

Non-amyloid specific treatment for transthyretin cardiac amyloidosis: a clinical consensus statement of the ESC Heart Failure Association

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Abstract

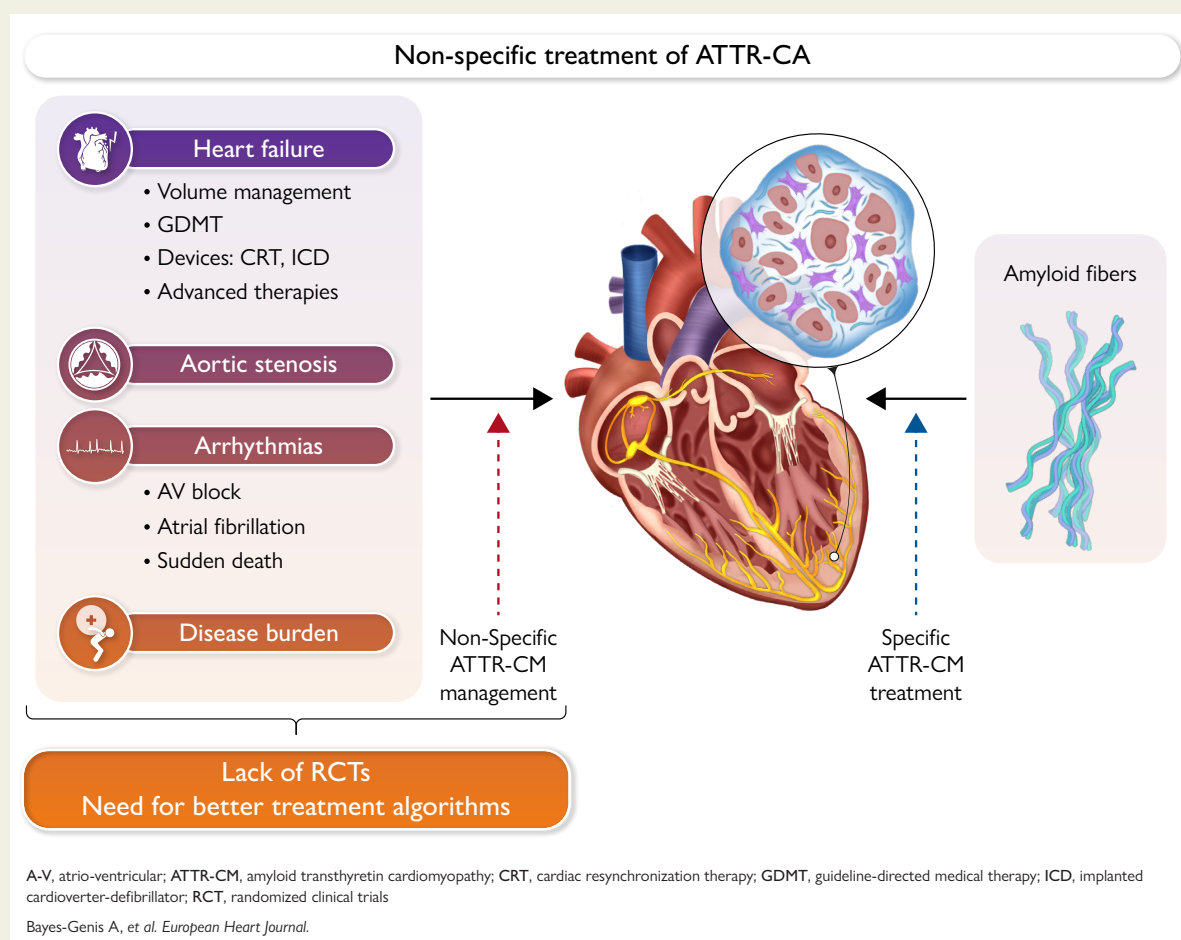
This clinical consensus statement, developed by the Heart Failure Association of the European Society of Cardiology, offers a detailed review of the non-specific management of transthyretin amyloid cardiomyopathy (ATTR-CM). This progressive and often fatal condition is increasingly recognized as a major contributor to heart failure. This document provides advice on symptom management and enhancing quality of life, with a focus on volume management, neurohormonal modulation, and tailored use of diuretics and other supportive therapies that address the distinct pathophysiology of ATTR-CM. It also explores advanced treatment modalities such as heart transplantation and mechanical circulatory support, which play crucial roles in managing advanced stages of the disease. Furthermore, it addresses the management of aortic stenosis in the context of ATTR-CM, advising transcatheter aortic valve replacement as the preferred treatment for these patients. The advice provided in this document relies primarily on expert opinion and retrospective studies due to a notable lack of randomized clinical trials, which underscores a critical research gap and the pressing need for evidence-based treatment protocols.

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Graphical Abstract



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Keywords

Cardiac amyloidosis • Treatment • Heart failure • Arrhythmias

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and often fatal disease that is increasingly recognized as a frequent cause of progressive heart failure (HF).¹ Treatment for ATTR-CM includes both disease specific and non-specific therapies.^{1–3} Disease specific treatments aim to stop or delay amyloid deposition, improving the disease natural course (i.e. 'disease-modifying therapies').³ In contrast, non-specific treatment (supportive) therapies do not target the amyloidogenic process directly but are used to manage cardiac manifestations and symptoms induced (or worsened) by amyloid infiltration.

Earlier identification of individuals with ATTR-CM, along with improvements in prognosis derived from disease specific therapies, have transformed the disease from one with a devastating prognosis into a condition that is not only more commonly diagnosed, but also has a much longer survival.⁴ As the number of patients increases and survival improves, there is growing interest in managing complications and enhancing the quality of life of these patients.

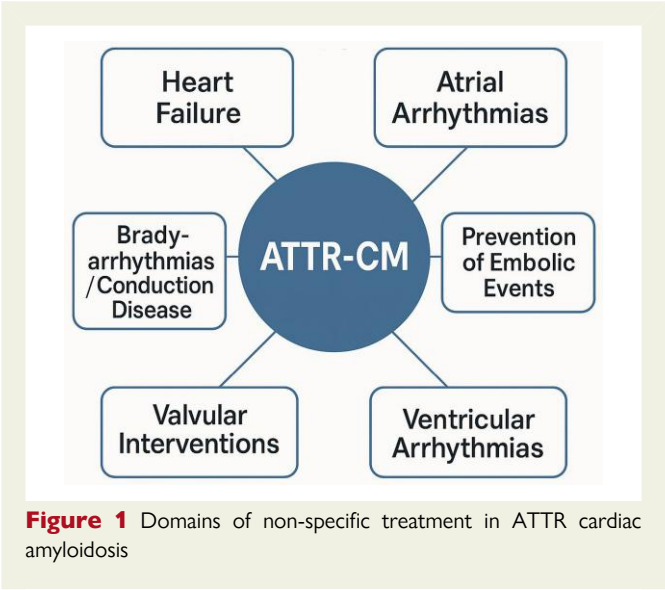
TTR amyloid infiltration affects all components of the heart, leading to a range of clinical manifestations and complications, from arrhythmias to HF and valvular disease.^{1,5} Consequently, supportive care for patients with

ATTR-CM involves addressing multiple areas, including the treatment of HF, management of atrial and ventricular arrhythmias (VAs), correction of conduction disturbances, prevention of thromboembolism, and management of aortic stenosis (AS; *Figure 1*).

Although the most appropriate treatments for cardiac complications associated with ATTR-CM have not been addressed in clinical trials, multiple retrospective studies have focused recently on these complications, aiming to shed light on this previously overlooked area. As a result, emerging evidence is now guiding important therapeutic decisions, despite the lack of formal randomized clinical trials.

The absence of randomized trials represents a significant challenge in formulating guideline-level recommendations. This clinical consensus statement seeks to review the available data and summarize expert opinions to inform best medical practices (*Figure 2*). It also aims to pinpoint knowledge gaps, discuss controversial issues, and offer advice for common scenarios encountered in clinical practice.

This consensus statement was developed under the auspices of the Heart Failure Association (HFA). The group comprises experts in both HF and cardiac amyloidosis. An initial online meeting was convened to establish the structure and objectives of the document. The first draft was prepared by P.G.-P., E.G.-L., and A.B.-G. and subsequently circulated among



STRENGTH OF ADVICE		Symbol
Clinical advice, based on robust published evidence		
Clinical advice, based on consensus of the writing group		
May be appropriate, based on published evidence		
May be appropriate, based on consensus of the writing group		
Areas of uncertainty		
STRENGTH OF EVIDENCE		Abbreviation
Randomized controlled trials		RCT
Meta-analysis		META
Observational studies		OBS
Expert opinion		OPN

Figure 2 Advice structure

all co-authors. Through multiple rounds of collaborative review and revision, full agreement was reached on all recommendations and tables.

Heart failure

HF is the primary manifestation in patients with ATTR-CM, present in most cases at the time of diagnosis. ATTR-CM is thought to account for 10%–15% of hospitalized elderly patients with HF and preserved ejection fraction (HFpEF) when increased LV wall thickness is observed,

with a prevalence of 6%–7% reported in community-dwelling patients.^{6–8} While the prevalence of ATTR-CM in patients with HF with reduced ejection fraction (HFrEF) is less studied, ATTR-CM patients can exhibit varying degrees of systolic dysfunction, and many present with impaired left ventricular ejection fraction (LVEF) at diagnosis.^{9–11} HFrEF appears to be more common in patients with ATTRv from the Val122Ile variant.¹² HF management in patients with ATTR-CM has specific nuances that differ from treatments for other forms of cardiac disease. As such, physicians caring for patients with ATTR-CM should be aware of special considerations related to HF therapies, including volume management, the use of drugs with survival benefit in HF, and specific therapies for end-stage HF.

Volume management

Patients with ATTR-CM frequently present with congestion and overt signs and symptoms of fluid overload. The accompanied elevated filling pressures are the consequence of severe diastolic dysfunction due to the restrictive physiology which in turn activate the neurohumoral system.¹³ The resulting sodium and water retention leads to an increased plasma volume. Furthermore, the activation of the sympathetic nervous system causes vasoconstriction, thereby reducing splanchnic capacitance and increasing circulatory volume.

The use of loop diuretics constitutes the cornerstone of diuretic therapy and is effective in lowering filling pressures in patients with ATTR-CM. Studies on how diuretics should be used in patients with amyloid cardiomyopathy are lacking. From a pathophysiological standpoint, patients with restrictive physiology depend on maintaining an adequate preload to maintain stroke volume and are potentially at risk for hypoperfusion, hypotension and acute renal dysfunction. This is particularly important in patients with hereditary ATTR-CM (ATTRv) where concomitant presence of dysautonomia is frequent.¹⁴ On the other hand, large observational studies in patients admitted with acute HF found that patients with HFpEF showed similar efficacy of decongestion therapy when compared with HFrEF.¹⁵ Furthermore, a recent study showed that an aggressive natriuresis-guided decongestion strategy was effective in both HFrEF and HFpEF patients.¹⁶ Considering these observations and the underlying pathophysiology, decongestion therapy as recommended by the European Society of Cardiology (ESC) guidelines on HF can be applied to patients with amyloidosis, however with the critical note of the potential elevated risk of organ hypoperfusion.¹⁷ The combination of restrictive physiology and lower preload reserve should be taken into account by the clinician when finely tuning diuretic administration and changes in systemic congestion (and filling pressures). Although this might pose an extra challenge to the clinician, quality of life and a proper balance between avoiding on the one hand congestion and on the other hand organ hypoperfusion should guide treatment. It is therefore critical to monitor renal function closely—particularly serum creatinine and estimated glomerular filtration rate (eGFR)—and adjust diuretic therapy to balance symptom relief with preservation of kidney function.¹⁶

Loop diuretics such as furosemide, torsemide, and bumetanide differ significantly in their pharmacokinetics. Furosemide, the most used, has highly variable oral bioavailability ranging from 10% to 90%, which can result in unpredictable diuretic effects. In contrast, torsemide and bumetanide have more reliable oral bioavailability (~80%–100%), and torsemide also has a longer half-life, offering a more sustained diuretic response. Bumetanide has a high degree of albumin binding, which may reduce its free circulating concentration and limit diuretic efficacy in patients with hypoalbuminaemia, such as those with nephrotic syndrome. These properties may be particularly advantageous in patients with gastrointestinal oedema or poor oral absorption—common in advanced HF and amyloidosis.

In selected cases, particularly in ATTRv, the use of midodrine, an α -adrenergic selective and peripheral receptor agonist, could be useful to treat orthostatic hypotension when diuretics are required at high or ascending doses. However, midodrine is advised to be used with caution in patients with HF as retrospective studies have suggested that midodrine use in patients with LVEF <35% is associated with worse prognosis.¹⁸

Loop diuretics, particularly furosemide, is typically the initial diuretic used, but for those with inadequate response, torasemide or bumetanide offers greater potency and bioavailability. Nevertheless, ultimately the choice of loop diuretic depends on physician's preference as there has not been head-to-head comparison.

Aldosterone antagonists (MRAs) can have a synergistic effect when used alongside loop diuretics and also increase potassium reabsorption, which is often needed when high doses of loop diuretics are needed. Amyloid referral centres have had good experience combining loop diuretics with MRAs in patients with cardiac amyloidosis. For loop diuretic-refractory congestion, dose augmentation combined with thiazides or acetazolamide could be beneficial.^{19,20}

Outpatient administration of intravenous (i.v.) diuretics may be effective in ATTR-CM patients with suboptimal response to oral regimens. In a recent study of an ambulatory diuresis clinic in patients with cardiac amyloidosis, i.v. diuretics were administered in 28% of visits. No participants experienced symptomatic hypotension or severe kidney injury.²¹ After establishing care at the so-called diuresis clinic, there was a significant decrease in emergency department visits and inpatient admissions.

In cardiac amyloidosis, diuretic management must also account for the risk of cardiorenal syndrome driven by elevated venous pressures. Persistent congestion can impair renal function by increasing renal venous pressure and reducing effective filtration. Thus, both over-diuresis and under-diuresis carry risks—while excessive fluid removal may lead to hypoperfusion, inadequate decongestion can also compromise end-organ function. Careful titration of diuretics, guided by clinical and biochemical monitoring, is essential to maintain optimal organ perfusion. In addition to diuretics, patient education and self-care including daily weight, fluid, and salt restriction as well as annual immunization are also crucial in volume management of patients with CA.¹⁷

Implantable monitoring devices, such as pulmonary artery (PA) pressure sensors like CardioMEMS, have emerged as valuable tools in the management of HF by enabling early detection of decompensation and guiding therapy adjustments. Although data specific to patients with cardiac amyloidosis are limited, these devices may offer potential benefits in this population, particularly given the challenges of volume assessment and the risk of rapid clinical deterioration. In patients with ATTR-CM, where symptoms may fluctuate and conventional clinical markers may be less reliable, continuous PA pressure monitoring could support more precise titration of diuretics and other HF therapies. However, further studies are needed to establish the safety, efficacy, and clinical utility of such devices in the context of cardiac amyloidosis.

Table of advice Volume management		
Advice TO DO	Evidence	Strength
Use diuretics to treat congestion as needed, including in combination therapies. Pay special attention to the risk of hypotension and organ hypoperfusion.	OBS	

Guideline-directed HF drugs

Until recently, the mainstay of management for patients with ATTR-CM was restricted to meticulous volume control with diuretics. However, there is an increasing focus on evaluating the usefulness of the four main pillars of HF management in this population.²²

Patients with ATTR-CM may have a similar and even possibly greater neurohormonal activation than patients with HF of other aetiologies.²³ Consequently, neurohormonal modulation might provide prognostic benefits for patients with ATTR-CM. Nevertheless, these patients might experience a different response to neurohormonal blockade based on the poor tolerance observed in clinical practice with some of the HF drugs, adding the risk of hypotension, exacerbation of conduction disorders, and exercise intolerance due to the decreased cardiac output, which is associated with greater mortality.²⁴

At present, there are no randomized trials supporting a prognostic benefit due to the use of beta-blockers, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor antagonists (ARBs), or mineralocorticoid receptor antagonists (MRAs) in ATTR-CM. Furthermore, patients with known ATTR-CM have been traditionally excluded from trials of conventional HF therapies. Therefore, assessment of safety and efficacy has been limited to observational small-scale and retrospective studies (confounded by indication and severity of the disease).

Neurohormonal blockade

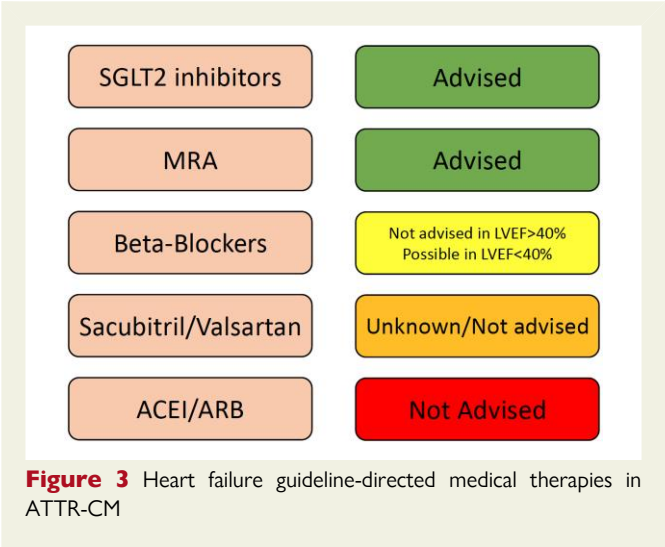
Historically, patients with ATTR-CM who discontinued beta-blockers or ACE inhibitors often experienced symptomatic improvement. This observation aligns with the disease pathophysiology, as these medications can exacerbate clinical deterioration by inducing hypotension and reducing cardiac output.

Indeed, early studies indicated that ATTRv patients who were treated with these drugs had poorer outcomes, while a neutral effect was observed with the use of beta-blockers and ACE inhibitors in patients with wild-type ATTR (ATTRwt).²⁵ More recently, a study involving 309 patients with ATTR-CM found no link between the use of neurohormonal blockade and survival.²⁶ In this cohort, stopping beta-blockers was associated with lower mortality, while the use of ACE inhibitors/ARBs or MRAs showed no improvement in survival rates.²⁶ Conversely, a retrospective involving 128 patients reported enhanced survival among those treated with beta-blockers.²⁷

The largest study to date assessing the use of beta-blockers, ACEis/ARBs, and MRAs is a retrospective and propensity score-matched cohort that included 2371 ATTR-CM patients without neuropathic involvement. Beta-blockers and ACEis/ARBs were prescribed at a low doses and often discontinued during follow-up, whereas MRAs appeared well tolerated and were rarely discontinued.²⁸ The prescription of HF medications in these patients seemed to be influenced by the presence of comorbidities and the severity of their cardiac condition. Notably, HF medications were more commonly prescribed in patients with atrial fibrillation (AF), diabetes, chronic kidney disease, and ischaemic heart disease.²⁸

Beta-blockers

In the aforementioned study, 63% of patients treated with beta-blockers (mostly bisoprolol) received <25% of the target dose for HF.²⁸ While beta-blockers were not associated with improved prognosis in the overall cohort, a propensity score-matched analysis demonstrated that low-dose beta-blockers were associated with a lower risk of mortality in patients with LVEF $\leq$ 40%.²⁸



Despite the reported positive effects, the use of beta-blockers in ATTR-CM remains controversial. Other studies have shown neutral or even negative outcomes in CA, highlighting the complexity of treatment efficacy in this condition. Furthermore, a recent small observational prospective study in 22 patients with LVEF $\geq 40\%$ showed that discontinuation of beta-blockers was associated with improvement in quality of life and increased functional capacity in the short term.²⁹ However this was an open-label study which may have introduced bias.

Considering all available evidence, including previous retrospective studies that have not demonstrated a survival benefit for patients with an LVEF $>40\%$, we advise against routinely prescribing beta-blockers to these patients (Figure 3). Furthermore, withdrawal of beta-blockers should be advised in ATTR-CM patients, particularly in those with lower heart rates. In patients with ATTR-CM with LVEF $<40\%$, the use of low-dose beta-blockers may be considered. In any case, fine tailoring of beta-blocker dose should be pursued.

Mineralocorticoid receptor antagonists

In the largest study conducted to date, survival analysis demonstrated a reduced risk of mortality in patients treated with MRAs in the overall population and in patients with a LVEF $>40\%$.²⁸ These results are further supported by retrospective analysis of the TOPCAT trial, whereby an enriched cohort of patients with echocardiographic characteristics suggestive of CA benefited from spironolactone treatment.³⁰ Given these observational studies, the use of MRA is advised in patients with ATTR-CM (Figure 3).

ACEis/ARBs/angiotensin receptor/neprilysin inhibitor

To date, no studies have shown benefit of ACE inhibitors or angiotensin receptor blockers (ARBs) in patients with ATTR-CM.^{25,26,28} The efficacy of sacubitril/valsartan for ATTR-CM patients with HF remains an unresolved question, with only a few isolated cases reported in the literature.³¹ An ongoing phase IV academic clinical trial is exploring the efficacy of starting open-label sacubitril/valsartan compared with no treatment in ATTR-CM patients with LVEF $<40\%$ (EUCT number: 2024-515661-34-00), with LVEF improvement as the primary endpoint. In this scenario, we advise against routine use of these drugs in ATTR-CM patients and to evaluate stopping RAS inhibitors in patients with low blood pressure (Figure 3).

Sodium-glucose-cotransporter-2 inhibitors

CA was an exclusion criterion in major HF clinical trials of sodium-glucose-cotransporter-2 inhibitors (SGLT2i). Despite no randomized clinical trials have specifically investigated safety and benefits of SGLT2i in CA, after their inclusion in HF guidelines, SGLT2i began to be used in clinical practice for CA patients. Beyond small series, the role of SGLT2i in ATTR-CM has been assessed in a recent multicentre observational study comparing 220 patients treated with SGLT2i with 220 matched controls and a larger study involving 2153 patients treated with SGLT2i and 2153 matched controls.^{32,33} Both studies concluded that SGLT2i were well tolerated and were associated with a reduction in mortality and HF hospitalization.^{32,33} Loop diuretic requirement and NTproBNP reduction were also observed in the smaller study while in the larger one iSGLT2 use was associated with reduced risk of ACM, MACE, and ischaemic stroke at 1 month, 1 year, and 3 year follow-up periods.^{32,33} A recent meta-analysis including 9766 participants confirmed SGLT2i benefits in ATTR-CM, demonstrating reductions in the odds of developing AF, ventricular tachycardia, and sudden cardiac arrest.³⁴

Considering the evidence, the consensus is that treatment with MRAs and SGLT2 inhibitors should be advised for patients with ATTR-CM (Figure 3).

Table of advice HF medications		
Advice	Evidence	Strength
Advice TO DO		
Treatment with MRAs and SGLT2i regardless of LVEF	OBS	
May Be Appropriate TO DO		
Treatment with low-dose beta-blockers for patients with LVEF <40%	OBS	
Advice NOT TO DO		
Treatment with ACEis/ARBs/ARNI, unless the patient is hypertensive	OBS	

Heart transplantation and mechanical circulatory support

Patients with ATTR-CM who progress to advanced HF can benefit from an evaluation for HT.³⁵ This is particularly relevant as the currently approved disease-modifying therapies can slow the progression of the cardiomyopathy but do not reverse it.^{2,17,35}

HT represents the optimal heart replacement therapy for patients with ATTR-CM, including both hereditary (ATTRv) and wild-type (ATTRwt) forms. Currently, outcomes for these patients are comparable with those seen with other heart transplant indications and are superior to those observed in AL amyloidosis. Most patients with advanced HF secondary to ATTRwt have an advanced age and, given

the shortage of donors, often do not qualify for HT. The rate of HT indication for patients with ATTRv ranges from 2% to 4.5% but can rise to as high as 18% in specific mutations, such as Glu109Lys.^{36–38} Advanced peripheral and autonomous polyneuropathy present in ATTRv due to mutations with a mixed phenotype can represent a caveat for HT, and appropriate patient selection is key to achieve good results. However, the need for HT may decrease in the near future as disease-modifying therapies become more widely used.

Most HT organizations prioritize patients with cardiac amyloidosis in the waiting list without distinguishing the type of amyloidosis, given the rapid progression of the disease, especially with AL amyloidosis, and without the need to be on mechanical circulatory support because these patients are poor candidates for long-term left ventricular assist devices (LVADs).³⁹ In ATTR-CM, disease progression tends to be more rapid in ATTRv, particularly with Val142Ile and Glu109Lys variants, which impacts the timing of HT indication.^{38,40,41} Improved outcomes after HT in patients with ATTR-CM have been achieved through better selection of candidates, specifically by excluding those with significant or severe extra-cardiac amyloid involvement that may impact patient survival.^{35,42} This and increased awareness of ATTR-CM have increased the number of HT indications during the last decade.^{43,44} Additionally, effective follow-up in multidisciplinary amyloidosis units enables early detection and treatment of extra-cardiac amyloid with disease-modifying therapies, further enhancing patient outcomes. In this regard, treatment with tacrolimus may worsen polyneuropathy symptoms, and, in this context, a change from standard to extended-release tacrolimus may be beneficial.⁴⁵

While liver transplant was previously advised alongside or following HT for patients with ATTRv, advances in disease-modifying therapies have largely obviated the need for this approach. The current recommendation is to treat patients with ATTR-CM with these therapies both before and after HT, according to current indications. Although

amyloid deposition could in theory occur in the transplanted heart, it has never been described.⁴⁶ Limited survival after transplantation in ATTRwt patients due to the age at which these patients received a HT coupled with the specific therapies that are used to treat polyneuropathy in ATTRv limit further the possibility of recurrence. No specific monitoring program is therefore recommended for ATTR-CM patients who have undergone HT.

Durable mechanical circulatory support is feasible in patients with ATTR-CM, but given the biventricular and restrictive cardiomyopathy, the International Society of Heart and Lung Transplantation guidelines recommend the use of the total artificial heart as a bridge to HT when timely HT is not feasible.⁴⁷ Some centres explored the use of long-term LVADs in patients with ATTR-CM,^{48,49} but the small left ventricular diameters in these patients are associated with suction events and worse outcomes.^{50,51} Additionally, patients with ATTR-CM also have a higher incidence of right ventricular failure and increased thrombotic and bleeding risk.⁵⁰ Despite innovative solutions aimed at addressing the physiological challenges associated with LVADs in restrictive cardiomyopathy, such as concomitant myectomy⁵² or left atrial implant of the inflow cannula,⁵³ LVAD generally remains unsuitable for most patients with ATTR-CM.

Atrial fibrillation and anticoagulation

Atrial arrhythmias are more prevalent in CA than in the general population. In ATTR-CM, reported prevalence varies widely but can reach up to 70% in ATTRwt.^{54–56} Atrial arrhythmias are often highly symptomatic and poorly tolerated. Managing AF in ATTR-CM is particularly challenging, as maintaining sinus rhythm in the long term is difficult due to restrictive physiology, progressive atrial dilatation, and amyloid infiltration.

When dealing with AF in ATTR-CM, two main aspects must be addressed: rate or rhythm control and thromboembolic risk with appropriate anticoagulation (Figure 4).

Evidence regarding rate or rhythm control in ATTR-CM is limited and controversial. No differences in survival have been demonstrated so far between both strategies although AF has been associated with higher prevalence and incidence of HF.^{54,55} Nonetheless, data come, mainly, from unicentric and retrospective analysis.

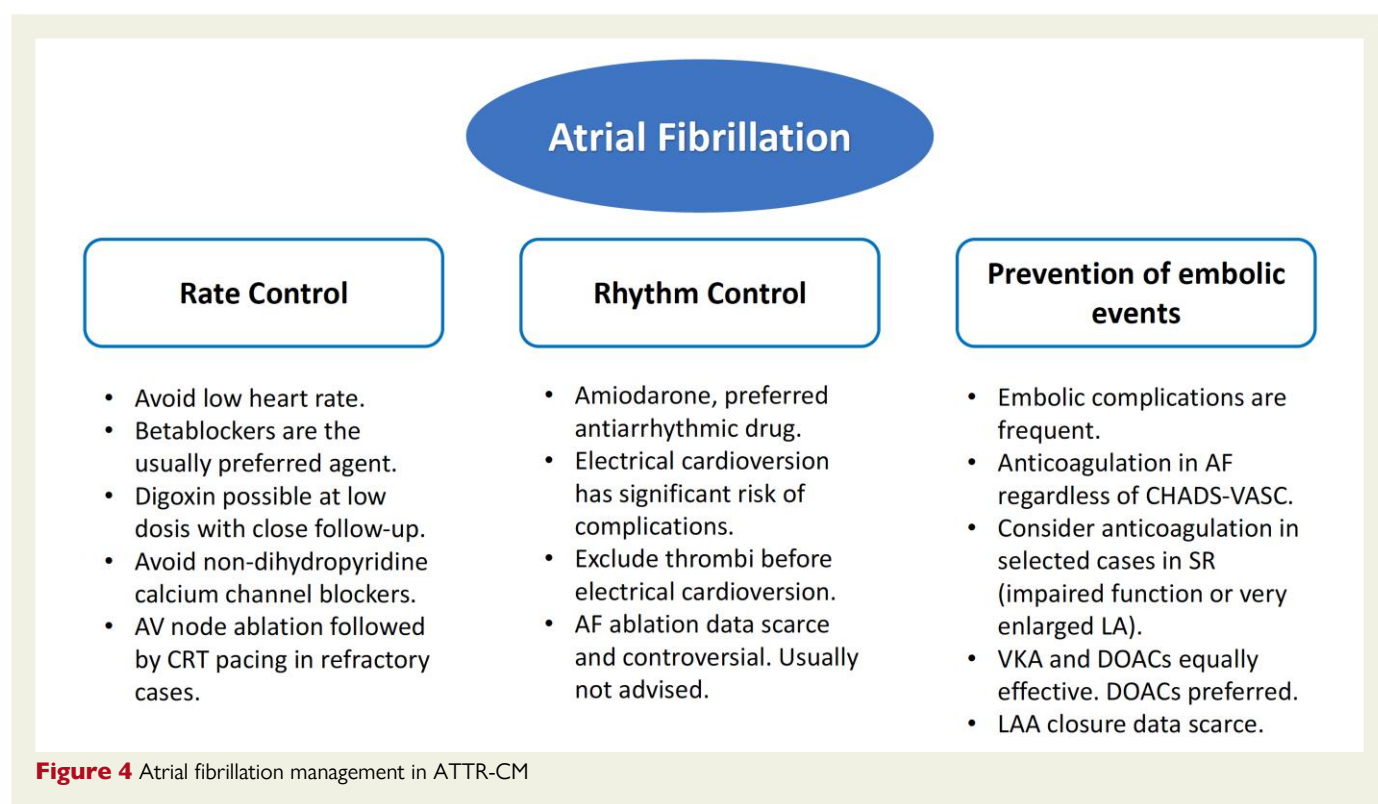
Loss of atrial contribution to ventricular filling in a restrictive heart can significantly worsen functional status. However, data on the success of rhythm control strategies are limited, and these approaches carry a higher risk of complications. A clinical scenario where rhythm control is usually preferred over rate control is when AF appearance acts as a precipitated factor that results in decline in LV ejection fraction and overt HF symptoms.

Rate control

Pharmacological therapy may include beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin. However, rate control medications are often poorly tolerated and carry risks such as hypotension, low cardiac output, HF decompensation, and conduction disorders.

Non-dihydropyridine calcium channel blockers are generally contraindicated in patients with cardiac amyloidosis based on old series reporting complete atrioventricular (AV) block and even cardiogenic shock associated with verapamil use.⁵⁷ Non-dihydropyridine calcium channel blockers are thought to bind to amyloid fibrils increasing levels of these drugs at heart level.

Table of advice Heart transplantation and mechanical circulatory support		
Advice	Evidence	Strength
Advice TO DO		
Assess the need for heart replacement therapies in cases of advanced HF, provided no contraindications are present	OBS	
Heart transplantation is the preferred heart replacement therapy in the absence of severe extra-cardiac involvement	OBS	
After heart transplantation, ensure adequate follow-up in multidisciplinary amyloidosis units for early detection and treatment of extra-cardiac amyloid	OPN	
Advice NOT TO DO		
Implant long-term LVAD	OPN	



Digoxin was contraindicated in cardiac amyloidosis based on older case reports reporting toxic effects from its binding to amyloid fibrils *in vitro*.⁵⁸ A recent retrospective cohort in patients with AL amyloidosis suggested that digoxin might be safe when started at low doses with close monitoring,⁵⁹ leading some centres to reconsider it as an option for heart rate control.⁶⁰

Overall, there is consensus to avoid non-dihydropyridine calcium channel blockers, while beta-blockers and digoxin could be possible used for rate control. In both cases, we advise to avoid aggressive control, use low doses, and closely monitor haemodynamics and signs of toxicity (including VAs). Moreover, monitoring of drug levels is advised in patients treated with digoxin despite toxicity can occur at therapeutic serum levels. For refractory cases despite pharmacological therapy, AV node ablation with permanent pacemaker (PPM) implantation may be advised.⁶¹ Patients that would require AV node ablation must be carefully selected as high heart rate frequently reflects a compensatory mechanism to maintain cardiac output. In case AV node ablation is pursued, paced rate is advised to be maintained high (usually between 80 and 90 bpm) to avoid HF decompensation. Furthermore, in these patients CRT is generally preferred over conventional PPM systems.

Rhythm control

There is paucity of studies investigating the efficacy and safety of antiarrhythmic drugs, but amiodarone is considered the drug of choice in most centres. Dofetilide is an alternative to amiodarone but it is not available in Europe, and it requires close dose adjustments in patients with significant renal insufficiency.

Direct current cardioversion (DCCV) is considered a high-risk procedure in ATTR-CM, based on a cohort study of CA patients that showed higher complications rate, including VAs, transient AV block requiring a temporary pacemaker, and stroke.⁶² Transoesophageal echocardiogram (TEE) is advised before DCCV, regardless of AF duration or

adequate anticoagulation, as the prevalence of left atrial appendage (LAA) thrombosis is high in this population.⁶³ A recent unicentric study challenges the routine use of pre-DCCV TEE in all CA patients, based on their experience in 132 DCCV procedures, approximately half of which did not include pre-procedural TTE. Despite a high rate of LAA thrombus, there were no strokes in adequately anticoagulated CA patients undergoing DCCV.⁶⁴

Finally, data on safety and efficacy of pulmonary vein ablation in ATTR-CM are limited, mostly derived from small unicentric series with high rates of AF recurrence.⁶⁵ A retrospective observational cohort of 24 patients from a referral amyloid centre reported excellent results, with ablation associated to improved survival and reduced mortality, particularly when performed early.⁶⁶ Unfortunately, this study did not analyse outcomes according to the severity of disease. As such, improvements observed could have been severely influenced by the type of patients included and their stage of the disease which was not advanced. In settings outside specialized referral centres and in less carefully selected cases, the role of AF ablation in patients with ATTR-CM remains under discussion. Given current evidence, the consensus is to consider it on a case-by-case basis rather than recommending it routinely.

Thromboembolic risk and anticoagulation

Recent data from an international cohort of over a thousand patients have shown that embolic events are common in ATTR-CM, particularly in those with AF who not receiving anticoagulation, but also in patients in sinus rhythm.⁶⁷

When to start anticoagulation in ATTR-CM?

Several studies have shown no significant association between the CHADS-VASc score and LAA thrombus, highlighting its limited value

in predicting embolic events in ATTR-CM.^{67,68} Therefore, anticoagulation is always advised in patients with ATTR-CM and AF, regardless of their CHA₂DS₂-VASc score.

Recommendations to start anticoagulation in ATTR-CM in sinus rhythm are lacking but may be advised in patients with impaired atrial function (reduced transmitral A wave of <20 cm/s in the absence of an obvious LV restrictive filling pattern, atrial standstill) or significantly enlarged atria (>50 mm diameter), though the risk–benefit balance should be evaluated on an individual basis, particularly in fragile ATTRwt patients.

There are not solid data about clinical results of active monitoring for occult AF either with periodic Holter monitoring or by using long-term monitoring devices or wearables. These devices offer an interesting opportunity to early identify patients with AF, and future studies should address this important unmet need. While this information emerges, we advise to perform yearly Holter ECG recordings that can help in identifying conduction abnormalities and also detect occult atrial arrhythmias.

Choice of anticoagulant

In the absence of randomized clinical trials, indirect data have shown that vitamin K antagonists and direct oral anticoagulants (DOACs) are equally effective in preventing embolism in ATTR-CM.^{67,69} DOACs may be preferred due to their ease of administration, fewer interactions with concomitant therapies, and relatively lower risk of intracranial haemorrhage. A retrospective study found that labile INR was observed in half of the population on warfarin, and those patients who had events or bleeding complications had labile INR.⁶⁹

Finally, although LAA closure devices have been barely studied in ATTR-CM, they are an option for patients with prohibitive bleeding risk or contraindications to anticoagulation, despite available data are limited.⁷⁰

Table of advice Atrial fibrillation and anticoagulation		
Advice	Evidence	Strength
Advice TO DO		
The choice between a rate or rhythm control strategy should be individualized	OPN	
Beta-blockers (preferred) and digoxin can be used for rate control, avoiding low heart rates, and should be administered in low doses with frequent monitoring	OBS	
TEE is advised before DCCV to identify intracardiac thrombi	OBS	
Anticoagulation should be initiated in AF, regardless of the CHADS-VASc score as recommended in SCD guidelines on cardiomyopathies	OBS	
Continued		

Table of advice Continued

Advice	Evidence	Strength
May Be Appropriate TO DO		
Consider anticoagulation in sinus rhythm in selected cases (very enlarged atria or impaired atrial function)	OBS/ OPN	
Consider yearly Holter ECG monitoring to detect occult AF	OPN	
Advice NOT TO DO		
Treatment with non-dihydropyridine calcium channel blockers	OBS/ OPN	

Conduction disease and pacemaker implantation

The pathophysiological mechanisms underlying the dysfunction of the heart’s electrical conduction system in ATTR-CM are not fully understood, but they involve several processes. These include the direct infiltration of amyloid fibrils into the cardiac conduction system,⁷¹ leading to altered electrical impulse transmission,^{72,73} particularly through the His–Purkinje system.⁶⁵ In addition, amyloid fibrils have a direct cytotoxic effect on cardiac tissue.⁷⁴ Finally, myocardial ischaemia, resulting from perivascular amyloid infiltration and chronic reduced blood supply to the cardiac conduction system, may also contribute to the dysfunction. Cardiac sympathetic denervation can also contribute to conduction system disease in ATTRv with autonomic neuropathy.

The evaluation of conduction abnormalities and chronotropic incompetence is essential in patients with suspected or established cardiac amyloidosis. A structured diagnostic approach is recommended, beginning with a standard 12-lead ECG to assess for baseline conduction system disease, including AV block, bundle branch block, prolonged PR or QRS intervals, and sinus node dysfunction. Ambulatory ECG monitoring, such as 24–48 h Holter monitoring, can detect transient arrhythmias or diurnal heart rate patterns suggestive of chronotropic incompetence. Exercise testing is particularly valuable for assessing the heart rate response to exertion, with a blunted increase in heart rate indicating chronotropic incompetence due to either sinoatrial node dysfunction or autonomic impairment. In patients with unexplained syncope or suspected infrequent arrhythmias, implantable loop recorders offer prolonged rhythm monitoring to capture rare events.

Sinus node dysfunction is relatively uncommon in ATTR-CM. A single-centre retrospective study found an incidence of 7% over an average follow-up period of 28 months (8% in ATTRv and 6% in ATTRwt).⁷⁵ In contrast, first-degree AV block was much more frequent (43% in ATTRv and 49% in ATTRwt).⁷⁵ Similarly, an Italian study reported a 33% prevalence of first-degree AV block in ATTRwt.⁷⁶ Overall, first-degree AV block affects ~35%–50% of patients. Advanced conduction disease is also common in patients with cardiac amyloidosis and frequently requires PPM implantation.^{77,78} Notably, patients with cardiac amyloidosis and HFpEF have a higher rate of PPM implantation compared with those with HFpEF alone (43.8% vs 11.5%).⁵ Several studies have described that ~9%–10% of patients

with cardiac amyloidosis have a PPM at diagnosis, though this rate could be significantly higher, reaching 41%.⁷⁹

Predictors of pacemaker implantation

A French single-centre study evaluated 262 ATTRv patients (61% with Val50Met variant) who received a prophylactic PPM if they met the following criteria: His-ventricular (HV) interval >70 ms, HV interval >55 ms in association with fascicular block, first-degree AV block, or an anterograde Wenckebach point <100 beats/min.⁸⁰ During a mean follow-up of 45 months, 25% of these patients developed complete AV block, with the risk being higher in those who had a first-degree AV block or a WA point ≤100 beats/min at baseline.⁸⁰

Other risk factors have emerged over the years, highlighting the role of prolonged QRS duration on the ECG. One study demonstrated an association between a QRS ≥120 ms at baseline ECG and the development of advanced AV block.⁷⁵ Another more recent study reported QRS duration and left ventricular thickness as independent risk factors for PPM implantation, proposing a predictive model for increased risk based on these parameters.⁷⁷ In a recent Italian study, the presence of AF at the baseline, a PR interval >200 ms and a QRS duration >120 ms (regardless of morphology) were associated with an increased risk of PPM implantation.⁷⁸ Notably, the combination of these three factors resulted in a significantly higher risk, while the absence of all three provided an excellent negative predictive value of 92%. Additionally, a PR interval >200 ms or a history of AF, combined with bifascicular block (right bundle branch block and left anterior fascicular block), identified patients at increased risk of requiring PPM.⁷⁸ Overall, these studies suggest that patients with these risk factors tend to have more advanced disease, revealing a relationship between a more extensive amyloid infiltration and conduction system disease.

Pacemaker implantation

Conduction disturbances in patients with CA are unpredictable, making the timing for the need for a PPM unclear. While progress has been made, current evidence does not support different indications for PPM application compared with the general population. However, certain ECG features, such as QRS duration, the presence of first-degree AV block, and AF, are factors associated with an increased risk of developing advanced AV block. Therefore, when these features are present along with episodes of syncope, PPM implantation may be advised. Alternatively, prolonged and frequent Holter ECG monitoring and the use of loop recorders are options to anticipate the diagnosis of advanced block in these patients.

Type of pacemaker

An observational, retrospective study analysed a cohort of 78 ATTR-CM patients (65% ATTRwt and 35% ATTRv mostly with Val142Ile variant) and demonstrated a significant worsening of New York Heart Association class (NYHA), degree of mitral regurgitation (MR), and LVEF in patients whose right ventricular pacing exceeded 40%, with a non-statistically significant trend towards increased mortality.⁸¹ In contrast, patients who received cardiac resynchronization therapy (CRT) devices showed improvement in these parameters.⁸¹ Another study of 34 patients followed for 3.1 ± 4 years showed a significant increase in the percentage of ventricular pacing over time, from 56 ± 9% at 1 year to 96 ± 1% at 5 years, with most patients experiencing near 100% pacing.⁷⁹ Based on these findings, CRT devices may be advised for patients undergoing PPM implantation and estimated ventricular pacing >40% or in those with LVEF <50%, NYHA class III-IV, or severe MR.

Left bundle branch area pacing (LBBAP) has recently been preliminarily explored in ATTR-CM.^{82,83} A retrospective analysis of 23 patients treated with LBBAP demonstrated it to be a feasible and safe pacing technique in this setting.⁸⁴ In this study, LBBAP was associated with significant QRS narrowing without changes in LVEF and NTproBNP at 6 months of follow-up.⁸⁴ Nevertheless, LBBAP should be approached with caution, as the absence of long-term outcome data presents a significant concern for potential pacing failure, which could lead to serious consequences, including patient death.

In patients with cardiac amyloidosis who require PPM, careful consideration should be given to programming lower rate limits. Due to frequent autonomic dysfunction and chronotropic incompetence in this population, setting an appropriately higher lower rate limit (e.g. 60–70 bpm) may help maintain adequate cardiac output and prevent symptoms such as fatigue or hypotension. Individualized programming based on symptom burden and haemodynamic response is recommended to optimize clinical outcomes. Finally, it should also be noted that amyloid infiltration may potentially influence the effectiveness of pacemakers in cardiac amyloidosis compared with other diseases. However, no solid data currently exist regarding specific PPM parameter evolutions during follow-up for these patients.

Ventricular arrhythmias and sudden cardiac death prevention

Cardiac amyloidosis is associated with an increased risk of VAs. Non-sustained ventricular tachycardia (NSVT) is commonly observed in patients with ATTR-CM.⁷⁹

Sudden cardiac death (SCD) is considered the second leading cause of cardiovascular death in patients with cardiac amyloidosis, regardless of LVEF, although the risk is higher in patients with AL amyloidosis compared with ATTR-CM.⁸⁵ In a recent retrospective study, SCD rate at 2 years was 1.8% in ATTR-CM compared with 8% in AL.⁸⁵ While some studies have demonstrated appropriate implantable cardioverter-defibrillator (ICD) therapies, none have convincingly shown improved survival.

Current guidelines indicate that there are insufficient data to provide recommendations beyond standard indications for ICD use as secondary prevention, emphasizing the need for individualized decision-making.

Most studies conducted to date provide observational data across various types of amyloidosis, with a relatively small number of patients with ATTR-CM included, and these studies were conducted before specific treatments were available.

Current evidence

Several small series of patients with cardiac amyloidosis and ICD have examined usefulness of ICDs to prevent SCD. Most studies have reported absence or very low appropriate ICD intervention rates including some studies that involved patients with severely reduced LVEF.^{86–88} The notable exception is a study including 45 patients (31 with ATTR-CM; 84% implanted for primary prevention), where appropriate ICD therapies were observed in 26.7% of patients over an average follow-up of 17 months (12 patients: four with AL amyloidosis and eight with ATTR-CM).⁸⁹ The time to the first event was short (4.7 months), while 92% experienced their first therapy within the first year after ICD implantation. No specific clinical, echocardiographic, or biological factors were identified as predictors of ICD therapy; however, patients with milder HF were more likely to experience VA. Mortality from terminal HF was high in patients with advanced cardiac involvement.⁸⁹ More recently, Brown *et al.* studied a cohort of 32

patients with ATTR-CM (25 ATTRv and 7 ATTRwt) who had ICDs implanted for primary prevention.⁹⁰ In this cohort, eight (25%) received appropriate ICD therapy (six ATTRv and two ATTRwt) while two (6%) experienced inappropriate therapy.⁹⁰ Of note, the rate of appropriate ICD therapy in this study (25%) was similar to that observed in historical trials such as the SCD-HeFT study in patients with HFrEF, where the rate was 21%.⁹¹

Clinical implications

Although several studies report successful ICD therapies, no study has shown a survival benefit, possibly due to patient selection factors. It remains uncertain whether ICD implantation offers greater benefit in AL compared with ATTR-CM, as most studies have predominantly included patients with AL, where the rate of VA is higher and prognosis generally worse.

While the effectiveness of ICDs for primary prevention of SCD is uncertain, many deaths in patients with cardiac amyloidosis do not appear to be preventable by an ICD.

The role of ICDs in ATTR-CM for SCD prevention is not yet established, and current available data do not support their use in primary prevention in these patients. However, with the advent of new specific treatments that may alter the natural history of the disease and extend survival in ATTR-CM patients, future recommendations regarding ICD implantation and SCD prevention could change. Of note, when considering ICD implantation, careful evaluation of tricuspid valve integrity and right heart function is essential to appropriately weigh the risk of right ventricular dysfunction associated with progressive tricuspid regurgitation.

Table of advice Pacemaker and ICD implantation

Advice	Evidence	Strength
Advice TO DO		
Implantation of a pacemaker in case of syncope associated with PR >200 ms + QRS ≥120 ms or PR >200 ms/AF history + bifascicular block	OBS	
Monitoring with 48 h Holter ECG every 6 months for patients with PR >200 ms/AF + QRS ≥120 ms or PR >200 ms/AF history + bifascicular block	OBS	
ICD implantation in ATTR-CM with resuscitated SCD or haemodynamically not tolerated VT (secondary prevention)	OBS	
May Be Appropriate TO DO		
Monitoring with internal loop recorders in patients PR >200 ms/AF and QRS ≥120 ms or PR >200 ms/AF history + bifascicular block	OBS	

Continued

Table of advice Continued

Advice	Evidence	Strength
CRT implantation in patients undergoing PM implantation if estimated ventricular pacing >40% or in the presence of LVEF <50%, or NYHA class III-IV, or severe MR	OBS	
ICD implantation in primary prevention in selected patients with ATTR-CM, LVEF <35%, and NSVT	OBS	
Advice NOT TO DO		
ICD implantation in primary prevention in ATTR-CM	OBS/ OPN	

Aortic stenosis and ATTR-CM

AS is common in ATTR-CM with a prevalence that ranges from 13% to 16% in candidates for transcatheter aortic valve replacement (TAVR).^{92,93} The pathophysiology of AS in cardiac amyloidosis is complex and still incompletely understood. The age-related calcification of the aortic valve generates elevated shear stress, which may trigger amyloid depositions.⁹⁴ The amyloid deposition, in turn, may stiffen the valve, exacerbating the severity of the disease. Assessment of AS severity in patients with cardiac amyloidosis and low stroke volume index presents unique challenges. In this setting, classical markers of severe AS, such as peak aortic jet velocity and mean transvalvular gradient, may be underestimated due to reduced left ventricular output. A comprehensive diagnostic approach is therefore essential, incorporating dobutamine stress echocardiography to distinguish true severe AS from pseudo-severe AS, particularly in cases with low-gradient AS and reduced ejection fraction. In addition, multimodality imaging with computed tomography to quantify aortic valve calcification can provide supportive evidence, especially in patients with discordant echocardiographic findings. Given the infiltrative nature of cardiac amyloidosis and its impact on myocardial contractility and haemodynamics, individualized assessment by a multidisciplinary heart team is strongly recommended.

Compared with lone AS, patients with ATTR-CM and AS exhibit worse right ventricular function, greater left ventricular hypertrophy, more severe diastolic dysfunction, and more frequently present low-flow low-gradient (both classical and paradoxical) AS pattern.⁹⁵ The prognosis for ATTR-CM and AS patients is notably poorer than for those with AS alone, especially without appropriate treatment.^{93,96–99} Due to the high surgical risk of these patients, a less invasive approach with TAVR has become the first option. Indeed, patients with ATTR-CM and AS treated with TAVR compared with SAVR show lower mortality and fewer peri-procedural complications such as acute kidney injury and septic or cardiogenic shock.^{99–101} Moreover, post-TAVR survival rates are similar between patients with lone AS and those with both ATTR-CM and AS, effectively dispelling the misconception that TAVR may be futile in ATTR-CM.^{93,94,99} The safety profile of TAVR is similar between ATTR-CM and lone AS with comparable risk of stroke, bleeding, vascular complications, and acute kidney injury. A trend towards a higher, despite not statistically significant, risk of PPM implantation after TAVR in CA has been suggested in a recent

meta-analysis.¹⁰² Furthermore, compared with those with lone AS, patients with ATTR-CM experience higher rate of HF hospitalizations.⁹⁶

Nitsche and co-authors demonstrated that 1 year after TAVR, patients with ATTR-CM showed a significant reduction of cardiac symptoms and NT-proBNP concentrations.¹⁰³ On echocardiography, mitral and tricuspid regurgitation improved, while left ventricular (LV) wall thickness an LV mass index remained unchanged, suggesting the absence of LV reverse remodeling in ATTR and AS after TAVR.¹⁰³

In conclusion, patients with both ATTR-CM and AS should not be denied treatment for AS, and TAVR is advised. It offers survival benefit over SAVR and a safety profile comparable with patients with lone AS. However, following TAVR, patients with ATTR-CM and AS may experience a higher incidence of HF related hospitalization and a lack of significant LV reverse remodeling compared with patients with lone AS.

Table of advice Aortic stenosis		
Advice	Evidence	Strength
Advice TO DO		
TAVR for patients with coexisting ATTR-CM and severe AS	OBS	
Advice NOT TO DO		
SAVR for patients with coexisting ATTR-CM and severe AS	OBS/ OPN	

Chronic kidney disease (CKD)

CKD affects almost one-third of patients with symptomatic ATTRv. CKD in amyloidosis requires a comprehensive approach that addresses both the underlying amyloid pathology and the renal complications. Renal-specific management focuses on reducing proteinuria with ACE inhibitors or ARBs, although caution is warranted due to the risk of hypotension, especially in patients with autonomic neuropathy. Blood pressure should be maintained below 130/80 mmHg, while avoiding overtreatment. Fluid and electrolyte imbalances, including volume overload and disturbances in sodium and potassium levels, must be carefully managed, often with the use of diuretics. Anaemia should be carefully evaluated and managed, with iron supplementation initiated when appropriate. Erythropoiesis-stimulating agents may be used in select patients, but their use should be approached with caution and tailored to individual clinical circumstances. Additionally, disturbances in mineral metabolism, such as elevated phosphorus or parathyroid hormone levels, should be addressed with phosphate binders and vitamin D analogues.¹⁰⁴

In advanced CKD or end-stage renal disease (ESRD), renal replacement therapy may be required. Dialysis, particularly peritoneal dialysis, may be better tolerated in patients with severe hypotension. Supportive care, including nutritional management, treatment of neuropathy and gastrointestinal symptoms, and regular monitoring of renal function, proteinuria, and treatment side effects, is essential. Given the complexity of the disease, a multidisciplinary approach involving nephrologists, haematologists, cardiologists, and neurologists is crucial for optimal patient outcomes.

Table 1 Gaps in evidence

Heart failure • Randomized controlled trials are needed to assess the efficacy of HF drugs in ATTR-CM • There is limited information on how to manage extra-cardiac amyloid and what disease-modifying therapies should be used in patients after HT • Long-term mechanical circulatory support devices that overcome the challenges imposed by the biventricular and restrictive cardiomyopathy
Arrhythmias and anticoagulation • Randomized studies to investigate whether AF ablation improves symptoms and prognosis in CA • Randomized studies comparing warfarin vs DOACs in ATTR-CM patients • Further evidence of starting anticoagulation to prevent thromboembolic event in patients in sinus rhythm is warranted • Need for further investigation to decide whether maintenance of sinus rhythm should be prioritized in ATTR-CM or not • The role of LAA closure in selected ATTR-CM cases requires further investigation
Conduction disorders • Evaluation if cardiac imaging parameters can help in predicting advanced AV blocks • Efficacy of specific therapies in reducing conduction disease progression • Efficacy of CRT in patients with ATTR-CM • Safety and efficacy of LBBAP in patients with ATTR-CM • Data on PPM parameters evolutions, in order to standardize PPM follow-up, are required
Sudden cardiac death • Additional studies are required to investigate if ICD improves the prognosis of patients with ATTR-CM both in primary and secondary prevention • Studies assessing the efficacy of wearable life vest are lacking
Aortic stenosis • The best timing for the treatment of AS in patients with CA is still unknown • The impact of specific therapies on patients with concomitant ATTR-CM and AS has still to be determined • It is unclear if patients with ATTR-CM and AS present a higher risk of PPM implantation after TAVR compared with patient with lone AS. The risk factors for pacemaker implantation after TAVR in ATTR-CM and AS are still unknown

ATTR-CM disease burden

Despite the advent of disease-modifying therapies, ATTR-CM remains a relentlessly progressive condition for most patients. Disease progression is associated with increasing symptoms, frailty, cachexia, and hospital admissions, and holistic multidisciplinary care with input from geriatricians, palliative care, and other specialists is advised.^{105–107}

An international multicentre, observational, real-world study into disease burden in ATTR-CM showed a median KCCQ overall score (KCCQ-OS) of 68, similar to other HF populations.^{108,109} However, ATTR-CM is characterized by relentless disease progression compared with other forms of HF. Analysis of data from the placebo arms of the DAPA-HF and DELIVER trials show small improvements in KCCQ-OS scores over time.¹¹⁰ In comparison, the ATTR-ACT trial demonstrates progressive deterioration in quality of life in untreated ATTR-CM patients, with an average fall of KCCQ score of 3.5 every 6 months for wild-type patients and 5.5 every 6 months in ATTRv, and 6 min walk distance fell by 5 m per month in both groups.¹¹⁰ Disease duration leads to falling KCCQ-OS scores, which also relate to NYHA class and disease stage.^{111,112} KCCQ-OS is reduced in NYHA class III vs NYHA I/II patients (KCCQ-OS 36 vs 71), and whereas 62% of patients overall report mobility issues and 29% were unable to complete normal household activities, this increases to 84% and 54%, respectively, for patients in NYHA class III. Clinically relevant anxiety/depression scores are also reported in 67% of NYHA III patients (HADs score >8).¹¹³

Advancing ATTR-CM places a heavy toll on caregivers. Caregivers report that patients in NYHA class II require around 2 h of care per week, compared with 17.5 h per week for patients in NYHA class III.¹⁰⁸ Caregivers provide essential support with daily tasks such as cleaning, cooking, walking, and bathing, and caregivers report that 11% of patients had some form of incontinence, increasing to 28% in NYHA III patients.¹⁰⁸ Most carers are the elderly spouse (female 85%); however, adult children are the main carers in a third of cases and may have other occupational and caring obligations.¹⁰⁸ Advanced planning is essential to address increasing care needs of ATTR-CM as the disease progresses, to avoid crises in care provision. Holistic care in ATTR-CM includes referral of patients and families to social services for support. However, a Delphi survey revealed that this practice is currently only core practice in 20% of centres.¹¹⁴ Access to palliative care services should also be available to ATTR-CM patients as needed throughout the course of their illness, both for symptom control and to aid the patient and family in determining appropriate goals of care.¹¹⁵

Gaps in evidence

In addressing ATTR-CM, significant evidence gaps persist, particularly in the realm of non-specific (supportive) therapies. While recent advancements have improved specific interventions aimed at decelerating amyloid deposition, the management of cardiac symptoms and

complications arising from amyloid infiltration remains underexplored in clinical trials. Table 1, compiled by the writing group of this clinical consensus statement, highlights these primary gaps in evidence. Additionally, important unanswered questions that would be required to be addressed are presented in Table 2.

Summary and future directions

This clinical consensus statement on ATTR-CM provides comprehensive advice for managing this progressive disease, emphasizing non-specific interventions for cardiac issues such as HF and arrhythmias. It includes advice on advanced treatments like HT and mechanical circulatory support and discusses managing AS, conduction disease, and the prevention of SCD. The working group highlights the importance of multidisciplinary and palliative care approaches to improve the quality of life for patients with advanced ATTR-CM.

This advice primarily stems from expert opinions and retrospective studies, highlighting a significant shortfall in comprehensive trial data. This lack of data underscores the critical need for more extensive research, especially randomized controlled trials. Such research is essential to propel evidence-based practices forward and refine treatment strategies for ATTR-CM.

Supplementary data

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

Declarations

Disclosure of Interest

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Table 2 Unanswered questions

- How to better tune diuretics and beta-blockers dose?
- Is there a role for sacubitril/valsartan in ATTR-CM?
- Should be atrial standstill an 'off label' anticoagulation indication in ATTR-CM?
- Is there a role for loop recorders in ATTR-CM monitoring?
- How to define the optimal heart rate for pacing in these patients?
- Which is the role of cardiac rehabilitation and exercise in ATTR-CM?
- How to manage end-stage HF and palliative care from a cardiac point of view?
- Which are the recommendations for caregivers?
- How do we prognosticate for patients in the era of evolving targeted TTR therapies?
- How to quantify extra-cardiac amyloidosis and its clinical burden?

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