ESC European Society of Cardiology

European Heart Journal (2025) **46**, 999–1013
https://doi.org/10.1093/eurheartj/ehae811

Transthyretin amyloid cardiomyopathy: a paradigm for advancing precision medicine

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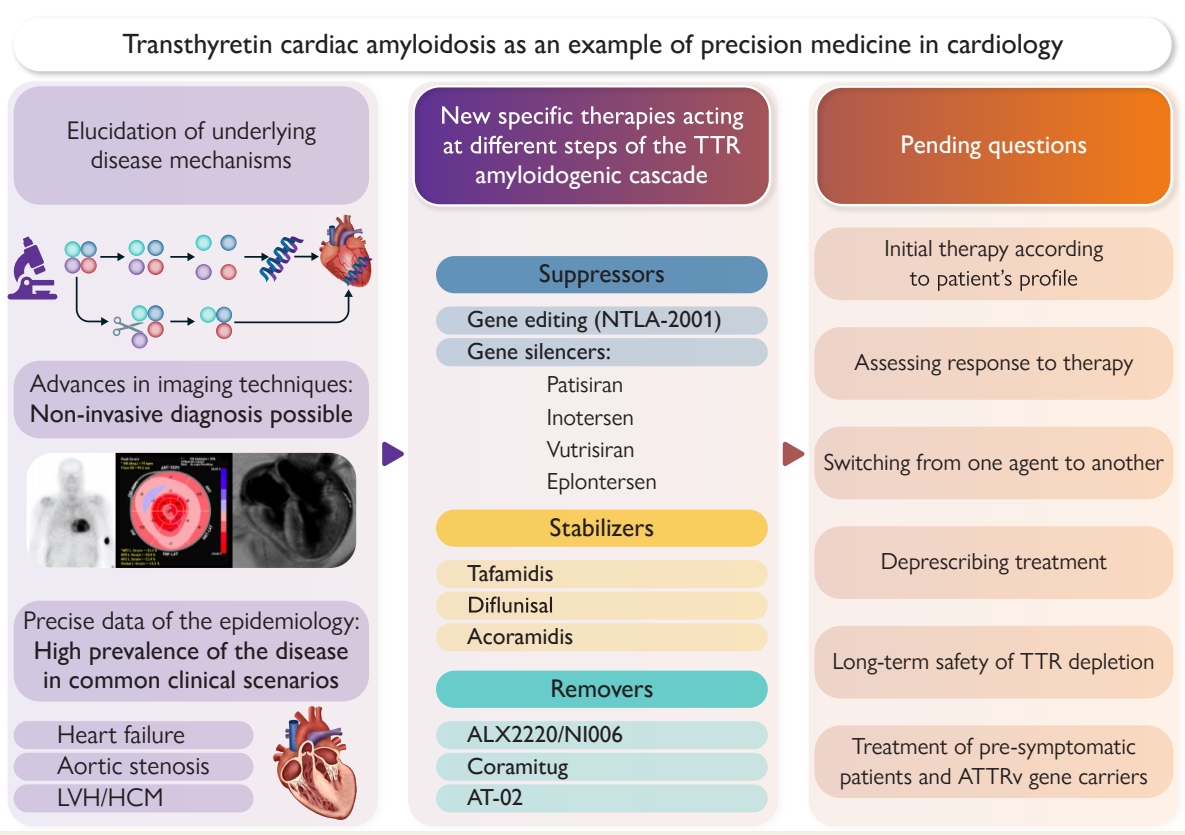
Received 25 May 2024; revised 25 July 2024; accepted 8 November 2024; online publish-ahead-of-print 10 January 2025

Graphical Abstract



Transthyretin cardiac amyloidosis (ATTR-CM) as a paradigm for advancing precision medicine: factors that have fostered the development of new specific therapies in ATTR-CM, available agents, and drugs under development along with unresolved questions in the therapeutic management of these patients.

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Abstract

Development of specific therapies addressing the underlying diseases' mechanisms constitutes the basis of precision medicine. Transthyretin cardiac amyloidosis (ATTR-CM) is an exemplar of precise therapeutic approach in the field of heart failure and cardiomyopathies. A better understanding of the underlying pathophysiology, more precise data of its epidemiology, and advances in imaging techniques that allow non-invasive diagnosis have fostered the development of new and very effective specific therapies for ATTR-CM. Therapeutic advances have revolutionized the field, transforming a rare, devastating, and untreatable disease into a more common disease with several therapeutic alternatives available. Three main types of therapies (stabilizers, suppressors, and degraders) that act at different points of the amyloidogenic cascade have been developed or are currently under investigation. In this review, the key advances in pathophysiology and epidemiology that have occurred in the last decades along with the different therapeutic alternatives available or under development for ATTR-CM are described, illustrating the role of precision medicine applied to cardiovascular disorders. Pending questions that would need to be answered in upcoming years are also reviewed.

Keywords Amyloid • Cardiac amyloidosis • Transthyretin • Heart failure

Introduction

Development of specific therapies addressing the underlying diseases' mechanisms constitutes the basis of precision medicine. Those therapeutic advances are possible due to a better characterization of diseases, a better understanding of their natural history, and underlying pathophysiology along with advances in imaging techniques and breakthroughs in gene sequencing techniques. Although other medical specialties like oncology or haematology have embraced this precision medicine approach years ago, only recently has the cardiovascular community witnessed how a personalized approach is becoming part of mainstream cardiology.[1] The field of heart failure (HF) and cardiomyopathies particularly exemplify the paradigm shift that will transform how we approach patients (and their families) in the next decades.[2]

Transthyretin cardiac amyloidosis (ATTR-CM), once considered a rare cause of restrictive cardiomyopathy, is an exemplar of this new paradigm where tailored therapies are progressively replacing the 'one-fits-all' model that has predominated clinical practice over the last 30 years. A better understanding of the underlying pathophysiology of transthyretin (TTR) amyloid formation,[3] advances in imaging techniques that facilitated a more precise epidemiology of the disease,[4–6] and the key driver of new specific and highly effective therapies[7–10] have revolutionized the field transforming what it used to be a rare disease with a devastating prognosis into a more common disease with several therapeutic alternatives (*Figure 1*). In this review, we describe the key advances in pathophysiology and epidemiology that have occurred in the last decades along with the different therapeutic alternatives available or under development for ATTR-CM to illustrate the role of precision medicine applied to cardiovascular disorders.

Pathophysiology and epidemiology

Transthyretin cardiac amyloidosis is a progressive disease caused by the extracellular deposition of TTR in the heart. Gene variants resulting in TTR instability cause hereditary ATTR (ATTRv), whereas an age-related failure of homoeostatic mechanisms among other unknown factors is responsible for the wild-type form of the disease (ATTRwt).

The formation process of amyloid fibrils (amyloidogenic cascade) is currently considered to be similar for both ATTRv and ATTRwt[11,12] (*Figure 2*). Transthyretin is a tetrameric protein mainly produced by the liver, which transports vitamin A–retinol-binding protein and thyroxin.[13] Instability of the TTR molecule and proteolytic cleavage leads to dissociation of the tetramer into dimers and monomers and subsequent monomer misfolding produce soluble misfolded aggregates and insoluble aggregates.[13] Insoluble aggregates ultimately generate amyloid fibrils and promote deposition of additional misfolded monomers fostering growth of amyloid fibrils.[14]

Transthyretin amyloidosis is a systemic disease, but cardiac involvement is responsible for most of the mortality and morbidity. Transthyretin deposition results in cardiac dysfunction and HF, recurrent hospitalizations, and ultimately death.[15,16] Given its progressive nature, ATTR-CM is characterized by worsening in quality of life and disability. Life expectancy was only of 2.5–3.5 years,[17,18] but has improved lately due to an earlier diagnosis, better management, and specific therapies.

Several studies conducted in the last decade have demonstrated the important contribution of ATTR-CM to common cardiovascular clinical scenarios such as HF with preserved ejection fraction (HFpEF), severe aortic stenosis in the elderly, or increased left ventricular (LV) wall thickness.[19–22] A recent meta-analysis grouped the screening studies performed up to January 2022 and found that ATTR-CM was present in 12% of patients with HFpEF, 10–15% of elderly patients with severe aortic stenosis undergoing valve replacement, and 7% of patients with LV wall thickness ≥15 mm.[3] Screening studies in other less explored scenarios like HF with reduced ejection fraction or cardiac conduction disorders[23,24] have also shown that ATTR-CM is not uncommon and is certainly far from being a rare disease for the practising cardiologist (*Figure 3*).

Disease-modifying therapies

Therapeutic advances in light chain amyloidosis (AL) and secondary amyloidosis over the last 20 years have shown that reducing the circulating concentration of the amyloid precursor proteins dramatically improves the prognosis of systemic amyloidosis.[25,26]

Transthyretin cardiac amyloidosis therapeutic approaches have historically followed the same premise of reducing the precursor protein. Until recently, the only therapy available (and only for some ATTRv patients) was liver transplantation. Liver transplantation allowed replacement of variant TTR by wild-type TTR but was associated with several limitations including donor shortage, surgical risks, complications derived from immunosuppression, and subsequent amyloid progression due to accumulation of wild-type TTR in the pre-existing ATTRv

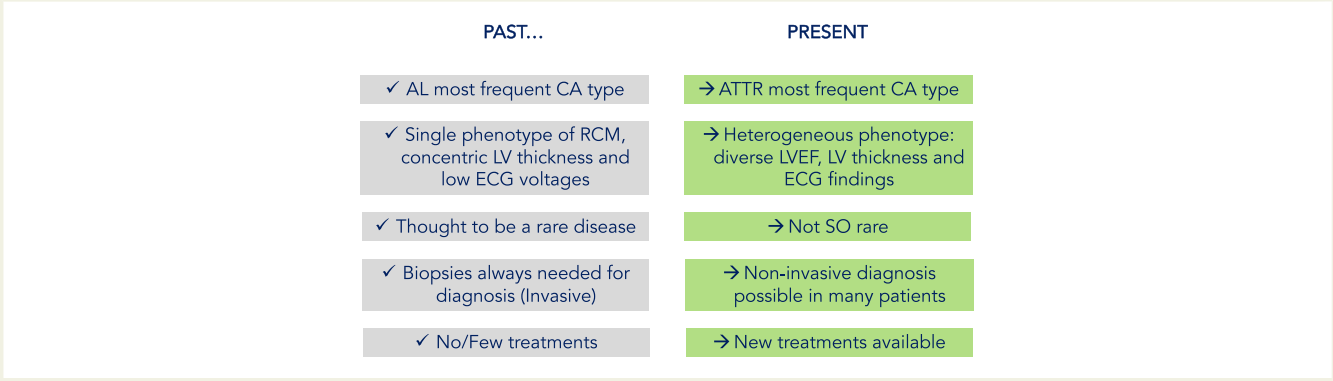

Figure 1 Advances in knowledge in transthyretin cardiac amyloidosis

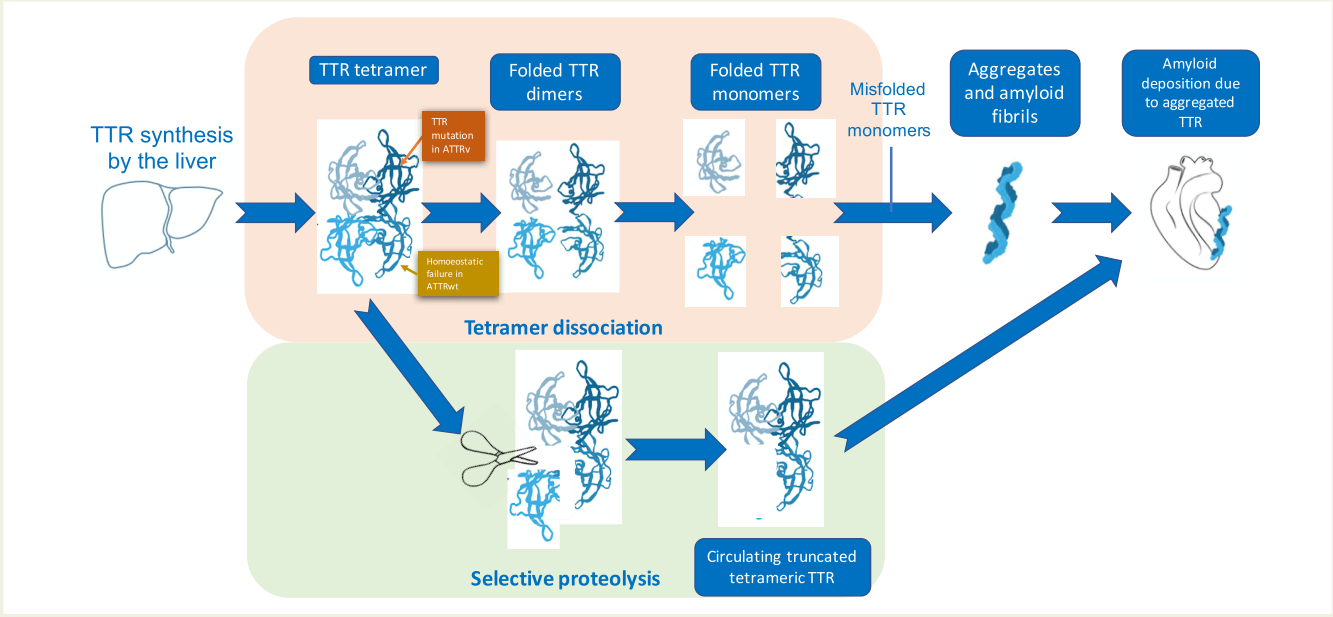

Figure 2 Transthyretin amyloidogenic cascade

deposits.[27] To overcome these limitations and based on a better understanding of the pathophysiology, new therapies acting at different points of the TTR amyloidogenic cascade have been developed or are currently under investigation.

Suppressors were designed to knockdown TTR production at the liver. Reduction of TTR production decreases circulating TTR limiting fibril formation. Stabilizers act by binding to the circulating TTR tetramers limiting their fragmentation and the formation of amyloid fibrils' precursors. Lastly, degraders are therapies designed to promote removal of amyloid fibrils (*Figure 4*). While degraders are under investigation in clinical trials, both reducers and stabilizers have already demonstrated efficacy in ATTR.

Transthyretin stabilizers

Transthyretin stabilizers prevent tetramer degradation into dimers and monomers. Three stabilizers have been studied in ATTR-CM: tafamidis, diflunisal, and acoramidis.

Tafamidis

Tafamidis stabilizes TTR by binding to the T4-binding site. Following the approval of tafamidis 20 mg for ATTRv with polyneuropathy, ATTR-ACT was the first trial assessing a specific therapy for ATTR-CM. ATTR-ACT enrolled 441 patients, randomized to 80 mg of tafamidis meglumine, 20 mg of tafamidis meglumine, or placebo in a 2:1:2 fashion and followed over 30 months. Histological diagnosis was required as well as a previous history of HF and a NTproBNP ≥600 pg/mL (*Table 1*).[7]

The trial showed a 30% relative reduction in mortality, with a number needed to treat (NNT) of 7.5 to prevent one death and a 32% relative reduction in the rate of cardiovascular (CV) hospitalization and a NNT of 4 to prevent one CV hospitalization per year.

Tafamidis-treated patients exhibited a significant reduction in the decline in the distance at the 6-min walk test (6MWT) and in quality of life assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[7]

Differences in survival emerged after 18 months of treatment, although improvements in 6MWT and KCCQ were evident at 6 months. Patients who were in NYHA III class showed an increase in the rate of

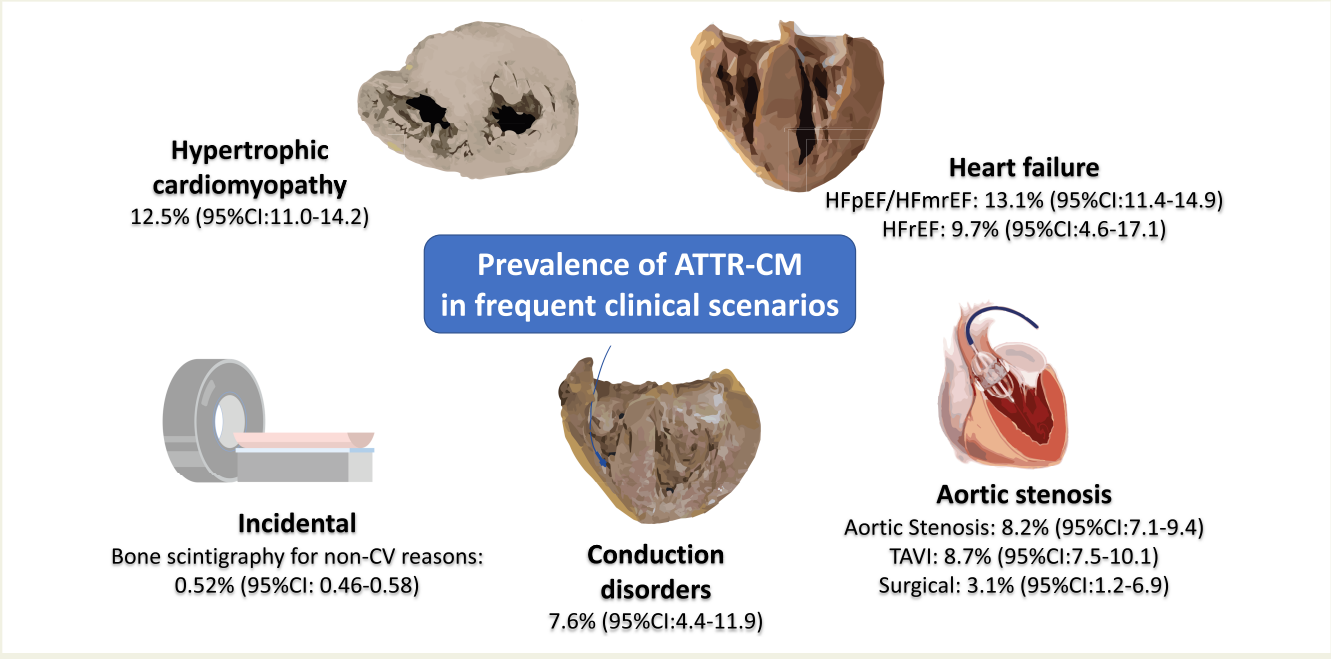

Figure 3 Epidemiology of transthyretin cardiac amyloidosis

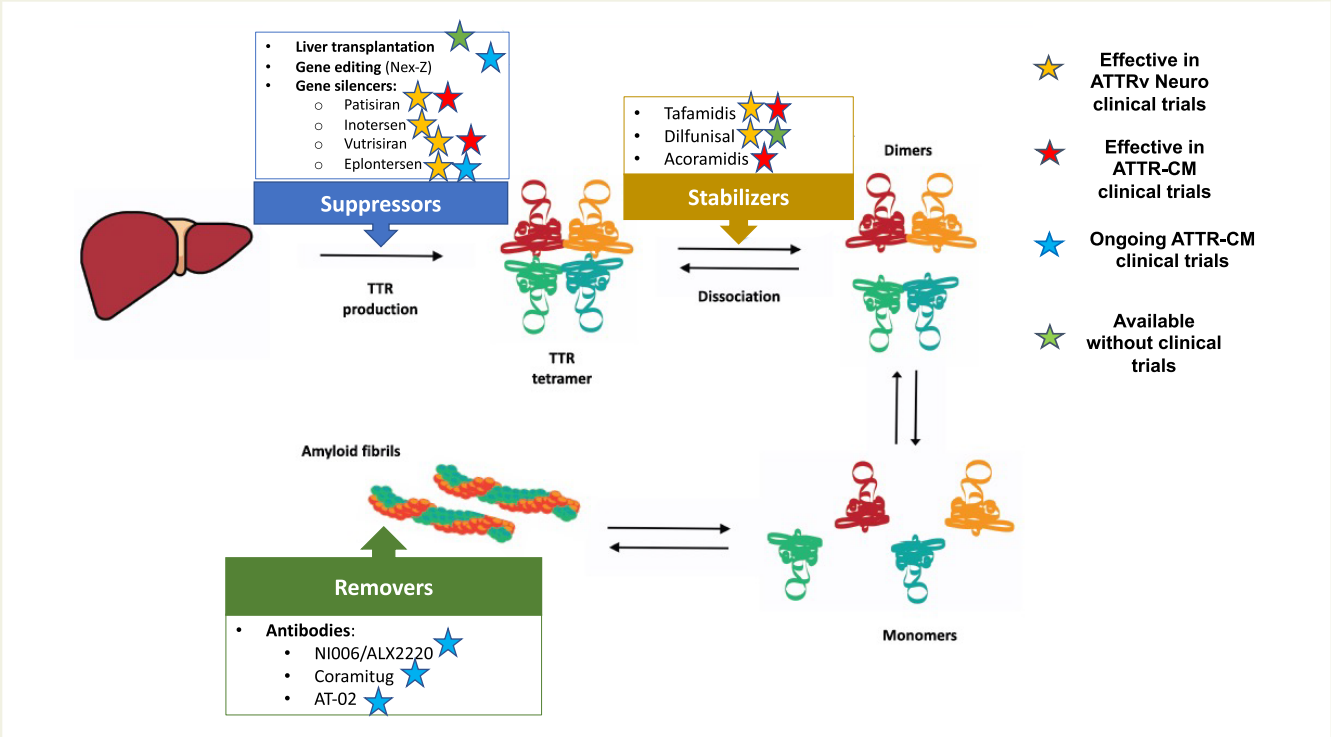

Figure 4 Transthyretin amyloidosis-specific therapies

CV hospitalizations, and the reduction in mortality in them was lower (16.3%) compared with individuals in NYHAs I and II (64.5% and 39.6%, respectively) leading to limitations of reimbursement in certain countries for patients at NYHA III and reinforcing the need of early diagnosis and prompt initiation of treatment.

ATTR-ACT was not designed to test dosage efficacy, and the primary endpoint was a pooled analysis of 80 and 20 mg, but subsequent analysis including the long-term extension (LTE) study showed that reduction in all-cause mortality was greater with 80 mg than with 20 mg, without dose-related side effects.[28] Latter development of tafamidis

61 mg free acid, bioequivalent to tafamidis meglumine 80 mg, simplified the number of pills to be taken.

Extended follow-up from the LTE study demonstrated a 41.2% relative risk reduction in mortality in patients initially treated with tafamidis 80 mg in ATTR-ACT compared to those initially treated with placebo and switched to tafamidis during LTE, highlighting the importance of early therapy.[29] Moreover, combination of ATTR-ACT with LTE data showed improved survival after 5 years among patients with NYHA III who initially received tafamidis 80 mg compared to those who initially received placebo, confirming that patients with advanced disease also benefit from tafamidis in the long term.[30] Tafamidis was also recently evaluated in patients ≥80 years who participated in ATTR-ACT. Albeit the group of patients was limited ($n = 88$), patients receiving tafamidis 80 mg during ATTR-ACT exhibited improved 6MWT distance, NTproBNP, and KCCQ than those receiving placebo.[31] Moreover, patients ≥80 years treated continuously with tafamidis trended towards longer median survival (45 vs. 27 months; $P = .15$) than those initially treated with placebo in ATTR-ACT.[31]

ATTR-ACT results lead to approval of tafamidis as the first specific ATTR-CM therapy. Tafamidis was also incorporated to the 2021 ESC HF guidelines for the treatment of ATTR-CM and NYHA class I or II to reduce symptoms, CV hospitalizations, and mortality as a class I recommendation. The 2022 ACC/AHA/HFSA guidelines also recommend tafamidis for selected patients with NYHA class III.[32]

Since approval, real-life data have demonstrated the association between tafamidis and a longer median time to HF decompensation, cardiac transplant, or death.[33]

Nonetheless, tafamidis has an unfavourable cost analysis with its high price limiting its access in many countries.[34,35]

Additional data on the role of tafamidis on biomarkers and imaging parameters are emerging. Tafamidis slows the rise in NTproBNP and troponin T levels,[36] and attenuates LV systolic and diastolic dysfunction.[37,38] Recent data also suggest that tafamidis could decrease cardiac uptake on scintigraphy in some individuals,[39] despite cardiovascular magnetic resonance (CMR) data have reported unchanged native T1 and extracellular volume (ECV) values after 1 year of treatment.[40] Finally, there are concerns about the interaction between tafamidis and statins and data are lacking in nonagenarians and in those with eGFR <25 mL/min/1.73 m^2.

Diflunisal

Diflunisal is a nonsteroidal anti-inflammatory drug that also binds to the T4-binding site preventing TTR dissociation and that is available in many countries.[41] Despite its stabilizing properties, diflunisal has potential side effects given its anti-inflammatory nature including worsening of hypertension, renal dysfunction, gastrointestinal bleeding, and HF decompensation.

Data of ATTR-CM patients treated with diflunisal come from single-centre studies and include limited number of patients.[42,43] Interestingly, several studies have shown clinical and echocardiography stability and even improved survival in ATTR-CM patients receiving diflunisal 250 mg twice daily.[42,43] Of note, discontinuation rate was high ranging from 23% to around 40% during initial years of treatment and variable rates of renal function worsening and gastrointestinal side effects have been reported.[42,43]

Diflunisal *in vitro* stabilization seems to be inferior to other stabilizers[44] but is an affordable drug that could be an option when other stabilizers are not accessible. In any case, a careful selection of patients and close monitoring of renal function are recommended.

Acoramidis

Acoramidis stabilizes TTR through hydrogen bonding as well as by binding to thyroxine-binding sites.[45,46] Acoramidis has been reported to be slightly more potent as a stabilizer than tafamidis and substantially more potent than diflunisal at a 10 μM plasma concentration.[44]

ATTRIBUTE-CM trial compared acoramidis to placebo in 632 patients with ATTR-CM (*Table 1*).[47] The study had two parts with two primary endpoints. Part A's primary endpoint, change from baseline to Month 12 in 6MWT, did not differ between groups while the primary endpoint of Part B, a hierarchical analysis of all-cause mortality, cumulative frequency of CV hospitalizations, change in NTproBNP, and change in 6MWT at 30 months, was in favour of acoramidis. Difference in all-cause mortality was not statistically significant between groups, despite an observed 25% relative reduction in all-cause mortality with acoramidis. In contrast, frequency of CV hospitalizations was significantly reduced in patients receiving acoramidis with a relative reduction approaching 50% ($P < .0001$). Other secondary endpoints like NTproBNP, KCCQ, and 6MWT were also favourable affected by acoramidis but the magnitude of the differences observed in these parameters between acoramidis and placebo was less than in ATTR-ACT, likely attributable to differences in the populations studied. Acoramidis had a side effect profile similar to placebo. Of note, patients with NYHA III receiving acoramidis did not show increased hospitalizations. Lastly, time to first event of all-cause mortality or CV hospitalization showed a relative reduction of 36% with a NNT of 7 at 30 months.[48]

Comparing stabilizers

Two stabilizers, tafamidis and acoramidis, have demonstrated benefit in randomized clinical trials. Both drugs have shown an excellent safety profile with curves of all-cause mortality diverging similarly at 18–19 months (*Table 2*).

Despite those similarities, inclusion criteria had important differences and likely account for the discrepancies found in the clinical endpoints. Patients enrolled in ATTRibute-CM had a less advanced disease with lower proportion of patients with NYHA III or ATTRv. Furthermore, NTproBNP inclusion threshold was lower, and the required 6MWT distance longer favouring inclusion of less advanced patients (*Table 2*).

ATTR-CM patients diagnosed nowadays have a better prognosis even in the absence of specific therapies due to earlier diagnosis and better overall treatment,[49] making it difficult to compare clinical trials conducted in different eras.

Although comparisons between trials are confounded by the differing populations, relative risk reduction in mortality was similar in both trials, whereas acoramidis demonstrated larger reduction in CV hospitalizations. Regarding changes in 6MWT and biomarkers, differences took longer to appear with acoramidis compared to tafamidis while differences in KCCQ appeared at similar timepoints with both drugs despite the magnitude of the benefit being larger in ATTR-ACT.

Transthyretin suppressors

Reduction of TTR levels can be achieved in ATTR-CM either by genetic silencing or through gene editing. Transthyretin gene silencers have been approved for several years for ATTRv with polyneuropathy, and data of cardiac efficacy are emerging. In contrast, gene editing has been used in a very limited number of patients and the phase 3 clinical trial has been initiated recently.

Table 1 Transthyretin cardiac amyloidosis clinical trials

	Mechanism of action	Route	Trial and *n*	Key inclusion criteria	Key exclusion criteria	Concomitant therapy	Primary endpoint	Results and status
Tafamidis	Stabilizer	Oral	ATTR-ACT Phase III (*n* = 441)	• 18–90 years • Invasive diagnosis of ATTR-CM • IVS >12 mm • History of HF: previous HF admission or volume overload requiring diuretics • NTproBNP >600 pg/mL • Distance on 6MWT >100 m	• NYHA IV • eGFR < 25 mL/min/1.73 m^2 • Liver transaminase >2 times upper limit • Severe malnutrition (mBMI <600)	• Diflunisal not permitted	Hierarchical all-cause mortality and frequency of CV-related hospitalizations	Positive Drug approved in several countries
Acoramidis	Stabilizer	Oral	ATTRibute-CM Phase III (*n* = 632)	• 18–90 years • Invasive or non-invasive diagnosis of ATTR-CM • History of HF: previous HF admission or volume overload requiring diuretics • NTproBNP >300 pg/mL • Distance on 6MWT >150 m	• Likely heart transplantation within a year • ALT/AST >2 times and bilirubin >3 times the upper limit • NTproBNP > 8500 pg/mL • eGFR <15 mL/min/1.73 m^2	• Tafamidis allowed after initial 12 months • Diflunisal not permitted	Part A: 6MWT at 12 months Part B: hierarchical combination of mortality, CV hospitalizations, NTproBNP, and 6MWT	Part A: not positive Part B: positive Drug approved by FDA and under evaluation by EMA
Diflunisal	Stabilizer	Oral	No randomized trial in TTR cardiomyopathy					Improved survival and clinical and echocardiography stability in retrospective observational single-centre studies
Patisiran	Gene silencer (siRNA, 1st generation)	IV Q3 weeks	APOLLO-B Phase III (*n* = 360)	• 18–85 years • Invasive and non-invasive diagnosis of ATTR-CM • IVS >12 mm • History of HF	• NYHA IV • NYHA III and NAC Stage 3 (NTproBNP >3000 pg/mL and eGFR <45 mL/min/1.73 m^2) • < 150 m on 6MWT • Polyneuropathy PND ≥ II	• Tafamidis allowed • Diflunisal not permitted	6MWT at 12 months 2°: KCCQ-OS at 12 months	Results positive Not approved by FDA for ATTR-CM Not evaluated by EMA

Continued

Table 1 *Continued*

	Mechanism of action	Route	Trial and *n*	Key inclusion criteria	Key exclusion criteria	Concomitant therapy	Primary endpoint	Results and status
Vutrisiran	Gene silencer (siRNA, 2nd generation)	SC Q3 months	HELIOS-B Phase III (*n* = 655)	• 18–85 years • Invasive and non-invasive diagnosis of ATTR-CM • HF: previous admission or clinical evidence of HF	• NYHA IV • NYHA III at high risk • eGFR <30 mL/min/1.73 m^2 • Polyneuropathy PND III or IV	• Tafamidis allowed • Diflunisal not permitted	Composite of all-cause mortality and recurrent CV events at 33–36 months in the overall population and in monotherapy (patients not on tafamidis at baseline)	Results positive
Eplontersen	Gene silencer (ASO, 2nd generation)	SC Q1 month	Cardio-TTRansform Phase III (*n* = 1443)	• 18–90 years • Invasive and non-invasive ATTR-CM diagnosis • IVS >12 mm • NYHAs I–III	• Liver or heart transplantation • Previous treatment with gene silencers • Current treatment with diflunisal	• Tafamidis allowed • Gene silencers not permitted.	Composite of CV mortality and recurrent CV clinical events	Recruitment completed. Results expected in mid 2026
Nexiguran ziclumeran (NTLA-2001)	Gene Silencer (CRISPR)	IV once	MAGNITUDE Phase III (*n* = 765)	• Medical history of HF • HF symptoms optimally managed and clinically stable within 28 days • NTproBNP ≥1000 or ≥2000 pg/mL in AF	• NYHA class IV • Polyneuropathy stage IV • RNA silencer within previous 12 months • Liver failure • eGFR <30 mL/min/1.73 m^2	• Stabilizers allowed • Gene silencers not permitted	Composite outcome of CV mortality and CV events	Recruiting
ALX2220 (NI006)	Recombinant human anti-TTR antibody	IV Q4 weeks	Phase I (*n* = 40)	• Confirmed diagnosis of ATTR • IVS >14 mm • LVEF >40% • NYHAs I–III • eGFR >30 mL/min/1.73 m^2 • NTproBNP 600–6000 pg/mL		• Tafamidis allowed • Diflunisal not permitted	Safety and pharmacokinetic profile Cardiac imaging parameters	Positive. Preliminary supporting efficacy data Phase II and III ongoing

Continued

Table 1 *Continued*

	Mechanism of action	Route	Trial and *n*	Key inclusion criteria	Key exclusion criteria	Concomitant therapy	Primary endpoint	Results and status
ALX2220 (NI006)	Recombinant human anti-TTR antibody	IV Q4 weeks	DepleTTR-CM Phase III ($n = 1000$)	• Confirmed diagnosis of ATTR • IVS >11 mm for women or >12 mm for men • NTproBNP > 2000 pg/mL • Loop diuretics for at least 30 days prior to screening • NYHAs II–IV • Life expectancy >6 months	• Leptomeningeal amyloidosis • PND score IV • LVEF < 30% • eGFR <20 mL/min/1.73 m^2	• Stabilizers and gene silencers permitted	Total Occurrence of all cause mortality and CV clinical events	Recruiting
Coramitug	Anti-TTR antibody	IV Q4 weeks	Phase II ($n = 99$)	• 18–85 years old • IVS >12 mm • NYHAs II and III • NTproBNP >650 or >1000 pg/mL if AF present • 150–450 m in 6MWT • eGFR >25 mL/min/1.73 m^2	• Prior organ transplant • >120 kg	• Stabilizers and gene silencers permitted	• Change in 6MWT and NTproBNP	Recruitment completed Results expected late 2025
AT-02	Pan-amyloid humanized IgG1-peptide fusion reagent	IV infusion	Phase I	Part 1: healthy volunteers Part 2: patients with systemic amyloidosis: • 18–80 years old • Confirmed AL, ATTR, or other forms of amyloidosis • AL patients should have VGPR or CR within 12 months Part 3: patients with systemic amyloidosis: same criteria as Part 2 plus imaging evidence of organ amyloid deposits		• Stabilizers and gene silencers permitted • Maintenance with daratumumab permitted in AL	• Safety, tolerability and pharmacokinetics of rising doses of AT-02	Recruiting

ATTRwt, wild-type transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; IVS, interventricular septum; HF, heart failure; 6MWT, 6-min walk test; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; mBMI, modified body mass index; CV, cardiovascular; AL, light chain amyloidosis; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TTR, transthyretin; ATTR-CM, transthyretin cardiac amyloidosis; KCCQ-OS, Kansas City Questionnaire–Overall Summary; IV, intravenous; RNA, ribonucleic acid; LVEF, left ventricular ejection fraction.

Table 2 Comparison between clinical trials with tafamidis and acoramidis

	ATTR-ACT	ATTRibute-CM
Compound	Tafamidis	Acoramidis
Mechanism of action	Binds to the T4-binding site	Promotes hydrogen bonding between the hydroxyl groups of adjacent S117 residues and binds to the T4-binding site
Inclusion criteria	• Invasive diagnosis • NTproBNP >600 pg/mL • eGFR >30 mL/min/1.73 m^2 • 6MWT >100 m	• Invasive and non-invasive diagnosis • NTproBNP >300 and <8500 pg/mL • eGFR >15 mL/min/1.73 m^2 • 6MWT >150 m • Tafamidis permitted after the initial 12 months
Number of participants	$n = 441$	$n = 632$
Primary endpoint	Hierarchical all-cause mortality and frequency of CV-related hospitalizations	Hierarchical death from any cause, CV-related hospitalization, change in NTproBNP, and in 6MWT
Secondary endpoint	• Change from baseline to Month 30 on the 6MWT • Change from baseline to Month 30 on KCCQ	• Death from any cause • Distance on 6MWT • KCCQ score • Serum TTR level
Duration (months)	30	30
Age, years	74 ± 7	77 ± 7
Gender (% males)	90.2	90.2
Race (% Black)	14.3	4.7
TTR genotype		
ATTRwt	76%	90.3%
ATTRv	24%	9.7%
NYHA class		
NYHA I	8.3%	10.8%
NYHA II	59.6%	72%
NYHA III	31.9%	17.2%
NTproBNP (ng/L)	3161 (1864.4–4825)	2326 (1278–3910)

TTR, transthyretin; eGFR, estimated glomerular filtration rate; 6MWT; 6-min walking test; ATTRwt, wild-type transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; NYHA, New York Heart Association; CV, cardiovascular; KCCQ-OS, Kansas City Questionnaire–Overall Summary.

Transthyretin silencers

Transthyretin silencers have been developed to reduce TTR production independently of the wild type or variant nature of TTR. Two different types of drugs have been studied:

- Small interfering RNAs (siRNAs) are double-stranded oligonucleotides containing sense and antisense strands. Within the cytoplasm, siRNA promotes a complex that binds to the target messenger RNA (mRNA) to form a RNA-induced silencing complex with subsequent degradation of the mRNA.[50]
- Antisense oligonucleotides (ASOs) are single-stranded molecules that act mainly at the nucleus, binding to the target mRNA and promoting its degradation.[50]

Both approaches have demonstrated to knockdown serum TTR levels. In both cases, daily vitamin A supplements are required.

First-generation transthyretin gene silencers

Patisiran

Patisiran, a siRNA formulated as a lipid nanoparticle, was approved in 2018 for ATTRv with polyneuropathy following APOLLO-A trial, which showed that patisiran halted or even reversed the progression of neuropathy at 18 months.[51]

Patients on patisiran receive intravenous infusions every 3 weeks and must be premedicated to mitigate infusion reactions mediated by the lipid nanoparticle delivery system.

Around half of the patients participating in APOLLO-A were considered to have cardiac involvement based on the presence of LV wall thickness ≥13 mm in the absence of hypertension and aortic stenosis. In this group of patients, patisiran showed LV wall thickness reduction, improvement in longitudinal global strain (LGS), and reduction of NTproBNP.[52]

APOLLO-B was a phase III, placebo-controlled trial in which 360 patients with wild-type and hereditary ATTR-CM were randomized 1:1 to patisiran or placebo during 12 months (*Table 1*).[9]

The study met its primary endpoints, demonstrating a lower decline in the 6MWT and an increase in KCCQ score at 12 months with patisiran.

Although differences in 6MWT and KCCQ were statistically significant, U.S. Food and Drug Administration (FDA) did not approve patisiran for ATTR-CM because of concerns regarding the clinical meaningfulness of the effect based on the differences found in endpoints: a median difference of 14.69 m in 6MWT and 3.7 points in KCCQ, below the minimal clinically significant difference of 30 m and 5 points.

While APOLLO-B did not demonstrate significant benefits for the secondary endpoint of a composite of death from any cause, CV events, and change in the 6MWT over 12 months, it provided evidence over the short term for a beneficial effect of gene silencing in ATTR-CM. Moreover, recent data have shown a sustained clinical benefit of patisiran in the open-label extension of the trial at 24 months, demonstrating that what patients lose in terms of function and quality of life is not regained.[53] Given that the trial was only 12 months, larger differences may be expected over time in clinical outcomes.

Inotersen

Inotersen is a first-generation ASO, administered subcutaneously every week. Inotersen was approved for ATTRv with polyneuropathy following the positive results from NEURO-TTR.[54] Approval was accompanied by the requirement of regular and frequent platelet and renal function monitoring to control severe thrombocytopenia and glomerulonephritis observed in the trial. These adverse events and the need of frequent monitoring counterbalanced in most patients the advantages of subcutaneous administration.

From a cardiac perspective, no significant differences by LGS or other echocardiographic variables were observed between patients treated with inotersen and those receiving placebo in patients with cardiomyopathy (same definition than in APOLLO-A). A small cohort of 33 patients with ATTR-CM either ATTRv or ATTRwt were treated with inotersen in a single-centre, open-label protocol.[55] Although follow-up was limited, preliminary findings of those patients who reached the 2- and 3-year time points included improvements in LV mass at CMR and in 6MWT.[55] With the advent of the second-generation genetic silencers, it is most likely that inotersen will become obsolete and its production will be halted as has already occurred in the USA.

Second-generation transthyretin genetic silencers

A second generation of subcutaneous TTR genetic silencers has been developed, showing increased stability, higher liver distribution, and less non-hepatocyte exposure. Moreover, the mean knockdown of serum TTR achieved is superior to the first generation of genetic silencers.

Vutrisiran

Vutrisiran is a siRNA conjugated to *N*-acetyl galactosamine (GalNAc) conferring high affinity to hepatocytes. Advantages over patisiran include the subcutaneous quarterly administration and that it does not require any premedication as it is not included in a lipid nanoparticle.

Compared to revusiran, a first-generation siRNA conjugated to GalNAc, whose phase III trial in ATTR-CM, ENDEAVOUR, was stopped prematurely due to an increase in mortality,[56] vutrisiran contains smaller dose and has longer dosing intervals.

Vutrisiran was approved in ATTRv with polyneuropathy following the results from HELIOS-A.[57] Exploratory prespecified cardiac endpoints showed significant decreased NTproBNP levels and improvements in some echocardiographic parameters at 18 months both in the overall cohort and in the cardiac subpopulation (defined in the same way as in APOLLO-A trial), compared with the external placebo group from APOLLO-A.[58] It is worth mentioning that this definition probably does not capture all patients with cardiac amyloidosis[59] and could have limited the results as some patients who did not qualify for the predefined subpopulation probably exhibited ATTR-CM.[58]

Interestingly, improvement in normalized LV total uptake and heart-to-contralateral lung ratio were observed in approximately two-thirds of patients who underwent serial scintigraphy at baseline and at 18 months. Furthermore, Perugini grade was reduced or unchanged compared with baseline in 55/57 (96.5%) evaluable patients.[58]

HELIOS-B, a phase III, randomized, double-blind, placebo-controlled multicentre study, has evaluated the efficacy and safety of vutrisiran in ATTR-CM. HELIOS-B enrolled 655 ATTR-CM patients with NYHAs I–III, with 40% of participants on tafamidis at baseline (*Table 1*).[60] The primary composite endpoint was a composite of all-cause mortality and recurrent CV events at 33–36 months in the overall population and in the monotherapy one (patients not taking tafamidis at baseline). Enrolled patients in HELIOS-B represent a contemporary cohort of patients with ATTR-CM, similar to ATTRIBUTE-CM, with male predominance (92.5%), median age of 76.5 years, and two-thirds of them in NYHA II (77.6%). Vutrisiran met its primary endpoint compared to placebo in both the overall population [HR 0.72; 95% confidence interval (CI): 0.56–0.93; $P = .01$] and the population of patients without concomitant tafamidis (HR 0.67; 95% CI: 0.49–0.93; $P = .02$). Additionally, vutrisiran was associated with a lower decline in the distance on 6MWT and KCCQ-OS at 30 months with a good safety and tolerability profile.[60]

Eplontersen

Eplontersen is a novel GalNAc-conjugated ASO, with the same base sequence as inotersen but with enhanced liver uptake. It is administered subcutaneously every 4 weeks. Eplontersen has demonstrated favourable outcomes in ATTRv with polyneuropathy in NEURO-TTRansform.[61] In the cardiomyopathy subgroup, defined by previous diagnosis or interventricular septum ≥13 mm in the absence of hypertension, eplontersen was associated with improvement in LV ejection fraction and stroke volume from baseline to Week 65 while other echocardiographic parameters remained stable compared with historical placebo group from NEURO-TTR despite notable differences at baseline parameters between both groups.[62]

Efficacy of eplontersen for ATTR-CM is currently being studied in the CARDIO-TTRansform trial that has enrolled 1443 patients with NYHAs I–III (*Table 1*). CARDIO-TTRansform is the largest trial conducted in ATTR-CM, with results expected by mid 2026. Its primary composite endpoint includes CV mortality and recurrent CV events up to Week 140. Additionally, it includes CMR and scintigraphy substudies to assess the effect of eplontersen on amyloid burden.

Transthyretin gene editing

Transthyretin amyloidosis is one of the first human diseases where clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 technology has been applied.

Nexiguran ziclumeran

Nexiguran ziclumeran (Nex-Z), formerly NTLA-2001, is a CRISPR-Cas9-based gene therapy designed to treat ATTR by displaying liver-directed lipid nanoparticles that contain *Streptococcus pyogenes* Cas9 mRNA and a TTR-specific sgRNA. The Cas9 mRNA is translated in the hepatocyte's cytoplasm, and the formed Cas9 endonuclease interacts with the TTR-specific sgRNA to form the Cas9-sgRNA ribonucleoprotein. This complex enters the nucleus, where it unwinds DNA and binds to DNA at the *TTR* gene to induce targeted DNA cleavage. Then, endogenous DNA repair introduces indel mutations in the *TTR* gene that ultimately prevent TTR synthesis.

Initial data have shown profound and long-lasting TTR knockdown, supporting its potential as a single-administration therapeutic option, avoiding serial infusions or injections. Phase I open-label trial was a single-ascending dose study conducted initially in ATTRv with polyneuropathy and then expanded to ATTR-CM. Part 1 was successful, with no major side effects and a TTR knockdown of up to 90% by Day 28, which was maintained up to 4–6 months.[8] Recently, additional data at 1 and 2 years showed maintenance of similarly reduced TTR levels and good safety profile.[63] Part 2 of the phase I trial is an ongoing open-label, dose expansion study to assess the effect on cardiac and neurological measures and will provide additional safety data.

MAGNITUDE, a phase III clinical trial, is currently recruiting ATTR-CM patients (*Table 1*). A total of 765 subjects will be randomized 2:1 to receive nexiguran ziclumeran or placebo with concomitant treatment with stabilizers being allowed whereas not with genetic silencers. The primary endpoint is a composite of CV mortality and CV events and the duration of the trial depends on event rates.

Removers

It was considered that amyloid fibrils were insoluble, with amyloid deposits evoking very little endogenous tissue reaction and being resistant to enzymatic degradation.

Although natural amyloid clearance was thought to occur in other cardiac amyloidosis, the process had not been documented in ATTR-CM until recently. Initial case reports with CMR followed by some scintigraphy studies of patients treated with both stabilizers and genetic silencers revitalized the concept that removing TTR amyloid was possible.[64] Three patients with spontaneous clearance of amyloid cardiac deposits who exhibited anti-amyloid antibodies provided further support to the possibility of enhancing amyloid removal.[65]

ALX2220

ALX2220, formerly NI006, is a recombinant human antibody that binds to a cryptic epitope that is exposed in misfolded TTR oligomers and aggregated TTR fibrils.[66]

In preclinical studies, ALX2220 has shown high affinity binding to ATTR fibrils facilitating their elimination via activation of phagocytic cells.[66]

Phase I clinical trial recruited 40 patients, predominantly ATTRwt (83%), with those receiving ALX2220, apparently, at a more advanced stage.[10] No serious adverse events were reported while mild or moderate side effects observed included cytokine release syndrome, non-severe thrombocytopenia, and musculoskeletal symptoms, which have been presumed to be associated with the activation of phagocytic immune cells aimed at musculoskeletal TTR deposits.[10]

The phase I trial also provided promising results in terms of efficacy. Cardiovascular magnetic resonance and scintigraphy data indicated a dose-related reduction of ECV and tracer uptake with the highest doses.[10] NTproBNP levels also showed a dose-related decrease with a median reduction of around 58% at 12 months in patients receiving the higher doses.[10]

After these promising findings, a phase 3 trial, DepleTTR-CM has been initiated. DepleTTR-CM plans to recruit 1000 patients with ATTR-CM and NYHAs II–IV who will be randomized in a 2:1 fashion to monthly intravenous infusions of ALX2220 or placebo for 24 to 48 months. The primary endpoint is a composite of events of all-cause mortality and CV events (*Table 1*).

Coramitug

Coramitug, formerly NNC6019-0001 and previously PRX004, is a humanized monoclonal antibody that targets an epitope of TTR that is exposed on monomeric, misfolded, and aggregated forms of TTR but hidden in native circulating tetramers.

By specific binding, coramitug clears TTR amyloid deposits through antibody-mediated phagocytosis and, in addition, it may prevent new amyloid fibril formation.

A phase I clinical trial showed that coramitug was safe and generally well tolerated in 21 patients with ATTRv. Moreover, a possible cardiac benefit was observed through LGS improvement in 7 patients.[67]

A phase II trial assessing its potential in ATTR-CM has recruited 99 patients who have been randomized to receive coramitug at doses of 10 and 60 mg/kg, or placebo. Patients receive monthly infusions for 12 months, and the primary outcomes are the change in 6MWT and NTproBNP (*Table 1*). Results are expected in late 2025.

AT-02

AT-02 is a humanized IgG1-peptide fusion reagent where the pan-amyloid reactive peptide p5R is fused to the C-terminal of the light chain. It binds to all types of amyloid deposits as peptide p5R binds the ubiquitous hypersulfated glycosaminoglycans and fibrils via electrostatic interactions. The same peptide technology with the AT-01 imaging agent (^{24}I-evuzamitide) has shown uptake in key organs in multiple amyloid types in phase 1 and 2 clinical trials.[68,69] Through the addition of the humanized IgG antibody, AT-02 promotes macrophage-mediated amyloid clearance and enhances amyloid phagocytosis.[70] Following successful animal data, phase I and II trials are currently recruiting healthy volunteers and patients with systemic amyloidosis including ATTR-CM.

Pending questions

As the new disease-modifying drugs approach clinical use, several questions arise (*Figure 5*).

Assessing response to therapy

Monitoring response is a clear unmet need in ATTR-CM. In the absence of longitudinal data, monitoring and progression criteria for ATTR-CM were proposed in 2021.[71] A set of 11 measurable features across 3 domains were considered: (i) clinical and functional endpoints, (ii) biomarkers and laboratory markers, and (iii) imaging and electrocardiographic parameters.[71] Progression in one marker from each domain is required to consider disease progression. Although several recent studies have applied these criteria to study disease progression on patients treated with tafamidis,[72,73] it is unknown whether these criteria could be used to assess response or failure to disease-modifying drugs.

A recent multicentre study has proposed and validated the increase at 1 year of NTproBNP (increase >700 ng/L and >30%) and outpatient

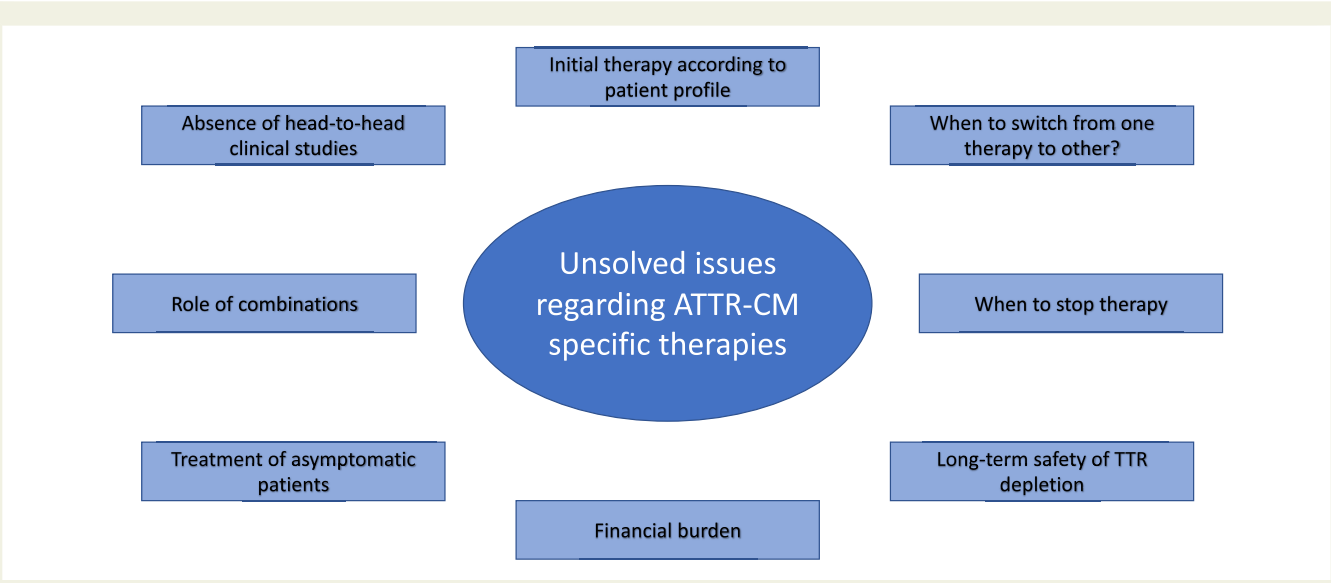

Figure 5 Unresolved questions regarding transthyretin cardiac amyloidosis-specific therapies

Table 3 Combination therapies in transthyretin cardiac amyloidosis clinical trials

Study	Number of participants	Combination therapy allowed	Participants with concomitant tafamidis	Participants with multiple specific therapies
ATTRIBUTE-CM	632 (611 primary analysis)	Acoramidis + tafamidis	107 (17.5%)	61 (14.9%)
APOLLO-B	360 (359 efficacy and safety analyses)	Patisiran + tafamidis	99 (27.6%)	51 (14.2%)
HELIOS-B	655	Vutrisiran + tafamidis	345 (52.7%)	174 (26.6%)
Cardio-TTRansform	1443	Eplontersen + tafamidis	No limit	Unknown

diuretic intensification as markers of disease progression.[74] Moreover, an absolute (>35 m) and relative (>5%) reduction of distance at 6MWT at 1 year predicted mortality in a single-centre study of 1118 patients.[75] Also, echocardiographic worsening of mitral and tricuspid regurgitation and stroke volume have been described to be associated with worse prognosis.[76] No study has examined these markers according to any treatment yet, and it is unknown if these parameters could be used to guide management and switch from one specific treatment to another.

Lastly, although there are not solid data with scintigraphy and CMR to asses progression in ATTR-CM, the relevance of both techniques has increased lately in other types of amyloidosis and in recent ATTR-CM trials to assess response to new therapies.[10,58] Accordingly, these techniques could have an important role in the future to determine treatment response.

Combined treatment

Combination of multiple specific therapies might enhance therapeutic efficacy, through targeting the amyloidogenic cascade at several points. Simultaneous targeting of TTR production and stabilization may have a synergistic effect as TTR knockdown is not complete and remaining circulating TTR can misfold and promote fibril formation. Although mean reduction of TTR levels achieved with second-generation silencers and gene editing is around 80%–90%, this value could be lower in certain patients. Moreover, it is unknown if there is an optimal knockdown (or stabilization) value beyond which fibril formation is halted. Therefore, it is unknown if the possible synergistic effect of combining treatments would translate into improved clinical outcomes. This question would be partially answered by analysing gene silencing clinical trials that have allowed background standard treatment including tafamidis. Unfortunately, the number of patients on tafamidis and the duration of therapy are highly heterogeneous across studies complicating meaningful conclusions (*Table 3*).

So far, the most solid data available about combined treatment arises from subgroup analysis of APOLLO-B where patisiran was not superior to placebo on 6MWT and KCCQ among the 90 participants who received tafamidis at baseline.[77] In ATTRIBUTE-CM, tafamidis was allowed after the initial 12 months and while 14.9% initiated tafamidis in the acoramidis group during the study, data point towards absence of benefit on combining both stabilizers.[47] In HELIOS-B, 40% of participants had tafamidis at baseline and 22% of those receiving vutrisiran in monotherapy started tafamidis during follow-up.[60] The trial was not powered to show differences according to baseline tafamidis

use, and patients were not randomly assigned to the stabilizer, therefore not allowing for a valid comparison of vutrisiran with tafamidis or of combination therapy with monotherapy.[60]

The trial that seems most prepared to address this question is Cardio-TTRansform that has enrolled enough participants to undertake subgroup analysis. Nevertheless, even if combination therapy has a role in the treatment of ATTR-CM, costs might turn combination treatment prohibitory and inaccessible for most patients.

Long-term safety of transthyretin depletion

Within an experience of 6–8 years now with first-generation gene silencers, short to medium term of TTR knockdown appears safe.[51,54] Long-term safety remains unknown though, and concerns increase with the irreversibility of gene editing.

From a physiological point of view, it seems there are other transporters that compensate TTR function as a carrier of vitamin A and thyroxine. Transthyretin knockdown does not appear to affect thyroid function, and vitamin A supplementation prevents ocular manifestations.

Nevertheless, it has been speculated that TTR might have a protective role at the central nervous system. Transthyretin knockdown in mice resulted in memory impairment compared to age-matched mice and absence of TTR in rats accelerated aging cognitive decline.[78,79] In patients with cerebral infarction, serum TTR levels were an independent predictor of good clinical outcomes.[80] Additionally, TTR seems to modulate food intake and body weight in animal models and retinol binding protein 4 is linked to insulin resistance, diabetes, and metabolic syndrome.[81,82] Therefore, long-term safety of TTR depletion is still uncertain and long-term studies are needed.

Central nervous system and ocular involvement

As prognosis of ATTRv patients improves, amyloid deposits at central nervous system and intraocular may become more common due to choroid plexus and retinal TTR production, setting a new challenge for management. Among the approved drugs for ATTRv, tafamidis is the only that has demonstrated to cross the blood–brain barrier despite showing low concentrations in cerebrospinal fluid.[83]

Specific treatment in presymptomatic patients

Advances in non-invasive diagnosis, the spread of knowledge about ATTR-CM, and a closer follow-up of ATTRv patients with polyneuropathy and asymptomatic genetic carriers have translated into the diagnosis of patients who do not exhibit HF at time of ATTR-CM diagnosis. This new population of patients is less prone to have events during follow-up, and new studies could struggle to show differences in clinical outcomes.

Clinical trials have focused on patients with overt HF with the current paradox of patients without HF, where the disease is less advanced and who likely benefit the most from treatments that halt disease progression, being deprived from treatment.

In this regard, a small multicentre study showed that ATTR-CM patients without HF who received tafamidis or diflunisal exhibited lower progression to HF and had improved survival than those who did not receive a stabilizer.[84] Although these data come from a small retrospective study, they provide support to consider early initiation of stabilizers in asymptomatic ATTR-CM patients.

Another group of patients that might benefit from preventive treatment is asymptomatic ATTRv variant carriers without signs of the disease. A placebo-controlled trial with acoramidis (ACT-EARLY) is currently being conducted in this population and will enrol 582 healthy TTR variant carriers (NCT06563895).[85]

Conclusions

ATTR-CM constitutes an example of precision medicine applied to cardiology. A better understanding of the pathophysiology of ATTR has boosted the development of several therapeutic options that leverage different mechanism of action. The future looks bright for ATTR-CM as several therapeutic alternatives are turning an untreatable disease into a treatable and potentially reversible one.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

E.G.-L. reports speaking fees from Pfizer, Eidos, and Alnylam; consulting fees from Pfizer, Akcea, Novo Nordisk, Alnylam, AstraZeneca, and Proclara. M.S.M. reports grants from Alnylam, BridgeBio, Attralus, Intellia, and Ionis and personal fees from Alnylam, Novo Nordisk, Astra Zeneca, Ionis, and Intellia. P.G.-P. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio, Intellia, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer and consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, ATTRalus, Bayer, BridgeBio, Intellia, Ionis Pharmaceuticals, Pfizer, Neuroimmune, and Novo Nordisk. E.G.-L. and P.G.-P. report research/educational support to their institution from Pfizer, BridgeBio, Novo Nordisk, AstraZeneca, Intellia, and Alnylam Pharmaceuticals.

Data Availability

No data were generated or analysed for this manuscript.

Funding

E.G.-L. and P.G.-P. are supported by Instituto de Salud Carlos III through the projects 'PI18/0765, PI20/01379 & PI24/02093' (co-funded by European Regional Development Fund/European Social Fund 'A way to make Europe'/'Investing in your future'). CNIC is supported by the ISCIII, MCIN, the PROCNIC Foundation, and the Severo Ochoa grant (CEX2020-001041-S). M.S.M. reports grant support from NIH R01HL139671 and AG081582

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