Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Guideline-Directed Medical Therapy for Heart Failure in Transthyretin Amyloid Cardiomyopathy

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ABSTRACT: Cardiac amyloidosis is an underdiagnosed cause of infiltrative cardiomyopathy, leading to heart failure across the spectrum of ejection fractions. Although there are approved disease-modulating therapies for the transthyretin subtype (transthyretin amyloid cardiomyopathy [ATTR-CM]), the role of heart failure medications remains uncertain and challenging in clinical practice. Their effects on clinical outcomes, such as mortality and hospitalization, are unknown for ATTR-CM. This review aims to explore the use of these medications in ATTR-CM, considering the disease's stage and patient-specific issues, such as fluid homeostasis, autonomic dysfunction, conduction disorders, low and fixed stroke volumes, and decreased functional capacity. As our understanding of this condition deepens, it is important to reassess the impact of contemporary heart failure medication in ATTR-CM. Finally, the relevance of guideline recommendations for heart failure drugs based on left ventricular ejection fraction should be reconsidered in the context of ATTR-CM.

Key Words: amyloidosis ■ cardiomyopathies ■ heart failure ■ hospitalization

Amyloidosis is a heterogeneous group of disorders linked to the misfolding of insoluble fibrils derived from endogenous proteins and then their deposition in various tissues and organs. There are 2 main subtypes of systemic amyloidosis that involve the heart: light-chain amyloidosis (AL) and TTR (transthyretin) amyloidosis (ATTR). Both manifest as cardiac amyloidosis (CA), a specific form of infiltrative heart disease. But the treatment approaches and prognosis for these 2 subtypes of systemic amyloidosis are different.[1] Several recent articles have reviewed the pathophysiology of each subtype.[2–5] Upon fibril infiltration, the myocardium can be altered; clinical manifestations include recurrent decompensated heart failure (HF), conduction disorders, and arrhythmias.[6] Yet the clinical course of individual patients is highly variable, and not all of these manifestations are present in every patient with ATTR-CM.

There is a lack of evidence about guideline-directed medical therapy for HF in patients with CA. At diagnosis, the stages of CA and the clinical presentation can vary from mild diastolic dysfunction without overt HF to restrictive cardiomyopathy with reduced cardiac output or to a phenotype characterized by a reduced ejection fraction.[7] The lack of clear evidence on the benefits and risks of managing HF in CA results in an approach that is empirical and highly individualized and needs to be frequently reevaluated based on disease progression. Scientific societies and experts have recommended randomized controlled trials to better guide the HF management of this cardiomyopathy.[8,9]

As proposed in the updated Heart Failure Guidelines of the European Society of Cardiology, medical treatment of HF is oriented toward 3 different subtypes defined by the left ventricular (LV) ejection fraction (LVEF): HF with preserved ejection fraction (HFpEF: LVEF ≥50%), HF with mildly reduced ejection fraction (HFmrEF: LVEF 41% to 49%), or HF with reduced ejection fraction (HFrEF: LVEF ≤40%).

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
Afib	atrial fibrillation
ARBs	angiotensin-1-receptor blockers
ARNIs	angiotensin-receptor-neprilysin-inhibitors
ATTR	transthyretin amyloidosis
ATTR-CM	transthyretin amyloid cardiomyopathy
BEST	β-blocker Evaluation in Survival Trial
CA	cardiac amyloidosis
DELIVER	Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction
EMPULSE	Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure
FINEARTS-HF	Finerenone in Heart Failure With Mildly Reduced or Preserved Ejection Fraction
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MRAs	mineralocorticoid receptor antagonists
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PARAGON-HF	Prospective Comparison of ARNI with ARB on Management of Heart Failure With Preserved Ejection Fraction
PARAMOUNT-HF	Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial
REDUCE-AMI	Randomized Evaluation of Decreased Usage of β-blocker After Acute Myocardial Infarction
SGLT-2i	sodium-glucose transport-2 inhibitors
THAOS	Transthyretin Amyloidosis Outcomes Survey
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With Aldosterone Antagonist
TTR	transthyretin

Based on several multicenter, prospective, randomized, blinded studies, 4 essential medication groups have emerged as the standard therapy for HF classified according to LVEF irrespective of the underlying etiologies. These fantastic 4 include (1) β-blockers, (2) ACE (angiotensin-converting enzyme) inhibitors or angiotensin-1-receptor blockers or angiotensin-receptor-neprilysin-inhibitors (ARBs/ARNIs), (3) mineralocorticoid receptor antagonists (MRA), and (4) sodium-glucose cotransporter-2 inhibitors (SGLT-2i). Guideline-directed medical therapy implies their combination at the highest tolerated dosage to achieve the greatest possible benefit. In addition to the 4 pillars, diuretics are used for symptom management in acute and chronic decompensated HF.

It is well known that therapy for HFrEF is most effective if all 4 classes of therapy are prescribed together, but this review intentionally considers HF medications separately, to address the potential benefits and risks of individual therapies and their compound effects in CA. This review mostly focuses on ATTR-CM because there is less evidence available for AL–CA and because ATTR-CM is much more common than heart involvement of light-chain amyloidosis. This review does not cover disease-specific amyloid therapies because this has been discussed in recent reviews.[10–12]

β-BLOCKERS

CA as a Confounder in Trials of β-Blockers

β-Blockers, especially the β1-selective blockers, are the most frequently studied medications in HF. They exert their effect by competitively blocking the β1-receptor to endogenous neurohormonal substances, such as (nor-)adrenaline, thereby attenuating the vicious cycle of continuous exposure to circulating catecholamines in HF patients. Several trials have demonstrated significant reductions of cardiovascular mortality in patients with HFrEF.[13,14] However, data on cardiovascular outcomes in the context of β-blocker therapy in patients with HFmrEF/HFpEF is less compelling.[15–18] International, multisociety guidelines recommend β-blocker prescription in HFpEF (Level IIa recommendation)

only in the presence of coronary artery disease or for rate control in atrial fibrillation (Afib).[19,20] Recently, this recommendation has been questioned within the REDUCE-AMI (Randomized Evaluation of Decreased Usage of β-blocker After Acute Myocardial Infarction) study, showing no substantial benefit of β-blocker treatment in patients with HFpEF with previous myocardial infarction.[18]

Importantly, all of the trials of β-blockers in HFrEF, HFmEF, or HFpEF, may have been confounded by the inclusion of patients with ATTR-CM.[21] The results of the BEST (β-Blocker Evaluation in Survival Trial) are an example of the confounding effect of including patients with ATTR-CM.[22] Briefly, the study showed a nonsignificant reduction of overall mortality with the nonselective β-antagonist bucindolol. In prespecified subgroup analysis, racial differences emerged with cardiovascular survival benefits for non–African-American participants. Genetic polymorphisms were suggested as causative for the observed difference in racial subgroups. Genome sequencing detected the pathogenic TTR-variant Val-122Ile (p.Val142Ile) in every 10th African-American patient aged ≥60 years in this trial.[23,24] This is hypothesis-generating regarding the potential confounding role of CA in the β-blocker trials conducted on HF patients, especially in the elderly.

Tolerance of β-Blockers in CA and Preexisting Hemodynamic Conditions

Depending on the degree of LV chamber stiffness, capacitance, and fixation of stroke volume, patients with ATTR-CM might carry the risk of decreased cardiac output and symptomatic deterioration with heart rate lowering.[25] Considering this pathophysiological mechanism, prescription of β-blockers may be harmful, irrespective of LVEF, disease stage, or genetic status. To date, 5 observational cohort studies on β-blockers in CA have been published, 3 of which specifically address their use in ATTR-CM. The results of these studies are difficult to compare to each other directly, due to the differences in patient samples and active ingredients studied. These studies have led to partly contradictory statements regarding the tolerability and potential benefit of β-blockers in ATTR-CM. Features and key messages of these observational studies are summarized in Table.

Most studies consistently show that patients, who were on low-dose β-blockers at the time of their ATTR-CM diagnosis, tolerated them well during follow-up.[9,26] β-blockers were mainly prescribed due to cardiovascular comorbidities such as coronary artery disease or Afib.[27] Yet the withdrawal rates were up to 30% in all studies, in part due to increased symptom burden such as fatigue, syncope, or worsening HF, especially in patients with HFrEF.[9,27]

Exposure to β-Blockers and All-Cause Mortality in Patients With ATTR-CM With Advanced HF

All observational studies suggest that the net survival benefit from β-blockers might apply only to selected patients with ATTR-CM. As current HF guidelines recommend an LVEF-based approach for the prescription of neurohormonal antagonists, retrospective studies on guideline-directed medical therapy in ATTR-CM have tried to clarify whether patients with HFrEF might obtain survival benefit from β-blocker therapy. In the largest study, a propensity score–matched cohort of patients with ATTR-CM HFrEF showed a significant 39% reduction in mortality risk when treated with β-blockers (bisoprolol or metoprolol; hazard ratio [HR], 0.61 [95% CI, 0.45–0.83]).[9] The study concluded that patients with ATTR-CM with LVEF ≤40% might benefit from low-dose (≤2.5 mg bisoprolol per day or ≤25% of target dose for HF) β-blocker treatment by antagonizing neurohumoral activation that promotes the vicious cycle in HFrEF.

However, a concern arises about the impact of neurohumoral activation in HFrEF in the presence of concurrent autonomic dysfunction in ATTR-CM. A smaller study on American patients with ATTR-CM treated with nonselective β-blocker (carvedilol), often at high dosages, revealed that patients with ATTR-CM might have difficulties counteracting the reduction in afterload with carvedilol.[27] Worsening HF symptoms and increased rates of hypotension and fatigue led to consideration for discontinuation in up to 43%, a higher percentage than in other studies.[27] Discontinuation of nonselective β-blockers resulted in improved mortality outcomes.[27] Mechanistically, carvedilol is thought to block the excessive adrenergic tone more comprehensively and to reduce reactive oxygen metabolites to a higher extent than its β1-selective peers.[32] It is still unknown whether this also has a modifying effect on the course of the disease of ATTR-CM, as oxidative stress and coronary microvascular dysfunction have previously been described as a driver of pronounced TTR-fibril deposition.[33]

Current studies suggest that treating HF in patients with ATTR-CM with β-blockers may not align with the standard therapeutic approach recommended in ischemic or dilated cardiomyopathy. The following questions should be addressed in the future to better characterize the applicability of β-blockers in ATTR-CM: (1) if β-blocker should be selective or nonselective, (2) what dosing should be aimed for, and (3) whether or not the prescription should be related to the disease stage.

β-Blockers in CA Might Deal With Comorbidities Irrespective of LV Function

Retrospective studies on larger cohorts have suggested potential benefits of β-blocker therapy for patients in the presence of comorbidities, such as arterial hypertension,

Table. Original Publications on Guideline-Directed Medical Treatment of Heart Failure in ATTR-CM

First author (year) ref. number (study design)	Amyloid type/age	CV comorbidities	Median follow-up time (months)	Type of medication and median dosage/use	TTR stabilizer	Key outcomes and other relevant findings according to substance classes
Ioannou et al (2023)[9] (retrospective, single center; 2020–2022)	n=2371; ATTRv: 22%; ATTRwt: 78%; mean age: 78 y	Afib: 52%; arterial hypertension: 35%; CAD: 20%	28	β-blockers: n=1313 (55%); bisoprolol (≤ 2.5 mg bid)	4% (within studies)	1. Discontinuation rate of β-blockers: 22%
						2. No association between β-blockers and risk of mortality in total cohort (HR, 0.89 [95% CI, 0.77–1.04]; *P*=0.149).
End point: all-cause mortality						3. 39% lower risk of mortality if on low-dose β-blockers and LVEF <40% (independently of CAD as comorbidity; HR, 0.61 [95% CI, 0.45–0.83]; *P*=0.002).
Statistics: propensity-score matched				ACE inhibitors/ARBs: n=1362 (57%); ramipril (≤2.5 mg bid)		1. Discontinuation rate of ACE inhibitors/ARBs: 33%
						2. No association of ACE inhibitors/ARBs with mortality, even if stratified by LVEF >40% or ≤40%, (HR, 1.09 [95% CI, 0.93–1.26]; *P*=0.283).
				MRAs: n=925 (39%); spironolactone (80%) and eplerenone (19%)		1. Discontinuation rate of MRAs: 8%
						2. 23% lower risk of mortality in patients treated with MRAs (HR, 0.77 [95% CI, 0.66–0.89]; *P*<0.001).
						3. No statistically significant evidence for prognostic benefit of MRA use in HFrEF (HR, 0.83 [95% CI, 0.62–1.10]; *P*=0.192).
Barge-Caballero et al (2021)[26] (retrospective, multicenter; 2018–2020)	n=128; ATTRv: 2%; ATTRwt: 90%; not tested: 9%; mean age: 82 y	Afib: 56%; arterial hypertension: 68%; CAD: 14%	17	β-blockers: n=65 (51%); bisoprolol (2.5 mg bid)	53%	1. Discontinuation rate of β-blockers: 34%
End point: all-cause mortality						2. Association of low-dose β-blocker intake and lower all-cause mortality (HR, 0.18 [95% CI, 0.0.8–0.41] on IPTW).
Statistics: IPTW						
Cheng et al (2021)[27] (retrospective, single-center; 2002–2018)	n=309; ATTRv: 34%; ATTRwt: 66%; mean age: 73 y	Afib: 17%; arterial hypertension: NA; CAD: 7%	72	β-blockers: n=154 (50%); carvedilol (mean equivalent dose: 10 mg bid)	18%	1. Discontinuation rate of β-blockers: 43%
						2. No association between β-blocker intake and mortality, even if stratified by LVEF <40% or ≥40%.
						3. Discontinuation of β-blockers was associated with better survival (HR, 0.36 [95% CI, 0.18–0.76]; *P*=0.007)
End point: all-cause mortality				ACE inhibitors/ARBs: n=108 (35%); mean dose: NA		1. Discontinuation rate of ACE inhibitors/ARBs: 58%
						2. No association of ACE inhibitors/ARBs with mortality if stratified by LVEF <40% (HR, 0.67 [95% CI, 0.34–1.31]; *P*=0.24).
Statistics: inverse probability of treatment weighting				MRAs: n=74 (24%); mean dose: NA		1. Discontinuation rate of MRAs: 25%
						2. No association of MRAs with mortality if stratified by LVEF <40% (HR, 0.98 [95% CI, 0.49–1.99]; *P*=0.964)
Tini et al (2021)[28] (retrospective, multicenter; 2016–2020)	n=642 (mixed); AL: 26%; ATTRv: 16%; ATTRwt: 58%; mean age: 77 y	Afib: 57%; arterial hypertension: 58%; CAD: 16%	14	β-blockers: n=250 (39%); substance not specified; dose ≥50%: in 25% of the cohort	NA	1. Prescription due to CV comorbidities (Afib/CAD/arterial hypertension)
						2. Discontinuation rate of β-blockers: 19%
Aim: prescription pattern				ACE inhibitors/ARBs: n=276 (44%); substance not specified		1. Prescription due to CV comorbidities (Afib/CAD/arterial hypertension)
						2. Discontinuation rate of ACE inhibitors/ARBs: NA

(*Continued*)

Table. Continued

First author (year) ref. number (study design)	Amyloid type/age	CV comorbidities	Median follow-up time (months)	Type of medication and median dosage/use	TTR stabilizer	Key outcomes and other relevant findings according to substance classes
Dobner et al (2023)[29] (retrospective, single-center; 2019–2021)	n=57; ATTRv: 5%; ATTRwt: 95%; not tested: 0.1%; mean age: 80 y	Afib: 26%; arterial hypertension: NA; CAD: NA	3	SGLT-2i: n=17 (30%); dapagliflozin (100%)	100%	1. SGLT-2i were well-tolerated with no adverse events within 3 mo after the start of treatment.
Aim: assessment of clinical adverse events						
Lang et al (2024)[30] (retrospective; single center: 2022–2023)	n=182; ATTRv: 16%; ATTRwt: 84%; median age: 79 y	Afib: 71%; arterial hypertension: 64%; CAD: 20%	7	SGLT-2i: n=87 (48%); dapagliflozin (41%); empagliflozin (59%)	93%	1. Discontinuation rate of SGLT-2i: 12% (due to genitourinary symptoms)
End point: changes in weight, diuretic dose, and cardiac/renal biomarkers						2. SGLT-2i treatment results in greater reductions from baseline in weight, loop diuretic dose, and uric acid, compared with controls.
Statistics: propensity-score matched						
Porcari et al (2024)[31] (retrospective, multicenter; 2014–2022)	n=440; ATTRv: 18%; ATTRwt: 82%; mean age: 77 y	Afib: 67%; arterial hypertension: 58%; CAD: 17%; diabetes: 42%	28	SGLT-2i: n=220; dapagliflozin (67%); empagliflozin (32%); canagliflozin (0.4%)	21% (within studies)	1. Discontinuation rate of SGLT-2i: 5%
End point: all-cause mortality						2. Association of SGLT-2i therapy with lower all-cause mortality (HR, 0.57 [95% CI, 0.37–0.89]; *P*=0.01), CV death (HR, 0.41 [95% CI, 0.24–0.7]; *P*<0.001), and HF hospitalization (HR, 0.57 [95% CI, 0.26–0.91]; *P*=0.014)
						3. SGLT-2i therapy attenuates deterioration of NYHA functional class, NT-proBNP increase, and the rate of eGFR decline.
Statistics: propensity-score matched						4. SGLT-2i treatment reduces the need for loop diuretic initiation over 12 mo by 86%.

A summary of the registry study trials that have investigated the efficacy, safety, and tolerability of neurohormonal blocking substances in the treatment of ATTR-CM. The table provides an overview of the different trials, their number of participants, substances used, and the key results. ACE indicates angiotensin-converting enzyme; Afib, atrial fibrillation; AL, light-chain amyloidosis; ARBs, angiotensin-1-receptor blockers; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CA, cardiac amyloidosis; CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT-2i, sodium-glucose transport-2 inhibitors; and TTR, transthyretin.

coronary artery diseases, and Afib or other arrhythmias, irrespective of their LV function.[28] In these studies, β-blockers were prescribed primarily because tachyarrhythmias such as Afib, which is common in wild-type ATTR-CM, even in early stages, and may be indicative of disease progression.[9,28,34–36] It remains unclear though if rate control or rhythm control strategies effectively reduce the symptom burden associated with Afib over the long term. Moreover, patients with ATTR-CM may require an elevated heart rate to maintain cardiac output, but the optimal targeted heart rate is unknown. Currently, international guidelines advise a cautious approach to using β-blockers for rate control in patients with ATTR-CM, acknowledging the importance of preserving functional capacity by maintaining a high heart rate.[34]

Interaction of β-Blockers With Autonomic Dysfunction, Predominantly in Hereditary Transthyretin Amyloid Cardiomyopathy

Autonomic dysfunction is often underestimated and underappreciated in ATTR-CM. TTR-fibril deposition in the cardiac autonomic nerves can lead to cardiac autonomic dysfunction. It remains unknown whether sympathetic and parasympathetic nerves are equally affected by fibril deposition, but changes may promote disease progression and arrhythmogenesis.[37] As β-blockers interfere with sympathovagal balance, they can potentially aggravate dysautonomia, including postural hypotension.

In the international multicenter THAOS (Transthyretin Amyloidosis Outcomes Survey), autonomic dysfunction

occurred more commonly and earlier in patients with variants than in wild-type ATTR-CM.[38] Autonomic dysfunction occurs early in the course of ATTR-CM, with delays between the onset of autonomic symptoms and disease confirmation in wild-type ATTR-CM of almost 10 years.[38] Detection of autonomic symptoms by the Composite Autonomic Symptom Score-31 is low in patients with wild-type ATTR-CM.[39] Hence, screening for the presence of cardiovascular autonomic neuropathy by formal testing (eg, with metaiodobenzylguanidine scans) may enhance decision-making about the possible benefits of β-blockers, especially in patients with hereditary transthyretin amyloidosis with mixed phenotype.[40]

In conclusion, β-blocker therapy in ATTR-CM presents both potential benefits and risks. It may be useful for rate control in Afib and for those with ATTR-CM with HFrEF but could exacerbate conduction disease and chronotropic incompetence. The studies discussed above suggest that disease stage and comorbidities might influence the potential benefits in this patient population. Randomized controlled trials or meta-analyses are warranted to better guide their use and tolerance in patients with CA.

Take-Home Message on β-Blockers

In patients with ATTR-CM, β-blocker prescription should be done cautiously, with close monitoring for adverse effects, at the lowest possible dose to achieve the desired effect. β-blockers may aggravate autonomic dysfunction. Screening for chronotropic incompetence by treadmill tests or bicycle exercise may be useful to review and monitor the indication of β-blockers, especially in the presence of Afib. Low-dose β-blockers may reduce overall mortality in patients with ATTR-CM who have concomitant HF with a reduced ejection fraction. Low and fixed LV stroke volume(s) should be taken into consideration for the prescription of β-blockers (Figure 1).

ACE INHIBITORS/ARBs/ARNIs

CA Is an Underestimated Confounder in HFpEF Trials of ACE Inhibitors, ARBs, and ARNIs

ACE inhibitors, ARBs, and the new generation ARNIs are well-studied and well-established components of HF therapy in patients with HFrEF, improving overall mortality in ischemic cardiomyopathies and dilated cardiomyopathies.[20,41] During the past decade, attempts have been made to demonstrate the beneficial effect of these agents in patients with HFpEF. The PARAGON-HF trial (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) compared ARNIs to valsartan in patients with LVEF ≥45%, but ARNIs failed to reach a statistically significant reduction in the combined primary end point of death from a cardiovascular cause and HF hospitalization.[42] Nonetheless, analysis of prespecified subgroups showed a favorable outcome of ARNI treatment in women, due primarily to a reduction of HF hospitalization.[43] Given the predominance of ATTR-CM in men, the lack of benefit might be attributable to the fact that this condition was not actively screened for in male participants.[44,45]

Similarly, in echocardiographic studies of the earlier PARAMOUNT-HF (Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction Trial), the HFpEF subcohort had substantially reduced longitudinal strains and reduced circumferential strains relative to a matched

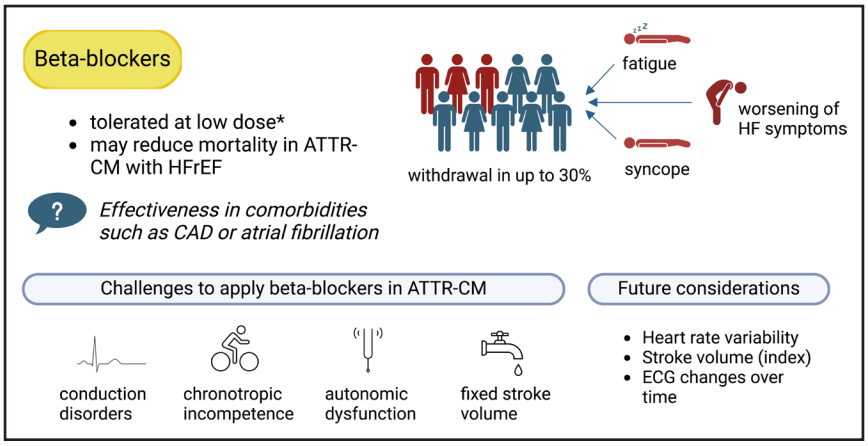

Figure 1. β-Blockers in transthyretin amyloid cardiomyopathy (ATTR-CM).
Current understanding of the effectiveness of β-blockers in ATTR-CM. Whether this class of medication is effective specifically in the presence of cardiac comorbidities remains to be addressed (question mark). In patients with ATTR-CM, clinicians should monitor conduction disorders (ECG) and evaluate the presence of chronotropic incompetence (eg, ergometry testing), autonomic dysfunction (tuning fork), and fixed stroke volume (faucet) before prescribing β-blockers. CAD indicates coronary artery disease; and HFrEF, heart failure with reduced ejection fraction. *Low-dose β-blockers denote ≤25% of the target dose for HF. Created in BioRender. Schwarting, S. (2025) https://BioRender.com/c32m291

hypertensive cohort, which is suggestive of unrecognized amyloidosis.[46] The investigators observed a subtle impairment of systolic contraction in speckle tracking analysis, which is typically found in infiltrative cardiomyopathies such as CA.[47]

Up to 15% of study participants of PARAMOUNT and PARAGON-HF met all the criteria of an ATTR-CM risk score (≥6 points), reflecting a potentially high prevalence of patients with CA in clinical trials on ACE inhibitors/ARBs/ARNis in HFpEF.[48] In addition, the selection criteria of PARAGON-HF could have been met by most of the patients with CA of a single-center registry, supporting the hypothesis that patients with CA were probably enrolled in the PARAGON-HF trial and may have confounded the results in these HFpEF trials.[21]

Tolerance and Outcomes of ACE Inhibitors/ARBs in CA and Preexisting Hemodynamic Conditions

To date, 3 retrospective registries have described the tolerability of ACE inhibitors/ARBs and their association with mortality in patients with CA (Table). Intake of ACE inhibitors/ARBs was associated with a previous medical history of arterial hypertension in two-thirds of the cohort. A possible association of the use of ACE inhibitors/ARB with cardiovascular outcomes has been assessed in 2 comparatively large ATTR-CM cohorts.[9,27] They found that up to 35% to 57% were prescribed ACE inhibitors/ARBs at baseline but one-third to half of these patients stopped these medications during follow-up due to intolerance and naturally decreasing blood pressure. Multivariate Cox regression and propensity score–matched analysis did not reveal a significant association of ACE inhibitors/ARBs with survival,[9,27] and there was no evidence for a significant survival benefit for patients with LVEF ≤40% treated with ACE inhibitors/ARBs.[9]

Effect of Cardiac Reverse Remodeling and Pulmonary Hypertension Under ARNIs in CA

Study results about ARNIs in ATTR-CM are scarce. The diagnosis of CA is often preceded by another disease that drives the indication for the prescription of ARNIs, such as ischemic cardiomyopathy with a reduced LVEF. It remains unknown whether patients with ATTR-CM benefit from guideline-directed medical treatment of their concomitant HF comorbidities.

ARNIs improve functional capacities and cardiac reverse remodeling indices including LV dimensions (eg, decrease in LV end-diastolic volume) in HFrEF.[49] Furthermore, this meta-analysis has shown that ARNIs outperform ACE inhibitors/ARBs for reducing LV mass index and left atrial volume index in patients with HFpEF.[49] However, in preclinical studies, the drug seems to achieve this effect by reducing cardiomyocyte hypertrophy, which has not been described in CA. Accordingly, it is unclear how well the clinical results of ARNIs in HFpEF might apply to patients with ATTR-CM. Pharmacological inhibition of the renin-angiotensin-aldosterone system by ARNIs or ACE inhibitors/ARBs could play an underestimated role in preventing adverse remodeling in the presence of cardiovascular comorbidities in patients with ATTR-CM. Neprilysin has previously been described as degrading enzymes in amyloid-β, of which aggregable isoforms are known to accumulate in Alzheimer disease. Thus, inhibition of neprilysin by sacubitril was thought to be associated with the development of dementia with long-term use.[50,51] Studies have not yet been performed on the potential role of neprilysin inhibition in TTR-fibril deposition. Finally, ARNIs can lead to a significant reduction of pulmonary pressures in patients with HFpEF independently of diuretic management,[52] but the efficacy of ARNIs on pulmonary pressures in patients with CA is unknown. Pulmonary hypertension resulting from increased LV filling, along with right ventricular to pulmonary artery uncoupling is associated with worse outcomes in patients with CA.[53] These findings underscore the potential rationale for considering ARNIs in these pathophysiological circumstances.[54]

Concern about side effects, such as systemic hypotension or worsening of preexisting renal dysfunction, has contributed to the reluctance to prescribe these drugs.

Take-Home Message on ACE Inhibitors/ARBs/ARNIs

In patients with ATTR-CM, renin-angiotensin-aldosterone system inhibition may mitigate adverse remodeling if cardiovascular comorbidities such as ischemic cardiomyopathy are present. The use of ACE inhibitors/ARBs/ARNIs has not shown any survival benefit in any HF phenotype in the absence of comorbidities. Renin-angiotensin-aldosterone system inhibition should be used cautiously, due to an increased risk of hypotension, especially in patients with autonomic dysfunction or advanced stages of disease (Figure 2).

MINERALOCORTICOID RECEPTOR ANTAGONISTS

CA in Treatment of Preserved Cardiac Function Heart Failure With Aldosterone Antagonist Study: Worse Prognosis but Same Benefit

MRAs block the intracellular receptor of aldosterone, thereby leading to increased sodium secretion and diuresis. The presence of mineralocorticoid receptors in cardiomyocytes and fibroblasts further supports the

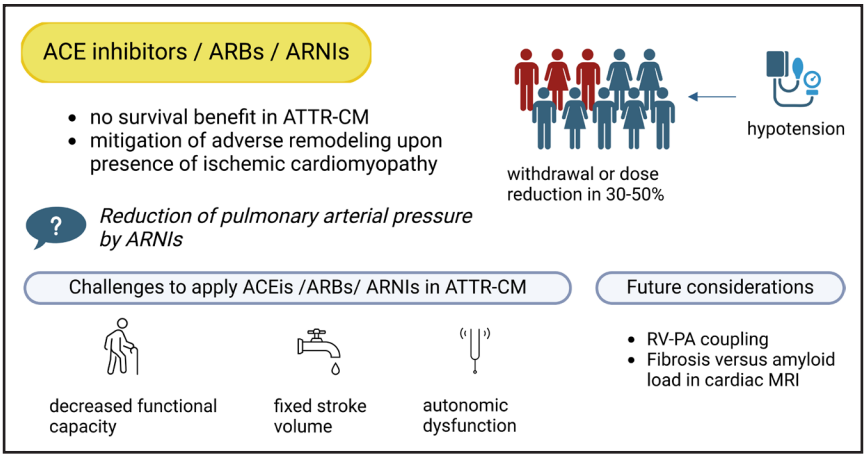

Figure 2. ACE (angiotensin-converting enzyme) inhibitors/angiotensin-1-receptor blockers (ARBs)/angiotensin-receptor-neprilysin-inhibitors (ARNIs) in transthyretin amyloid cardiomyopathy (ATTR-CM).
Current understanding of the effectiveness of ACE inhibitors/ARBs/ARNIs in ATTR-CM. It remains unclear to what extent pulmonary arterial pressure will be reduced in patients with ATTR-CM if treated with ARNI. Hypotension was the main cause for withdrawal or dose reduction of ACE inhibitors/ARBs/ARNIs in patients with ATTR-CM. Decreased functional capacity (disabled person), as well as fixed stroke volume (faucet), should be considered if ACE inhibitors/ARBs/ARNIs will be prescribed in patients with ATTR-CM. MRI indicates magnetic resonance imaging; and RV-PA coupling, right ventricular to pulmonary artery coupling. Created in BioRender. Schwarting, S. (2025) https://BioRender.com/j93d934

hypothesis that MRAs also exert an additive effect in preventing the development of cardiac fibrosis.[55] The 2 main agents recommended by HF guidelines are spironolactone and eplerenone. A nonsteroidal MRA, finerenone, was approved by the European Medicines Agency in 2022 for the treatment of chronic kidney disease with albuminuria and type 2 diabetes.[56] More recently, data of the FINEARTS-HF (Finerenone in Heart Failure With Mildly Reduced or Preserved Ejection Fraction) demonstrated a significant reduction of HF events and cardiovascular deaths in patients with LVEF ≥40% treated with Finerenone.[57]

European Society of Cardiology guidelines on HF recommend MRAs (Level IA) simultaneously with β-blockers and ACE inhibitors/ARBs in patients with HFrEF. In HFmrEF and HFpEF, MRAs have a Class IIb recommendation as an additional treatment option.[20] The TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With Aldosterone Antagonist) failed to show a significant reduction in all-cause mortality or cardiovascular mortality in patients with LVEF ≥45%.[58] However, post hoc analysis revealed that the trial results were confounded by the enrollment of patients who did not fulfill all HFpEF criteria in the 2 participating east-European countries.[58] An exploratory substudy of TOPCAT showed that 23% of the participants exhibited echocardiographic features indicative of CA such as an interventricular septal wall thickness of ≥1.2 cm or reduced mitral annular systolic velocity (s').[59] In addition, myocardial contraction fraction was lower in this group compared with the others.[59] At baseline, this subgroup was slightly older, predominantly male, had a higher prevalence of Afib, and had pronounced left atrial enlargement, factors that collectively suggest the presence of ATTR-CM. The primary outcome of the TOPCAT trial was similar in patients with characteristics suspicious for CA to those without such features, with a positive benefit of spironolactone in comparison to placebo.[59]

Tolerance of MRAs in Patients With CA

MRAs have been well-tolerated, with no need for dose reduction during follow-up, both in large ATTR-CM cohorts and in most patients with a mixed phenotype.[9,27] Patients treated with MRAs in these studies included those in advanced stages of the disease, and MRAs were combined with other guideline-directed medical therapies in up to two-thirds of these patients.

In their propensity score–matched analysis, Ioannou et al[9] reported a 23% lower relative risk of mortality in patients with ATTR-CM treated with MRAs (HR, 0.77 [95% CI, 0.66–0.89]; $P<0.001$). The positive effect of MRA use was seen in particular in patients with HFmrEF and HFpEF (LVEF ≥40%) who were treated with MRAs (HR, 0.75 [95% CI, 0.63–0.90]; $P=0.002$); whereas use in patients with HFrEF was not significantly beneficial (HR, 0.83 [95% CI, 0.62–1.10]; $P=0.192$),[9] consistent with previous, smaller retrospective studies.[27]

Use of MRAs in patients with ATTR-CM with concomitant chronic kidney disease, which is prevalent in progressive disease stages, may add a renal protective effect.[60]

Take-Home Message on MRAs

In patients with ATTR-CM, MRAs appear to be safe and well-tolerated, regardless of LVEF or disease stage, and

may improve survival across the entire spectrum of HF, particularly for HFmrEF and HFpEF (Figure 3).

SODIUM-GLUCOSE TRANSPORTER-2 INHIBITORS

SGLT-2i: Broad Range of Cardioprotective Mechanisms

During the past decade, SGLT-2i have emerged as a key component of effective HF therapy. Regardless of concomitant renal dysfunction or type 2 diabetes, treatment with empagliflozin, or dapagliflozin significantly reduced the combined risk of cardiovascular death or HF hospitalization in all phenotypes of chronic HF, from HFrEF to HFpEF.[61] This drug class appears to favorably influence the energetic work of cardiomyocytes and positively affect cardiac reverse remodeling by inhibiting proinflammatory pathways and diminishing fibrosis formation in response to stress.[61–63] These drugs induce stable maintenance of fluid homeostasis without compromising systemic blood pressure.[63] The results of the EMPULSE (Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure) show that these mechanisms may be particularly important in the setting of acute decompensation within the first 3 days of hospitalization.[64,65] Moreover, SGLT-2i have shown favorable effects on renal function. They reduce glomerular filtration and albuminuria, thereby maintaining a consistent oncotic pressure.[61] In addition, they substantially lower uric acid, a marker of inflammatory states that has been shown to independently predict survival in ATTR-CM[66–68] and in light-chain amyloid cardiomyopathy.[68]

Profound efficacy across all ranges of kidney disease severity and HF phenotypes makes them widely applicable in the range of cardiovascular comorbidities, but data on SGLT-2i in patients with ATTR-CM specifically are only recently emerging. Unfortunately, infiltrative diseases were listed as an exclusion criterion in the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction).[69] But the sister trial DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) aimed specifically to test this substance class in a heterogeneous group of patients with HFpEF. However, patients with structural heart diseases and hypertrophic phenotypes were potentially enrolled.[70,71] The primary composite end point was mainly driven by the reduction of cardiovascular hospitalization events.[70]

SGLT-2i Are Well-Tolerated and May Be Beneficial in Patients With ATTR-CM

Tolerability of SGLT-2i in ATTR-CM has previously been shown by 2 small observational studies with a follow-up time of up to 8 months. SGLT-2 inhibition was accompanied by an early decline in kidney function as observed by an initial drop in glomerular filtration rate, which recovered to baseline by 3 months.[29] Similarly, the short-term effectiveness of SGLT-2i have recently been investigated in a retrospective, controlled cohort of 87 patients with ATTR-CM by Lang et al.[30] Newly prescribed SGLT-2i treatment was associated with a reduction in loop diuretic dose, a significant reduction in body weight, and a urate-lowering effect in the initial 6 months of therapy in comparison to the propensity-matched control group.[30] In a recent multicenter retrospective study, SGLT-2i treatment in patients with ATTR-CM was associated with a reduced risk of HF hospitalization and a reduced risk of cardiovascular and all-cause mortality over a median follow-up of 28 months, regardless of the presence of diabetes or LVEF, in propensity score–matched analyses.[31] In addition, a

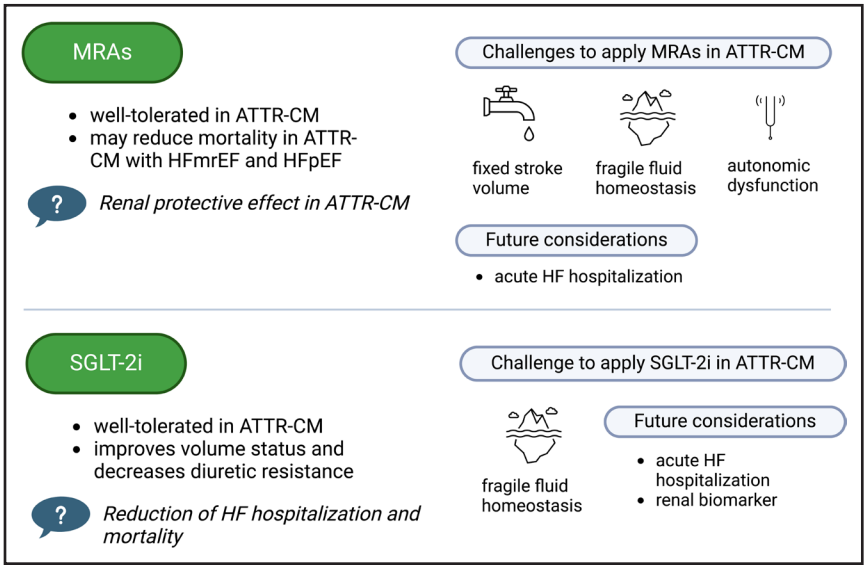

Figure 3. Mineralocorticoid receptor antagonists (MRAs) and sodium-glucose transport-2 inhibitors (SGLT-2i) in transthyretin amyloid cardiomyopathy (ATTR-CM). Current understanding of the effectiveness of MRA and SGLT-2i in ATTR-CM. Their renal protective effect, as well as their potential benefit in reducing hospitalization for heart failure (HF) and mortality, remains unclear and is currently under investigation. Fixed stroke volume (faucet) and fragile fluid homeostasis (iceberg) may challenge the use of MRAs and SGLT-2i, respectively, in patients with ATTR-CM. HFmrEF indicates HF with mildly reduced ejection fraction; and HFpEF, HF with preserved ejection fraction. Created in BioRender. Schwarting, S. (2025) https://BioRender.com/e18w493

worsening of renal function, an increase of NT-proBNP (N-terminal pro-B-type natriuretic peptide), and a deterioration of the New York Heart Association functional class were attenuated in the SGLT-2i treated cohort at 12 months.[31] These results suggest that SGLT-2i are well-tolerated in ATTR-CM and may be beneficial in combating diuretic resistance.

In conclusion, large-scale randomized prospective studies of SGLT-2i in patients with ATTR-CM are lacking, but their broad applicability and multiple mechanisms of action, as well as level III studies reporting effectiveness, suggest that SGLT-2i are promising therapies for patients with ATTR-CM.[72]

Take-Home Message on SGLT-2i

In ATTR-CM, SGLT-2i are well-tolerated by most patients and appear to improve volume status and combat diuretic resistance, without compromising systemic blood pressure. The use of SGLT-2i appears promising and beneficial across the spectrum of ATTR-CM (Figure 3).

COMBINED HF THERAPY IN ATTR-CM

Current HF guidelines have recommended combination therapy,[9] but there has only been 1 study about this in the context of ATTR-CM.[9] About one-sixth of the cohort was prescribed triple therapy consisting of β-blockers, ACE inhibitors/ARBs, and MRAs. In a propensity score–matched analysis, the risk of mortality was significantly reduced on triple therapy (MRAs, β-blockers, and ACE inhibitors/ARBs) in comparison to dual therapy (β-blockers and ACE inhibitors/ARBs; HR, 0.63 [95% CI, 0.49–0.80]; $P<0.001$).[9] However, treatment with only 2 classes of HF medication (β-blockers and ACE inhibitors/ARBs) did not show any survival benefit in comparison to single treatment (HR, 1.06 [95% CI, 0.81–1.39]; $P=0.677$). Due to the small subsample size, combinations with SGLT-2 inhibitors were not included in that analysis.[9] It is noteworthy that patients on triple therapy were sicker in terms of cardiovascular comorbidities, which along with LVEF seems again to be the driving factor for the implementation of medical HF therapy.[9]

CONCLUSION AND FUTURE PERSPECTIVES

ATTR-CM covers the entire spectrum of HF classifications by ejection fraction, but implementation of guideline-based medical treatment for HF remains a major challenge due to the disease's complexity. The patient-specific approach should consider potentially low

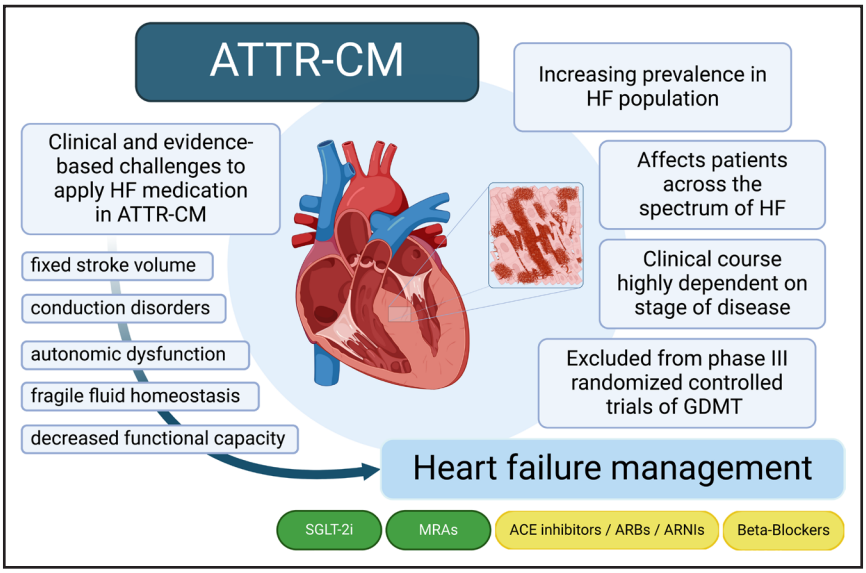

Figure 4. Current understanding of the challenges and effectiveness of guideline-directed medical therapy of heart failure (HF) in transthyretin amyloid cardiomyopathy (ATTR-CM).
Guideline-directed medical therapy (GDMT) of HF in patients with ATTR-CM. ATTR-CM is a complex, multisystemic disease. Its prevalence in the general HF population is increasing, and it affects patients across the whole spectrum of HF. Patients with ATTR-CM present with highly variable clinical courses of HF and their disease. Individual challenges need to be considered before prescription of GDMT. These include a fixed stroke volume, conduction disorders, autonomic dysfunction, fragile fluid homeostasis, and decreased functional capacity. To date, HF management in ATTR-CM has a low level of evidence due to limited available data. The current understanding of effectiveness is mainly based on propensity score–matched cohorts. Sodium-glucose transport-2 inhibitors (SGLT-2i) and mineralocorticoid receptor antagonists (MRAs; green boxes; good tolerability and survival benefit) can be applied safely irrespective of left ventricular ejection fraction, whereas low-dose β-blockers and inhibitors of renin-angiotensin-system (yellow boxes; individual tolerability but low evidence of beneficial use) need to be prescribed cautiously. ACE inhibitors/ARBs/ARNIs indicates angiotensin-converting enzyme inhibitors/angiotensin-I-receptor blockers/angiotensin-receptor-neprilysin-inhibitors. Created in BioRender. Schwarting, S. (2025) https://BioRender.com/k61q898

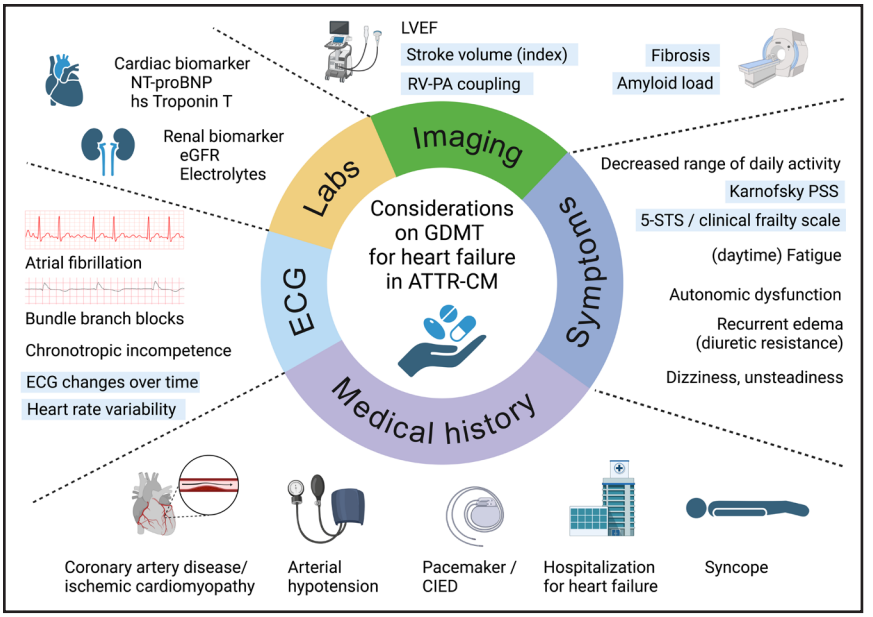

Figure 5. Present and future considerations on guideline-directed medical therapy of heart failure (HF) in transthyretin amyloid cardiomyopathy (ATTR-CM). Imaging, laboratory values, ECG, past medical history, and current leading symptoms should be systematically and repeatedly assessed in patients with ATTR-CM. Further considerations, highlighted in blue, may facilitate future tailoring of guideline-directed medical therapy of HF in this specific HF entity. 5-STS indicates 5 times Sit to Stand Test; CIED, cardiac implantable electronic devices; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PSS, Performance Status Scale; and RV-PA coupling, right ventricular to pulmonary artery coupling. Created in BioRender. Schwarting, S. (2025) https://BioRender.com/e36y619

and fixed LV stroke volumes (resulting in a higher risk for symptomatic hypotension), reduced functional capacity, impaired fluid homeostasis, concomitant autonomic dysfunction, and conduction disorders (Figure 4). The phenotypic diversity and progression of ATTR-CM are still incompletely understood, leading to the inclusion of varying degrees of disease severity in data analyses. The greatest unmet needs are high-quality data to determine the risks and benefits of guideline-based HF therapies. Discovery of reliable clinical markers that facilitate risk stratification concerning response to HF therapy would also be useful. The present narrative review paper is limited by the primary studies from which observations and recommendations are drawn, as they are all retrospective, nonrandomized studies. In addition to performing randomized controlled trials, it is necessary to reconsider whether guideline-suggested classification by LVEF is also useful in guiding HF treatment in ATTR-CM or whether other prognostic factors (such as biomarker staging, echocardiographic (eg, strain measurements and stroke volume index), hemodynamic (eg, stroke volume index) measures, or symptoms and frailty (eg, 5 times Sit to Stand Test or Clinical Frailty Scale) would more reliably guide HF treatment decision-making in these patients (Figure 5). Large-scale multinational registries could address this question.

ARTICLE INFORMATION

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