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# TRANSTHYRETIN AMYLOIDOSIS – OVERVIEW OF TREATMENT METHODS

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**ABSTRACT**

ATTR amyloidosis is a rare disease associated with abnormal folding of the transthyretin (TTR) protein, leading to the deposition of amyloid fibrils in the heart and nervous system. Treatment to date has focused primarily on alleviating symptoms such as heart failure and neuropathy. Currently available disease-modifying therapies include TTR stabilizers (tafamidis, acoramidis), which prevent TTR tetramer dissociation, and gene silencers (siRNA and ASO), which reduce TTR production and slow the progression of polyneuropathy. Modern experimental strategies, including CRISPR-Cas9 gene editing and anti-ATTR monoclonal antibodies, offer the potential for one-time treatment and removal of existing amyloid deposits. The choice of therapy should be tailored to the patient's phenotype, disease stage, and clinical capabilities, and ongoing research will better determine the long-term efficacy and safety of new drugs.

The aim of this paper is to present contemporary therapeutic strategies in the treatment of transthyretin amyloidosis (ATTR), with particular emphasis on disease-modifying drugs such as TTR stabilizers, gene silencers, CRISPR-Cas9 gene editing therapies, and anti-ATTR monoclonal antibodies. The paper aims to evaluate the efficacy and safety of available therapies, discuss their clinical indications depending on the patient's phenotype (polyneuropathy, cardiomyopathy), and present directions for the development of new therapeutic strategies based on current clinical trials.

**KEYWORDS**

ATTR Amyloidosis, Transthyretin, TTR Stabilizers, Gene Silencers, CRISPR-Cas9, Monoclonal Antibodies, Tafamidis, Acoramidis, Patisiran, Vutrisiran, Eplontersen, Inotersen

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## Introduction

Transthyretin amyloidosis (ATTR) is a rare, progressive disease resulting from abnormal folding of the transthyretin (TTR) protein, leading to amyloid deposition in the heart, peripheral nervous system, and other organs. Depending on the genetic variant and clinical phenotype, hereditary polyneuropathy (ATTRv-PN) and cardiomyopathy (ATTR-CM) are distinguished, with possible coexistence of both forms in some patients.

In recent years, there have been significant advances in the treatment of ATTR, including both symptomatic and disease-modifying therapies. Modern therapeutic strategies focus on three main mechanisms: stabilizing the TTR tetramer, silencing TTR gene expression, and removing pathologically deposited amyloid fibrils. TTR stabilizers, such as tafamidis and acoramidis, prevent tetramer dissociation, reducing amyloid accumulation. Gene silencers, including siRNA (patisiran, vutrisiran) and ASO (inotersen, eplontersen), reduce the production of both wild-type protein and TTR mutant variants. Emerging approaches, including CRISPR-Cas9 gene editing (e.g., nexiguran ziklumeran) and anti-ATTR monoclonal antibodies (Coramitug, ALXN2220), offer the potential for one-time treatment or direct removal of amyloid deposits, which may slow or reverse disease progression.

The aim of this review is to present the current status of clinical trials and approved therapies for the treatment of ATTR, with particular emphasis on efficacy, safety, clinical indications, and prospects for the development of new therapeutic strategies. This review focuses on current therapeutic options for the treatment of ATTR amyloidosis, including TTR stabilizers, gene silencers, and novel strategies such as gene therapy and monoclonal antibodies.

**Methodology**

To ensure the reliability and timeliness of the review, a systematic literature search was conducted in databases such as PubMed, Scopus, and Web of Science. Selected studies were included based on criteria of clinical relevance, methodological quality, and timeliness of publication, focusing primarily on phase II and III studies and expert recommendations in the field of ATTR treatment. Publications from recent years were included, focusing on studies describing ATTR treatment, including TTR stabilizers, gene silencers, and newer therapeutic approaches. The selected articles are characterized by high methodological quality, clear descriptions of clinical trials, and references to everyday medical practice.

**Results**

According to *Treatment of transthyretin cardiac amyloidosis* (2024), tafamidis remains the only approved agent for treating ATTR-CM. At the same time, new research data has emerged in recent years as two large phase III clinical trials have been completed and others are nearing completion. This review discusses current therapeutic options and directions for further work on the treatment of ATTR-CM. The ATTRibute-CM study showed that acoramidis, which stabilizes TTR protein, reduces the risk of death and hospitalization compared to placebo. Patisiran, which works by silencing RNA, maintained exercise capacity and quality of life in participants in the APOLLO-B study, although it has not been approved by the FDA for this disease entity. In turn, a phase I project involving ALXN2220, an antibody that removes amyloid deposits, suggests the possibility of reversing changes in the heart muscle. Phase III trials are also underway involving various forms of RNA-silencing therapies, CRISPR-Cas9 gene editing methods, and additional amyloid-targeting antibodies. Treatment based on various mechanisms related to the pathophysiology of ATTR-CM paves the way for new therapeutic solutions. Further research should aim to compare the effectiveness of available strategies, analyze the possibilities of combining methods from different categories, and determine which patient groups can benefit most from specific interventions.

According to *Real-world treatment management in hereditary transthyretin amyloidosis - an experience report and proposal for therapy switch decision criteria* (2025), hereditary transthyretin amyloidosis progresses rapidly and leads to death, but the emergence of new therapies affecting the course of the disease has significantly improved the prognosis. With the expansion of treatment options, new questions have arisen regarding patient response to therapy and the timing of therapy changes. The aim of this study was to review the reasons for modifying therapy in recent years and to formulate conclusions that may guide clinical practice in the future. In a retrospective analysis covering a single center, data were collected on 13 patients with hereditary transthyretin amyloidosis who had undergone one or more therapy changes prior to January 2024. Demographic information and reasons for treatment modification were evaluated using descriptive and exploratory analysis. During the study period, the following amyloid-targeting drugs were available: tafamidis 20 mg, tafamidis 61 mg, patisiran, inotersen, and vutrisiran. The most common reason for discontinuing tafamidis 20 mg was disease progression, which occurred in 83.3% of cases. Changes in therapy in patients treated with patisiran occurred mainly after the introduction of wutrisiran, which was associated with a preference for subcutaneous administration and longer intervals between doses (65%). In two cases, discontinuation of inotersen was due to severe adverse events. In the analyzed group, the motivations for changing treatment varied and included, among others, deterioration of neurological or cardiac condition, adverse events, patient choices, and the emergence of new therapeutic options. Therefore, it is important to comprehensively consider these factors when further planning treatment for patients with hereditary transthyretin amyloidosis.

Hereditary transthyretin amyloidosis (ATTRv) is a genetic disorder transmitted in an autosomal dominant manner. More than 150 TTR gene mutations have been described, with p.Val50Met being the most common change. Mutations lead to instability of transthyretin tetramers, resulting in their breakdown into monomers with altered conformation, prone to forming oligomers and amyloid fibrils. These, in turn, accumulate in the peripheral nerves and heart, among other places, leading to gradual organ damage. The most common symptoms are bilateral sensory-motor polyneuropathy and autonomic disorders, as well as cardiomyopathy. In many patients, both systems are affected simultaneously. In addition, disorders of the gastrointestinal tract, kidneys, eyes, and central nervous system may occur. Depending on the patient's ability to move, the progression of polyneuropathy in FAP is divided into: stage 1, in which the patient can walk independently; stage 2, in which the patient requires assistance; and stage 3, in which the patient becomes wheelchair-bound. Due to the varied course and severe consequences of the disease, treatment targeting the amyloidogenesis process is crucial to slowing it down.

By June 2025, several drugs modifying the course of ATTRv were available — both FDA/EMA-approved, off-label, and those in advanced clinical trials. This paper focuses on FDA/EMA-approved drugs that work by silencing TTR gene expression (siRNA and ASO) and stabilizing tetramers. siRNA drugs inhibit TTR gene expression at the post-transcriptional level. Patisiran, delivered to the liver in lipid nanocapsules, was approved in 2018 for the treatment of FAP in stages 1 and 2. The decision was based on the results of the APOLLO-A study, which demonstrated improvement in neurological parameters (mNIS+7), improvement in quality of life (Norfolk QoL-DN), and a reduction in TTR concentration of approximately 80% compared to placebo.

In 2022, another siRNA therapy, vutrisiran, was approved. The HELIOS-A study achieved its goals of improving neurological outcomes. In 2025, the drug was also approved for the treatment of ATTR-CM. TTR gene silencing can also be achieved through the use of antisense oligonucleotides (ASOs).

Inotersen was approved for the treatment of FAP in 2018 after demonstrating its efficacy in the NEURO-TTR study. Another drug in this class, eplontersen, was introduced in the US in 2023 and in Germany in 2025, further expanding the range of therapies available.

Transthyretin stabilizers work by mimicking thyroxine binding, which prevents tetramer breakdown. Tafamidis 20 mg was the first drug approved for patients with stage 1 FAP in 2011, and its efficacy was confirmed in the Fx-005 study. In subsequent years, the indications were expanded to include transthyretin amyloid cardiomyopathy (ATTR-CM), and acoramidis, another tetramer stabilizer, was also added to the therapy.

For a long time, tafamidis was the only drug available that targeted amyloid. With the introduction of new therapies, there was a need to better understand their safety, mode of action, and the best strategies for their sequential use. However, there is a lack of comparative studies directly comparing individual methods, and the criteria used in clinical trials vary. There are also no clear guidelines on when to start or change therapy.

For this reason, the aim of this study is to analyze the actual experiences of patients who underwent treatment changes, which may provide additional information on the practical use of available methods. The analysis was conducted at Charité Berlin as part of the Amyloidosis Registry. The project was approved by the ethics committee and was conducted in accordance with the Declaration of Helsinki. The information was collected from electronic medical records. Inclusion in the study required a confirmed TTR mutation, legal age, and patient consent. Of the 65 people with ATTRv, 39 had not previously undergone treatment and were therefore not included. Ultimately, the analysis was performed in a group of 13 patients who had undergone at least one change in therapy and in a matched control group without changes in treatment. The choice of therapy was determined by a team of specialists covering several fields of medicine. Documentation was maintained using the TBase system. The study was descriptive and observational. Demographic and clinical data were presented using descriptive statistics. Therapy changes were assessed by analyzing the reasons for discontinuation of treatment and the course of medications used. Both patient self-assessment and standardized tools were used to assess neurological progress, while changes in clinical parameters were measured using NIS, COMPASS-31, NT-proBNP, and interventricular septal thickness. A group with no changes in treatment was also evaluated for comparison. The cohort included 13 individuals diagnosed with ATTRv amyloidosis. Most were men, and the predominant mutation was not always p.Val50Met. The vast majority presented with neurological or mixed symptoms, while no cases of isolated cardiomyopathy were reported. The first treatment was started on average about two years after the onset of symptoms, while the current therapy was implemented later, after a period of previous treatment, which usually lasted from one to three years. The most commonly used initial therapy was tafamidis at a dose of 20 mg, which was received by 76.9% of patients (patients 1–10). Individual patients were treated with inotersen (patient 13), patisiran (patient 11), or a combination of tafamidis 20 mg and patisiran (patient 12), which together accounted for 7.7% of the study group. It is worth noting that for most patients starting treatment with tafamidis 20 mg (60%), it was the only drug registered by the FDA and EMA at that time. In 83.3% of patients (n = 10), the reason for switching from tafamidis 20 mg was disease progression. In three patients, the severity of neuropathy was predominant, as confirmed by an increase in the NIS score (median +10 points) over approximately 16 months. Patient 2 switched to patisiran due to increasing polyneuropathy, weight loss, and autonomic gastrointestinal dysfunction. Patient 4 switched to patisiran after developing gait disturbances and an increase in NIS of +12.5 points, and then to vutrisiran due to further progression (total +64 points) and infusion intolerance. Patient 10 experienced an increase in NIS of +34 points and features of axonal demyelinating neuropathy, leading to a switch to patisiran and later to vutrisiran due to symptoms associated with intravenous administration. Neurological deterioration affected 80% of patients who underwent a change in treatment (patients 1, 2, 3, 4, 5, 6, 9, 10). Half of the patients

(patients 1, 5, 6, 7, 8) also showed signs of cardiac progression, as confirmed by an increase in NT-proBNP levels (median +583 ng/L in approximately 9 months). Patient 1, after liver transplantation and treatment with 20 mg tafamidis, developed pericardial effusion and progressive cardiomyopathy, and NT-proBNP increased by +1652 ng/L over three years. At the same time, IVSd increased from 19 to 27 mm, and the NIS score rose by +52 points in seven years. The patient died due to complications of sepsis and multiple organ failure under immunosuppression. In patient 5, the switch from tafamidis 20 mg to inotersen was preceded by symptoms of heart failure and gastrointestinal disorders, as well as an increase in NT-proBNP of +1009 ng/L in the last year before the switch. In patient 6, the reason for switching to patisiran was increasing NT-proBNP values (+1562 ng/l), IVSd thickening of +4 mm, and an increase in NIS of +10 points over 9 months. Patient 8 first received a higher dose of tafamidis (61 mg) and then patisiran due to progressive heart failure and polyneuropathy, which was associated with a reduction in walking distance to less than 150 m and an increase in COMPASS-31 of +18 points to 45.3. Ultimately, it was decided to switch to vutrisiran due to difficult venous access. Changes from inotersen (n = 2) were due solely to adverse events. Patient 5 developed thrombocytopenia, glomerulonephritis, and hemorrhagic cystitis, requiring discontinuation of therapy and temporary return to tafamidis 61 mg prior to heart transplantation. Patient 12 experienced transient delirium and difficulty speaking. The switch from patisirane to vutrisiran was mainly due to patient preference regarding the route of administration. Infusion-related reactions were observed in two individuals (patients 4 and 10), while 65% of patients (n = 6) chose vutrisiran because of the possibility of subcutaneous administration every few months (patients 3, 8, 9, 11, 12, 13). For example, patient 3, who had been treated with patisiran for a long time, cited the psychological burden of frequent infusions as the main reason for the change. In the final assessment, vutrisiran was the most commonly used drug (66.7%, n = 8). Two patients were treated with patisiran (2 and 6) and two with tafamidis 61 mg (5 and 7). The group of patients with no change in treatment (n = 13) was comparable in terms of age (median 67 years) but differed in gender distribution (38.5% male). During the approximately one-year observation period, all key indicators remained stable: NIS (0 points), COMPASS-31 (median +1.03), NT-proBNP (median +0.5 ng/L), and IVSd (no change). Based on the collected data, a set of criteria was proposed to aid in the decision to change treatment. The first step is to assess adverse events and clinical changes. Both neuropathy- and heart-related parameters should be monitored, with no single mandatory progression threshold. Another element is conditions related to the method of drug administration, such as kidney and liver function, platelet count, or difficulties with venous access or swallowing. Patient preferences also play an important role, including, among others, organizational possibilities related to visits to the center. The final aspect is the availability of new therapies and financial considerations, which may vary between countries and insurance systems. Treatment decisions should be based on interdisciplinary discussion and regularly reviewed during follow-up visits. A single-center analysis evaluated the reasons for treatment changes in patients with ATTRv amyloidosis, demonstrating their complex nature. Although the choice of initial therapy depends mainly on the stage of the disease, the data presented document the first experiences with modifying regimens involving different mechanisms of action. The most common reason for change was disease progression, which is consistent with the current expert opinion recommending early response to deterioration in health. In the case of TTR stabilizers such as tafamidis, progression of neuropathy was a common reason for discontinuation of treatment, as confirmed by previous publications. siRNA treatment may improve disease control in individuals who progress during therapy with stabilizers, as confirmed by both this analysis and the literature. At the same time, frequent infusions of patisiran may affect its long-term tolerance, which explains the frequent switch to less frequently administered vutrisiran. Adverse events such as nephropathy or thrombocytopenia during inotersen therapy and infusion-related reactions with patisiran are well documented. In turn, the possibility of increasing the dose of tafamidis to 61 mg or switching to vutrisiran offered new therapeutic options available at the time of the analysis. Differences between countries in terms of reimbursement and use of specific drugs indicate the growing importance of economic factors in clinical decisions. Changes in therapy in patients with ATTRv amyloidosis are common and result from many factors, such as disease progression, adverse effects, patient preferences, and the availability of newer drugs. Despite the development of disease-modifying therapies, there is still a lack of uniform guidelines on the sequence of their use. Further studies involving larger populations are needed to compare treatment strategies, identify biomarkers to aid decision-making, and enable the development of recommendations based on clinical practice data.

*Current and future treatment of transthyretin amyloid cardiomyopathy* (2025) describes transthyretin amyloid cardiomyopathy (ATTR-CM), a disease in which insoluble amyloid fibrils formed from misfolded transthyretin (TTR) accumulate in tissues. This protein has a tetrameric structure, is produced mainly by the

liver, and participates in the transport of retinol and thyroxine. In the course of ATTR-CM, amyloid is formed from TTR with a normal sequence (wild type, ATTRwt), where factors related to age and oxidative stress promote the deposition of deposits, or from mutant TTR (ATTRv), transmitted autosomal dominantly with incomplete penetrance. In both forms of the disease, unstable tetramers break down into monomers that are prone to misfolding and further assembly into fibrils. The deposits accumulate in the intercellular space of various organs, disrupting their structure and function. In the heart, this leads to thickening of the walls, difficulty in diastole, and increased filling pressure, which, as the changes progress, causes heart failure and can result in death. Without treatment, the median survival is approximately two to five years. For a long time, treatment options were limited to symptom relief, as there were no methods to influence the progression of the disease. In recent years, however, numerous targeted therapies have been introduced that have changed the existing approach, and ongoing research is expanding the range of available solutions. This review discusses current and developing therapeutic strategies and shows how new possibilities are influencing clinical practice. Therapies developed for ATTR-CM target different phases of the disease process. Stabilizers bind to the TTR tetramer at the site where thyroxine normally binds, which is intended to prevent its breakdown into monomers that promote amyloid formation. Drugs that suppress TTR expression, based on siRNA or antisense oligonucleotides, act in hepatocytes by blocking TTR mRNA and reducing protein production in the liver. This limits the supply of monomers that can form deposits. At the same time, work is underway on therapies that attach to already formed amyloid and facilitate its removal by the immune system. Tafamidis was the first drug for ATTR-CM approved by the FDA in May 2019. It is administered orally once a day and binds to the thyroxine site in TTR, maintaining the stability of the four-molecule structure of the protein. The ATTR-ACT study showed a clear improvement in prognosis. Over 30 months, the mortality rate in the tafamidis-treated group was 29.5%, compared with 42.9% in the placebo group (HR 0.67; 95% CI 0.51–0.96). Patients taking the drug also had a 32% reduction in hospitalizations for cardiovascular reasons (RRR 0.68; 95% CI 0.56–0.81). In addition, the results of the 6-minute walk test and the overall health assessment in the KCCQ-OS questionnaire deteriorated more slowly. Acoramidis is a newer generation stabilizer designed to mimic the action of the natural T119M mutation, which increases the resistance of the TTR tetramer to degradation. The drug not only binds at the thyroxine binding site, but also forms additional hydrogen bonds with serine residues at position 117, similar to the T119M variant mentioned above. This allows it to achieve over 90% TTR stabilization. Acoramidis is taken orally twice daily and in November 2024 became the second drug approved by the FDA for the treatment of ATTR-CM in patients with wild-type and variant forms. The decision was preceded by the results of the ATTRibute-CM study, in which acoramidis clearly outperformed placebo. This was assessed using a four-element hierarchical analysis of the win ratio, including overall mortality, cardiovascular hospitalizations, change in NT-proBNP concentration, and 6MWT score. The resulting odds ratio of 1.8 (95% CI: 1.4–2.2; $p < 0.001$) indicated a beneficial effect of treatment. Some patients also underwent serial CMR examinations, which showed signs of a possible reduction in amyloid burden, encouraging further analysis. The study protocol allowed tafamidis therapy to be initiated after one year of follow-up. Ultimately, 14.9% of participants in the acoramidis group and 22.8% in the placebo group received it, and the time to treatment initiation was similar in both cases. Patisiran is an siRNA drug originally approved in 2018 for the treatment of hereditary ATTR polyneuropathy. It is administered intravenously every three weeks and requires prior premedication. Its use in patients with ATTR-CM was evaluated in the phase III APOLLO-B study. It showed a slower rate of deterioration in 6MWT and KCCQ-OS scores, although the absolute differences were small despite reaching statistical significance. Additional analyses of mortality, cardiovascular events, hospitalizations, and urgent visits for heart failure were inconclusive, partly due to insufficient study power. Approximately one-quarter of participants continued tafamidis treatment initiated prior to randomization, and a small percentage in both groups initiated treatment during the one-year follow-up. In October 2023, the FDA declined to expand the indication for patsirane to ATTR-CM due to the limited clinical utility of the results, as the statistical benefits were mainly related to surrogate endpoints and associated with small absolute differences. As in the ATTRibute-CM study observations, the problem may have been too short a follow-up period or too few events, making it difficult to demonstrate the superiority of the therapy in hard endpoints. Vutrisiran is a second-generation TTR expression silencer that acts through an siRNA mechanism similar to patisirane, but is administered subcutaneously once every three months. The FDA approved it for the treatment of ATTRv-PN in June 2022 and for ATTR-CM in March 2025. The efficacy of vutrisiran was evaluated in the Phase III HELIOS-B study, which included patients with variant and wild-type forms of the disease. A reduction in overall mortality and recurrent cardiovascular events was demonstrated (HR 0.72; 95% CI 0.56–0.93; $p = 0.01$). The drug also slowed the deterioration of functional outcomes: the

difference in favor of vutrisiran was 26.5 m in the 6MWT and 5.8 points in the KCCQ, which was statistically significant. At baseline, 60% of participants in both groups were not taking tafamidis, but after randomization, about one-fifth started this therapy. The greatest benefits were seen in people who had not previously been treated with tafamidis, who had a lower risk of death and recurrent cardiovascular events (HR 0.67; 95% CI 0.49–0.93; p = 0.02). Among the newer therapies are further inhibitors. Eplontersen is an antisense oligonucleotide that reduces TTR synthesis in the liver by blocking its mRNA. It is administered subcutaneously once a month, and the patient can perform the injections themselves, unlike vutrisiran, which requires administration in a medical facility. The drug was approved by the FDA in December 2023 for the treatment of ATTRv-PN, as indicated by the results of the NEURO-TTRansform study, which showed a reduction in serum TTR levels and alleviation of neuropathy symptoms. Post hoc analyses also suggested possible cardiological benefits, such as improvement in selected echocardiographic parameters related to heart structure and function. Although eplontersen is not yet registered for ATTR-CM, its effect on cardiomyopathy is being evaluated in the CARDIO-TTRansform study, which, upon completion, will be the largest research project in this disease entity. It includes over 1,400 participants and tests whether the therapy reduces cardiovascular mortality and the number of subsequent hospitalizations. The protocol allows for the parallel use of tafamidis, which will allow for the evaluation of the potential value of combination therapy based on a stabilizer and a silencer. Nukresiran (ALN-TTRsc04) is another siRNA therapy designed to block hepatic production of both wild-type and variant TTR mRNA. It is administered subcutaneously at long intervals, ranging from six to twelve months. Phase 1 studies showed a very strong and long-lasting reduction in TTR levels, exceeding 96% at higher doses, with the effect lasting for at least 180 days. On this basis, the phase 3 TRITON-CM trial was launched, comparing nukesiran with placebo in patients with ATTR-CM treated with standard therapy. Approximately 1,200 people with wild-type or variant forms, including those already using stabilizers, are planned to be enrolled. The project will also evaluate the potential benefits of a combination approach using different classes of drugs. Nexiguran ziclumeran (Nex-z, NTLA-2001) is a one-time therapy using the CRISPR-Cas9 system that is designed to permanently reduce TTR gene expression after intravenous administration. A phase I study found an 89% reduction in serum TTR after one month, which persisted for one year (95% CI from –93 to –87). No serious adverse events were reported. Functional outcomes remained stable: NT-proBNP levels were unchanged, the 6MWT showed a mean increase of 5 meters, and the KCCQ-OS score improved by eight points. The MAGNITUDE phase III trial is currently underway, analyzing the impact of therapy on cardiovascular mortality, recurrent events, and amyloid accumulation. Initially, individuals with more advanced disease and NT-proBNP above 1000 pg/mL were enrolled, but the threshold was lowered to 600 pg/mL, bringing the study population closer to previous projects evaluating silencers. The study uses repeated cardiac magnetic resonance imaging to determine changes in extracellular volume and monitor response to treatment.

The landscape of ATTR-CM treatment is changing rapidly, with recent advances influencing the entire approach to the disease. At the current rate of development, it is likely that the available treatments will look completely different in a few years. Current solutions focus on stabilizing TTR, limiting its production, or accelerating the elimination of deposits. However, there is still uncertainty about how to select individual therapies for different patients, in what order to use them, and when to combine different approaches. Effective patient management requires regular assessment of response to treatment, recognition of worsening symptoms, and decisions about possible intensification of therapy. The currently available response markers are not sufficiently precise. This raises the question of whether we are actually monitoring the signals that best reflect the course of the disease. Serum TTR levels are sometimes used as a measure of the effect of stabilizers, with higher increases associated with a better prognosis. In comparative studies, acoramidis increased TTR concentration by 39% after one year, while tafamidis increased it by 30%. However, it is not known whether changes in TTR concentration alone are sufficient to assess the actual clinical effect. Attention is also drawn to circulating amyloid aggregates, which may reflect disease severity and decrease after treatment initiation. If their usefulness is confirmed, they could become a non-invasive tool for assessing residual amyloid burden and deciding on a different therapeutic approach. Determining the progression of ATTR-CM can be difficult in practice. Clinical trials use functional outcomes, biomarkers, and survival data, but in everyday practice, physicians often observe more subtle changes that are not captured by standard tools. It is unclear whether signals such as an increase in the dose of diuretics should be part of a broader classification of disease progression. In practice, however, they are often perceived as a clear sign of deterioration. The growing number of therapeutic options makes the decision to change treatment increasingly difficult. There is a lack of uniform criteria that would facilitate such decisions. Although further studies will provide new data, they will not

resolve many everyday clinical dilemmas, especially those concerning patients with advanced disease or those already treated with disease-modifying drugs. A multicenter registry of patients with amyloidosis could help fill this gap by providing data on long-term response to treatment, changes in therapies used, and comparisons of the effectiveness of monotherapy and combination therapies. It would also provide a better understanding of the factors that influence treatment decisions, including symptoms, test results, imaging parameters, and patient preferences. Without such data, there is a risk of both abandoning effective treatment too quickly and changing the approach too late, when another type of therapy could still influence the course of the disease. In the coming years, it may be possible to shift the treatment of ATTR-CM from slowing the progression of the disease to reversing it. Antibody-based therapies such as ALXN2220, coramitug, and AT-02 offer the possibility of removing existing amyloid rather than merely stabilizing TTR or limiting its production. It is not known whether the elimination of fibrils will improve heart function or whether the immune responses triggered by these therapies will lead to fibrotic processes. However, if their effectiveness is confirmed, they may also benefit people with more advanced disease. Such solutions could also reduce the consequences of late diagnosis, as they would enable real reversal of changes. With the emergence of new therapies, clinical decision-making will have to change. More individualized treatment models will be needed, combining data from biomarkers, clinical observation, and real-world studies. The treatment of ATTR-CM increasingly requires an approach tailored to the individual patient. The coming years will determine not only what therapies will be available, but also how they will be used in practice.

*Treatment of amyloidosis: present and future. Eur Heart J Suppl.* (2023) states that the treatment of cardiac AL amyloidosis requires a team effort involving specialists in oncohematology and cardiology, and preferably also centers with experience in the treatment of amyloidosis. Patients with AL have a hematological malignancy, often involving several organs. The management and prognosis depend primarily on the degree of heart damage. In people with symptomatic heart failure, mortality within the first six months is high. In recent years, survival rates have increased significantly thanks to modern chemotherapy regimens. The basis of treatment remains autologous stem cell transplantation and chemotherapy or immunotherapy targeting pathological plasma cell clones. However, transplantation has limitations related to age and, above all, heart function. It is contraindicated in people with severe cardiac involvement. Chemotherapy can also be used before such a procedure. Current guidelines indicate a combination of cyclophosphamide, bortezomib, dexamethasone, and daratumumab as the first-line treatment for patients with newly diagnosed AL. Bortezomib is a proteasome inhibitor. Proteasomes are involved in controlling proteotoxicity and regulating proteins responsible for proliferation and processes leading to cell death. Plasma cells that produce amyloid respond particularly strongly to proteasome inhibition, as it is essential for them to reduce the toxicity of light chains. Daratumumab is a monoclonal antibody directed against CD38, a glycoprotein found on the surface of plasma cells. Binding to CD38 leads to their death. This preparation is the only registered drug used in AL amyloidosis in combination with CyBorD. The effectiveness of this regimen is very high. In almost eight out of ten patients, a significant hematologic response is observed, understood as a complete response or a very good partial response. In a small comparative analysis, the survival of patients treated with CyBorD was 655 days on average, compared to 178 days in the group receiving other regimens based on melphalan and dexamethasone. However, these therapies have side effects. Among them, cardiac disorders are particularly troublesome, often leading to dose reduction, discontinuation of treatment, or the need for milder, albeit less effective, options. Isatuximab, another anti-CD38 antibody, is currently being evaluated as a treatment for plasma cell dyscrasias that lead to AL. Research is also ongoing on three monoclonal antibodies, namely birtamimab, CAEL-101, and AT-03. Their task is to remove amyloid fibrils that accumulate in organs. The results of these studies may provide evidence that the elimination of light chain deposits improves the functioning of affected tissues. In transthyretin amyloidosis, TTR is a protein involved in the transport of thyroxine and retinol-binding protein. Produced in the liver, TTR has a structure rich in beta filaments, which easily form insoluble amyloid fibrils. In the familial form, a single missense mutation leads to disturbances in the protein structure and produces a variety of clinical pictures. Phenotypes with predominant neuropathy and autonomic dysfunction, mixed forms, and forms in which cardiac involvement predominates are observed. The most common variant associated with cardiomyopathy, V122I, occurs in more than one-third of African Americans. Wild-type transthyretin amyloidosis, formerly known as senile amyloidosis, is a sporadic disease that mainly affects older men. This disease should be suspected in people with heart failure, fainting or arrhythmias, ventricular wall thickening, symptoms of dysautonomia, a history of carpal tunnel syndrome, or biceps tendon rupture. The prognosis for ATTR with cardiac involvement is more favorable than for AL. The median survival time is approximately 75 months, while in AL it is only 11 months. Despite this, ATTR

cardiomyopathy progresses and, until recently, there were few treatment options available. Recently, there have been many studies on drugs developed for amyloidosis, which show promising results. One of the most important conclusions is the need for early diagnosis of the disease, as treatment in the early stages gives much better results in terms of neurological and systemic symptoms. Current recommendations include therapies that modify the synthesis, production, and aggregation of fibrils, symptomatic treatment to control neurological and cardiovascular complications, general medical support, and genetic counseling in hereditary forms. TTR-targeted therapies are based on two main approaches: limiting TTR synthesis and expression, and stabilizing the protein to slow its breakdown. Other solutions are also being evaluated, such as agents that promote amyloid elimination, antisense therapies, and substances that inhibit TTR aggregation. The liver accounts for almost all of the TTR present in serum. For this reason, since the 1990s, liver transplantation has been considered the first-line treatment for patients with familial amyloidosis (ATTRv), as it removes the source of the protein prone to forming deposits. This method is not used in the ATTR-wt variant. Young people who underwent surgery at an early stage of the disease had a high 20-year survival rate. However, the effectiveness of the transplant depends on the type of mutation. Some variants respond better to this form of treatment, while others respond less well, such as V122I, which is associated with heart strain. In selected cases, simultaneous liver and heart transplantation is possible, which gives better results in patients with ATTRv and cardiomyopathy than heart transplantation alone. Therapies aimed at reducing TTR levels are designed to inhibit its synthesis. One of the available solutions is antisense oligonucleotides (ASOs), such as inotersen (Tegsedi, Akcea Therapeutics). These molecules bind to the mRNA encoding TTR, blocking its production. Studies have shown that inotersen administered subcutaneously once a week at a dose of 300 mg can stabilize cardiac symptoms in people with ATTRv cardiomyopathy. The drug also improves neurological function, although in rare cases it can lead to severe thrombocytopenia and kidney damage. For this reason, in the US, it is used in specialized centers under intensive supervision. In Italy, the drug has been approved for the treatment of adult patients with hereditary TTR amyloidosis and stage 1 or 2 polyneuropathy. The second group of therapies consists of siRNA molecules, such as patisiran (Onpatro, Alnylam Pharmaceuticals). These are short, double-stranded RNAs that recognize TTR mRNA and lead to its degradation. The drug uses lipid nanoparticles, which facilitate its delivery to hepatocytes. The APOLLO study involved 225 patients with NYHA class I–II ATTR-PN. Patrisiran administered at a dose of 0.3 mg/kg every three weeks for 18 months inhibited the progression of polyneuropathy and led to neurological improvement in some patients. In a subgroup of patients with cardiac involvement, a reduction in left ventricular wall thickness, improvement in global longitudinal strain, and a decrease in NT-proBNP were observed. Data analysis also showed a lower incidence of hospitalizations and deaths than in the placebo group. A small study using magnetic resonance imaging reported a reduction in extracellular volume in the heart muscle. Patisiran was also studied in a group of 300 patients with ATTR amyloidosis and NYHA class I–III heart failure. The APOLLO B project, evaluated after 12 months of therapy, showed improved exercise capacity in the 6-minute walk test and better quality of life. The safety profile of the drug was assessed as favorable. However, no effect was observed in several secondary endpoints, including mortality. Currently, patisiran is only approved for use in ATTR-PN. The therapy requires premedication with corticosteroids and antihistamines, which limits allergic reactions associated with the administration of the drug. Both patisiran and inotersen significantly reduce the concentration of TTR, which serves as a vitamin A transporter. For this reason, vitamin A supplementation is necessary during treatment. Vutrisiran (Amvuttra, Alnylam Pharmaceuticals) is a second-generation siRNA that easily reaches hepatocytes thanks to its combination with N-acetylgalactosamine (GalNAc). The drug is administered subcutaneously at a dose of 25 mg once every three months and does not require prior premedication because it does not use lipid nanoparticles. In a phase I study involving healthy volunteers, an approximately 83% decrease in TTR concentration was observed after six weeks, which persisted for the next three months. The HELIOS-A project showed that, compared to placebo, vutrisiran reduces NT-proBNP levels, improves selected echocardiographic parameters, and increases tracer uptake in bone scintigraphy in people with ATTRv and polyneuropathy. A phase III trial is currently underway involving approximately 600 patients with ATTR amyloidosis and NYHA class I–III heart failure. Participants were randomly assigned to receive vutrisiran or placebo (HELIOS-B, NCT04153149). Some of the study participants may take tafamidis in combination with other medications. The observation period will last 30–36 months, during which deaths and recurrence of cardiovascular events will be assessed. Vutrisiran is currently approved for the treatment of ATTR-PN. Transthyretin stabilization is another therapeutic approach used in TTR amyloidosis. The goal of this treatment is to maintain the tetrameric structure of the protein, which limits its breakdown into monomers susceptible to aggregation. To achieve stabilization, it is necessary to occupy both thyroxine binding sites

simultaneously, which requires the use of high concentrations of the preparation. Diflunisal is a nonsteroidal anti-inflammatory drug with the ability to stabilize the TTR tetramer. At a dose of 250 mg per day, used in amyloidosis and lower than in anti-inflammatory treatment, it is usually well tolerated. Small studies have confirmed its efficacy in patients with ATTR-PN. Attention is also drawn to its potential effect on slowing the progression of cardiac amyloidosis in stable heart failure. The most commonly observed side effects include fluid retention, worsening heart failure, renal dysfunction, and gastrointestinal bleeding. For this reason, the drug requires careful use and systematic monitoring, especially in people with heart and kidney disorders. Tafamidis (Vindaquel, Pfizer) is an oral preparation that binds with high selectivity to thyroxine sites in both wild-type and mutant TTR. This reduces tetramer breakdown without exhibiting the anti-inflammatory effects characteristic of diflunisal. The efficacy of tafamidis was evaluated in the ATTR-ACT study, which included 441 patients with cardiac TTR amyloidosis. Participants were randomly assigned to receive 80 mg, 20 mg of tafamidis, or placebo for 30 months. The results showed that the 80 mg dose maintains stable TTR levels in most cases, is associated with fewer deaths (29.5% vs. 42.9%), and reduces hospitalizations for heart failure in NYHA class I and II patients. A slower decline in exercise tolerance as assessed by the 6-minute walk test was also observed. In the subgroup of patients with more advanced heart failure (NYHA class III), no similar benefit was observed; on the contrary, the hospitalization rate was higher than in the placebo group. Nevertheless, recent data presented at the European Society of Cardiology Congress (May 2022, Barcelona) suggest better 5-year survival in NYHA class III patients treated with tafamidis. A long-term analysis of the ATTR-ACT study also showed that the reduction in mortality persists up to 58 months, and earlier initiation of the drug is associated with better outcomes than later initiation. In 2019, tafamidis at a dose of 61 mg as free acid (equivalent to the 80 mg dose used in the study) became the first drug approved by the FDA, followed by the EMA and AIFA, for the treatment of wild-type and variant ATTR-CA. Acoramidis (AG10/ALXN2060, Eldos Therapeutics) is another TTR stabilizer being evaluated for the treatment of ATTR amyloidosis. Studies indicate that it may inhibit disease progression in patients with the polyneuropathy variant. The molecule binds to TTR more selectively than tafamidis and diflunisal, leads to an increase in blood TTR levels, and is well tolerated. The ATTRIBUTE-CM study (NCT03860935) plans to enroll 510 patients with ATTR amyloidosis and cardiomyopathy. In a 2:1 ratio, patients will receive 800 mg of acoramidis or placebo twice daily for 30 months. Changes in distance in the 6-minute walk test after 12 months and mortality and hospitalizations for cardiovascular causes after 30 months will be evaluated.

In recent years, the treatment of amyloidosis has evolved. Although relatively few drugs are currently available to modify the course of amyloid cardiomyopathy (AC), cardiologists will have a range of promising therapeutic strategies at their disposal in the near future. It is very important to maintain a high level of diagnostic suspicion when typical “red flags” appear, as this enables early diagnosis of the disease. Future research will prioritize individualized treatment, the development of drug combinations to maximize clinical effects, the establishment of criteria for eligibility for therapy, and the precise determination of prognostic indicators. It will also be necessary to deepen our knowledge of screening, monitoring, and therapeutic approaches in subclinical forms of CA-ATTR. Finally, the challenge is to refine supportive care and strategies dedicated to patients with advanced heart failure, in whom the risk of death and complications remains high.

According to *New therapies to treat cardiac amyloidosis* (2025), tafamidis continues to be the main drug used in ATTR-CM and has been in clinical use for over five years. Another transthyretin stabilizer, acoramidis, was recently approved by the FDA following positive results from the ATTRibute-CM study. Wutrisiran, which works by silencing the TTR gene, has shown good results in the HELIOS-B trial and is awaiting regulatory approval. The CARDIO-TTRansform trial with eplonterson, the largest ATTR-CM research project to date, is expected to be completed by the end of 2025. Work is also underway on new therapeutic technologies, such as CRISPR-Cas9-based NTLA-2001, as well as drugs targeting amyloid deposits, including ALXN2220 and coramitug. In the treatment of AL-CM, a regimen based on daratumumab, cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) has become a widely used strategy. Researchers are working on a new generation of cell and immune therapies, including CAR-T cells, bispecific antibodies such as teklistimab, and drugs that reduce fibrils. Birtamimab has shown improved survival in people with advanced AL-CM in the VITAL trial and is being further evaluated in the AFFIRM-AL project. Anselamimab is in phase III CARES trials, while AT-02 is undergoing early testing in both ATTR-CM and AL-CM. Therapeutic progress in ATTR-CM and AL-CM is rapid and includes methods that target different stages of the disease process. Ongoing clinical trials offer real hope for further improvements in treatment and prognosis for patients with cardiac amyloidosis.

*The search in Pharmacological Management of transthyretin amyloid cardiomyopathy: a scoping review* (2024) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature review was performed using several databases, including observational and clinical studies on ATTR-CM therapy. The most important information was extracted from each study found, including a description of the population, the outcomes assessed, and the adverse events reported. Nineteen publications were included in the review, of which eight were clinical and 11 were based on observational data. The therapies evaluated included tafamidis, acoramidis, revusiran, doxycycline, tauroursodeoxycholic acid, diflunisal, inotersen, eplontersen, and patisiran. Tafamidis showed the best results, especially when treatment was started in the earlier stages of the disease. Drugs based on RNA interference and antisense oligonucleotides had a beneficial effect on patients' daily functioning. However, the review noted a lack of data on longer-term follow-up, comparisons between therapies, and their relationship to healthcare costs. The available drugs can modify the course of ATTR-CM, but a complete picture of their potential is still lacking. Further analyses are needed to better assess the effectiveness of individual therapies and their impact on prognosis. The material for the review was collected through an extensive search of the PUBMED, ScienceDirect, Google Scholar and ClinicalTrials.gov databases, covering publications from the inception of these resources until 12 January 2024. The selection of keywords was tailored to the subject matter of the study in order to obtain the most comprehensive range of data possible. The initial search yielded 837 publications. After removing duplicates, 643 records were selected for further evaluation. Of these, 584 were rejected after analysis of titles and abstracts, leaving 59 studies for full evaluation. Ultimately, 19 studies were included in the review. The most common reasons for rejection were inadequate methodology, mainly review articles, and lack of data on the efficacy or safety of pharmacological therapies used in ATTR-CM. Nine drugs under evaluation were identified: tafamidis, acoramidis, revusiran, TUDCA, doxycycline, diflunisal, inotersen, eplontersen, and patisiran. In 2015, the results of a phase II study by Maurer et al. were published, involving 35 people with ATTR (including 31 with ATTRwt) who were administered tafamidis. The drug works by stabilising transthyretin and limiting its breakdown process leading to amyloid deposition. The main objective of the study was to evaluate the maintenance of stable TTR concentrations using an immunoturbidimetric assay. Assessments were performed after 6 weeks, 6 months and 1 year of treatment. Tafamidis maintained TTR stability in 96.8% of participants at week 6, 90% at 6 months and 89.3% at 1 year. During the 12-month treatment, 7 patients required hospitalisation for cardiac reasons, mainly due to worsening heart failure or the onset of atrial fibrillation. Another, much larger study – ATTR-ACT – was conducted by Maurer and his team in 2018. The trial included 441 patients with ATTR cardiomyopathy, 335 of whom had the wild-type form. Participants received tafamidis or placebo. The analysis included all-cause mortality and the incidence of hospitalisation for cardiovascular disease. Treatment with tafamidis was associated with lower mortality (HR 0.70; 95% CI 0.51–0.96), fewer hospitalisations for cardiac reasons (RR 0.68; 95% CI 0.56–0.81), better 6-minute walk test results, and more favourable KCCQ-OS questionnaire results. The most commonly reported adverse events were similar to those in the phase II study: heart failure and atrial fibrillation. In 2023, another TTR stabiliser, acoramidis, was evaluated in the ATTRibute-CM trial. The project included 632 people with transthyretin cardiomyopathy, including 571 with the wild-type form. The therapy lasted 30 months, and the primary analysis covered four areas: total mortality, hospitalisations due to cardiovascular disease, change in NT-proBNP values, and change in distance covered in the 6MWT. The results clearly favoured acoramidis ($P < 0.001$), showing a hazard ratio of 1.8 (95% CI 1.4–2.2). No differences in the incidence of adverse events were found between the groups (54.6% vs. 64.9%). A single-arm study by Castano et al. in 2012 evaluated the safety and efficacy of diflunisal in 13 patients with ATTR-CM, seven of whom had the wild-type form. No changes in left ventricular mass, ejection fraction or laboratory markers were reported. However, a 6% decrease in estimated glomerular filtration rate was observed during follow-up. In 2018, Rosenblum and colleagues presented a retrospective analysis of the survival of patients treated with TTR stabilising agents. The study included 120 individuals, 84 of whom had the wild-type form. Of these, 29 patients received stabilising treatment (tafamidis in 16 patients, diflunisal in 13), while 91 patients did not receive such therapy. The use of stabilising drugs was associated with a lower risk of death and the need for heart transplantation (HR 0.31; $p < 0.001$). No differences were found between the preparations used in this group. The year 2018 also saw a study by Ikram and colleagues, which analysed the tolerance of diflunisal in 23 patients with ATTR-CM, including 13 with the wild-type form. After approximately 15 months of therapy, there were no deaths or episodes of heart failure. Three individuals discontinued treatment due to adverse events such as erosive gastritis or epigastric pain. In 2019, Lohrmann and colleagues conducted another retrospective analysis of 33 patients receiving diflunisal and 48 patients not receiving such treatment. In the treatment group, serum TTR

concentrations were significantly reduced and left atrial volume increased compared to the control group. However, no changes in left ventricular ejection fraction or BNP levels were observed. In 2021, Falk and colleagues evaluated the effect of tafamidis on TTR levels in 72 patients with ATTR-CM, including 67 with the wild-type form. Baseline values were compared with measurements taken 3–12 months after the start of therapy. A 34.5% increase in TTR was achieved, confirming that tafamidis effectively stabilises the protein. Three further retrospective analyses were published in 2022. The study by Ochi et al. examined 82 patients with ATTRwt cardiomyopathy, 38 of whom started tafamidis therapy. Advanced disease stage and frailty were the most common barriers to treatment initiation. Among those receiving the drug, there were no discontinuations due to adverse events. Patients receiving treatment were less likely to be hospitalised for cardiovascular disease (19% vs. 59%) and less likely to die (8% vs. 34%). The most commonly reported symptoms were related to heart failure. A second study from 2022, by Giblin and colleagues, included 45 individuals, 23 of whom received tafamidis. After one year of follow-up, a marked deterioration in global longitudinal strain and myocardial function parameters was observed in the untreated group, which was not observed in patients receiving the drug. The differences did not apply to ejection fraction, radial or circumferential strain, left ventricular torsion parameters, or Doppler velocity. These results are consistent with a post hoc analysis of the 2023 ATTR-ACT study, which showed that tafamidis slowed the deterioration of left ventricular systolic and diastolic function over more than 30 months of follow-up. In addition, the ATTR-ACT post hoc analysis confirmed fewer cardiac hospitalisations among those treated with tafamidis and shorter hospital stays, which translated into an average of 2.62 fewer hospitalisation days per patient per year. In 2023, a cohort analysis using the TriNetX database was also published, comparing individuals taking tafamidis with untreated patients. After propensity score matching, there were fewer exacerbations of heart failure and lower overall mortality in treated patients, confirming the observations from the ATTR-ACT study in real-world clinical practice. The phase 3 ENDEAVOUR study, conducted by Judge and co-authors in 2020, involved 206 people with hereditary transthyretin amyloidosis with cardiomyopathy. Participants were randomly assigned to receive either revusiran, a drug that uses RNA interference to reduce TTR production, or a placebo. The trial was terminated early due to a noticeable difference in the number of deaths between the two groups. Among those taking revusiran, 23 people (16.4%) died, compared to 7 people (10.6%) in the placebo group. The majority of deaths were due to heart failure (78%). The overall mortality rate was 18% in the revusiran group and 2% in the placebo group (HR 5.3; 95% CI 1.2–22.8). There was no significant difference in the results of the 6-minute walk test between the two groups. Patisiran, another RNA interference drug, was evaluated in the APOLLO-B study, which included 360 people with ATTR-CM, most of whom were wild-type patients (288 people). Patisiran administration was associated with a slower decline in distance covered in the 6-minute walk test (estimated difference 14.69 m, $p = 0.02$) and a slight improvement in KCCQ-OS score compared to placebo (difference 3.7 points, $p = 0.04$). The most commonly reported adverse events included joint pain, muscle cramps and infusion reactions. A retrospective analysis by Karlstedt et al. from 2019 included 53 individuals with ATTR-CM, most of whom had the wild-type form. All patients received therapy based on doxycycline and ursodiol, which work by inhibiting the formation of amyloid fibrils. Six patients discontinued treatment due to skin changes or gastrointestinal complaints. After approximately 22 months of follow-up, there were no significant differences in NYHA class, cardiac biomarkers or echocardiography results. However, a noticeable improvement was observed in global longitudinal systolic strain, which increased in 38% of patients ($p < 0.01$), especially in those with less advanced disease. The study described by Dasgupta and co-authors in 2019 evaluated the safety and efficacy of inotersen, an antisense oligonucleotide targeting TTR mRNA. Thirty-three patients were enrolled, including 23 with wild-type disease. The observation period was three years. MRI scans showed a gradual reduction in mean left ventricular mass: 0.54% after one year, 8.5% after two years and 11.5% after three years. The ejection fraction remained stable, but cardiac load varied depending on the type of disease. The hereditary group showed an improvement of 1.3, while the wild-type group showed a slight decrease of 1.4. In all patients, BNP levels decreased during therapy, especially in those with the hereditary variant. At the same time, platelet counts decreased by an average of 14–15% over three years, although this did not lead to serious bleeding or severe thrombocytopenia, even though many patients were taking anticoagulants. One death was reported due to complications following emergency cholecystectomy. In the 2023 NEURO-TTRansform study of 144 adults with ATTRv polyneuropathy, 34% of participants also had cardiomyopathy. Patients were randomly assigned to receive eplontersen or placebo. An additional analysis of the results allowed the effect of treatment on the heart to be assessed. In the cardiomyopathy group, a 4.3% improvement in left ventricular ejection fraction ($p = 0.049$) and a 10.64 ml increase in stroke volume ($p = 0.002$) were observed at week 65 of follow-up. Tafamidis

confirmed its efficacy by affecting the incidence of complications and survival. At the same time, the safety signals described in the ENDEAVOR study and the results obtained in APOLLO-B, compared with other therapies with similar effects, show that the response to treatment may vary and depend on the patient's profile. Despite the available data, the review revealed several gaps in the literature, particularly in the area of long-term effects, comparisons between drugs, and analyses relating these results to financial burdens. The directions for the development of ATTR-CM therapies remain broad, and further research in the coming years may significantly change the prognosis for people with this disease.

According to *Transthyretin Amyloid Cardiomyopathy — 2025 Update: Current Diagnostic Approaches and New Therapeutic Options* (2025), ATTR amyloidosis is a progressive multiorgan disease that is fatal if left untreated. Survival ranges from 8 to 10 years on average for ATTRv and 3 to 4 years for ATTR-CM, counting from the onset of the first symptoms. Diagnosis can be difficult because the clinical picture is variable and often non-specific. Patients with predominantly cardiac manifestations usually develop worsening HFpEF resulting from amyloid deposition in the heart muscle. This leads to restrictive cardiomyopathy with features of hypertrophy and other cardiac dysfunction. In individuals with greater nervous system involvement, sensory-motor disorders and symptoms of dysautonomia are observed. Traditionally, patients are classified into ATTR-CM or ATTR-PN groups based on their predominant symptoms. However, approximately 33% of patients worldwide present with a mixed picture, including both cardiac and neurological symptoms, which makes accurate diagnosis and treatment selection difficult. In addition, ATTR amyloidosis is classified according to genotype, as different TTR variants lead to different clinical presentations, disease dynamics and organ involvement. The disease is considered rare, although the estimated number of cases — 200,000–300,000 for ATTRwt and 10,000–40,000 for ATTRv — may be underestimated. More recent data indicate that in selected populations, especially among older people with valvular heart disease, left ventricular hypertrophy or HFpEF, the prevalence may be as high as 15%. Early diagnosis is crucial, especially given the availability of therapies that slow the progression of the disease. The review presents current diagnostic methods, discusses therapies for ATTRv and ATTRwt, and outlines directions for treatment development, with a particular focus on patients with ATTR-CM and mixed phenotype. It also emphasises the need for further research into both improving diagnostic tools and optimising existing therapeutic strategies, which must respond to the diverse course of the disease. The development of new treatments should aim to halt progression, improve survival and quality of life, while reducing adverse effects and adherence issues. The THAOS registry (NCT00628745), a global observational study conducted between 2007 and 2023, includes both patients with ATTR amyloidosis and asymptomatic mutation carriers. It was found in 48% of the subjects, followed by p.Val142Ile (6%) and p.Glu109Gln (2.4%). ATTRwt accounted for 25% of cases. There are significant geographical differences — p.Val50Met predominates in Asia (48%), Europe (54%) and South America (79%), while in North America, patients with ATTRwt were most frequently recorded (59%). According to epidemiological data, the majority of patients are men (71%), and the average age of onset is 57 years. In the case of ATTRwt, the disease develops almost exclusively in men (over 90%) and usually begins after the age of 70. Of all symptomatic patients, 32% were classified as predominantly ATTR-CM, 39% as predominantly ATTR-PN, and 24.5% presented with a mixed picture. Although cardiac manifestations usually predominate in patients with ATTRwt, a significant proportion of patients in Europe (30%) and North America (50%) also experience polyneuropathic symptoms. This requires diagnostic vigilance on the part of cardiologists, especially in the presence of additional neurological signs. In most patients with ATTRwt and in some patients with specific ATTRv variants (including p.Val142Ile, p.Thr80Ala, p.Ile88Leu), there is predominant amyloid deposition in the myocardium. In the THAOS registry, all symptomatic patients with wt-ATTR were classified as having ATTR-CM (76%) or a mixed phenotype (24%).The presence of amyloid deposits leads to restrictive cardiomyopathy with concentric left ventricular hypertrophy (≥12 mm). Changes in valve structure and conduction disturbances contribute to arrhythmias and heart failure. Usually, the left ventricle is affected, but the process may also involve the right ventricle and atria. Due to the fact that the effectiveness of disease-modifying therapies depends on their rapid initiation, the diagnosis must be confirmed without delay after cardiac amyloidosis is suspected. Patients with cardiac amyloidosis exhibit characteristic cardiac manifestations that may suggest ATTR-CM. Extracardiac symptoms result primarily from amyloid deposition in the nervous system and musculoskeletal structures. Cardiological symptoms include clinical symptoms of heart failure, aortic valve stenosis, persistently elevated cardiac troponin levels, and abnormally high NT-proBNP levels indicative of heart failure. An exercise test can complement the functional assessment of cardiac amyloidosis, especially when evaluating response to therapy or in the differential diagnosis in the early stages of the disease. Typical echocardiography findings include a granular, flickering image of the myocardium,

thickening of the left ventricular walls (sometimes also the right ventricle and valves), weakened longitudinal function with preserved apical wall motion (so-called 'apical sparing') and pericardial effusion. Analysis of left atrial deformation has become useful in differentiating cardiac amyloidosis from other hypertrophic phenotypes, especially when apical sparing is not observed. New echocardiographic techniques, such as myocardial function analysis, can expand our knowledge of cardiac mechanics and help distinguish amyloidosis from hypertrophic cardiomyopathy or hypertensive heart disease. ECG findings typically include pseudo-infarction patterns with prolonged QTc interval, low QRS voltage (disproportionate to left ventricular hypertrophy) and atrioventricular conduction disturbances. CMR imaging typically shows gadolinium kinetics abnormalities and typical late gadolinium enhancement patterns, such as subendocardial or transmural LGE, as well as significantly elevated native T1. Quantitative measurement of extracellular volume (ECV) allows assessment of the extent of interstitial expansion and accurately reflects the degree of amyloid infiltration. Elevated ECV values are common in ATTR-CM and can be used to differentiate it from other causes of left ventricular hypertrophy. ATTR-CM is sometimes misdiagnosed as other heart diseases. The differential diagnosis should include hypertrophic cardiomyopathy, other restrictive cardiomyopathies, other types of cardiac amyloidosis (AL, AA) and storage diseases such as Fabry disease, Danon disease, Pompe disease and Gaucher disease. The vast majority of cases of cardiac amyloidosis involve AL or ATTR amyloidosis. According to the results of one meta-analysis, ATTR-CM is diagnosed in approximately 7% of patients with left ventricular wall thickness ≥15 mm, in 12% of patients with HFpEF, and in 10–15% of elderly patients with aortic valve stenosis referred for valve replacement. The most reliable method for confirming cardiac amyloidosis remains endomyocardial biopsy with histological staining and identification of the protein type using immunohistochemistry or mass spectrometry. Despite significant advances in imaging, Congo red staining remains the diagnostic standard, especially in AL amyloidosis. In clinical practice, a non-invasive pathway based on typical imaging results and positive bone scintigraphy in the absence of monoclonal gammopathy is increasingly being used. The diagnosis of ATTR-CM is considered confirmed when scintigraphy using 99mTc tracers shows grade 2 or 3 myocardial uptake at least equal to bone uptake, and tests for monoclonal proteins (free light chains in serum, electrophoresis and immunofixation) do not indicate AL amyloidosis. In patients with normal monoclonal protein levels and grade 1 uptake, a cardiac or extracardiac tissue biopsy with further immunohistochemical or mass spectrometry analysis is necessary. Once ATTR-CM is confirmed, each patient undergoes genetic testing for TTR gene mutations to distinguish ATTRv from ATTRwt. If a mutation is found, genetic counselling and screening of first-degree relatives is recommended. In addition to symptomatic therapies targeting heart failure, neuropathic pain or autonomic disorders, there are an increasing number of treatment options available that modify the course of ATTR-CM and ATTR-PN. Currently approved drugs in the US and EU are divided into two groups according to their mechanism of action. TTR stabilisers are small-molecule drugs that bind to the TTR tetramer. This prevents its breakdown into monomers, further misfolding and amyloid fibril deposition. Gene silencers use small interfering RNAs or antisense oligonucleotides that direct TTR mRNA to degradation. As a result, the production of both mutant and wild-type TTR proteins is reduced. TTR stabilisers protect the tetramer from breaking down into monomers by stabilising its structure. Diflunisal, a non-steroidal anti-inflammatory drug with TTR-stabilising properties in vitro, has been used off-label in ATTRv-PN. However, its lack of registration and the risk of gastrointestinal, renal and cardiac toxicity make its use unfavourable in patients with cardiac involvement in ATTRv or ATTRwt. More modern and selective stabilisers have been introduced. Tafamidis, a derivative of diflunisal, binds to thyroxine binding sites on the TTR tetramer, protecting the protein from dissociation. Maintaining the native structure reduces the rate of amyloid fibril formation. Acoramidis is a newer generation stabiliser that acts on the same binding sites as tafamidis, but is designed to mimic the protective T119M variant. This gives it a stronger affinity and more effective pharmacological stabilisation of TTR. Tafamidis is a small molecule drug that stabilises the TTR tetramer by binding at the T4 site. In 2019, it was approved in the United States for the treatment of ATTR-CM. In the double-blind, placebo-controlled Phase III ATTR-ACT trial involving 441 patients with ATTR-CM (76% with ATTRwt), administration of 20 mg of tafamidis meglumine was associated with a hazard ratio of 1.70, a 30% reduction in mortality, and a 32% reduction in cardiovascular hospitalisations over 30 months compared to placebo. The benefits were most pronounced in patients with early-stage disease (NYHA ≤ II), which is why the EMA initially limited the approval of tafamidis to this group. In 2020, tafamidis (61 mg) was approved by the European Commission for the treatment of ATTR-CM in a broader population. In 2011, tafamidis meglumine (20 mg) was approved in the European Union for the treatment of stage 1 ATTR-PN because it demonstrated the ability to slow disease progression and preserve neurological function. The approval was based on the Phase III Fx-005 trial, in which

tafamidis reduced disease progression in 60% of patients, compared with 38% in the placebo group. Tafamidis is not approved by the FDA for the treatment of ATTR-PN. Acoramidis (formerly AG10) is an oral small molecule drug designed to mimic the protective TTR T119M variant, a natural mutation that increases tetramer stability and reduces the risk of amyloidosis even in the presence of pathogenic variants. The drug strengthens hydrogen bonds between TTR monomers, including the stabilising salt bridge with Ser117, providing greater affinity and better thermodynamic stability than tafamidis. In vitro studies have shown greater selectivity and a stronger stabilising effect compared to tafamidis and diflunisal, which may translate into better protection against disease progression. In November 2024, the FDA approved acoramidis for patients with ATTRwt and ATTRv with ATTR-CM cardiomyopathy, and in January 2025, it was approved in the European Union for the same indication. The approval was based on the Phase III ATTRibute-CM study, in which 632 patients were randomly assigned to acoramidis (800 mg twice daily) or placebo for 30 months. The drug showed a significant benefit compared to placebo, including a reduction in mortality and cardiovascular hospitalisations. Long-term data up to 42 months showed a 43% reduction in mortality or first hospitalisation for cardiovascular causes in patients continuing treatment. The ACT-EARLY study is currently underway to evaluate the efficacy of acoramidis in asymptomatic patients with ATTRv in preventing or delaying the onset of symptoms. TTR gene silencing involves inhibiting TTR gene expression at the post-transcriptional level, leading to a reduction in the production of wild-type and mutant TTR protein. Silencers include small interfering RNAs (siRNAs), which bind to mRNA and initiate its degradation by the RISC complex, and antisense oligonucleotides (ASOs), which trigger mRNA degradation via RNase H. Currently approved therapies include the siRNA vutrisiran and the next-generation ASO eplontersen, optimised for delivery to the liver. In the past, liver transplantation was a form of TTR gene silencing, but with the advent of specific therapies, its importance has diminished. Eplontersen is a subcutaneous ASO conjugated to GalNAc, which is the successor to inotersen. Conjugation to GalNAc enables specific uptake of the drug by the liver. In the NEURO-TTRansform study in patients with ATTRv-PN, a 70% reduction in serum TTR was demonstrated after a monthly dose, slowing the progression of neuropathy and significantly improving quality of life. The drug is administered once a month in the form of a subcutaneous autoinjector. In March 2025, eplontersen was approved in the EU for adult patients with stage 1 or 2 ATTRv-PN. The efficacy of eplontersen in ATTR-CM is being evaluated in the CARDIO-TTRansform trial, the largest clinical trial to date in this population, involving approximately 1,438 patients. The primary endpoints are cardiovascular events, changes in 6MWT and the KCCQ score. Results are expected in mid-2026, and the drug has received Fast Track designation from the FDA for accelerated review in the treatment of ATTR-CM. Vutrisiran is a subcutaneously administered successor to patisirane, the first siRNA drug approved for patients with ATTRv-PN. Like eplontersen, vutrisiran is conjugated to GalNAc, which enables specific delivery of the drug to the liver and subcutaneous administration. The efficacy of vutrisiran was evaluated in the Phase III HELIOS-A study, in which administration of 25 mg every 12 weeks slowed the decline in neurological function and quality of life at 9 months of treatment, as measured by mNIS+7 and the Norfolk QoL-DN questionnaire. In 2022, the drug was approved by the FDA and EMA for patients with stage 1 and 2 ATTRv-PN. In a subsequent phase III study, HELIOS-B, vutrisiran demonstrated efficacy in 655 patients with ATTR-CM, reducing the risk of all-cause mortality and cardiovascular events by 28% at 36 months compared to placebo. Secondary endpoints also improved, including NYHA class, six-minute walk test score, and quality of life as assessed by the KCCQ-CSS. Vutrisiran has also been approved by the FDA and EMA for the treatment of ATTR-CM. To date, the FDA and EMA have approved four gene silencing drugs for the treatment of patients with stage 1 or 2 ATTRv-PN: patisiran (intravenous siRNA), vutrisiran (subcutaneous GalNAc siRNA), inotersen (subcutaneous ASO), and eplontersen (subcutaneous GalNAc-ASO). In the European Union, the TTR stabiliser tafamidis meglumine (20 mg) is approved for patients with stage 1 ATTRv-PN. Tafamidis is approved by the FDA for the treatment of ATTR-CM, but not for ATTR-PN. Depending on the severity of neuropathy and local guidelines, patients with ATTRv-PN may be treated with tafamidis (stage 1) or gene silencers such as vutrisiran or eplontersen (stages 1–2). Older drugs, patisiran and inotersen, are now less commonly used in clinical practice. For patients with additional cardiac amyloidosis (ATTR-CM), special recommendations described in the following chapters apply. The 2021 ESC guidelines and the 2023 ACC expert consensus recommend the use of tafamidis in patients with NYHA class I–II ATTR-CM. The AHA/ACC/HFSA guidelines for the treatment of heart failure also recommend tafamidis for patients in NYHA class III to reduce morbidity and mortality associated with cardiovascular disease. A second stabilizer, acoramidis, has also recently been approved for patients with ATTR-CM. The choice between tafamidis and acoramidis should take into account clinical trial results and individual patient characteristics. Tafamidis reduces all-cause mortality and cardiovascular hospitalizations, particularly in NYHA classes I–II.

Acoramidis improves functional capacity and quality of life and effectively stabilizes TTR in over 90% of patients, which can be monitored through serum TTR levels. In the ATTRibute-CM study, the mean increase in TTR over 28 days was 9.1 mg/dL, and each additional 5 mg/dL was associated with a 31.6% reduction in the risk of death over 30 months. Although there are no direct comparisons between tafamidis and acoramidis, both drugs effectively stabilize TTR, and the choice in practice depends, among other things, on drug availability, cost, kidney function, frequency of administration, and patient preference. Tafamidis remains the standard first-line therapy, while acoramidis is a promising alternative, especially where monitoring TTR levels can support the assessment of treatment efficacy. Vutrisiran and eplontersen have also been evaluated in phase III trials in ATTR-CM, offering a promising alternative not only for ATTRwt-CM but also for patients with a mixed phenotype with additional polyneuropathic symptoms. Most approved therapies target patients with a dominant phenotype, posing a challenge in treating patients with a mixed phenotype, who account for approximately one-third of symptomatic patients. Patients with ATTRv-CM and additional polyneuropathy may be treated with TTR stabilizers such as tafamidis or acoramidis, which are approved for ATTR-CM. The approval of tafamidis for the treatment of ATTR-PN is limited to stage 1 in the EU. Neither tafamidis nor acoramidis are approved by the FDA for the treatment of isolated ATTR-PN. In patients with a mixed phenotype and marked neurological impairment, gene silencers may be considered, which requires close collaboration with neurologists. The CRISPR-Cas9 system has revolutionized genetic engineering by offering a precise and efficient tool for DNA modification. It allows for the one-time treatment of serious genetic diseases. Until March 2025, the only approved CRISPR-Cas9-based therapy was a treatment for sickle cell anemia. Other therapies, including for ATTR amyloidosis, are currently in Phase III clinical trials. The first CRISPR-Cas9-based therapy tested in humans was Nexiguran ziklumeran (Nex-Z, formerly NTLA-2001). In an open-label Phase I study, a single intravenous infusion of Nex-Z in patients with ATTR-CM reduced serum TTR levels by 90% after 12 months. Ninety-two percent of patients had improvement or no worsening in their NYHA class. Nex-Z was well tolerated, with infusion-related reactions being the most common side effect. The international Phase III MAGNITUDE study is currently underway and is expected to enroll approximately 765 patients. The primary endpoint is a composite of death and cardiovascular events, and secondary endpoints include TTR changes and KCCQ-OS score at 18 months. The study is scheduled to be completed in 2028. In addition to stabilizing TTR tetramer and reducing TTR production, therapies targeting pathological amyloid deposition are being developed. The goal of these so-called ‘TTR depletors’ is to reverse the disease and prevent re-accumulation, especially in patients with advanced disease. Monoclonal antibodies bind to misfolded TTR and enable its removal by phagocytes, resulting in the elimination of amyloid fibrils in the heart and peripheral nervous system. Coramitug (NNC6019-0001, formerly PRX004) is a humanized IgG antibody that removes ATTR deposits. It is currently being studied in a global Phase II trial in patients with ATTR-CM (NYHA II-III). It is administered intravenously every 4 weeks in two doses or placebo. Primary endpoints include changes in 6MWT and NT-proBNP up to week 52, and secondary endpoints include time to death, number of cardiovascular events, and changes in KCCQ-CSS and NIS. The study is expected to be completed in mid-2025. ALXN2220 (formerly NI006 and NI301A) is a human IgG monoclonal antibody that selectively binds misfolded TTR aggregates and ATTRv and ATTRwt fibrils. Following a positive Phase I study, ALXN2220 is being evaluated in the Phase III DepleTTR-CM study. An estimated 1,000 patients with ATTR-CM and heart failure (NYHA II-IV) are expected to participate in the study. The primary endpoint is the number of deaths and cardiovascular events up to 48 months, and secondary endpoints include changes in KCCQ-OS and 6MWT. The study is scheduled to be completed in 2028.

**Discussion**

The data confirm that the ATTR treatment strategy should be multifaceted, involving TTR stabilization, gene silencing, and, in selected cases, direct removal of amyloid deposits. Ongoing and planned Phase III trials will better define the place of new therapies in treatment regimens and allow for the assessment of their impact on survival, quality of life, and disease progression in patients with different ATTR phenotypes. An analysis of current clinical trials and approved therapies for transthyretin amyloidosis (ATTR) shows that treatment of this disease is evolving toward targeted strategies that not only alleviate symptoms but also modify the course of the disease. TTR stabilizers, such as tafamidis and acoramidis, have been shown to be effective in reducing the progression of ATTR cardiomyopathy, with acoramidis offering near-complete stabilization of TTR protein, which may translate into additional clinical benefits and the ability to monitor treatment efficacy using serum TTR levels. Gene silencers, both siRNA (patisiran, vutrisiran) and ASO (inotersen, eplontersen), have been shown to significantly reduce TTR expression, which translates into a slowdown in the progression of

neuropathy and an improvement in patients' quality of life. The advantage of these therapies is their specificity and adaptability to patients with different disease phenotypes.

Subcutaneous drugs conjugated with GalNAc appear particularly promising, as they enable targeted delivery to the liver, which improves safety and reduces the required dose. Modern approaches, such as CRISPR-Cas9 gene editing (nexiguran ziklumeran) and anti-ATTR monoclonal antibodies (Coramitug, ALXN2220) open up prospects for potentially one-time or reversible therapies for advanced amyloid changes. Phase I/II studies to date confirm high efficacy in reducing TTR and removing amyloid deposits, with an acceptable safety profile, which gives hope for further improvement in clinical outcomes in the future. A comparison of current therapeutic strategies suggests that the choice of therapy should be tailored to the patient's phenotype, disease stage, and drug availability. TTR stabilizers remain a well-documented option for the treatment of ATTR-CM, while gene silencers dominate the treatment of stage 1 and 2 ATTRv-PN. New gene therapies and antibodies may expand the treatment spectrum in the future, especially in patients with mixed phenotypes or advanced disease. The selection of optimal therapy for patients with a mixed phenotype, who have both cardiomyopathy and polyneuropathy, remains a challenge.

In practice, treatment decisions must take into account both clinical trial data and individual patient characteristics, including disease stage, cardiovascular risk, renal function, drug availability, and patient preferences.

**Conclusions**

1. Previous treatments have focused mainly on symptoms (e.g., heart failure, neuropathy). Currently available and investigational therapies target the underlying mechanism of the disease—stabilizing TTR or reducing its production. These therapies show potential in slowing or stopping disease progression, which is an improvement over symptomatic treatment.

2. Tafamidis and acoramidis effectively stabilize the TTR tetramer, limiting amyloid formation. Tafamidis has established clinical evidence, particularly in NYHA class I–II ATTR-CM, while acoramidis shows higher TTR stabilization and may be a promising alternative. Both drugs remain the main choice for treating patients with a predominantly cardiac phenotype.

3. Drugs such as patisiran, vutrisiran, inotersen, and eplontersen effectively reduce TTR production, slowing the progression of polyneuropathy in patients with ATTRv-PN. The clear clinical effect includes improved neurological function, slowed progression of neuropathy, and improved quality of life. They also show potential in treating patients with a mixed phenotype involving both the heart and nervous system.

4. CRISPR-Cas9 therapies, such as Nexiguran Ziclumeran, enable one-time gene editing, leading to a permanent decrease in TTR concentration and stabilization of heart function. Anti-ATTR monoclonal antibodies (Coramitug, ALXN2220) offer the possibility of removing existing amyloid deposits, which is a new direction in the treatment of advanced disease.

5. The choice of therapy should take into account the patient's phenotype (cardiac, neurological, or mixed), disease stage, drug availability, and patient preferences. TTR stabilizers remain the primary choice for ATTR-CM, while gene silencers are preferred for patients with a predominantly neurological or mixed phenotype.

6. Ongoing phase III and IV trials will allow for a better assessment of the long-term efficacy and safety of new therapies. New approaches, such as gene editing and monoclonal antibodies, may in the future enable not only slowing down but also partial reversal of the disease, especially in patients with advanced ATTR.

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