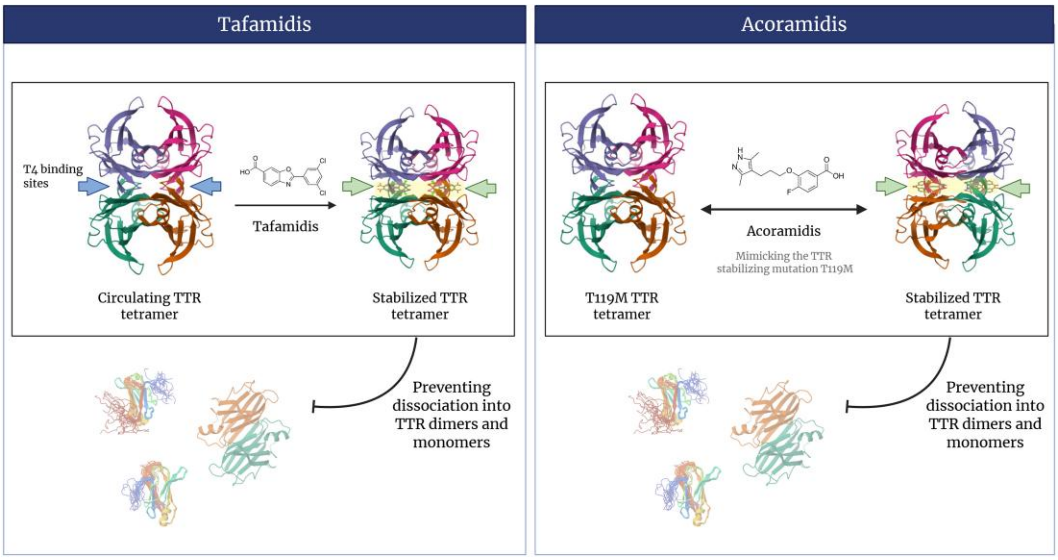

Figure 1 Transthyretin tetramer stabilization: tafamidis and acoramidis. Schematic representation of the mechanism of action of TTR tetramer stabilizers. Tafamidis binds to the thyroxine (T4) binding sites on the circulating TTR tetramer, increasing its stability and reducing dissociation into amyloidogenic dimers/monomers. Acoramidis is designed to achieve more pronounced stabilization by 'mimicking' the protective effect of the Thr119Met (T119M) variant, with the same final objective: to maintain TTR in its tetrameric form and limit the formation of new misfolded species. Source: Fontana *et al.* (2025).[12]

serum vitamin A levels and therefore require its supplementation.[10]

The main therapeutic platforms include small interfering RNA (siRNA), which act via the RNA-induced silencing complex (RISC) to degrade TTR mRNA, and antisense oligonucleotides (ASOs), which bind TTR mRNA and promote its degradation, thereby reducing hepatic TTR synthesis (*Figure 2*).

siRNA

Patisiran is a TTR-directed siRNA delivered via lipid nanoparticles, administered intravenously every 3 weeks, and is approved for hereditary ATTR polyneuropathy.[10] In the APOLLO-B clinical trial in patients with ATTR-CM, patisiran resulted in a smaller decline in 6-min walk distance (median difference 14.7 m) and in KCCQ-OS score (3.7 points) compared with placebo over 12 months.[11] The magnitude of the effect was considered modest and insufficient to clearly demonstrate a clinically meaningful benefit on overall cardiomyopathy outcomes; consequently, the FDA did not approve patisiran for the treatment of ATTR-CM.

Vutrisiran is a next-generation GalNAc-conjugated siRNA administered subcutaneously every 12 weeks.[10] The Phase 3 HELIOS-B trial in ATTR-CM demonstrated a reduction in the risk of all-cause mortality and recurrent cardiovascular events, together with improvements in functional capacity (6-min walk test) and quality of life (KCCQ-OS) compared with placebo, with an overall safety profile that was largely comparable.[12] On the basis of these results, vutrisiran has been approved in the United States and Europe for the treatment of ATTR-CM.

Nucresiran is an investigational siRNA developed to achieve profound and sustained TTR reduction and potentially longer dosing intervals, up to 6 months. In a Phase 1 study, a single dose of ≥300 mg produced a rapid reduction in TTR, with decreases maintained at least through day 180 and a >70% reduction at day 360 (300 mg dose), with low interindividual variability and good tolerability.[13] A Phase 3 trial has recently been initiated (NCT07223203).

Antisense oligonucleotides

Inotersen is an unconjugated ASO administered subcutaneously once weekly and is indicated for the treatment of polyneuropathy in hereditary ATTR.[10] In the pivotal NEURO-TTR trial, it demonstrated a slowing of neurological progression and deterioration in quality of life compared with placebo.[14] However, its clinical use is limited by a safety profile that requires particular caution. In the study, the most characteristic serious adverse events were glomerulonephritis (3%) and thrombocytopenia (3%).[14] These risks have restricted its use in routine clinical practice.[10]

Eplontersen is a 'next-generation' GalNAc-conjugated antisense oligonucleotide, which enhances hepatocyte targeting and allows for once-monthly subcutaneous administration. It is approved for the treatment of polyneuropathy in hereditary ATTR. With regard to cardiac involvement, the Phase 3 CARDIO-TTRansform trial (NCT04136171) is evaluating the efficacy and safety of eplontersen in ATTR-CM in a randomized, double-blind, placebo-controlled design, with monthly dosing and a large sample size; study completion is expected in 2026.

Gene editing (CRISPR–Cas9)

In vivo gene editing represents a potentially single-administration therapeutic approach. Nexiguran

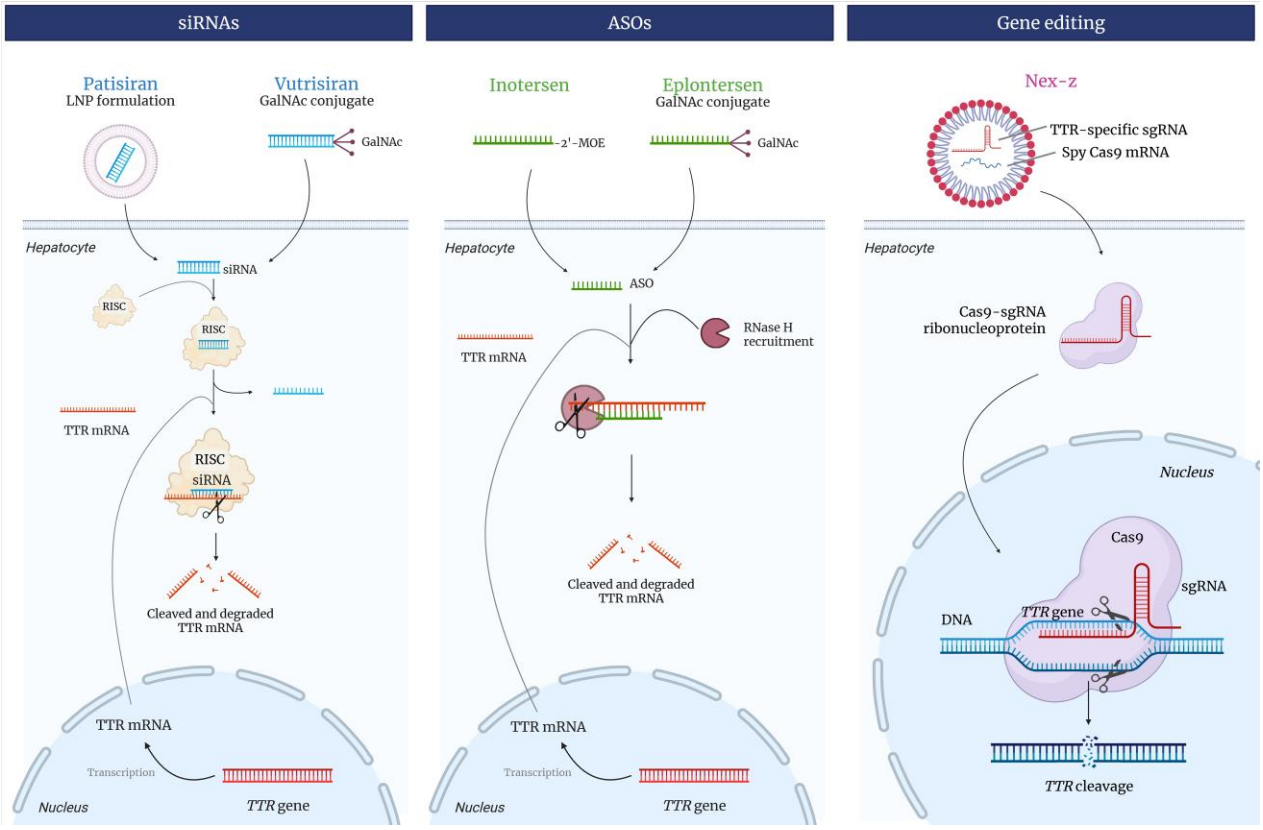

Figure 2 Reduction of TTR: siRNA, antisense oligonucleotides, and gene editing. Overview of the main strategies to reduce hepatic TTR production. siRNAs (patisiran delivered in lipid nanoparticles; GalNAc-conjugated vutrisiran) enter hepatocytes and, through the RNA-induced silencing complex (RISC), induce degradation of TTR mRNA. Antisense oligonucleotides (inotersen; GalNAc/LICA-conjugated eplontersen) bind TTR mRNA and recruit RNase H, promoting its degradation. Gene editing (nexiguran ziclumeran, nex-z) uses CRISPR–Cas9 guided by single-guide RNA to cleave the TTR gene in the nucleus, inducing repair with insertions/deletions and resulting in more durable suppression of TTR production. Source: Fontana *et al.* (2025).[12]

ziclumeran (nex-z; formerly NTLA-2001) uses CRISPR–Cas9 technology to induce small insertions/deletions in the TTR gene within hepatocytes through non-homologous end-joining repair, resulting in sustained suppression of TTR production. In a Phase 1 study in patients with ATTR-CM, a single infusion led to a mean reduction in TTR levels of 90% at 28 days, which remained stable at 12 months.[15] The ongoing Phase 3 trial (MAGNITUDE, NCT06128629) has been temporarily suspended (October 2025) following a case of fatal liver disease.

Open issues and future directions in research

Tetramer stabilizers and gene-silencing therapies currently represent the cornerstones of disease-modifying strategies in transthyretin amyloidosis. Although they share the common goal of reducing the availability of the precursor protein and slowing the formation of new amyloid, the two classes act at different steps of the amyloidogenic cascade and offer complementary therapeutic opportunities.

From a clinical perspective, stabilizers maintain TTR in its tetrameric form, limiting dissociation and, consequently, the generation of amyloidogenic species. The most robust evidence derives from tafamidis, which demonstrated benefits on major clinical outcomes in ATTR cardiomyopathy and established a crucial principle: the earlier treatment is initiated—before organ damage becomes irreversible—the greater the clinical benefit. The advent of next-generation stabilizers, such as acoramidis, expands therapeutic options and further underscores the importance of understanding whether, and in which subgroups, more 'complete' stabilization translates into additional clinical benefit compared with conventional stabilization alone.

Gene-silencing therapies (siRNA and ASOs) reduce hepatic TTR synthesis and induce a marked lowering of circulating protein levels. This class has long been established in hereditary neuropathy but has, in recent years, assumed an increasingly important role also in ATTR-CM, with results suggesting benefits on clinical and functional outcomes. Nevertheless, specific issues remain to be considered: the need for vitamin A supplementation and the fact that TTR production in the central nervous system and the eye is not abolished, with potential implications for phenotypes predisposed to leptomeningeal or ocular manifestations. Moreover, in ATTR-CM it is not yet fully established whether greater depth and persistence of TTR knockdown translate linearly into improved cardiovascular outcomes.[10]

Despite the expansion of the therapeutic armamentarium, areas of uncertainty persist that directly involve both stabilizers and silencers. First, the lack of head-to-head comparative studies precludes a definitive definition of the optimal initial strategy and the most appropriate sequencing across different stages of disease. Second, the increasing alignment of clinical trials with real-world practice—through the use of concomitant therapies or the introduction of additional treatments during follow-up—enhances generalizability but complicates attribution of benefit to a single therapeutic class and makes it more challenging to establish shared criteria for treatment intensification. Consequently, management within specialized centres, supported by registries and multidisciplinary care pathways, remains essential for patient selection, response monitoring, and longitudinal treatment adaptation.

Another key issue is the definition of a clinically meaningful response. Cardiac biomarkers, functional testing, and quality-of-life measures are indispensable but may be influenced by comorbidities and supportive therapy. In this context, integration of additional biomarkers—such as transthyretin levels, at least in patients receiving stabilizer therapy[8]—with imaging-based quantification of amyloid burden (e.g. extracellular volume on cardiac magnetic resonance or quantitative bone tracer techniques) may help identify more sensitive and reproducible indicators. These tools could prove valuable both in clinical practice and in research, facilitating shared definitions of 'responders' and 'non-responders'.

Finally, the most promising perspective for both stabilizers and silencers lies in rational combination strategies capable of acting simultaneously on protein stability and precursor availability. However, the adoption of combination approaches will require dedicated evidence on incremental efficacy, long-term safety, and economic sustainability. In parallel, refinement of selection criteria based on disease stage, phenotype, and amyloid burden will be essential to maximize the benefit–risk ratio and the efficiency of resource allocation. Closely related to this is the issue of cost-effectiveness of single vs. combined treatments, particularly in relation to equity of access to care and the sustainability of healthcare systems, on the one hand, and to recent epidemiological data that appear to challenge the classification of ATTR as a rare disease and its therapies as orphan drugs, on the other. From this perspective, two additional factors merit consideration: first, it is likely that in the future, through the use of screening strategies in at-risk populations, improvements in diagnostic capabilities, and increased clinician awareness, diagnosis will be made earlier than at present, when patients are often treated at a stage of established disease and long disease duration; second, silencers and stabilizers are likely to be used in combination with amyloid-depleting agents currently under evaluation in Phase III trials.

In conclusion, stabilizers, gene-silencing therapies and amyloid-depleting agents are going to transform the natural history of ATTR, shifting the focus towards early diagnosis, timely intervention, and longitudinal monitoring. The challenge of the coming years will be to use these classes coherently into a personalized therapeutic model, grounded in comparative evidence, more sensitive biomarkers, and specialized clinical networks capable of ensuring equitable access and continuity of care.

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