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REVIEW ARTICLE

# Evolving Therapies for Transthyretin Cardiac Amyloidosis: New Clinical Trials with Amyloid Fibrils Depleter

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## Abstract

Amyloidosis is caused by the extracellular deposition of insoluble protein arrangements, formed from structural changes in different precursor proteins. The prominent clinical and epidemiological relevance of transthyretin amyloid cardiomyopathy (ATTR-CM), whose increased incidence is associated with the aging of the global population, given its high prevalence in the elderly population, has motivated the intensification of the search for specific therapeutic targets capable of altering the natural course of the disease. The past few years have been especially prolific with the emergence of significant new therapies for ATTR-CM, with important trials demonstrating positive results and changing the natural history of an inexorable and deadly disease. Up to now, the available drugs mainly promote stabilization of disease progression in patients with no advanced heart disease but grant no reversal of the structural cardiac disease in most cases. The transthyretin (TTR)-depleters based on monoclonal antibodies directed against the deposited amyloid fibers hold promise to fulfill these expectations. The DepleTTR-CM will test the safety and efficacy of a monoclonal antibody directed against TTR fibrils deposited in the myocardium of patients with ATTR-CM. This will be the first multicenter randomized controlled trial to test this new class of anti-amyloid treatment, the "amyloid fibril depleters". This is a strategy designed to revert the amyloid accumulation in the cardiac interstitium, which is expected to translate into relevant clinical benefits, with the potential to close a gap in the ATTR-CM treatment strategies, mainly in patients with more severe disease.

## Keywords

Amyloidosis; Heart Failure; deplete; Prealbumin.

## Introduction

Amyloidosis results from the extracellular deposition of insoluble protein arrangements, formed from structural changes in different precursor proteins.[1] These amyloidogenic proteins disaggregate and rearrange themselves, forming a unique fibrillar protein structure[2] that is deposited, infiltrating different organs, and causing tissue damage and functional changes. There are more than 30 proteins described as being involved in the formation of amyloid deposits.[3] When considering infiltration of the myocardial interstitium with the development of cardiac amyloidosis, the main proteins (about 95% of cases) are immunoglobulin light-chains, generating AL amyloidosis[4] and transthyretin (TTR), leading to amyloidosis transthyretin amyloid (ATTR).[5]

TTR is a protein synthesized by the liver that is involved in the transport of retinol (vitamin A) and thyroid hormone (thyroxine).[6,7] It is released into the bloodstream after its release in the liver, and to a lesser extent proportion in choroid plexuses and retinal epithelial cells.[8,9] Physiologically, TTR is found in the form of tetramers.[10] However, due to pathological processes, involving changes in the conformation of the protein and its consequent anomalous folding, TTR tetramers can be disaggregated into dimers and dissociate into monomers, which can aggregate abnormally, forming insoluble amyloid fibrils that are deposited in tissues[11,12]

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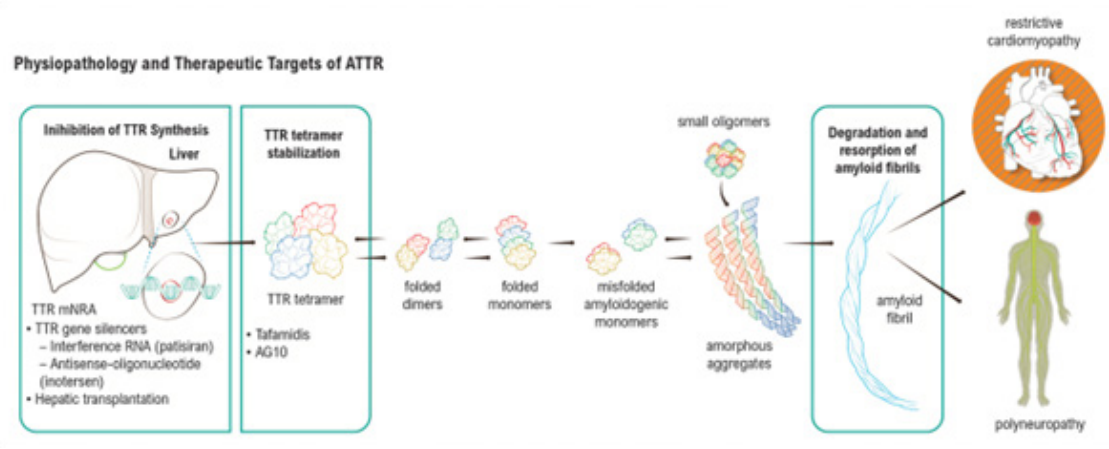


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*The "amyloidogenic cascade" of ATTR, pointing out the potential therapeutic targets and the respective drugs. Adapted from Simões et al.[25]*
*TTR: transthyretin; mNRA: messenger ribonucleic acid; RNA: Ribonucleic acid.*

(Figure 1). TTR abnormalities that lead to amyloidosis may result from mutations in the genes that encode protein synthesis (hereditary form or ATTRv, where v stands for variant)[13] or due to post-transcriptional changes in protein synthesis, related to aging (wild form or "wild type", ATTRwt).[14] These post-transcriptional changes may be present even in hereditary forms and in the involvement of a mechanoenzymatic mechanism, with the cleavage of TTR, in which plasmin appears to be involved.[15,16]

The clinical manifestations of ATTR are divided into neurological, cardiological and other systemic manifestations, such as orthopedic, renal, ocular, and central nervous system.

Cardiac involvement in ATTR refers to the infiltration of amyloid material into the walls of the heart, both atria and ventricles, causing thickening and the development of an infiltrative ATTR cardiomyopathy (ATTR-CM) with a restrictive pattern, with reduced relaxation and increased ventricular filling pressures.[17,18]

The most frequent clinical manifestation of this form of cardiomyopathy is heart failure syndrome,[19] most commonly with preserved ejection fraction (HFpEF) but which can progress to a drop in ejection fraction in the more advanced stages of the disease.

The presence of cardiac involvement by amyloidosis is the most powerful marker of a worse prognosis in the disease, both in the cases of AL amyloidosis and in the ATTRv form.[20]

Patients with ATTRv have a variable prognosis depending on the existing mutation, with the V122I mutation worsening and a median survival of two years.[21,22] In addition to the link with increased mortality, the presence of heart failure contributes significantly to the increase in morbidity and compromised quality of life in patients with amyloidosis.[21]

In the ATTRwt form, the prognosis is slightly better, with a median survival of 3.6 to 6 years, which varies depending on the age at diagnosis and the degree of cardiac involvement. To assist in prognostic assessment, a score composed of elevated biomarkers was developed: troponin T >0.05 ng/ml, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) >3000 pg/ml, with the patient being classified according to the cutoffs into three stages. (I, II, and III).[23] Other classic prognostic factors involved are the functional class of advanced NYHA (New York Heart Association) and the need for pacemaker implantation.[24]

## New therapies modifying the natural history of TTR amyloid cardiomyopathy

The prominent clinical and epidemiological relevance of ATTR-CM, whose increased incidence is associated with the aging of the global population, given its high

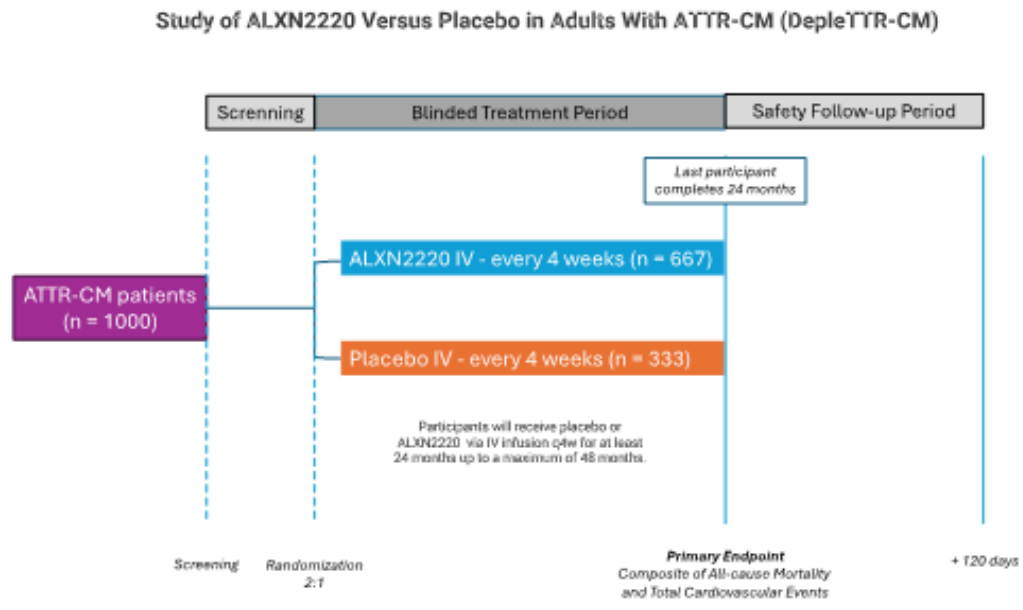


**Figure 1 – The DepleTTR-CM trial design.**

prevalence in the elderly population, has motivated the intensification of the search for specific therapeutic targets capable of altering the natural course of the disease.

Central Illustration demonstrates the therapeutic targets identified in the ATTR amyloidogenic cascade that have been explored for the development of new drugs. Up to now, two classes of drugs have been tested in this clinical scenario, including TTR tetramers stabilizers and inhibitors of the hepatic synthesis of TTR.

## The TTR tetramers stabilizers

### Tafamidis

Tafamidis was the first drug tested in a multicenter randomized controlled trial for the treatment of ATTR-CM. This drug binds to TTR with high affinity, at the thyroxine binding sites, increasing the stability of the tetramer and preventing its disaggregation and the consequent formation of monomers and the subsequent formation of insoluble amyloid fibrils (Central Illustration).[26]

The effects of tafamidis were evaluated in a multicenter phase III, randomized, placebo-controlled clinical study (ATTR-ACT study),[27] involving 441 adult patients with ATTR-CM, both ATTRv and ATTRwt, with a previous diagnosis of heart failure, in NYHA class I to III, with high levels of NT-proBNP, and being treated over 30 months.[27] Patients receiving tafamidis exhibited a 30% reduction in all-cause mortality (relative risk [RR] 0.70, 95% confidence interval [CI] 0.51–0.96) and a 32% reduction in hospitalizations due to cardiovascular causes (RR 0.68, 95%CI 0.56–0.81). In addition to these results in cardiovascular outcomes, tafamidis was also associated with a reduction in the rate of worsening of functional capacity and quality of life, effects that were demonstrated as early as six months of treatment.[27]

Analysis of the results of the ATTR-ACT study indicate that tafamidis has a greater positive impact when started in less-advanced stages of the disease, as the benefits appear to be attenuated in patients with NYHA functional class III. As an exclusion criterion, the study did not consider patients with NYHA FC IV. Therefore, the role of tafamidis in advanced heart disease is uncertain.[27] This aspect makes early diagnosis the key to changing the prognosis and truly improving quality of life. On the other hand, patients with more severe ATTR-CM and advanced symptoms were not included in those trials and were perceived as patients with a low probability of benefit from this drug.

### Acoramidis

Acoramidis is a TTR stabilizer whose mechanism of action simulates the effects of a mutation that increases the binding strength between TTR tetramers and reduces their dissociation rate. This medication was tested in a recently published randomized, placebo-controlled, multicenter study (ATTRibute-CM study).[28] In this phase III, double-blind trial, patients with ATTR-CM were randomly assigned in a 2:1 ratio to receive acoramidis hydrochloride at a dose of 800 mg twice daily or a matching placebo for 30 months. The statistical analysis employed a four-step primary hierarchical analysis including death from any cause, cardiovascular-related hospitalization, the change from baseline in the NT-proBNP level, and the change from baseline in the 6-minute walk distance. A total of 632 patients were randomly assigned. The primary results analysis favored acoramidis over placebo. The win ratio was 1.8 (95%CI 1.4–2.2, p<0.001); with 63.7% of pairwise comparisons favoring acoramidis and 35.9% favoring placebo. Together, death from any cause and cardiovascular-related hospitalization contributed more than half of the wins and losses to the win ratio (58% of all pairwise comparisons). The drug presented good level of tolerance and safety profile, with an incidence of adverse events similar in the acoramidis and placebo groups (98.1% and 97.6%, respectively).[28]

## TTR synthesis inhibitors

### Patisiran

Patisiran is a TTR hepatic synthesis silencer based on small-interference ribonucleic acid (RNA) technology. The results of a phase III, double-blind, randomized, and controlled trial testing patisiran in 360 ATTR-CM patients, both ATTRv and ATTRwt, were recently published. Patients were randomized in a 1:1 ratio, to receive patisiran (0.3 mg per kilogram of body weight) or placebo once every three weeks for 12 months. The main results showed at month 12 the decline in the 6-minute walk distance was lower in the patisiran group than in the placebo group (Hodges–Lehmann estimate of median difference, 14.69 m; 95%CI 0.69–28.69; p = 0.020); the Kansas City Cardiomyopathy Questionnaire – overall summary (KCCQ-OS) score increased in the patisiran group and declined in the placebo group (least-squares mean difference, 3.7 points; 95%CI 0.2–7.2; p = 0.040).

### Eplontersen

Eplontersen is another class of TTR hepatic synthesis silencer that is based on anti-sensing oligonucleotide technology, that has demonstrated beneficial effects on the ATTR polyneuropathy, and is currently been tested in a phase III, double-blind, randomized, and controlled trial in patients with ATTR-CM, with the final results been expected to be published in a near future.

## Effect of currently available drugs and unmet needs

As we briefly reviewed above, the past few years were especially prolific with the emergence of significant new therapies for ATTR-CM, with three important trials demonstrating positive results and changing the natural history of an inexorable and deadly disease.

But it is important to remark that, up to now, the available drugs mainly promote stabilization of disease progression in patients with no advanced heart disease but grant no reversal of structural cardiac disease in most cases. Therefore, the next step in this clinical scenario is the development of drugs able to promote the depletion of TTR deposits in myocardial tissue that could more deeply impact disease progression. The TTR-depleters based on monoclonal antibodies directed against the deposited amyloid fibers hold promise to fulfill these expectations. A recently launched multicenter randomized phase III clinical trial, the DepleTTR-CM, was the first trial, so far, designed to test this hypothesis.

## The rational basis of the DepleTTR-CM study

The objective of the DepleTTR-CM study is to evaluate the safety and efficacy of a depleter of amyloid fibrils deposited in the myocardial interstitium, a monoclonal antibody anti-ATTR, currently called ALXN2220, but previously called NI006.

The reason for using this type of medication is based on the notion that reducing myocardial TTR load can translate into restoration of cardiac function and improved patient survival. Myocardial deposits of ATTR accumulate in the cardiac interstitium, impacting the mechanical and functional properties of the myocardium such as changes in diastolic relaxation, and with the progression of the disease, there is also impairment of systolic function. In peripheral sensorimotor neurons, ATTR deposits also cause polyneuropathy, which together with cardiomyopathy, are the main clinical manifestations of TTR amyloidosis.[29-31] Drugs that act

as TTR tetramer stabilizers, silencers, and gene-editing therapies have been designed to prevent the accumulation of ATTR but these drugs do not directly target amyloid that has already been deposited in the heart.[32]

In preclinical studies, NI006, a recombinant human anti-ATTR monoclonal IgG1 antibody that selectively binds to the amyloid conformations of ATTRv and ATTRwt, but not physiologically folded TTR, eliminated the protein by inducing phagocytosis of TTR fibrils with consequent removal of TTR deposits from tissues.[33]

A recently published randomized phase I (Ia-Ib), double-blind, placebo-controlled, multicenter (in four European countries), combined single-dose progressive clinical trial was the first investigational study in humans and aimed to evaluate the safety profile and side effects of intravenous infusions (ranging from 0.3 to 60 mg per kilogram of body weight) in patients with ATTR-CM. Patients with ATTR-CM and chronic heart failure were randomized (in a 2:1 ratio) to receive intravenous infusions of NI006 or placebo every four weeks for four months.[34]

In this study, the use of NI006, particularly at doses of at least 10 mg per kilogram administered every four weeks, was associated with changes in extracellular volume on cardiac magnetic resonance imaging and radiotracer uptake on scintigraphy, two image-based surrogate markers of cardiac amyloid burden. These observations were supported by changes in cardiac biomarker levels and functional measures. The safety profile of NI006 and the absence of anti-drug antibodies may be related to the amino acid sequence of the medicine of human origin and its selectivity for misfolded TTR, without binding to physiological TTR.[33] No variation in plasma TTR level was observed between the different dose cohorts. The type, frequency, and severity of cardiac adverse events in this study appeared to be similar to those reported in the phase III studies of tafamidis[16] and patisiran,[17] in which the patient population was larger but patient characteristics were similar.[34] A notable difference in this trial was the occurrence of arthralgias, which may be more common with NI006 and possibly related to the activation of phagocytic immune cells targeting musculoskeletal TTR deposits.[35,36]

## DepleTTR-CM trial design

According to information available on https://clinicaltrials.gov, under the number NCT06183931, the phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of amyloid depleter ALXN2220 in adult participants with ATTR-CM — the DepleTTR-CM study — is predicated upon the hypothesis that ALXN2220, a novel therapeutic agent, will demonstrate efficacy in treating ATTR-CM. It is hypothesized that ALXN2220, through its mechanism of action, will effectively reduce the burden of amyloid deposits in cardiac tissue, leading to improved cardiac function and clinical outcomes compared to placebo. This hypothesis is based on preclinical data and early clinical trials suggesting the potential of ALXN2220 to inhibit the formation and deposition of amyloid fibrils, thereby addressing the underlying pathology of ATTR-CM.

The study will enroll adult patients with ATTR-CM, ATTRv or ATTRwt, with symptomatic heart failure and increased NT-proBNP levels.

The specific criteria for participant eligibility are summarized in Table 1:

The study exclusion criteria for participant eligibility are depicted in Table 2:

### Randomization groups, doses, and procedures

The allocation method is randomized, ensuring an unbiased distribution of participants into different treatment arms. The interventional model is characterized by parallel assignment, where participants are distributed to either the experimental group receiving ALXN2220 or the control group receiving placebo. To maintain blinding and minimize bias, quadruple masking is employed, involving masking of participants, care providers, investigators, and outcomes assessors. In the experimental arm, participants receive ALXN2220 via intravenous infusion every four weeks for a duration of at least 24 months, with the possibility of extension up to 48 months, while those in the control arm receive placebo following the same administration schedule. Both ALXN2220 and placebo are administered via intravenous infusion, with dosing based on weight for the experimental group. These design elements are implemented to rigorously evaluate the efficacy and safety of ALXN2220 compared to placebo in the treatment of ATTR-CM, with the goal of informing clinical practice and improving patient outcomes.

**Table 1 - Inclusion criteria of the DepleTTR-CM study.**

| Inclusion criteria |
|---|
| Centrally confirmed diagnosis of ATTR-CM with either wild-type or variant TTR genotype. |
| End-diastolic interventricular septal wall thickness ≥ 11 mm for women or ≥ 12 mm for men on echocardiography measured at screening. |
| NT-proBNP > 2,000 pg/mL at screening. |
| Treatment with a loop diuretic for at least 30 days prior to screening. |
| History of heart failure NYHA class II–IV at screening. |
| Life expectancy of ≥ 6 months as per the investigator's judgment. |
| Males and females of childbearing ability must use contraception. |

*ATTR-CM: Transthyretin amyloid cardiomyopathy; NYHA: New York Heart Association; TTR: transthyretin; NT-proBNP: N-terminal pro–B-type natriuretic peptide.*

**Table 2 - Exclusion criteria of the DepleTTR-CM study.**

| Exclusion criteria |
|---|
| Known leptomeningeal amyloidosis. |
| Known AL, or secondary AA, or any other form of systemic amyloidosis. |
| Acute coronary syndrome, unstable angina, stroke, transient ischemic attack, coronary revascularization, cardiac device implantation, cardiac valve repair, or major surgery within three months of screening. |
| Uncontrolled clinically significant cardiac arrhythmia, per investigator's assessment. |
| LVEF < 30% on echocardiography. |
| Renal failure requiring dialysis or an eGFR < 20 mL/min/1.73 m2 at screening. |
| Polyneuropathy disability score IV. |

*AL: light-chain; AA: amyloidosis; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.*

### Study conducting and planned outcomes

The primary outcome measure of the study focuses on a composite of events comprising all-cause mortality and total cardiovascular clinical events. This measure will be evaluated from baseline throughout the duration of the study, extending up to month 48.

Secondary outcome measures include: (1) another composite measure of all-cause mortality and total heart failure events, assessed from baseline to the end of the study; (2) changes from baseline in the KCCQ-OS score, measured at month 24, offering insights into participants' perceived quality of life; (3) time to cardiovascular-related mortality, monitored from baseline to the end of the study; (4) changes from baseline in the 6-minute walk test (6MWT) at month 24, providing objective measures of functional capacity; (5) number of participants experiencing cardiovascular clinical events; and (6) time to all-cause mortality, recorded throughout the study period up to month 48. These outcome measures collectively aim to comprehensively evaluate the efficacy and impact of the intervention on clinical events, quality of life, functional capacity, and mortality rates among participants with ATTR-CM. Figure 1 illustrates the trial design.

The study officially started on January 11, 2024, the date of the first patient randomization, and is estimated to complete the enrollment with 1,000 patients, on August 29, 2025.

## Conclusions

The DepleTTR-CM will test the safety and efficacy of a monoclonal antibody directed against the TTR fibrils deposited in the myocardium of patients with ATTR-CM. This will be the first multicenter randomized controlled trial to test this new class of anti-amyloid treatment, the "amyloid fibril depleters", a strategy designed to revert the amyloid accumulation in the cardiac interstitium, which is expected to translate into relevant clinical benefits, with the potential to close a gap in the ATTR-CM treatment strategies, mainly in patients with more severe disease.

## Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Simões MV, Fernandes F, Dabarian A, Mesquita CT, Valicelli FH.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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