Heart Failure Management in Cardiac Amyloidosis: Towards a Paradigm Shift

Giorgia Panichella [1], Alberto Aimo [2,3] Vincenzo Castiglione [2,3] Giuseppe Vergaro [2,3] and Michele Emdin [2,3]

1. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; 2. Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy; 3. Fondazione Gabriele Monasterio, Pisa, Italy

Abstract

Heart failure (HF) and cardiac amyloidosis (CA) are significant clinical challenges, with evolving epidemiological patterns reshaping the understanding of these conditions. Traditionally linked with HF with preserved ejection fraction, CA is increasingly recognised for its specific characteristics, including a considerable subset of patients presenting with reduced left ventricular ejection fraction. This review explores how the neurohormonal activation observed in CA impacts on disease progression and management strategies. Historically, neurohormonal antagonists were considered contraindicated in CA owing to concerns about autonomic dysfunction and chronotropic incompetence. However, recent evidence suggests a paradigm shift, indicating that such agents may offer therapeutic benefits even in these patients. By examining these developments, this review provides a comprehensive overview of current therapeutic approaches, the role of neurohormonal modulation and the need for personalised care strategies to address the complexities of HF in the context of CA.

Keywords

Heart failure, cardiac amyloidosis, neurohormonal, β-blockers

Received: 20 October 2024 **Accepted:** 17 March 2025 **Citation:** *Cardiac Failure Review* 2025;11:e15. **DOI:** https://doi.org/10.15420/cfr.2024.33

Disclosure: The authors have no conflicts of interest to declare.

Correspondence: Michele Emdin, Fondazione Toscana Gabriele Monasterio, Via Giuseppe Moruzzi 1, 56124, Pisa, Italy. E: m.emdin@santannapisa.it

Cardiac amyloidosis (CA) is an increasingly recognised cause of heart failure (HF); it results from the deposition of amyloid fibrils within the myocardium and leads to progressive cardiac dysfunction.[1] CA can result from various types of amyloid proteins, with transthyretin CA (ATTR-CA) and light-chain CA (AL-CA) being the most prevalent forms affecting the heart.

The deposition of these amyloid fibrils disrupts the normal architecture and function of the heart, leading to restrictive cardiomyopathy, arrhythmias and HF. This condition, while less common than other HF aetiologies, poses a significant challenge owing to its complex pathophysiology and the severe impact it has on cardiac function.

In recent years, novel pharmacological treatments and targeted therapies have been transforming the management of CA, offering hope for improved outcomes. Therapies targeting the amyloidogenic cascade can modify the natural history of the disease, albeit only after a period of latency following treatment initiation (for example, around 18 months after starting tafamidis to impact on all-cause mortality).[2]

Cardiac involvement remains a crucial determinant of morbidity and mortality, and the evolution of this is partially independent from the underlying disorder. Supportive therapies may play a key role in counteracting cardiac remodelling and preserving cardiac function, mitigating the progression of HF while disease-modifying treatments gradually take effect.

Conventional HF therapies have been traditionally contraindicated in CA patients. This is attributed to poor haemodynamic tolerance of these therapies because of an altered pressure–volume loop, potential ventricular–vascular decoupling and chronotropic incompetence.[3] However, consensus documents recommendations rely upon weak evidence and expert opinion.[4]

Recent evidence suggests there has been a paradigm shift in managing HF in these patients, with a potential benefit from some neurohormonal drugs at least in ATTR-CA and/or in the early stage of the disease.

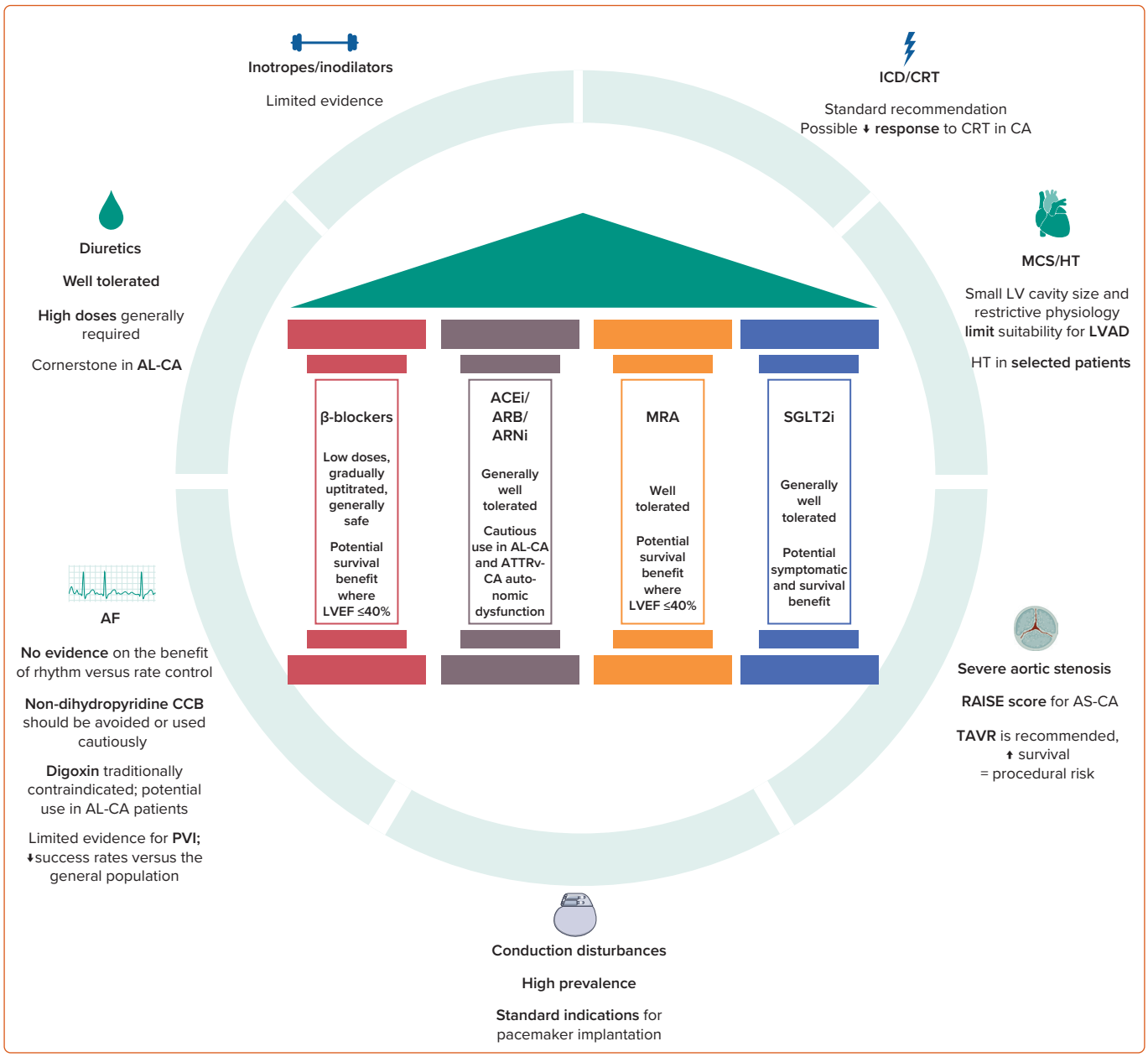
This review aims to explore the evolving epidemiology of HF and CA, focusing on understanding the role of neurohormonal activation in CA and its implications. Additionally, it will evaluate current therapeutic strategies for managing CA, while also addressing comorbidities and complications associated with HF (*Figure 1*).

Epidemiology

Within the spectrum of HF aetiologies, CA represents a critical but often overlooked cause of HF. While CA accounts for a relatively small proportion of HF cases overall, its prevalence is markedly higher in some groups, notably in elderly populations and individuals with CA red flags.[5,6] Conversely, HF is a common manifestation in patients with CA as amyloid infiltration compromises cardiac structure and function.

Until recently, epidemiological studies on CA were primarily single-centre and limited in sample size. However, a recent Spanish prospective multicentre study evaluated the prevalence of CA among 453 patients aged ≥65 years with HF and a left ventricular (LV) wall thickness >12 mm.[7] CA was diagnosed based on current recommendations in one in five

Figure 1: Heart Failure Treatment in Cardiac Amyloidosis



ACEi = angiotensin-converting enzyme inhibitor; AL-CA = light chain cardiac amyloidosis; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitor; AS = aortic stenosis; CA = cardiac amyloidosis; CCB = calcium channel blocker; HT = heart transplantation; LVAD = left ventricular assist device; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; PVI = pulmonary vein isolation; RAISE = Remodeling, Age, Injury, Systemic involvement and Electrical abnormalities; SGLT2i = sodium–glucose cotransporter 2 inhibitor; TAVR = transcatheter aortic valve replacement.

(20.1%) patients, with ATTR-CA in 84.6% and a higher prevalence in men (60.1% versus 39.9%; p=0.019). In this series, 26.5% of the patients with CA had a LV ejection fraction (LVEF) of <50%.[7]

In a previous study by Lindmark et al., 20% of 134 investigated patients in a Swedish cohort with HF and an LV wall thickness >14 mm had wild-type ATTR-CA (ATTRwt-CA).[8] Calculated for the whole population of HF patients, the prevalence is just over 1.1%. Comparing this number to the total population would give an estimated prevalence of 1:6,000.[8]

CA has been traditionally associated with HF with preserved ejection fraction (HFpEF), owing to extracellular accumulation of misfolded protein fragments causing a restrictive filling pattern. The reported prevalence of CA in HFpEF is in the range of 5–14%.[9–11] In a study by Hahn et al., 108 patients with HFpEF were prospectively subjected to endomyocardial biopsy. CA was diagnosed in 15 (14%) patients: seven patients with ATTRwt-CA; four with variant CA (ATTRv-CA); three with AL-CA; and one patient with AA amyloidosis.[12] Patients with HFpEF-CA were older, with a lower BMI, higher LV mass index and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin I levels.[12]

In a cohort of elderly patients with HFpEF without LV hypertrophy (LV wall thickness <12 mm), the prevalence of ATTRwt-CA was 5%.[13] A prospective study using bone scintigraphy to screen for ATTR-CA in HFpEF patients showed that ATTRwt amyloidosis accounts for 13% of patients with LV hypertrophy aged >60 years hospitalised for HFpEF.

Finally, in a cohort of 1,235 patients with HFpEF (LVEF ≥40%) aged ≥60 years and with an LV wall thickness of ≥12 mm, CA was diagnosed in 16 patients (1.3%); prevalence increased from 0% in patients aged 60–69

years old to 21% in those aged ≥90 years (p<0.001).[14]

Nonetheless, CA is emerging as an important cause of HF with reduced EF (HFrEF). In a systematic review including 11 studies and 3,303 patients, the pooled prevalence of CA in HF was 13.7%. The overall prevalence of CA in HFpEF was 15.1%, and that of HFrEF was 11.3%. The main factors associated with a diagnosis of CA in HF included older age, being male, raised NT-proBNP, increased interventricular septal thickness, apical sparing and reduced LV systolic function.[15]

The epidemiology of CA is steadily expanding and evolving, driven by increased awareness of red flags for CA and the possibility of a non-invasive diagnosis through the algorithm by Gilmore et al.[16,17] This trend is further influenced by the rising life expectancy of the general population and the introduction of disease-modifying therapies.

Advances in non-invasive diagnostic modalities and serum biomarkers have significantly enhanced the detection of CA among HF patients. Recognising the bidirectional relationship between HF and CA is crucial for timely diagnosis and appropriate therapeutic intervention.

Neurohormonal Activation

Over the decades, our understanding of HF has evolved considerably. Until the 1960s, HF was seen mainly as a cardiorenal disorder, primarily linked to sodium retention by the kidneys, resulting in increased fluid volume and thus leading to pulmonary and/or peripheral oedema.[18]

In the 1960s to the 1980s, the perspective shifted to a haemodynamic model, with an emphasis on the roles of reduced contractility and peripheral vasoconstriction in symptom occurrence and exercise intolerance. [18]

In the 1990s, HF was reinterpreted as a neurohormonal disorder, highlighting the role of activated endogenous neurohormonal mechanisms in disease progression.[18] Neurohormonal activation in HF is a critical factor in the pathophysiology and progression of the disease. Among these systems, the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) are particularly significant.[19]

The SNS plays a pivotal role in HF by increasing catecholamine levels, which cause excessive vasoconstriction, persistent tachycardia and cardiac arrhythmias. Elevated plasma catecholamines, resulting from heightened SNS activity, lead to a reduction in β-adrenergic receptor density within the failing myocardium, thereby diminishing the heart's responsiveness to inotropic and chronotropic stimuli.[20]

Chronic SNS activation also depletes the norepinephrine stores in the heart, forcing reliance on circulating catecholamines to maintain cardiac output, which contributes to a vicious cycle of worsening HF.[21]

Finally, increased sympathetic activity is associated with chronotropic incompetence, which is characterised by an insufficient increase in the heart rate during exercise. This may result from β-adrenergic receptor downregulation, β-blocker use or high-baseline heart rates, and leads to exercise intolerance and reduced exercise capacity.[22]

The RAAS promotes sodium and water retention, vasoconstriction and myocardial fibrosis. Overactivation of the RAAS leads to the production of angiotensin II, a potent vasoconstrictor, which raises blood pressure and contributes to adverse cardiac remodelling. Additionally, aldosterone promotes myocardial fibrosis and endothelial dysfunction.[23]

Pharmacological interventions targeting the RAAS, including angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs) and the more recent angiotensin receptor-neprilysin inhibitor (ARNi) sacubitril/valsartan, have proven highly effective in improving clinical outcomes in HF patients.[24–26] Mineralocorticoid receptor antagonists (MRAs) inhibit aldosterone's action, leading to reduced sodium and water retention, decreased blood pressure and improved outcomes in HF.[27] All these agents not only reduce mortality and hospitalisation rates but also help reverse maladaptive cardiac remodelling.

The pathophysiology of HFpEF differs from that of HFrEF, with neurohormonal activation having a much less prominent role. Accordingly, all neurohormonal antagonists have failed to prolong the survival of patients with HFpEF in large randomised trials.[28,29]

Despite its typical presentation with a hypertrophic phenotype, CA cannot be assimilated to HFpEF for many reasons, including its different pathophysiology (with an extracellular accumulation of amyloid fibrils producing a pseudohypertrophy) and natural history. Furthermore, the effects of AL-CA and ATTR-CA on the neurohormonal axes might be partially different, with a greater toxic effect of light-chain than transthyretin fibrils, causing cardiomyocyte damage and increased wall stress (both leading to natriuretic peptide release), a more rapid development of cardiac dysfunction (with the need of SNS and RAAS activation to sustain haemodynamics) and a direct toxic effect of light-chain amyloid fibrils on cardiac sympathetic terminals.[30]

Neurohormonal activation in CA was researched for the first time in a study by Vergaro et al.[30] The authors matched 47 patients with AL-CA and 61 with ATTR-CA to HF patients based on age, sex, LVEF ranges, renal function and HF therapies. Patients with AL-CA had: a 10-fold higher NT-proBNP than HF patients (6,548 ng/l; 95% CI [2,059–15,097] versus 692; 95% CI [243–2,241]; p<0.001); and slightly higher norepinephrine (595 ng/l; 95% CI [383–869] versus 416; 95% CI [250–693]; p=0.047). Patients with ATTR-CA had: higher NT-proBNP (3,984 ng/l; 95% CI [2,275–9,505] versus 1,751 ng/l; 95% CI [470–4,768]; p=0.006); norepinephrine (552 ng/l; 95% CI [344–855] versus 441; 95% CI [323–601]; p=0.020), and renin (14 mU/l; 95% CI [8–80] versus 10 mU/l; 95% CI [4–34]; p=0.017).

Patients with AL-CA or ATTR-CA more often had two or three neurohormones above the corresponding upper reference limits than matched HF patients. NT-proBNP and aldosterone were univariate predictors of the primary endpoint of 1-year cardiovascular death or HF hospitalisation in patients with ATTR-CA, but not in matched controls. NT-proBNP and renin predicted the secondary endpoint of 5-year cardiovascular death in patients with AL-CA, but not in matched controls.

These findings show that CA patients have a higher neurohormonal activation than non-CA HF patients and confirm the prognostic value of NT-proBNP in ATTR-CA, thus suggesting the potential benefit of MRAs or ARNis in patients with ATTR-CA.[31]

Therapeutic Strategies

Therapies targeting the amyloidogenic cascade can modify the natural history of the disease, albeit only after a period of latency following treatment. In the meantime, cardiac involvement remains a crucial determinant of morbidity and mortality, and its evolution is partially independent from the underlying disorder.

Four Pillars

Historically, the use of β-blockers and ACEi/ARB/ARNis has been contraindicated in CA by most consensus documents (*Table 1*).[4]

β-blockers are theorised to be poorly tolerated in people with CA because of patients' fixed stroke volume and dependence on a chronotropic response to maintain cardiac output.[1] This is especially critical in cases with overt restrictive physiology, where cardiac output relies heavily on heart rate.[32]

Additionally, ACEi/ARB/ARNis are believed to exacerbate hypotension from amyloid-associated autonomic dysfunction in AL-CA and ATTRv-CA.[33] Similarly, they can also be poorly tolerated, particularly in patients who are hypotensive. A retrospective study indicated no survival benefit from β-blocker or ACEi/ARB therapy in patients with ATTR-CA.[34] Moreover, β-blocker discontinuation seemed to be associated with decreased mortality.[34]

Several consensus guidelines advise against the use of β-blockers or ACEi/ARBs, and the European Society of Cardiology (ESC) position statement suggests to deprescribe β-blockers and avoid ACEi/ARBs in all patients.[35] However, nearly 30% of patients in the ATTR-ACT trial were receiving β-blockers or ACEi/ARBs.[2]

In a study on 99 patients with CA (72% men; mean age 80 years; 33% AL-CA and 67% ATTR-CA), β-blockers were successfully prescribed in up to 87% of patients, ACEi/ARB in up to 75% and MRAs in up to 63%.[36] Furthermore, the vast majority of patients tolerated these therapies without major adverse events, provided that no contraindications were present, and that the medications were initiated at low doses, gradually uptitrated and closely monitored.[36]

Similar results supporting the safe use of HF therapies in CA patients with HFrEF or HF with mid-range EF were reported in a study by Yan et al., where ARNis were also included.[37] The study showed no statistically significant differences in rates of potential adverse effects in treated versus untreated patients. Moreover, there was no association with hospitalisation or mortality for baseline or follow-up β-blocker, ACEi/ARB/ARNi or MRA use.[37]

As stated above, patients with CA exhibit greater neurohormonal activation than those with HF, and this activation may contribute to the progression of cardiac disease over time.[30] Additionally, endomyocardial biopsies from patients with CA show significant fibrosis, which may influence the clinical manifestations of heart disease and could potentially be mitigated by antifibrotic drugs such as ACEis/ARBs or MRAs.[38]

Besides these considerations, a recent study by Ioannou et al. characterised HF treatment in over 2,000 patients with ATTR-CA followed at the National Amyloidosis Centre over 2000–22.[39] Patients with a more severe cardiac phenotype were found to be more frequently treated with HF medications. During a median follow-up of 27.8 months, 21.7% of patients discontinued β-blockers and 32.9% discontinued ACEi/ARBs compared to only 7.5% for MRAs. Propensity score-matched analysis showed that MRAs were independently associated with a reduced risk of mortality in the overall population (HR 0.77; 95% CI [0.66–0.89]; p<0.001) and in patients with LVEF >40% (HR 0.75; 95% CI [0.63–0.90]; p=0.002).

This is in line with a retrospective analysis of the TOPCAT trial in a subcohort enriched for echocardiographic characteristics consistent with CA.[40] Low-dose β-blockers were associated with reduced mortality in patients with an LVEF ≤40% (HR 0.61; 95% CI [0.45–0.83]; p=0.002), while ACEis/ARBs showed no significant benefit.[39]

These results suggest that MRAs and low-dose β-blockers may offer a survival benefit in ATTR-CA, challenging current recommendations. The relative risk reduction with β-blockers and MRAs is similar to that demonstrated in the ATTR-ACT study with tafamidis for all-cause mortality, but at a much lower medication cost.[2,3] However, randomised controlled trials would be needed to investigate further these therapies in ATTR-CA.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have been shown to improve the outcome of patients with HF with either preserved or reduced EF, but patients with CA have been excluded from all phase III trials on empagliflozin and dapagliflozin.[41–44]

The slight diuretic effect and multiple proposed cardiac-protective mechanisms may prove beneficial even in patients with CA.[45] A small, single-centre, retrospective study compared patients with ATTR-CA and on tafamidis (n=40) with patients on tafamidis who were starting dapagliflozin (n=17). Over 3 months, dapagliflozin was well tolerated but changes in NT-proBNP did not differ between the two groups (p=0.557).[46]

In a recent multicentre, longitudinal, observational study performed across 14 referral centres for CA, 220 ATTR-CA patients treated with SGLT2i (mean age: 77 years; mean LVEF: 46%) were compared to 220 propensity-matched controls.[47] SGLT2i treatment in ATTR-CA patients was well tolerated, with only 4.5% of patients discontinuing therapy. Moreover, it was associated with a decreased rate of worsening in HF symptoms, less increase in NT-proBNP, a slower decline in renal function and a lower diuretic agent requirement over time.

Over 28 months, SGLT2i therapy was associated with lower all-cause mortality (HR 0.57; 95% CI [0.37–0.89]; p=0.010), cardiovascular mortality (HR 0.41; 95% CI [0.24–0.71]; p<0.001), HF hospitalisation (HR 0.57; 95% CI [0.36–0.91]; p=0.014), and the composite outcome of cardiovascular mortality and HF hospitalisation (HR 0.57; 95% CI [0.38–0.84]; p=0.003).[47]

In a recent, small-scale, retrospective study on patients with AL-CA, SGLT2i therapy was generally well tolerated, though some patients experienced volume depletion symptoms that required temporary discontinuation.[48] The therapy was associated with reductions in diuretic dosage and NT-proBNP levels (p<0.05), suggesting potential benefits in patients with AL-CA who have symptomatic HF and/or high diuretic requirement.[48]

The evidence on the safety and efficacy of HF therapies in CA is outlined in *Table 2*.

Diuretics, Inotropes and Inodilators

Patients with CA usually have dyspnoea and tissue oedema because of increased pressures in the pulmonary vessels and the venous system. Diuretics (loop diuretics and MRAs) are often needed in high doses, are well tolerated and may be combined. In AL-CA, diuretics are the cornerstone of therapy since autonomic dysfunction often hinders the use of RAAS inhibitors.[49]

Diuretic dose has also been demonstrated to be a strong independent prognostic measure in ATTR-CA patients. A daily mean diuretic dose of 0.6 ± 1.0 mg/kg was associated with all-cause mortality (adjusted HR 1.43; 95% CI [1.06–1.93]) in a cohort of 309 patients with ATTR-CA. Moreover,

Table 1: Recommendations for Drugs for Heart Failure in Cardiac Amyloidosis

Drug	European Society of Cardiology[35]	German Cardiac Society (DGK)[59]	Canadian Cardiovascular Society/Canadian Heart Failure Society[3]	American Heart Association[5]	Japanese Circulation Society[58]
Loop or thiazide diuretic	Recommended*	Recommended*	Recommended*	Recommended, but avoid underfilling and worsening renal function from restrictive physiology*	Recommended*
β-blocker	Not recommended, deprescribe*	Avoid or very cautious use*	Avoid or very cautious use*	No data for benefit; may not be tolerated given fixed stroke volume*	Tolerated dosing might be considered*
ACEi/ARB	Not recommended*	Avoid or very cautious use*	Avoid or very cautious use*	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction*	Tolerated dosing might be considered*
Sacubitril/valsartan	No recommendation	No recommendation	No recommendation	No data for benefit; may exacerbate amyloid-related hypotension from autonomic dysfunction*	No recommendation
MRA	No recommendation	No recommendation	Recommended*	Might be considered in conjunction with loop diuretics if adequate blood pressure and renal function*	Tolerated dosing might be considered*

**Expert consensus opinion. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DGK = Deutsche Gesellschaft für Kardiologie; MRA = mineralocorticoid receptor antagonist. Source: Rapezzi et al. 2022.[4] Adapted with permission from Elsevier.*

adding diuretic dose as categories (0 mg/kg; >0–0.5 mg/kg; >0.5–1 mg/kg; and >1–2 mg/kg) to previously published ATTR risk scores provided significant incremental value (the area under the curve of the Mayo risk score increased from 0.693 to 0.767 and the UK risk score from 0.711 to 0.787).[50]

Care should be taken to avoid worsening renal function, electrolyte disturbances and excessive preload reduction.

There is also evidence that ambulatory diuresis clinics are safe and feasible management strategies in these patients, often reducing acute care need.[51]

The evidence about inotropes and inodilator therapy in CA is very limited. In a small, retrospective cohort of patients with CA receiving levosimendan during an episode of acute HF, according to clinical indication, levosimendan proved to be well tolerated and safe, though with a limited impact on in-hospital and post-discharge outcome.[52]

Even in patients with cardiogenic shock, inotropic therapy does not seem to improve outcome. In a single-centre, retrospective study, 26 patients with CA were admitted to the intensive care unit because of cardiogenic shock. Dobutamine was administered to 21 of them, with norepinephrine added in 10 of these patients; two were switched from dobutamine to levosimendan. The response to inotrope therapy was poor, with 17 patients (81%) dying during hospitalisation and the other four (15%) within 3 months.[53]

Digoxin, a cardiac glycoside, exerts its positive inotropic effects by reversely inhibiting the myocardial Na^+/K^+ ATPase; its role in CA will be discussed in the section on AF under the heading of comorbidities.

Defibrillation and CRT

Ventricular arrhythmias often represent the terminal events for patients with CA, especially those with AL-CA compared to ATTR-CA, with non-sustained ventricular tachycardia prevalence ranging from 5% to 27% and reaching 100% during stem cell transplants.[54,55]

In the past, it was argued that ICD implantation might be less beneficial for CA patients owing to a higher defibrillation threshold.[56] However, it is now known that ICDs can effectively treat sustained ventricular arrhythmias in these patients.[57]

In the absence of dedicated studies, all consensus documents agree that an ICD should be offered to patients with standard indications for secondary prevention, with the partial exception of the Japanese guidelines, which do not give a class I indication for secondary prevention; this is because of the lack of demonstrated prognostic benefit and the frequency of pulseless electric activity as the ultimate cause of death.[4,58]

Attitudes toward ICD implantation for primary prevention range from 'rather generous (primary prophylactic) indication' (German Cardiac Society position statement) to the 'usually not recommended' (ESC position statement).[35,59] The general consensus is that ICD implantation should be avoided in patients with a life expectancy of <1 year.[4]

In CA patients, despite the high prevalence of LV dysfunction and conduction disturbances, the potential of cardiac resynchronisation therapy (CRT) to promote cardiac remodelling and improve survival has been scarcely explored and all consensus documents refer to the recommendations by corresponding national and international societies.[4]

The ESC statement is the only one recommending that CRT be considered in patients requiring pacemaker (PM) implantation if the paced burden is predicted to be high; this is likely based on the finding that a higher right ventricular pacing burden is associated with deleterious remodelling and congestive HF in patients with ATTR-CA, while biventricular pacing is associated with improvements in LVEF, New York Heart Association (NYHA) class and degree of mitral regurgitation.[35,60] Nonetheless, indications for CRT have been established in patients with non-amyloidotic HF, which warrants further investigations in the specific setting of CA.

In a small study by Donnellan et al., 30 patients with ATTR-CA who underwent CRT implantation were matched based on age, sex, LVEF, NYHA functional class and ATTR-CA stage with 30 ATTR-CA patients who did not receive a CRT device.[61] CRT implantation was not only

Table 2: Characteristics of the Studies Investigating Safety and Efficacy of Heart Failure Medications in Cardiac Amyloidosis

Reference	Study Characteristics	Population				NYHA Class III–IV (%)	Median LVEF	Median NT-proBNP (ng/l)	HF Therapies at CA Diagnosis	Discontinuation Rates	Safety	Outcomes
		Number of Patients	Women (%)	Median Age (Years)	CA type							
Aimo et al. 2020[36]	Single-centre, retrospective (2009–19)	99	28% (100% white)	80 years	33% AL-CA 66% ATTR-CA	54%	50% (15% HFrEF, 26% HFmrEF, 58% HFpEF)	3,984 ng/l	87% BB 75% ACEi/ARB 63% MRA	7% BB 0% ACEi/ARB 0% MRA	*__ACEi/ARB and MRA__ can be safely used in CA	–
											*Patients starting or starting/up-titrating a __BB__ did not show a higher frequency of adverse events	–
Cheng et al. 2021[34]	Single centre, retrospective (2002–18)	309	16% (72% white)	73 years	100% ATTR-CA (66% ATTRwt, 34% ATTRv)	45%	45% (47% HFpEF, 19% HFmrEF, 34% HFrEF)	BNP or NT-proBNP elevated in 40% of cases	50% BB 35% ACEi/ARB 24% MRA	50% BB 59% ACEi/ARB 25% MRA	–	†__BB__ discontinuation was associated with ↓mortality
											–	‡No association with mortality for __ACEi/ARBs__
											–	‡No association with mortality for __MRAs__
Yan et al. 2023[37]	Single centre, retrospective (2012–22)	82	17% (61% white)	72 years	19% AL-CA, 45% ATTRwt-CA, 35% ATTRv-CA	N/A	38% (35% HFmrEF, 65% HFrEF)	4,591 ng/l	63% BB 51% ACEi/ARB/ARNi 44% MRA	21% BB 22% ACEi/ARB/ARNi 16% MRA	__BBs, ACEis/ARBs/ ARNis and MRAs__ can all be safely used	‡__BB, ACEi/ARB/ARNis and MRA__ use does not appear to improve mortality or hospitalisation
Ioannou et al. 2023[39]	Single centre, retrospective (2000–22)	2,371	10% (80% white)	77 years	78% ATTRwt-CA 22% ATTRv-CA	20%	48% (78% HFpEF or HFmrEF, 22% HFrEF)	2,925 ng/l	55% BB 57% ACEi/ARB 39% MRA	22% BB 33% ACEi/ARB 7.5% MRA	–	*Treatment with __low-dose BB__ was independently associated with ↓mortality in patients with LVEF ≤40%
											–	‡No convincing differences for treatment with __ACEi/ARBs__
											–	*Treatment with __MRAs__ was independently associated with a ↓ risk of mortality in the overall population and in patients with LVEF >40%
Porcari et al. 2024[47]	Multicentre, longitudinal, observational	220 patients treated with SGLT2i versus 220 controls	10%	77 years	81% ATTRwt-CA, 19% ATTRv-CA	23%	46% (66% HFpEF or HFmrEF, 34% HFrEF)	2,693 ng/l	60% BB 45% ACEi/ARB 47% MRA	4.5% SGLT2i	*__SGLT2i__ is safe and associated with favourable effects on HF symptoms, renal function and diuretic requirement	*__SGLT2i__ treatment was associated with ↓risk of HF hospitalisation and cardiovascular and all-cause mortality
Lang et al. 2024[48]	Single centre, retrospective (2022–24)	17 patients with AL-CA treated with SGLT2i versus 21 non-treated	29%	66 years	100% AL-CA	29%	52% (59% HFpEF, 18% HFmrEF, 23% HFrEF)	1,338 ng/l	6% BB 6% ACEi/ARB/ARNi 82% MRA	7.4% SGLT2i permanent discontinuation 22% SGLT2i temporary discontinuation 27 patients in the safety analysis cohort	‡__SGLT2i__ treatment was generally well tolerated in patients with AL-CA, but volume depletion symptoms may limit continuous use	*__SGLT2is__ may aid management of congestion in AL-CA, as evidenced by reduced loop diuretic dosage and NT-proBNP levels

**Favourable findings. †Potentially harmful findings. ‡Indifferent findings. ACEi = angiotensin converting enzyme inhibitors; AL-CA = light-chain cardiac amyloidosis; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor neprilysin inhibitors; ATTR-CA = transthyretin cardiac amyloidosis; ATTRv-CA = variant transthyretin cardiac amyloidosis; ATTRwt-CA = wild-type transthyretin cardiac amyloidosis; BB = β-blocker; CA = cardiac amyloidosis; HF = heart failure; HFmrEF = HF with mid-range ejection fraction; HFpEF = HF with preserved ejection fraction; HFrEF = HF with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal fraction of pro-B-type natriuretic peptide; NYHA = New York Heart Association; SGLT2i = sodium–glucose cotransporter 2 inhibitors.*

significantly associated with improved LVEF and NYHA class, but also associated with improved survival (HR 0.39; 95% CI [0.21–0.74]; p=0.003).[61]

Nonetheless, a small multicentre retrospective French study has demonstrated that CA patients seem to have a lower rate of CRT response (absolute delta LVEF ≥10%) and, consequently, a worse cardiovascular prognosis after CRT implantation compared to propensity-matched dilated cardiomyopathy patients.[62]

Mechanical Circulatory Support and Heart Transplantation

A small LV cavity size and restrictive physiology make CA patients poor candidates to LV assist device implantation.[63] Retrospective studies suggest that intra-aortic balloon pumps may be viable as a bridge to heart transplantation (HT) or total artificial heart implantation.[64]

HT remains a viable option for individuals with ATTRv—either as a standalone procedure or in conjunction with liver transplantation—as well as for selected patients aged <65 years with ATTRwt-CA and certain cases of AL-CA.

For ATTRv-CA patients, a multidisciplinary approach involving cardiologists, hepatologists and neurologists is recommended to evaluate the necessity of combined heart and liver transplantation, as outlined in the 2016 International Society for Heart and Lung Transplantation guidelines (class IIA; level of evidence B).[65] Stanford's HT evaluation guidelines can provide additional guidance in selecting HT candidates.[66]

In cases of AL-CA, HT is typically considered only after effective chemotherapy has controlled the underlying haematologic disorder; if disease-specific treatments are contraindicated because of HF, early planning for autologous stem cell transplantation is advised. Severe extracardiac amyloid organ dysfunction is generally a contraindication for HT (class IIA; level of recommendation B).[65]

Guidance on disease-modifying therapies post-transplantation, including in cases involving combined heart and liver transplants or domino transplants, remains unaddressed.

Comorbidities

AF

AF is a prevalent arrhythmia in patients with CA with a mean prevalence of 15% that reaches 40% in ATTRwt-CA.[67] It often exacerbates symptoms and complicates disease management owing to the structural and functional abnormalities characteristic of amyloid infiltration in the atria.

However, no evidence on the prognostic benefit of maintaining sinus rhythm versus controlling the heart rate is available, and the consensus documents do not provide any specific recommendation.[4] A pragmatic approach is to pursue a rhythm-control strategy when the atria are not extensively remodelled, i.e., enlarged and dysfunctional.

Among antiarrhythmic drugs, non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should be avoided or used with extreme caution because of the risk of precipitating HF decompensation.[4] The Japanese guideline allows the use of these drugs, on a case-by-case basis, in patients with ATTR-CA and preserved EF.

Amiodarone is presented as the first-choice antiarrhythmic drug primarily because of concerns about the other drugs.[4] Its adverse effects, particularly during long-term administration, are well known.

Digoxin was traditionally contraindicated in patients with CA because of old case reports reporting toxic effects attributed to the binding of digoxin to amyloid fibrils; this was attributed to the accumulation of digoxin in amyloid deposits, although such accumulation has never been demonstrated.[68,69] Recent retrospective cohorts suggest that – at least in AL-CA – digoxin is safe when started at low doses and patients are closely monitored.[70]

Evidence on pulmonary vein isolation (PVI) for AF is very limited. The success rate in patients with CA seems lower than in the general population (75% at 1 year and 60% at 3 years).[71] Only the Japanese guideline provides specific recommendations on PVI, stating that patients with paroxysmal AF without left atrium dilatation or LV hypertrophy (i.e., those without extensively remodelled atria) may be candidates for PVI (Class IIb; level C). Conversely, PVI is contraindicated for patients with AL-CA, poor prognosis, severe left atrium dilatation and LV hypertrophy (Class III, level C).[58]

Conduction Disturbances

Many patients with CA experience atrioventricular (AV) conduction disturbances owing to amyloid infiltration or compression of the AV node and the bundle of His. The basal segments of the septum are often early sites of amyloid deposition.[72] The right atrium is less affected, making sinus node disease less common than AV conduction disturbances.[73]

Data on the prevalence of AV conduction disturbances in CA are fragmented. In a cohort of 25 patients with AL-CA, 92% had prolonged *infra*-His conduction times, while 88% had normal sinus node function.[74]

In a multicentre study of 405 patients (29% AL-CA; 15% ATTRv-CA; 56% ATTRwt-CA) without a PM at baseline, 9% received a PM within 3 years. Factors independently associated with PM implantation included a history of AF (HR 3.80; p=0.002), a prolonged PR interval (HR 1.013; p=0.002) and a QRS duration of >120 ms (HR 4.7; p=0.001). The combined presence of these factors increased the risk of PM implantation sixfold (HR 6.26; 95% CI [1.90–20.60]), while their absence had a negative predictive value of 92% over 6 months.[75]

Severe Aortic Stenosis

The coexistence of calcific aortic stenosis (AS) and CA increases with age and is not uncommon in the elderly.

A meta-analysis found a median CA prevalence of 8% in patients with severe AS referred for valve replacement; 67% were men, the median age was 84 years and nearly all (98%) had ATTR-CA.[6] Identifying CA in patients with AS is challenging because they have overlapping features.[76,77]

A clinical score (RAISE) that uses LV Remodeling (hypertrophy/diastolic dysfunction), Age, Injury (high-sensitivity troponin T), Systemic involvement (e.g. carpal tunnel syndrome) and Electrical abnormalities (right bundle branch block/low voltages) was developed to predict the presence of AS-CA among patients with AS.[78]

When CA is diagnosed, AS severity should be assessed per current guidelines, noting that around 50% of CA patients exhibit a paradoxical low-flow, low-gradient AS pattern.[76] This may be owing to factors such as severe LV concentric remodelling and impaired diastolic filling.[76]

Patients with severe AS and CA have similar outcomes to those with lone AS when LV thickness is <16 mm, but have worse prognoses with greater thickness.[79]

Finally, transcatheter aortic valve replacement (TAVR) should not be withheld in patients with CA since there is evidence that it improves survival versus medical management independent of the presence of CA; moreover, periprocedural complications are similar in patients with and without CA.[78] AS-CA can also be predicted by the CT routinely performed prior to TAVR by calculating the extracellular volume, which has demonstrated a strong correlation with the degree of amyloid infiltration, as well as with the amount of accompanying fibrosis.[38,80]

Conclusion

The nuanced interaction between HF therapies and CA presents a challenging yet critical area for clinical research and practice. Evidence from recent studies offers valuable insights but also raises numerous questions regarding the optimal use of neurohormonal blockade in CA patients, challenging the traditional contraindications of such drugs in this setting.[34,36,37,39]

It is crucial to recognise that CA often requires supportive therapies to stabilise cardiac function, providing the necessary time for disease-modifying treatments to influence the natural progression of the disease. While certain HF medications, such as low-dose β-blockers and MRAs, may offer survival benefits, their efficacy can vary based on patient-specific factors such as disease severity and tolerance to the medication.

This highlights the urgent need for randomised clinical trials to better understand the potential benefits and risks of neurohormonal blockade in this population. Future research should focus on identifying which patients are most likely to benefit from these treatments and at what doses, ensuring that therapy is both effective and safe.

Effective management also necessitates close collaboration between centres specialising in CA and referring cardiologists to optimise care and ensure timely intervention. In summary, until more data are available, clinicians should be aware that neurohormonal antagonist therapies are generally well tolerated, particularly in patients with ATTR-CA and/or in the early stages of the disease. ❑

1. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation* 2020;142:e7–22. https://doi.org/10.1161/CIR.0000000000000792; PMID: 32476490.
2. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;379:1007–16. https://doi.org/10.1056/NEJMoa1805689; PMID: 30145929.
3. Cheng RK, Cuddy SAM. Neurohormonal blockade in transthyretin amyloidosis: perhaps one size does not fit all? *Eur Heart J* 2023;44:2908–10. https://doi.org/10.1093/eurheartj/ehad357; PMID: 37224517.
4. Rapezzi C, Aimo A, Serenelli M, et al. Critical comparison of documents from scientific societies on cardiac amyloidosis: *JACC* state-of-the-art review. *J Am Coll Cardiol* 2022;79:1288–303. https://doi.org/10.1016/j.jacc.2022.01.036; PMID: 35361352.
5. Aimo A, Vergaro G, Castiglione V, et al. Wild-type transthyretin cardiac amyloidosis is not rare in elderly subjects: the CATCH screening study. *Eur J Prev Cardiol* 2024;31:1410–17. https://doi.org/10.1093/eurjpc/zwae093; PMID: 38456769.
6. Aimo A, Merlo M, Porcari A, et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail* 2022;24:2342–51. https://doi.org/10.1002/ejhf.2532; PMID: 35509173.
7. Ruiz-Hueso R, Salamanca-Bautista P, Quesada-Simón MA, et al. Estimating the prevalence of cardiac amyloidosis in old patients with heart failure – barriers and opportunities for improvement: the PREVAMIC study. *J Clin Med* 2023;12:2273. https://doi.org/10.3390/jcm12062273; PMID: 36983274.
8. Lindmark K, Pilebro B, Sundström T, Lindqvist P. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. *ESC Heart Fail* 2021;8:745–9. https://doi.org/10.1002/ehf2.13110; PMID: 33205581.
9. Magdi M, Mostafa MR, Abusnina W, et al. A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. *Am J Cardiovasc Dis* 2022;12:102–11. PMID: 35873185.
10. González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;36:2585–94. https://doi.org/10.1093/eurheartj/ehv338; PMID: 26224076.
11. Mohammed SF, Mirzoyev SA, Edwards WD, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2014;2:113–22. https://doi.org/10.1016/j.jchf.2013.11.004; PMID: 24720917.
12. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail* 2020;8:712–24. https://doi.org/10.1016/j.jchf.2020.04.007; PMID: 32653448.
13. Devesa A, Camblor Blasco A, Pello Lázaro AM, et al. Prevalence of transthyretin amyloidosis in patients with heart failure and no left ventricular hypertrophy. *ESC Heart Fail* 2021;8:2856–65. https://doi.org/10.1002/ehf2.13360; PMID: 33963812.
14. AbouEzzeddine OF, Davies DR, Scott CG, et al. Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol* 2021;6:1267–74. https://doi.org/10.1001/jamacardio.2021.3070; PMID: 34431962.
15. See See ASY, Ho JSY, Chan MY, et al. Prevalence and risk factors of cardiac amyloidosis in heart failure: a systematic review and meta-analysis. *Heart Lung Circ* 2022;31:1450–62. https://doi.org/10.1016/j.hlc.2022.08.002; PMID: 36137915.
16. Westin O, Butt JH, Gustafsson F, et al. Two decades of cardiac amyloidosis: a Danish nationwide study. *JACC Cardiooncol* 2021;3:522–33. https://doi.org/10.1016/j.jaccao.2021.05.004; PMID: 34729524.
17. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;133:2404–12. https://doi.org/10.1161/CIRCULATIONAHA.116.021612; PMID: 27143678.
18. Mann DL. The evolution of modern theory and therapy for heart failure. *Prog Pediatr Cardiol* 2014;37:9–12. https://doi.org/10.1016/j.ppedcard.2014.10.002.
19. Manolis AA, Manolis TA, Manolis AS. Neurohumoral activation in heart failure. *Int J Mol Sci* 2023;24:15472. https://doi.org/10.3390/ijms242015472; PMID: 37895150.
20. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;307:205–11. https://doi.org/10.1056/NEJM198207223070401; PMID: 6283349.
21. Heinsimer JA, Lefkowitz RJ. The beta-adrenergic receptor in heart failure. *Hosp Pract (Off Ed)* 1983;18:103–25. https://doi.org/10.1080/21548331.1983.11702685; PMID: 6138306.
22. Grosman-Rimon L, Wright E, Sabovich S, et al. Relationships among norepinephrine levels, exercise capacity, and chronotropic responses in heart failure patients. *Heart Fail Rev* 2023;28:35–45. https://doi.org/10.1007/s10741-022-10232-y; PMID: 35325323.
23. Sayer G, Bhat G. The renin-angiotensin-aldosterone system and heart failure. *Cardiol Clin* 2014;32:21–32. https://doi.org/10.1016/j.ccl.2013.09.002; PMID: 24286576.
24. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75. https://doi.org/10.1056/NEJMoa010713; PMID: 11759645.
25. Garg R, Yusuf S, Bussmann WD, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450–6. https://doi.org/10.1001/jama.1995.03520420066040; PMID: 7654275.
26. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004. https://doi.org/10.1056/NEJMoa1409077; PMID: 25176015.
27. Ferreira JP, Rossello X, Eschalier R, et al. MRAs in elderly HF patients: individual patient-data meta-analysis of RALES, EMPHASIS-HF, and TOPCAT. *JACC Heart Fail* 2019;7:1012–21. https://doi.org/10.1016/j.jchf.2019.08.017; PMID: 31779922.
28. Kjeldsen SE, von Lueder TG, Smiseth OA, et al. Medical therapies for heart failure with preserved ejection fraction. *Hypertension* 2020;75:23–32. https://doi.org/10.1161/HYPERTENSIONAHA.119.14057; PMID: 31786973.
29. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020;17:559–73. https://doi.org/10.1038/s41569-020-0363-2; PMID: 32231333.
30. Vergaro G, Aimo A, Campora A, et al. Patients with cardiac amyloidosis have a greater neurohormonal activation than those with non-amyloidotic heart failure. *Amyloid* 2021;28:252–8. https://doi.org/10.1080/13506129.2021.1966624; PMID: 34396857.
31. Hutt DF, Fontana M, Burniston M, et al. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017;18:1344–50. https://doi.org/10.1093/ehjci/jew325; PMID: 28159995.
32. Milani P, Dispenzieri A, Scott CG, et al. Independent prognostic value of stroke volume index in patients with immunoglobulin light chain amyloidosis. *Circ Cardiovasc Imaging* 2018;11:e006588. https://doi.org/10.1161/CIRCIMAGING.117.006588; PMID: 29752392.
33. Bhuiyan T, Helmke S, Patel AR, et al. Pressure-volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail* 2011;4:121–8. https://doi.org/10.1161/CIRCHEARTFAILURE.109.910455; PMID: 21191093.
34. Cheng RK, Vasbinder A, Levy WC, et al. Lack of association between neurohormonal blockade and survival in transthyretin cardiac amyloidosis. *J Am Heart Assoc* 2021;10:e022859. https://doi.org/10.1161/JAHA.121.022859; PMID: 34729989.
35. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur J Heart Fail* 2021;23:512–26. https://doi.org/10.1002/ejhf.2140; PMID: 33826207.
36. Aimo A, Vergaro G, Castiglione V, et al. Safety and tolerability of neurohormonal antagonism in cardiac amyloidosis. *Eur J Intern Med* 2020;80:66–72. https://doi.org/10.1016/j.ejim.2020.05.015; PMID: 32475765.
37. Yan CL, Gallo RA, Martinez MV, et al. Safety and efficacy of traditional heart failure therapies in patients with cardiac amyloidosis and heart failure. *Am J Cardiol* 2023;204:360–5. https://doi.org/10.1016/j.amjcard.2023.07.140; PMID: 37573615.
38. Pucci A, Aimo A, Musetti V, et al. Amyloid deposits and fibrosis on left ventricular endomyocardial biopsy correlate with extracellular volume in cardiac amyloidosis. *J Am Heart*

Assoc 2021;10:e020358. https://doi.org/10.1161/JAHA.120.020358; PMID: 34622675.
39. Ioannou A, Massa P, Patel RK, et al. Conventional heart failure therapy in cardiac ATTR amyloidosis. *Eur Heart J* 2023;44:2893–907. https://doi.org/10.1093/eurheartj/ehad347; PMID: 37216684.
40. Sperry BW, Hanna M, Shah SJ, et al. Spironolactone in patients with an echocardiographic HFpEF phenotype suggestive of cardiac amyloidosis: results from TOPCAT. *JACC Heart Fail* 2021;9:795–802. https://doi.org/10.1016/j.jchf.2021.06.007; PMID: 34509404.
41. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451–61. https://doi.org/10.1056/NEJMoa2107038; PMID: 34449189.
42. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–24. https://doi.org/10.1056/NEJMoa2022190.
43. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008. https://doi.org/10.1056/NEJMoa1911303; PMID: 31535829.
44. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286; PMID: 36027570.
45. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020;17:761–72. https://doi.org/10.1038/s41569-020-0406-8; PMID: 32665641.
46. Dobner S, Bernhard B, Asatryan B, et al. SGLT2 inhibitor therapy for transthyretin amyloid cardiomyopathy: early tolerance and clinical response to dapagliflozin. *ESC Heart Fail* 2023;10:397–404. https://doi.org/10.1002/ehf2.14188; PMID: 36259276.
47. Porcari A, Cappelli F, Nitsche C, et al. SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol* 2024;83:2411–22. https://doi.org/10.1016/j.jacc.2024.03.429; PMID: 38866445.
48. Lang FM, Teruya S, Cuomo M, et al. Safety and efficacy of SGLT2 inhibitors for amyloid light-chain cardiomyopathy. *J Card Fail*. 2024;30:1641–6. https://doi.org/10.1016/j.cardfail.2024.06.009; PMID: 38997000.
49. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation* 2005;112:2047–60. https://doi.org/10.1161/CIRCULATIONAHA.104.489187; PMID: 16186440.
50. Cheng RK, Levy WC, Vasbinder A, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *JACC Cardiooncol* 2020;2:414–24. https://doi.org/10.1016/j.jaccao.2020.06.007; PMID: 33073249.
51. Vaishnav J, Hubbard A, Chasler JE, et al. Management of heart failure in cardiac amyloidosis using an ambulatory diuresis clinic. *Am Heart J* 2021;233:122–31. https://doi.org/10.1016/j.ahj.2020.12.009; PMID: 33352187.
52. Aimo A, Rapezzi C, Arzilli C, et al. Safety and efficacy of levosimendan in patients with cardiac amyloidosis. *Eur J Intern Med* 2020;80:114–6. https://doi.org/10.1016/j.ejim.2020.06.037; PMID: 32631802.
53. d'Humières T, Fard D, Damy T, et al. Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure. *Arch Cardiovasc Dis* 2018;111:582–90. https://doi.org/10.1016/j.acvd.2018.03.004; PMID: 29709420.
54. Goldsmith YB, Liu J, Chou J, et al. Frequencies and types of arrhythmias in patients with systemic light-chain amyloidosis with cardiac involvement undergoing stem cell transplantation on telemetry monitoring. *Am J Cardiol* 2009;104:990–4. https://doi.org/10.1016/j.amjcard.2009.05.040; PMID: 19766769.
55. Khanna S, Lo P, Cho K, Subbiah R. Ventricular arrhythmias in cardiac amyloidosis: a review of current literature. *Clin Med Insights Cardiol* 2020;14:1179546820963055. https://doi.org/10.1177/1179546820963055; PMID: 33088185.
56. Dhoble A, Khasnis A, Olomu A, Thakur R. Cardiac amyloidosis treated with an implantable cardioverter defibrillator and subcutaneous array lead system: report of a case and literature review. *Clin Cardiol* 2009;32:E63–5. https://doi.org/10.1002/clc.20389; PMID: 19455567.
57. Halawa A, Woldu HG, Kacey KG, Alpert MA. Effect of ICD implantation on cardiovascular outcomes in patients with cardiac amyloidosis: a systematic review and meta-anaylsis. *J Cardiovasc Electrophysiol* 2020;31:1749–58. https://doi.org/10.1111/jce.14541; PMID: 32391952.
58. Kitaoka H, Izumi C, Izumiya Y, et al. JCS 2020 guideline on diagnosis and treatment of cardiac amyloidosis. *Circ J* 2020;84:1610–71. https://doi.org/10.1253/circj.CJ-20-0110; PMID: 32830187.
59. Yilmaz A, Bauersachs J, Bengel F, et al. Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society (DGK). *Clin Res Cardiol* 2021;110:479–506. https://doi.org/10.1007/s00392-020-01799-3; PMID: 33459839.
60. Donnellan E, Wazni OM, Saliba WI, et al. Cardiac devices in patients with transthyretin amyloidosis: impact on functional class, left ventricular function, mitral regurgitation, and mortality. *J Cardiovasc Electrophysiol* 2019;30:2427–32. https://doi.org/10.1111/jce.14180; PMID: 31515942.
61. Donnellan E, Wazni OM, Hanna M, et al. Cardiac resynchronization therapy for transthyretin cardiac amyloidosis. *J Am Heart Assoc* 2020;9:e017335. https://doi.org/10.1161/JAHA.120.017335; PMID: 32633203.
62. Fischer K, Lellouche N, Damy T, et al. Cardiovascular outcomes after cardiac resynchronization therapy in cardiac amyloidosis. *ESC Heart Fail* 2022;9:740–50. https://doi.org/10.1002/ehf2.13663; PMID: 34734471.
63. Fine NM, Davis MK, Anderson K, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement on the evaluation and management of patients with cardiac amyloidosis. *Can J Cardiol* 2020;36:322–34. https://doi.org/10.1016/j.cjca.2019.12.034; PMID: 32145862.
64. Witteles RM. Cardiac transplantation and mechanical circulatory support in amyloidosis. *JACC Cardiooncol* 2021;3:516–21. https://doi.org/10.1016/j.jaccao.2021.05.007; PMID: 34729523.
65. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;35:1–23. https://doi.org/10.1016/j.healun.2015.10.023; PMID: 26776864.
66. Varr BC, Liedtke M, Arai S, et al. Heart transplantation and cardiac amyloidosis: approach to screening and novel management strategies. *J Heart Lung Transplant* 2012;31:325–31. https://doi.org/10.1016/j.healun.2011.09.010; PMID: 22051505.
67. Longhi S, Quarta CC, Milandri A, et al. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. *Amyloid* 2015;22:147–55. https://doi.org/10.3109/13506129.2015.1028616; PMID: 25997105.
68. Cassidy JT. Cardiac amyloidosis. Two cases with digitalis sensitivity. *Ann Intern Med* 1961;55:989–94. https://doi.org/10.7326/0003-4819-55-6-989; PMID: 13877133.
69. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981;63:1285–8. https://doi.org/10.1161/01.cir.63.6.1285; PMID: 7014028.
70. Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? *Amyloid* 2018;25:86–92. https://doi.org/10.1080/13506129.2018.1449744; PMID: 29529877.
71. Tan NY, Mohsin Y, Hodge DO, et al. Catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2016;27:1167–73. https://doi.org/10.1111/jce.13046; PMID: 27422772.
72. Grigoratos C, Aimo A, Rapezzi C, et al. Diphosphonate single-photon emission computed tomography in cardiac transthyretin amyloidosis. *Int J Cardiol* 2020;307:187–92. https://doi.org/10.1016/j.ijcard.2020.02.030; PMID: 32081469.
73. Barbhaiya CR, Kumar S, Baldinger SH, et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm* 2016;13:383–90. https://doi.org/10.1016/j.hrthm.2015.09.016; PMID: 26400855.
74. Reisinger J, Dubrey SW, Lavalley M, et al. Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. *J Am Coll Cardiol* 1997;30:1046–51. https://doi.org/10.1016/s0735-1097(97)00267-2; PMID: 9316537.
75. Porcari A, Rossi M, Cappelli F, et al. Incidence and risk factors for pacemaker implantation in light-chain and transthyretin cardiac amyloidosis. *Eur J Heart Fail* 2022;24:1227–36. https://doi.org/10.1002/ejhf.2533; PMID: 35509181.
76. Ternacle J, Krapf L, Mohty D, et al. Aortic stenosis and cardiac amyloidosis: JACC review topic of the week. *J Am Coll Cardiol* 2019;74:2638–51. https://doi.org/10.1016/j.jacc.2019.09.056; PMID: 31753206.
77. Aimo A, Camerini L, Fabiani I, et al. Valvular heart disease in patients with cardiac amyloidosis. *Heart Fail Rev* 2024;29:65–77. https://doi.org/10.1007/s10741-023-10350-1; PMID: 37735319.
78. Nitsche C, Scully PR, Patel KP, et al. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol* 2021;77:128–39. https://doi.org/10.1016/j.jacc.2020.11.006; PMID: 33181246.
79. Ricci F, Ceriello L, Khanji MY, et al. Prognostic significance of cardiac amyloidosis in patients with aortic stenosis: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2021;14:293–5. https://doi.org/10.1016/j.jcmg.2020.07.011; PMID: 32828772.
80. Scully PR, Patel KP, Saberwal B, et al. Identifying cardiac amyloid in aortic stenosis: ECV quantification by CT in TAVR patients. *JACC Cardiovasc Imaging* 2020;13:2177–89. https://doi.org/10.1016/j.jcmg.2020.05.029; PMID: 32771574.