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Concomitant cardiac amyloidosis and aortic stenosis: update on diagnosis and management

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Abstract

Concomitant aortic stenosis (AS) and cardiac amyloidosis (CA) represent a significant and increasingly recognized clinical challenge, particularly in elderly populations. This review aims to present current knowledge on the prevalence, clinical characteristics, imaging findings, outcomes and management strategies for patients with both AS and CA. Studies indicate that transthyretin cardiac amyloidosis (ATTR-CA) frequently coexists with AS, especially in patients undergoing transcatheter aortic valve replacement (TAVR), with prevalence rates ranging from 4% to 16%. The dual pathology exacerbates heart failure risk, increases mortality, and complicates therapeutic decision-making. Diagnosing CA in the presence of AS is complex due to overlapping clinical and imaging features. A multi-parametric diagnostic approach is essential, incorporating clinical assessment, advanced echocardiography, cardiac magnetic resonance imaging, and bone scintigraphy of the heart. The presence of CA influences the management of AS, often favoring TAVR over surgical valve replacement due to increased surgical risk. Emerging pharmacological treatments for ATTR-CA offer survival benefits and may alter the natural disease progression. This review highlights the need for heightened clinical awareness, early diagnosis through advanced imaging modalities, and tailored therapeutic strategies to improve outcomes in patients with concomitant AS and CA.

Keywords

amyloidosis<concomitant conditions, echocardiography<diagnosis and imaging, electrocardiography<diagnosis and imaging, imaging<diagnosis and imaging, multimodality imaging<diagnosis and imaging, scintigraphy<diagnosis and imaging, transthyretin cardiac amyloidosis, aortic stenosis<specific heart valve disease conditions

Key points

- Concomitant aortic stenosis (AS) and cardiac amyloidosis (CA) are increasingly recognized, particularly in the elderly. Diagnosing CA in the presence of AS presents a challenge due to overlapping clinical features.
- Early detection through clinical evaluation and advanced imaging techniques, such as echocardiography, cardiac magnetic resonance and bone scintigraphy of the heart is crucial. Enhanced diagnostic strategies and a multidisciplinary approach are essential for accurately diagnosing these patients.
- The dual pathology of AS and CA raises heart failure risk and mortality, complicating treatment. TAVR is often preferred over surgical options due to lower risks, with emerging targeted therapies for CA offering new management possibilities.
- Future research should evaluate the best approaches to combine new CA therapies with treatments like TAVR for AS. Establishing clear clinical guidelines will be crucial for improving diagnosis, treatment, and patient outcomes.

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Introduction

Life expectancy has dramatically increased across the globe, mainly due to improvements in living standards, advancements in medicine, public health policies, and better nutrition. However, this rise in longevity has brought with it an ageing population that is increasingly being affected by age-related cardiovascular disorders, neurodegenerative diseases, cancers, and geriatric syndromes such as frailty.[1] With current projections indicating that the number of individuals over 65 years of age will exceed two billion by 2050, a corresponding rise in the prevalence of these diseases is expected, alongside inevitable increases in related morbidity, mortality and healthcare expenditures.[2]

Among age-related conditions, calcific aortic stenosis (AS) stands out the most common age-related valvular heart disease, with its prevalence ranging from approximately 3% of individuals over 65 and exceeding 10% in people aged 75 years and older.[3,4] Furthermore, recent studies have suggested that the prevalence of AS may be growing.[5,6] If not treated, symptomatic AS presents with disabling symptoms of syncope, angina, and dyspnoea and portends a poor prognosis.[7] However, treatment of severe symptomatic AS with surgical or transcatheter aortic valve replacement (SAVR or TAVR, respectively) significantly improves patient symptoms, quality of life, and life expectancy.[8,9] Importantly, moderate AS—for which close follow up is recommended—is also now being associated with a significantly higher long-term mortality risk.[10,11]

Cardiac amyloidosis (CA), particularly wild-type transthyretin CA (ATTRwt-CA) involving the deposition of amyloid fibrils in the heart, is also a disease of ageing, seen in up to 25% of octegenarians.[12,13] Hence AS and ATTRwt-CA can frequently co-exist in elderly patients. Since the first reports of CA co-occurrence with AS,[14–18] several studies identified co-existant ATTRwt-CA in 4% to 16% of AS patients referred for aortic valve replacement (AVR) (Table 1). Furthermore, CA in these patients was an independent risk factor of higher all-cause post-AVR mortality.[15,19]

From a diagnostic standpoint, AS and ATTRwt-CA exhibit overlapping clinical and pathologic features, such as concentric left ventricular hypertrophy (LVH), advanced diastolic dysfunction, and heart failure (HF) with either preserved or mildly reduced ejection fraction, rarely with reduced ejection fraction.[20] Moreover, amyloid deposition into the peri-valvular and myocardial spaces can lead to progression of AS severity,[21] but because these findings can be related either to the progression of AS or the restrictive cardiomyopathy caused by ATTRwt-CA,[21] the manifestations of AS can mask the detection of concurrent CA if clinicians are not aware of this association. Advanced imaging modalities particularly technetium^{99} (^{99}Tc)-based bone scintigraphy of the heart when combined with the exclusion of a monoclonal protein component in blood and urine can reliably establish the diagnosis of CA after identifying findings ('red flags') suggestive of co-existing ATTRwt-CA on clinical valuation, laboratory tests, electrocardiography, and trans-thoracic echocardiography in AS patients.[20–23]

Recent studies have reported a lower prevalence of AS-CA than previous ones, and demonstrated comparable peri-procedural and long-term outcomes in co-existent ATTRwt-CA and AS versus AS alone.[24,25] Those studies have expanded upon the echocardiographic indicators that can effectively distinguish between concomitant ATTRwt-CA and AS *versus* AS alone. Novel medical therapies aim at reducing transthyretin production or stabilising non-amyloidogenic transthyretin, which have shown promise in slowing the progression of ATTRwt-CA and patient functional decline, and in decreasing N-terminal pro-B type natriuretic peptide (NT-proBNP) levels, cardiovascular-related hospitalisations and all-cause mortality, in patients with hereditary and ATTRwt-CA.[26–28] Therefore, determining whether the presence of AS impacts the response of ATTRwt-CA patients to these medical therapies is an important question.

Our review aims to delve into the recent epidemiological updates of ATTRwt-CA with AS, describe the clinical, laboratory, and imaging findings indicative of co-existing AS and ATTRwt-CA, and review the diagnostic approaches and management strategies in this population. As more long-term data on the natural history of AS-CA patients and their outcomes to medical and invasive therapies becomes available, developing evidence-based guidelines for clinical screening, diagnostic algorithms, and positioning of medical/surgical intervention for these patients will be imperative.

The interplay between the pathophysiology of cardiac amyloidosis and aortic stenosis

Amyloidosis is an ensemble of several diseases characterised by the misfolding of soluble precursor proteins into insoluble amyloid fibrils, which then deposit in the extracellular space of various organs, thereby inducing tissue damage.[29] Cardiac involvement occurs in 50–80% of patients with systemic amyloidosis and is a significant predictor of patient prognosis.[30] CA generally arises either from misfolded immunoglobulin light chains in AL amyloidosis secondary to a plasma cell dyscrasia, or from misfolded transthyretin, *ie,* ATTR-CA.[31]

There are two main subtypes of ATTR-CA: senile/wild-type (ATTRwt-CA) and hereditary (or variant; ATTRv-CA). ATTRwt-CA is typically prevalent in elderly individuals, particularly in octogenarians.[32] It is characterised by the deposition of structurally unaltered transthyretin, whereas its aetiology remains poorly understood; however, it is likely multifactorial and not solely dependent on the ageing process.[33] On the other hand, ATTRv is an inherited, autosomal dominant disorder associated with over 100 driver mutations, with some pathogenic variants differently associated with cardiac involvement.[34] Phenotypically, patients

Table 1. Studies investigating the association between aortic stenosis and cardiac amyloidosis.

Author, year	Study Context	Country of study	Diagnosis Modality	N	Mean age of lone AS patients (yrs)	Prevalence of CA (%)	Mean Age of CA patients (yrs)	Male (%)	Outcomes
Galat, 2016	Retrospective; analysis of patients with concomitant AS and ATTR-CA	France	Bone scintigraphy (HMDP/DPD), endomyocardial biopsy	16	NA	NA	79	81	Mortality was 44% in patients with AS-CA.
Treibel, 2016	Observational; patients with severe AS undergoing SAVR	UK	Endomyocardial biopsy	112	75	5.4	77	67	50% of patients with ATTR-CA and AS died versus 7.5% without ATTR-CA (HR 9.5 CI 2.5–35.8, P < 0.001)
Longhi, 2016	Prospective; AS patients referred for AVR (surgical or transcatheter)	Italy	Bone scintigraphy (PYP), endomyocardial biopsy	43	NA	11.60	84*	80	NA
Cavalcante, 2017	Retrospective; moderate/severe AS referred for CMR	USA	LGE pattern on CMR	113	70	8.0	88	89	Higher all-cause mortality in CA versus no CA (56% vs 20%, P < 0.001). CA was an independent predictor of mortality (P = 0.04).
Castaño, 2017	Observational; severe AS referred for TAVR	USA	Bone scintigraphy (PYP)	151	83	16.0	86	92	NA
Scully, 2018	Observational; severe AS referred for TAVR	UK	Bone scintigraphy (DPD)	101	86#	14.0	88	50	NA
Nitsche, 2020	Observational; severe AS referred for TAVR	Austria	CMR, bone scintigraphy (DPD), endomyocardial biopsy	191	82*	8.4	84*	63	No difference in hospitalizations and deaths following TAVR between the 2 groups.
Scully, 2020	Prospective; severe AS referred for TAVR	UK	Bone scintigraphy (DPD)	200	85	13.0	88	62	Lone AS versus AS-amyloid mortality overall was 21% and 23% (P = 0.71). TAVR improved outcome in AS-CA patients (P = 0.03) compared to medical management.
Rosenblum, 2020	Prospective; severe AS referred for TAVR	USA	Bone scintigraphy (PYP)	204	82	13.2	86	93	After TAVR, lone AS versus AS-CA mortality was 31% and 33% (P = 0.9423). Rate of hospitalization for patients with ATTR-CA was higher (P = 0.041).
Nitsche, 2021	Prospective; severe AS referred for TAVR	UK, Austria	Bone scintigraphy (DPD), Endomyocardial biopsy	407	84	11.5	87	66	Unadjusted all-cause mortality of AS-ATTRCA was higher compared with lone AS (P = 0.001). AVR improved survival in AS-CA patients compared with medical management (P = 0.003).

(continued)

Table 1. Continued.

Author, year	Study Context	Country of study	Diagnosis Modality	N	Mean age of lone AS patients (yrs)	Prevalence of CA (%)	Mean Age of CA patients (yrs)	Male (%)	Outcomes
Singal, 2021	Prospective; severe AS referred for SAVR	India	Bone scintigraphy (PYP), endomyocardial biopsy	32	69*	9.4	70	33	2 patients had died; 1 in the myocardial TTR-negative and 1 in the TTR-positive group (P = 0.477).
Dobner, 2023	Prospective; severe AS referred for TAVR	Switzerland	Bone scintigraphy (DPD)	315	83	9.5	86	83	All-cause and CV death not affected by concomitant CA. In patients undergoing TAVR, mortality was similiar between DPD+ and DPD- patients (P > 0.05).
Abadie, 2023	Prospective; severe AS referred for TAVR	USA	Bone scintigraphy (PYP)	380	83	4.7	88	90	NA
Jakstaite, 2024	Prospective; severe AS referred for TAVR and fulfilled criteria for red flags of ATTR	Germany	Bone scintigraphy (DPD), Endomyocardial biopsy	85	82	7.0	85	100	The all-cause mortality of lone AS versus AS-ATTR was 12% and 0% (P = 0.228)
Beuthner, 2024	Prospective; severe AS referred for TAVR	Germany	Endomyocardial biopsy	162	80	4.9	81	88	Mortality (P > 0.05) and first rehospitalization due to HF (P = 0.093) did not differ significantly between the two subgroups. Patients with AS-CA suffered more from sudden cardiac death (P = 0.017).

Values given for male (%) are for patients with concomitant AS-ATTRCA. *: Reported values are medians. #: Mean age of all patients in the cohort. AS: aortic stenosis; CA: cardiac amyloidosis; CMR: cardiac magnetic resonance; CV: Cardiovascular; DPD: 3,3-diphosphono-1,2-propanodicarboxylic acid; HF: Heart failure; HMDP: hydroxymethylene diphosphonate; PYP: pyrophosphate; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.

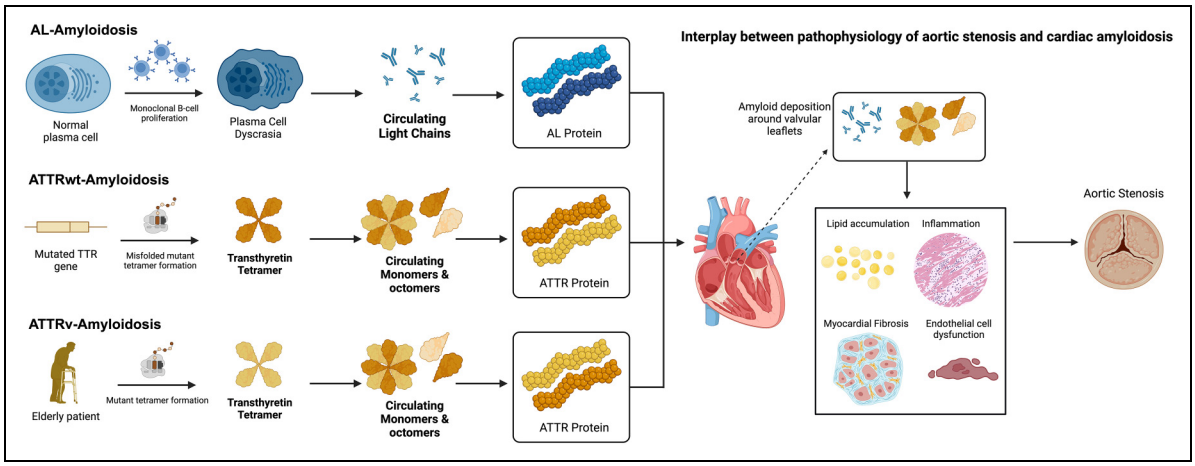

Figure 1. The pathological processes of the three main types of cardiac amyloidosis—AL, ATTRv, and ATTRwt—are illustrated. AL commonly arises due to plasma cell dyscrasia and subsequent monoclonal immunoglobulin light chain secretion, whereas ATTRv and ATTRwt arise from a mutated transthyretin gene and age-related misfolding, respectively. These pathways collectively lead to the deposition of amyloid protein in cardiac tissue, triggering structural and functional changes that contribute to aortic stenosis. The pathophysiology of aortic stenosis is underpinned by an inflammatory milieu which arises due to lipid accumulation and structural stress, consequently leading to the onset of endothelial dysfunction and the subsequent calcification, fibrosis, and sclerosis of the aortic valve leaflets. The presence of amyloid deposits close to the aortic valve leaflets may contribute to the inflammatory milieu in aortic stenosis, particularly relating to the remodelling of the extracellular matrix and the proliferation of myofibroblasts.

with ATTRv tend to be younger than those with ATTRwt and present predominantly with cardiovascular and neurologic symptoms.[35] The overwhelming majority of concurrent AS and CA cases are seen with ATTRwt-CA, whereas AL-CA is rarely present in the setting of concomitant AS.[20,36]

Involvement of the LV myocardium in CA proceeds from the base to the cardiac apex, leading to increased biventricular wall thickness and restrictive cardiomyopathy with longitudinal systolic and marked diastolic dysfunction.[37,38] CA typically manifests as HFpEF, though about a third of CA patients develop HF with reduced ejection fraction (HFrEF).[39] Degenerative AS, the most common valvular disease in developed countries, is associated with cardiac remodelling and sometimes a restrictive cardiac phenotype.[40,41] This phenotypic shares similarity between AS and CA may mask the presence of the latter in patients with AS.

Amyloid deposition is blind and thus is not limited to the myocardium and can involve the cardiac valves, the endocardium, the conduction system, the atrial wall, the pericardium and microvasculature.[42] Aortic valve infiltration may contribute to the initiation or progression of secondary AS among CA patients[43,44] (Figure 1). The pathophysiology of AS is initiated by an inflammatory milieu secondary to lipid accumulation and shear stress, leading to endothelial dysfunction and calcification, fibrosis and sclerosis of the aortic valve cusps.[45,46] Several studies have demonstrated the presence of amyloid deposits adjacent to areas of calcification within structurally abnormal aortic valves.[43,47–49] There is also growing evidence suggesting that amyloid deposition within or in proximity to the aortic valve leaflets may contribute to the inflammatory milieu in AS, thereby promoting the proliferation of myofibroblasts and remodelling of the extracellular matrix.[50] Additionally, amyloid infiltration proximal to the valvular leaflets may amplify pre-existing AS by worsening the transvalvular pressure gradient and LV afterload.[21]

Natural history of aortic stenosis with cardiac amyloidosis

Prevalence of concurrent AS and ATTR-CA

The prevalence of both ATTR-CA and AS increases with age; therefore, the incidence of concurrent ATTR-CA and AS is often observed in elderly patients.[21] Initially, the association between ATTR-CA and AS was reported across several case reports and case series; however, many observational cohort studies have emerged over the previous decade, on the actual epidemiological burden of this association (Table 1).

Treibel *et al* conducted an observational study in 146 AS patients undergoing surgical aortic valve replacement.[15] Based on endomyocardial biopsy, 4.1% of patients were determined to have concurrent ATTR-CA and varying degrees and types of AS. Among the subgroup with severe calcific type AS (n = 112), the prevalence of concomitant ATTR-CA was 5.6%.

Following this study, Cavalcante *et al* enrolled 113 patients with moderate to severe AS and suspected CA, and utilised cardiac magnetic resonance imaging (CMR) for ATTR-CA diagnosis.[19] The prevalence of concurrent

ATTR-CA and AS within this study was 8.0%, of which patients were 88 year-old on average, and 89% males.

Castaño et al conducted an observational study among 151 patients with severe AS referred for TAVR (mean age 84 y). Using technetium-99 m pyrophosphate (99mTc-PYP) bone scintigraphy of the heart, the prevalence of concurrent ATTR-CA and AS was 16.0%.[36] Patients with co-existent ATTR-CA and AS were 86 year-old on avergae, and approximately 92% males. Following these initial observational cohort studies, several recent studies emerged focusing on patients with severe AS undergoing TAVR. In a observational study of 200 patients with severe AS referred for TAVR, Scully *et al* found a prevalence of dual ATTR-CA and AS of 13.0%.[51] Rosenblum *et al* conducted a similar study including 204 patients with severe AS undergoing TAVR and found a comparable prevalence of concurrent ATTR-CA and AS of 13.2%.[52]

Nitsche *et al* conducted the largest observational study among 407 patients with severe AS referred for TAVR, where the mean age was 83 years.[53] The prevalence of concurrent ATTR-CA and AS was 11.5%, with patients being 87 year-old on average, and unlike previous studies approximately 65% of them only were males suggesting that female may have been underdiagnosed in previous cohorts. However, Dobner et al found a 9.5% prevalence of ATTR-CA among patients undergoing TAVR and Abadie et al reported a low prevalence of only 4.7% in a similiar population.[25,54]

In summary, across 15 observational studies including 2546 participants, the overall mean age of participants with concurrent ATTR-CA and AS was approximately 83 years, wheras the mean age for patients with lone AS was approximately 80 years. The prevalence of concurrent ATTR-CA and AS varied from 4.1% to 16.0%, with an average prevalence of approximately 10%. These variations could be due to differences in baseline inclusion criteria and diagnostic methods in each cohort (Table 1).

Outcomes of concurrent ATTR-CA and AS

The presence of ATTR-cardiomyopathy exacerbates myocardial damage, increases the risk of HF, and significantly heightens the morbidity and mortality burden in patients with AS, who already suffer from myocardial injury.[21,53]

In an early cohort of patients with severe AS requiring SAVR, Treibel *et al* found that overall mortality was significantly higher in patients with concurrent wtATTR-CA and AS compared to those with severe AS alone, at 50% versus 7.5% ($P < 0.001$) respectively at a median 2.3 years follow-up[15] (Table 1). Similarly, in the Cavalcante *et al* study, CA was statistically associated with mortality among a cohort of 113 patients with moderate to severe AS referred for CMR.[9]

However, in a more recent prospective study of 191 patients with severe AS referred for TAVR, Nitsche *et al* found no difference in terms of hospitalisations or deaths 15 months in average following TAVR between patients with lone AS or those with concomitant CA and AS.[55] Similarly, Scully *et al* found no significant difference in mortality after 19 months follow-up among patients with lone AS or patients with concurrent ATTR-CA and AS referred for TAVR, with 21% versus 23% overall mortality rates, respectively.[56] Moreover, in the same study, TAVR was superior to medical management in patients with concurrent ATTR-CA and severe AS ($P = 0.03$). Rosenblum *et al* found similar rates of mortality among patients with lone AS versus those with concurrent ATTR-CA and AS; though, the rate of hospitalisations among patients with concomitant ATTR-CA and AS was higher ($P = 0.041$).[52] Nitsche *et al* found that the unadjusted all-cause mortality of AS-ATTR-CA patients was higher when compared to those with lone AS ($P = 0.001$), but TAVR was superior to medical management among patients with concomitant ATTR-CA and AS.[53] The two most recent large-scale observational studies exploring concurrent ATTR-CA and AS in patients with severe AS referred for TAVR have demonstrated no significant differences in mortality after TAVR among patients with AS-ATTR-CA compared to those with lone AS,[25,57] despite an increased rate of sudden cardiac death in the mixed disease group ($P = 0.017$). Finally a nationwide study from the USA of 245 020 hospitalisations for TAVR, of which 273 patients also had CA, has shown no difference in mortality or 30-day readmission rates between patients with lone AS versus those with concurrent ATTR-CA and AS.[58] However, the same study found a heightened risk of thromboembolic stroke among patients with concurrent ATTR-CA and AS compared to AS alone ($P = 0.005$).

Therefore, previous observations showed conflicting reports of whether or not concurrent ATTR-CA and AS increase the risk of mortality when compared to lone AS following AV intervention. This heterogeneity in study outcomes can be explained by a multitude of factors, such as differences in inclusion criteria (*eg,* biopsy-proven CA *vs* non-invasive imaging) and the sampling of patients with differing severities of both AS and CA, differences in follow-up times, and other confounding factors such as other patient comorbidities and the availability of disease-modifying therapies in later cohorts. Larger and prospective studies with longer follow-up periods are required to establish a clear difference in mortality between the two groups. The presence of concurrent ATTR-CA and AS is associated with a increased risk of morbidities, including ischemic thromboembolism and rehospitalization for acute decompensated HF. With respect to treatment, meta-analyses have shown that survival of patients with combined CA-AS after TAVR is comparable to that of lone AS,[59] although patients with co-existent disease appear to have a higher risk of acute kidney injury, stroke, and pacemarker implantation post-TAVR.[60,61] Additionally, TAVR intervention provides a significant survival benefit over medical management.[62,63] However, these pooled estimates are based off a handful of

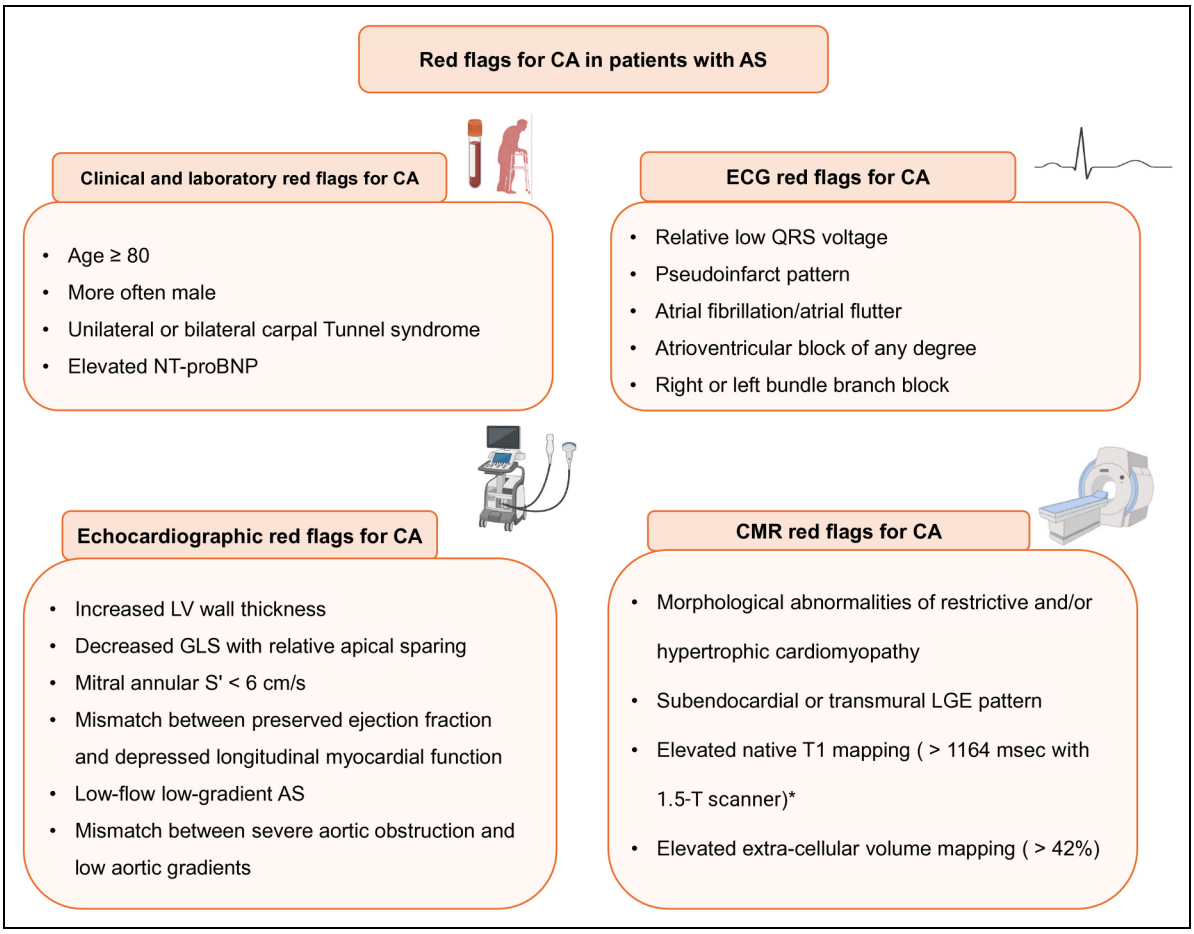

Figure 2. Red flags of cardiac amyloidosis in patients with aortic stenosis.
*: T1 values can change according to scanner and sequence. CA: cardiac amyloidosis; CMR: cardiovascular magnetic resonance imaging; IVS: interventricular septum; mitral annular S': mitral annular systolic velocity; NT-proBNP: N-terminal probrain natriuretic peptide.

observational studies; the lack of randomized data is an unmet need in this field. Nevertheless, promptly diagnosing and managing cases of co-existent AS and ATTR-CA is critical.

Red flags of aortic stenosis with cardiac amyloidosis

The diagnostic algorithm of AS is well established; clinical signs and routine investigations—*eg,* electrocardiography, and transthoracic echocardiography—typically reveal the diagnosis. In contrast, the definitive diagnosis of ATTR-CA cannot be made on routine investigations and always requires bone scintigraphy of the heart or sometimes histological confirmation by either cardiac or extra cardiac tissue biopsy. Furthermore, the clinical, electrocardiographic, and echocardiographic features of CA may be similar to AS, and the diagnosis of AS can be made by these investigations. Thus, a clinician may appropriately diagnose AS but not conduct more advanced diagnostic tests to detect CA if their index of suspicion is not high.[64] In light of this problem, we have attempted to curate the 'red flags' of ATTR-CA from history/physical examination, electrocardiogram, and echocardiography, on the basis of which more advanced testing such as CMR, bone scintigraphy of the heart, and even biopsy for histological examination should be initiated (Figure 2). Overall, "a mismatch" between findings can suggest the presence of concomitant AS and ATTR-CA, such as disproportionate increased LV wall thickening contrasting with low QRS voltages, preserved/borderline LVEF contrasting with markedly reduced longitudinal myocardial function, and severe aortic obstruction by aortic valve area contrasting with low flow and low transaortic pressure gradient. These findings are covered in more detail in the subsequent sections, and the relative ranges of sensitivities and specificites reported across individual studies is summarized in Table 2.[53,54,65–75]

Clinical and laboratory findings

The presence of the following findings should raise a clinician's suspicion for CA: a diagnosis of unilateral or bilateral

Table 2. Diagnostic sensitivities and specificities of key red flags in suspecting cardiac amyloidosis.

	Sensitivity (%)	Specificity (%)	References
Biomarkers			
Elevated NT-proBNP	76–90	54–70	54,65
Electrocardiography			
Low QRS Voltage	74	82	66
Echocardiography			
Increased wall thickness (mm)	64–70	34–79	65,67
Decreased GLS (%)	67–88	42–74	54,68,70,76
RELAPS	46–77	66–94	54,68,71,76,77
LF-LG AS	65	70	54
Cardiac Magnetic Resonance Imaging			
LGE pattern	85–90	85–90	72
Elevated T1 values (ms)	80–97	66–100	54,73–75
Elevated ECV (%)	82–85	93–97	72,75
RAISE Score			
≥2	94	52	53
≥3	72	84	53

All numbers provided represent the range of sensitivities and specificities observed in the literature for each diagnostic parameter. GLS: global longitudinal Strain; LGE: late gadoliniume enhancement; LF-LG AS: low-flow low-gradient aortic stenosis; ms: milliseconds; NT-proBNP: N-terminal pro b-type natriuretic peptide; RAISE: remodeling, age, injury, system, and electrical; RELAPS: relative apical sparing pattern.

carpal tunnel syndrome/carpal tunnel surgery, lumbar spinal stenosis, spontaneous biceps tendon rupture, unexplained deafness, and poorer functional status with more decompensated heart failure episodes along with more episodes of hypotension or patients previously hypertensive becoming spontaneously normotensive with no medications. Some other manifestations more commonly seen in AL amyloidosis are macroglossia/submandibular gland enlargement, periorbital purpura, and acquired factor X deficiency.[78–80] An important sign of co-existant ATTR-CA and AS is marked AS progression with HF-related symptoms unexplained by a proportionate severity of AS (*eg,* based on performance on a 6-min walk test, though it is rarely used in clinical practice).[20,21] AL amyloidosis most commonly involves the heart and the kidney, the latter manifesting as severe nephrotic syndrome (*ie,* generalised oedema, hyperlipidemia, and nephrotic-range proteinuria and fatty casts on urinalysis).

On laboratory testing, cardiac markers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) are often found to be chronically higher in patients with dual pathology.[53,54,56,65] Low-level but persistent elevation of high-sensitivity troponin-T (hs-TnT) time without electrocardiographic changes, regional wall motion abnormalities, or positive MIBI scan after ruling out ischemic heart disease should raise suspicion for CA in patients with AS. Table 3 summarises the laboratory and imaging findings that can distinguish between concomitant AS and ATTR-CA and sole AS.

Electrocardiogram

Absolute low voltages (Sokolow-Lyon Index of S wave in V1 + R wave in lead V5 or V6 < 1.5 mV) despite significant increase in LV wall thickness is considered a specific sign of CA.[66] However, its prevalence varies between studies from 20% and up to 60% and actually may be only present at later stages of the disease.[81,82] It is also more common in patients with AL CA.[83] The relative low voltage-to-mass ratio is more sensitive for identifying CA than absolute low voltages alone and is also an independent predictor of ATTR-CA in patients with AS.[36,53,55–57] Thus, its absence does not exclude the diagnosis of CA.[81] In a prospective study of 191 patients with AS referred for TAVR, the relative voltage-to-mass ratio could effectively distinguish between AS with CA and lone AS (AUC, 0.770), which is comparable to the performance of another parameter only obtained by CMR—extracellular volume mapping (AUC, 0.756).[55] Another electrocardiography-based red flag for CA is the presence of pathologic Q waves (*ie,* Q waves at least 1/fourth of the height of the R wave) in two consecutive leads in the absence of regional wall motion abnormalities, ischemic heart disease, or left bundle branch block—termed the pseudo-infarct pattern. Alongside low voltage, the pseudo-infarct pattern is the most common electrocardiographic finding (almost 70% of the cases of patients with biopsy-proven ATTR.[84]

Amyloid infiltration may occur into the conduction system, leading to the development of arrhythmias (*eg,* sino-atrial node dysfunction, atrioventricular blocks, bundle branch blocks, and atrial fibrillation/flutter). Indeed, studies comparing the prevalence of conduction abnormalities between AS-ATTR and AS patients have reported significantly higher prevalences of right bundle branch block (37.5% *vs* 15.8%, respectively; $p = 0.023$) and atrial fibrillation/flutter (67% *vs* 20.2%, respectively; $p = 0.006$) in mixed disease.[19,36] Corroborating these findings, a more recent study by Rosenblum *et al* also reported significantly higher

Table 3. Laboratory and imaging parameters of aortic stenosis-cardiac amyloidosis patients.

Author, year	Nt-proBNP (pg/ml)	VMR	LVEF (%)	IVST (mm)	LV SVi (mL/m2)	LV mass index (g/m2)	LF-LG AS (%)	GLS (%)
Treibel, 2016	2560	0.13	67.0	16.7	NA	NA	NA	−12.6
Galat, 2016	4380	NA	50.0	18.4	27	NA	86	−7
Longhi, 2016	NA	NA	Reduced in 40% of ATTR-CA patients	18.0	NA	NA	80	NA
Cavalcante, 2017	NA	NA	52.0 versus 43.0	13.0 versus 18.0*	37 versus 25*	NA	45 versus 78	NA
Castaño, 2017	18 960 versus 32 200	1.4 versus 1.0*	56.1 versus 47.6*	11.0 versus 13.0*	36 versus 30*	97.9 versus 129.8*	11 versus 29*	−15.7 versus −12.4*
Scully, 2018	NA	NA	NA	NA	38 versus 32	NA	NA	NA
Nitsche, 2020	18 390 versus 36 340	1.6 versus 0.9*	62.0 versus 62.0	15.0 versus 15.5*	47 versus 27*	135.0 versus 159.0*	25 versus 56*	−16.9 versus −13.8
Scully, 2020	1250 versus 3700*	2.5 versus 1.7*	54.0 versus 54.0	13.0 versus 14.0*	38 versus 34*	118.0 versus 136.0*	24 versus 31	−14.0 versus −15.0
Rosenblum, 2020	NA	0.23 versus 0.18	55.0 versus 48.0*	12.0 versus 14.0*	35 versus 31*	106.0 versus 136.0*	26 versus 37	NA
Nitsche, 2021	1610 versus 4860*	1.84 versus 1.06	58.0 versus 51.0	14.0 versus 16.0*	40 versus 36*	127.0 versus 150.0*	39 versus 56	−15.6 versus −13.7
Singal, 2021	3550 versus 5180	NA	54.4 versus 33.5	14.2 versus 14.5	NA	NA	10 versus 33	−18.7 versus −14.2
Dobner, 2023	2520 versus 3850*	Discordance in 12% versus 48% of patients*	58.4 versus 49.0*	12.8 versus 15.8*	NA	117.2 versus 144.7*	49 versus 85*	NA
Abadie, 2023	812 versus 2502*	NA	61.0 versus 53.0*	13.0 versus 15.0*	38 versus 29*	103.0 versus 136.0*	30 versus 65*	−15.1 versus −9.3*
Jakstaite, 2024	NA	1.5 versus 1.7	52.0 versus 52.0	16.0 versus 18.0	NA	149.7 versus 162.1	34 versus 50	−13.0 versus −12.1*
Beuthner, 2024	1938 versus 4356*	1.46 versus 0.73*	54.0 versus 52.0	15.0 versus 17.0	33 versus 25*	142.1 versus 149.6	28 versus 25	NA

Each value pair represents the mean value for Lone AS versus the mean value for AS-ATTRCA. Values with an asterisk (*) indicate that the difference between the groups was statistically significant. Lone values in the table represent data for the AS-ATTRCA group only. AS: aortic stenosis; CA: cardiac amyloidosis; GLS: global longitudinal strain; IVST: interventricular septal thickness; LF-LG: low-flow low-gradient; LV: left ventricle; LVEF: left ventricular ejection fraction; SVi: stroke volume index; VMR: voltage-to-mass ratio.

rates of right bundle branch block in mixed disease than lone AS (39% vs 17%, respectively; $p = 0.011$).[52] These conduction abnormalities do not appear to increase risk of mortality,[85,86] but their presence should raise suspicion of CA in patients with AS.

Echocardiogram

Echocardiography is the best non-invasive imaging modality for screening co-existent ATTR-CA in patients with AS. It is also the gold standard modality for diagnosing and grading the severity of AS using aortic valve area, peak and mean transaortic valvular gradients. Other parameters usually reported are left ventricle (LV) size and degree of LVH, systolic and diastolic function, left atrial volume, RV size and function, and pulmonary artery pressure and presence of pericardial effusion.

Both AS and CA may lead to concentric LVH. However, normal LV thickness or assymetrical LVH cannot exclude a diagnosis of CA because approximately a third of patients with AL-CA exhibit normal LV thickness and as many as 79% of patients with ATTR-CA can present with asymmetric hypertrophy rather than a diffuse concentric pattern.[87] Nevertheless, severe LVH (≥15 mm), and relative wall thickness (>0.5) that are disproportionate to/unexplained by the severity of AS can point to concurrent CA.[65,67,88]

Patients with AS-CA may also present with significantly lower LVEF and stroke volume index than lone AS.[19,25,36,52,53,55] In addition, more advanced diastolic dysfunction and restrictive patterns are also more often found in CA-AS. Finally, the pattern of low-flow, low-gradient with small aortic valve area <1 cm^2 can be found in more than 50% of patients with dual AS and ATTR-CA.[14,16,19,25,36,54] However, although low-flow low-gradient is a red flag for co-existent disease, it is not specific of CA and can be seen in several other etiologies (severe associated mitral stenosis, severe tricuspid regurgitation, rapid atrial fibrillation, etc). In this context, calculating the myocardial contraction fraction—the ratio of LV stroke volume to myocardial volume—by Doppler echocardiography can reveal impaired myocardial contractility despite preserved ejection fraction and has been shown to be significantly lower in AS-CA patients as compared with patients with lone AS.[88,89] LV involvement in CA proceeds from the base to the apex and initially leads to markedly reduced longitudinal systolic function, seen on imaging as reduced mitral annular septal/lateral systolic velocity (S') using Doppler Tissue Imaging or reduced global longitudinal strain (GLS) using advanced strain imaging. Accordingly, a pooled comparison of echocardiographic features in AS-CA patients *versus* those with AS alone revealed significantly lower mitral annular S' in AS-CA.[88] In the Castano *et al* study, a mitral annular S' cut-off <6 cm/s demonstrated 100% sensitivity in predicting a positive 99mTc bone scintigraphy of the heart for CA.[36] We do not, however, recommend using mitral annular S' as the primary modality for diagnosis of CA, though its presence may be used to rationalize further workup for CA. Similarly, parameters of right ventricular systolic function—indicated by tricuspid annular plane excursion and tricuspid annular systolic wave S'—are more severely impaired in co-existent AS and CA patients than in those with AS alone, implying more severe biventricular systolic dysfunction in this group.[88]

Global longitudinal strain imaging has an increasing role in identifying CA with or without AS. GLS has been consistently shown to be decreased at earlier stage of any cardiomyopathy, including CA.[36,54,68–70,90] Pagourelias *et al* reported that the LVEF/GLS ratio showed the best performance (AUC, 0.95; 95% CI, 0.89—0.98) in distinguishing CA from other hypertrophic cardiac states with diastolic dysfunction (*eg,* hypertrophic cardiomyopathy and hypertension).[69] However, assessment of regional differences in deformation may provide more information about the underlying pathology. In CA, amyloid infiltration preferentially deposits in the basal and middle segments of the LV with a relatively lower total amyloid mass at the apex.[91] Hence, the impairment of LV longitudinal strain is most profound at the base with relative apical sparing[54,68,69,71,77,85,92]—called 'cherry on top' pattern. A high apical sparing to longitudinal strain ratio (>0.9 or 1) may be more sensitive and specific for identifying ATTR-CA as compared with just the cherry on top appearance.[93] Yet, there has not been a direct comparison of the accuracy, sensitivity, and specificity between the qualitative appearance and apical sparing ratio in ATTR-CA. However, the optimal cutoff of the apical sparing ratio also varies in the literature, with studies typically using a ratio between 1.0 and up to 2.0. In an international, multi-center study of 544 patients with confirmed ATTR-CA, Cotella *et al* demonstrated that even the optimal cut-off of the apical sparing ratio of 1.67 demonstrated an AUC-ROC of 0.74, a sensitivity of 72%, and a specificity of 66%, with apical sparing seen in 32% of control patients (CA ruled out) and 6% of healthy subjects.[70] However, relative apical sparing is not unique to CA and can be seen in patients with severe AS referred for AVR or with severe end stage renal disease.[94,95] Reduced GLS with relative apical sparing in sole AS is typically reversible after AVR, distinguishing it from CA.[94] These findings indicate that there is likely no single best echocardiographic marker of concomitant ATTR-CA in AS patients, underscording the importance of integrating the patient's clinical presentation, laboratory tests, electrocardiogram, and imaging findings (including CMR and bone scintigraphy of the heart).

The decrease in left ventricular compliance and its restricted filling can lead to diastolic dysfunction, resulting in an increased early-filling-velocity to atrial-filling-velocity (E/A) ratio and left atrial volume enlargement, especially in patients with advanced AS and ATTR-CA.[53,88] An increase in atrial afterload because of a stiff LV and consequent

atrial dilatation is most likely the cause of the increased E/A ratio rather than an intrinsic failure of the left atrium secondary to amyloid deposition.[96] Impaired emptying of the left atrium can lead to blood stasis and thrombosis; CA is associated with a higher incidence of atrial fibrillation and intracardiac thrombi.[86,97,98] Hence, evaluating left atrial volume and function may provide additional information about the patient's clinical trajectory.

Atrial strain can assess left atrial function during distinct phases of the cardiac cycle, such as during atrial relaxation/filling in systole (reservoir function), during rapid ventricular filling in early diastole (conduit function), and during atrial contraction in late diastole.[99] Analysis of left atrial strain by speckle-tracking imaging can effectively distinguish CA from other causes of diastolic dysfunction, such as hypertensive heart disease[100–102] and is a significant predictor of prognosis for both AS and CA.[103–107] In ATTR-CA and AL-CA, left atrial function in all three phases is significantly impaired, though reservoir and contractile function may be disproportionately impaired in ATTRwt-CA as compared to hereditary ATTR-CA and AL-CA.[108] Oike *et al* reported that the relative apical longitudinal strain was significantly higher and left atrial peak longitudinal strain rate significantly lower in patients with mixed disease; both were significant predictors of positivity on bone scintigraphy scans to diagnose concomitant ATTR-CA. The AUC-ROC of peak left atrial longitudinal strain rate in predicting the diagnosis of ATTR-CA was 0.79, the best cut-off value being 0.47 per second (sensitivity: 78.6%; specificity: 72.3%).[109] Additionally, a cut-off of LV apical longitudinal strain of $\geq$1 (sensitivity: 43.8% and specificity: 87.5%) was established. Cardiac tracer uptake on bone scintigraphy was positive in 83.3% of patients with values above these cut-offs, and negative in 96.6% (28/29 patients) with values below these cut-offs.[109] Nevertheless, because of the single-center nature and small sample size of this study, whether left atrial strain measurements can distinguish between isolated AS and mixed AS-CA—and what cut-off is sufficiently sensitive and specific for mixed disease—remains an open question. Presently, these measurements are better utilized as prognostic markers of a patient's clinical trajectory—supplementing electrocardiographic, echocardiographic, laboratory, and imaging results—rather than diagnostic tools for separating mixed disease from lone AS.

Cardiac magnetic resonance imaging (CMR)

CMR can provide added information about the presence of concomitant CA because it provides more detailed myocardial tissue characterisation. CMR is particularly useful for the workup of CA if other causes of restrictive cardiomyopathies are suspected because of its ability to distinguish nonamyloid causes of LV thickening, such as hypertrophic cardiomyopathy and hypertension.[95] The characteristic finding of CA on CMR is circumferential late gadolinium enhancement (LGE) throughout the LV subendocardium, with or without myocardial extensions and a base-to-apex gradient.[72] However, this pattern reflects the greatest degree of interstitial amyloid deposition and, therefore, can be absent in early disease stages with low sensitivity (despite high specificity) for diagnosis in patients with dual AS and ATTR-CA.[21,55,110] Indeed, amyloid deposition represents a continuum from no LGE to subendocardial and transmural; hence, particularly early forms of ATTRwt-CA are difficult to differentiate from advanced AS remodeling based solely on CMR-LGE.[110] Furthermore, a third of patients with severe AS can exhibit non-ischaemic patchy or mid-wall LGE (reflecting focal fibrosis), which may lead to varying LGE patterns in patients with dual pathology.[111,112]

In contrast, CMR parametric mapping techniques, namely native T1-mapping and extracellular volume (ECV) mapping, can identify associated CA before LGE is detectable and can effectively distinguish ATTR-CA from other causes of equivalent myocardial hypertrophy with diastolic dysfunction (*eg,* hypertrophic cardiomyopathy and hypertensive heart disease).[73–75,87,113,114] It is worth noting native T1 values are higher in AL-CA, while ECV is relative higher in ATTR-CA.[115] ECV, because it is more specific for the myocardial interstial and intravascular spaces than native T1 and is less influenced by intracellular myocardial edema, offers greater prognostic value than native T1 because it more directly indicates amyloid burden.[75] The ECV is increased moderately in other cardiac pathologies with fibrosis (*eg,* hypertension, HCM, and severe AS) but seems to increase massively in amyloidosis—higher than any other disease.[116] A meta-analysis by Pan *et al* demonstrated that an elevated ECV demonstrated significantly greater diagnostic odds ratio and hazard of adverse events for CA than LGE and native T1 mapping.[117] Furthermore, Kravchenko *et al* demonstrated that an ECV cut-off >30% was the single best parameter in distinguishing CA from other causes of LVH (AUC: 0.97; 95% CI: 0.89—0.99; $P<0.0001$).[118] The authors also reported that T2 relaxation was the best parameter in distinguishing ATTR-CA and AL-CA. A cut-off T2 relaxation time of 61 milliseconds along with LGE patterns (transmural for ATTR-CA and subendocardial for AL-CA) improved differentiation between ATTR-CA and AL-CA (AUC: 0.96; 95% CI 0.89–0.99; $P=0.05$).[118]

An alternative to CMR, cardiac computed tomography (CT) is widely performed in severe AS before TAVR to assess valve annulus dimensions, vascular access, and the anatomy of the coronary arteries, but can also be used to calculate the ECV that correlates well to CMR-ECV in both AS and CA and, in the case of the latter, with bone scintigraphy amyloid burden.[116,119] Thus, ECV quantification by CT may represent a more cost- and time-effective alternative to CMR.

In AS, myocardial fibrosis leads to high native T1 and ECV,[120,121] and this may be exacerbated in concomitant

amyloid deposition. Studies by Cavalcante *et al* and Nitsche *et al* have demonstrated significantly higher native T1 and ECV values in patients with dual AS-CA as compared with patients with lone AS.[19,55] While LGE had low sensitivity, incorporating ECV into CMR assessment improved diagnostic accuracy in distinguishing mixed disease from sole AS (AUC: 0.756).[21,55]

Alternatively, quantification of the ECV with CT also reveals significantly higher global ECV in patients with mixed AS-CA as compared to patients with lone AS.[122] In agreement with this finding, Scully *et al* showed that, in 109 patients with severe AS referred for TAVR, of which 15% (16/109) has grade 1 or 2 amyloid on bone scintigraphy, quantification of ECV by CT as part of routine preprocedural evaluation showed significantly higher measurements in those with positive scintigraphy than those with lone AS.[123] It is worth noting, however, that the mean age in this cohort was 86 years, hence the prevalence of CA was likely higher in this cohort as compared with younger AS patients. Nevertheless, setting a cut-off ECV value to predict positive grade 2 cardiac uptake on bone scintigraphy (based on which CA can be diagnosed), a cut-off CT-ECV of 33.4% had an AUC of 0.95 (95% CI, 0.89–1.00; sensitivity 100%; specificity 64%; negative predictive value of 100%).[123] Hence, ECV can be a useful tool when determining which patients should undergo bone scintigraphy. Furthermore, regional ECV quantification can reflect the pattern of amyloid infiltration and fibrosis in AS-CA (*eg,* predilection for involvement of the base, subendocardium, and inferior wall). Septal ECV mearuemnt by CT also demonstrate prognostic utility in ATTR amyloidosis, being associated with hsTnT and NT-proBNP elevations, LV wall thickness, and all-cause mortality.[124] In another study, Patel *et al* demonstrated that epicardial ECV (cut-off: 27.05%) was a significant predictor of overall survival in independent cohorts of patients with severe AS and mixed AS-CA (HR = 1.21; 95% CI = 1.08 to 1.36; P = 0.02).[122]

However, although we recommend CMR in the diagnostic and prognostic evaluation of CA, the findings on CMR are highly influenced by stage of amyloidosis, the severity of AS, and potentially other presently unknown factors, which may lead to variable findings. For instance, Triebel *et al* performed CMR in 6 patients among 146 with severe AS referred for TAVR who had histologically-proven ATTRwt-CA and showed that CMR findings—including LGE pattern, LVEF, LV mass index, myocardial contraction fraction, maximal wall thickness, and ECV—were consistent with CA in only 2 patients.[15] In these patients, CMR revealed classical findings of CA, such as hypertrophy out of proportion to AS severity, global transmural LGE, elevated native T1, and ECV > 50%; however, values of these parameters could be explained by severe AS in the other four cases.[15] Hence, relying solely on CMR for diagnosis of CA is not recommended, and negative findings should not obviate the need for further workup by scintigraphy if clinically suspicion for CA is high.

Diagnosis of cardiac amyloidosis

Based on the above-mentioned clinical, electrical, and echocardiographic red flags, Nitsche *et al* developed the RAISE clinical prediction tool for detecting concomitant ATTR-CA and AS composed of the following five parameters: remodelling (marked LVH or diastolic dysfunction —1 point), age (≥85 years—1 point), injury (high-sensitivity troponin-T > 20 ng/L—1 point), systemic (positive history of carpal tunnel syndrome—3 points), and electrical (right bundle branch block (2 points) or low voltages (1 point)). This score demonstrated good accuracy in cases of co-existent ATTR-CA and AS (AUC = 0.86; 95% CI: 0.78 to 0.94; $p < 0.001$), validated on an external cohort (AUC: 0.83; 95% CI: 0.75 to 0.92; $p < 0.001$). A score of at least two on this prediction had high sensitivity (93.6%) with modest specificity (52.1%) in detecting the presence of ATTR-CA with AS.[53]

The definitive diagnosis of CA includes ruling out AL amyloidosis and evaluating for cardiac tracer uptake on technetium-99 m (99mTc)-based bone scintigraphy—such as with 99mTc-labelled pyrophosphate (99mTc-PYP)/3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD)/ or hydroxy methylene diphosphonate (99mTc-HMDP) radiolabelled tracers.[125,126] This forms the basis of the non-biopsy diagnostic criteria (NBDC) for ATTR-CA. The result of the scintigraphy scan is graded from 0–3 according to the intensity of cardiac uptake relative to bone uptake, with Perugini grade 0 meaning no cardiac uptake, Perugini grade 1 describing mild uptake but less intense than bone, Perugini grade 2 describing comparable cardiac uptake to bone uptake, and Perugini grade 3 describing greater cardiac than bone uptake. Single-photon emission computed tomography (SPECT) imaging is necessary to confirm that tracer uptake is located within the myocardium and not within the blood pool. Perugini grades 2–3 can be used to make the diagnosis of CA, grade 0 rules out cardiac amyloidosis, while grade 1 can either represent a false-positive scan or early-stage CA.[127–129] However, although high grade uptakes are more specific for CA, stratification by Perugini Grade does not reliably predict patient prognosis,[129] underscoring the need for a comprehensive evaluation with the aforementioned, prognostically relevant clinical, laboratory, and imaging parameters. Accordingly, the NBDC comprises the following elements: a clinical phenotype of cardiomyopathy, evidence of cardiac infiltration on echocardiography or cardiac magnetic resonance imaging (CMR), the absence of a monoclonal gammapathy, and a grade 2–3 cardiac tracer uptake.[125,130] Fulfilling these criteria obviates the need for a confirmatory endomyocardial biopsy to detect and subtype amyloid via histological assessment.

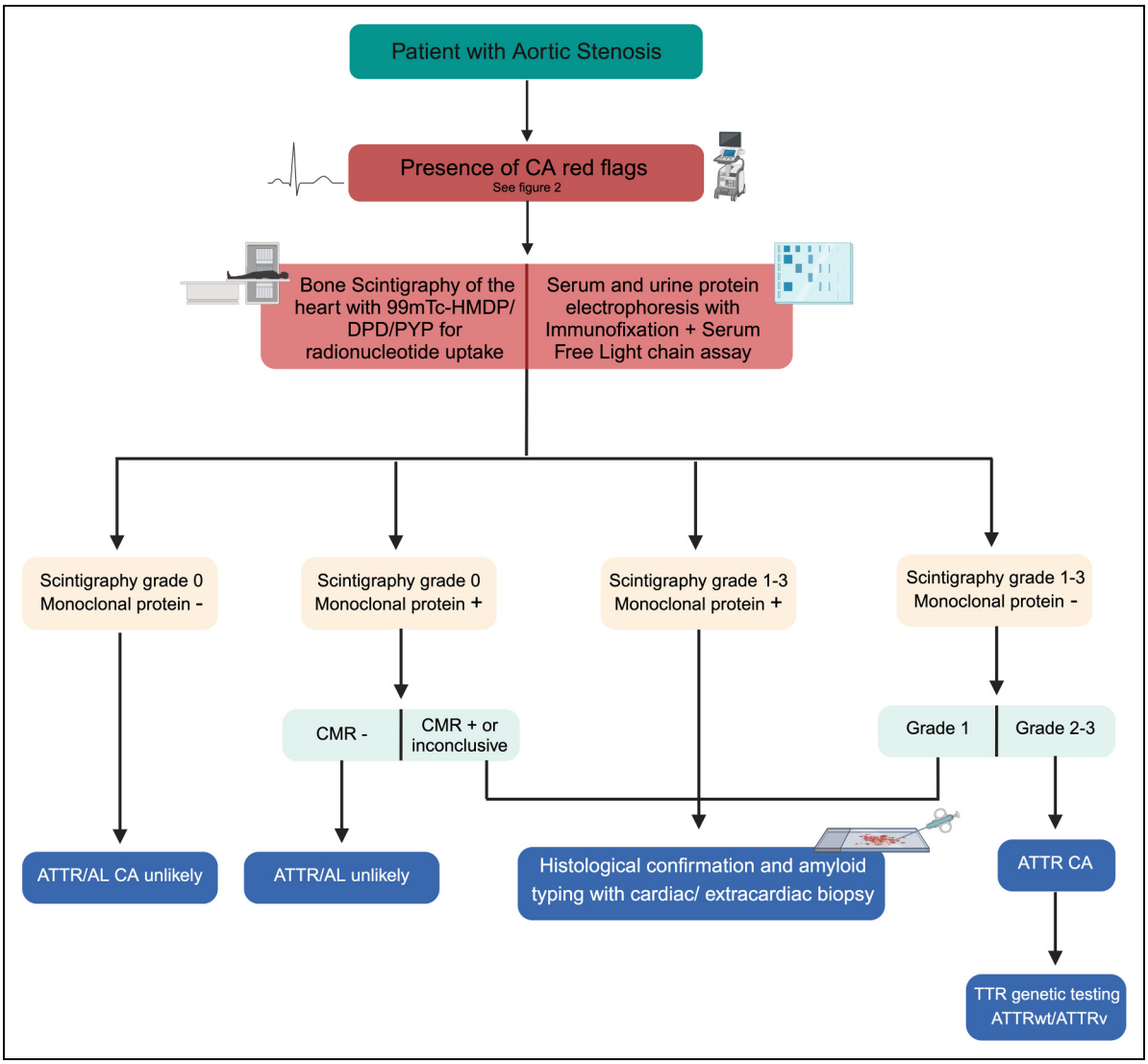

Figure 3. Diagnostic algorithm of cardiac amyloidosis in patients with aortic stenosis. Patients with suspected CA should undergo assessment for monoclonal proteins by SPIE, UPIE, and quantification of serum FLC coupled to bone scintigraphy for myocardial radiotracer uptake. Cardiac uptake in bone scintigraphy is graded from 0–3 (0 = absent cardiac uptake, 1 = mild uptake less than bone, 2 = moderate uptake equal to bone, 3 = high uptake greater than bone). ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; CA: cardiac amyloidosis; CMR, cardiac magnetic resonance imaging; DPD, 3,3-diphosphono-1,2-propanodicarboxilic acid; HMDP, hydroxymethylene diphosphonate; PYP, pyrophosphonate; SPIE, serum protein electrophoresis with immunofixation; TTR, transthyretin; UPIE, urine protein electrophoresis with immunofixation.

Serum and urine electrophoresis and serum free light chains must be measured to rule out monoclonal component/light chain abnormalities; only when AL amyloidosis has been excluded then a diagnosis of ATTR-CA be made. In the case that findings of bone scintigraphy of the heart are equivocal, such as Perugini Grade 1 uptake on 99mTc-based scintigraphy, or in any other scenario where the elements mentioned above are not fulfilled, further workup with either another follow-up bone scintigraphy in addition to CMR is suggested. If these tests are still unclonclusive and clinical /biological/ echo suspicion is strong, then endomyocardial or tracardiac biopsy may be needed (Figure 3). Indeed, since Perugini grade 1 may represent either a false positive result or early-stage ATTR or AL CA (findings in the literature have been conflicting), further histological confirmation and amyloidosis typing is currently recommended for these patients.

Once the diagnosis of ATTR-CA is established, genetic testing (*ie,* sequencing of the *TTR* gene on chromosome 18) is indicated for all patients to differentiate between ATTRwt-CA and ATTRv-CA. Making this distinction is

critical for several reasons. For instance, because alleles for the *TTR* gene are inherited in an autosomal dominant fashion, genotyping is crucial for counselling of family members is crucial because different genetic variants (*eg,* Val122Ile and Val30Met) have varying ages of onset and degrees of cardiac and neurologic involvement; for example, Val122Ile is associated with later age of onset and greater degree of cardiac involvement.[35,131] Hence, decisions of cascade genetic testing in first-degree relatives and subsequent clinical monitoring for early detection of ATTRv amyloidosis differ based on the variant detected. Secondly, the identification of variants associated with nervous system or gastrointestinal involvement warrant referrals to the relevant specialities in order to establish multidisciplinary care. This is especially relevant as two agents therapeutic agents, patisiran and inotersen, are approved for the treatment of ATTRv-associated neuropathy irrespective of cardiac involvement. Hence, genotyping is also important for treatment, as certain medications are only indicated for ATTRv amyloidosis.[132] The importance of genetic testing will only increase in the future with phase 3 trials evaluating novel therapeutic avenues such as CRISPR/Cas9 gene editing technologies, antisense oligonucleotides (ASO) and small interfering RNAs (siRNAs) for ATTRv amyloidosis.[133,134] is worth noting that a negative family history should not preclude genetic testing because the transmission of *TTR* variants have incomplete penetrance and the the possibility of missed diagnosis in the parent or death of the parent prior to the development of amyloidosis. These considerations also hold for patients with dual AS-CA because genetic testing, despite their old age, has important implications for treatment, referral to relevant medical specialties, and family counselling/monitoring.

Management of concurrent aortic stenosis and cardiac amyloidosis

The concurrence of ATTR-CA and AS requires timely diagnosis and the subsequent initiation of appropriate intervention strategies. Nonetheless, there remains equivocation as to which of the two diseases is the primary prognosticator. For instance, a number of studies have reported similar outcomes among patients with co-existent ATTR-CA and AS compared to those with ATTR-CA alone.[17,21] Similarly, the survival rate of patients with lone AS have closely resembled those of patients with concurrent ATTR-CA and AS in certain studies.[56] On the other hand, a growing body of evidence has demonstrated worsening outcomes among patients with co-existent ATTR-CA and AS compared to either disease alone.[52,55,135] Thus, it is likely that there is a potential interplay between the pathophysiology of both disorders resulting in worsening cardiovascular outcomes and subsequently a potential higher mortality risk.

Management of cardiac amyloidosis in patients with concurrent aortic stenosis

Recent evidence has suggested that in cases of co-existent ATTR-CA and AS, the primary phenotype of cardiac remodeling resembles amyloidotic pathology.[136] Furthermore, following treatment of AS, the pathological phenotype purely resembles that of cardiac amyloidosis.[137] Hence, the focus of management after treating the stenotic aortic valve is to target and manage the complications of the amyloidosis deposition. The treatment of cardiac amyloidosis primarily focuses on two aspects: (1) targeted (*ie,* disease-modifying) therapy to stop, stabilize or decrease amyloid deposition, and (2) general or supportive measures to decrease the effect of complications of amyloid deposition of affected organ particularly cardiac involvement (Figure 4).

The general management of cardiac amyloidosis is outlined by the CHAD-STOP guidelines: Conduction and rhythm disorders prevention, High heart rate maintenance, Anticoagulation, Diuretic agents, STOP ß-receptor and calcium-channel blockers, digoxin, RAAS inhibitors.[20] Cardiac amyloidosis frequently infiltrates the conduction system resulting in a myriad conduction and rhythm disturbances.[138] Amiodarone is the first-line drug for conduction disorders among patients with CA, whereas digoxin should be used cautiously given the risk of its accumulation within amyloid deposits. Moreover, given the high prevalence of conduction disorders among patients with CA, pacemaker insertion should be considered in patients with first degree AV block, unexplained syncope, and patients awaiting aortic valve replacement.[139] Amyloid infiltration of the myocardium results in a restrictive cardiomyopathy phenotype with marked impairment of LV filling. Consequently, preload decreases, rendering an increase in heart rate the only compensatory mechanism to maintain adequate cardiac output.[20] Therefore, β-receptor and calcium-channel blockers are contraindicated in CA due to their negative chronotropic effects. Additionally, renin-angiotensin-aldosterone system inhibitors should be prescribed with caution prescribed given the risk of severe hypotension. In the setting of CA presenting with heart failure with reduced ejection fraction and evident systolic dysfunction, the use of RAAS inhibitors and ß-blockers should be preceeded by a case by case evaluation based on hemodynamic parameters. In cases of decompensated heart failure the initiation of diuretic agents is critical; however, excessive depletion of intravascular volume can severely impede cardiac output. Cardiac amyloidosis is associated with a heightened risk of thromboembolic events.[140] Additionally, the co-existence of ATTR-CA and AS has been associated with a significantly increased risk of thromboembolic events.[58] Therefore, prompt initiation of anticoagulant therapy is required among patients with supraventricular arrhythmias and those with thromboembolic complications. The initiation of anticoagulation among CA patients with supraventricular arrhythmias should

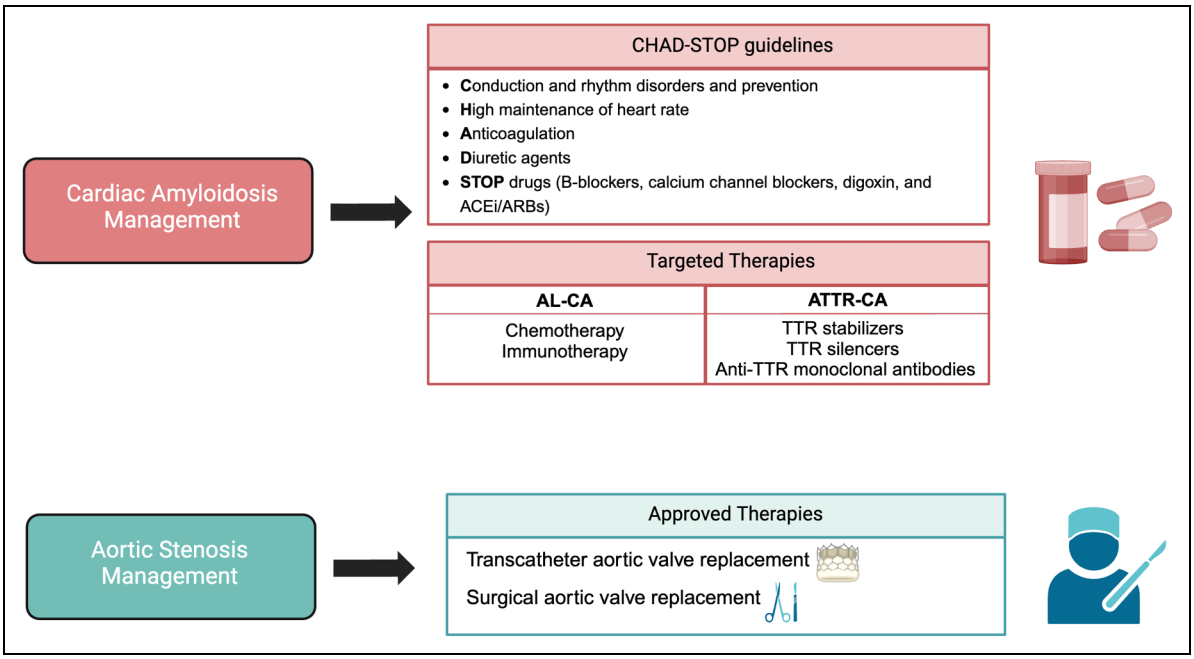

Figure 4. Current medical and surgical treatment of patients with cardiac amyloidosis and aortic stenosis. AL-CA, amyloid light chain–cardiac amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis.

be initiated irrespective of the CHA_2DS_2-VASC score. This is supported by a recent study which found no association between the CHA_2DS_2-VASC score and left atrial appendage thrombus in patients with ATTR-CA In addition, patients with CA may display left atrial electro-mechanical dissociation resulting in the presence of atrial thrombi despite the persistence of sinus rhythm.[141–143] Consequently, anticoagulation in sinus rhythm ought to be considered on a case by casis basis among CA patients with evident electro-mechanical dissociation.[144] More recently, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown promising efficacy in the treatment of ATTR-CA-related heart failure. Despite the heightened theoretical risks of adverse events due to SGLT2is in patients with ATTR-CA as a consequence of their older age and their predisposition to severe hypotension, small cohort studies have shown the ability of SGLT2is to improve volume status and overcome diuretic resistance in patients with ATTR-CA induced heart-failure.[145,146] Importantly, SGLT2is were well tolerated in this patient subgroup, with no severe adverse events.

Patients with ATTR-CA frequently develop advanced heart failure wherein medical therapy is no longer effective. Mechanical circulatory support or cardiac transplantation may be required in this setting.[131] In the case of mechanical circulatory support, a number of important limitations arise among patients with ATTR-CA.[147] In particular, patients with CA possess small ventricular cavities which hinders the placement of inflow cannulas and heightens the potential for suction events. Additionally, patients with ATTR-CA have biventricular dyfunction, predisposting them to right ventricular failure if left ventricular support devices are utilzed alone. Nonetheless, despite the aforementioned limitations, mechanical circulatory support can be a viable option for certain patients. A study of 28 patients (including 9 with ATTR-CA) with restrictive cardiomyopathies who received left ventricular assist devices, reported an average survival time of 536 days.[148] Notably, patients with larger left ventricular cavities experienced significantly longer survival, highlighting the importance of carefully selecting patients with desirable charecterstics prior to the initiation of mechanical circulatory support. In a separate single-center study, 11 amyloidosis patients received mechanical circulatory support as a bridge to heart transplantation.[149] All of these patients required biventricular support, either with a total artificial heart or biventricular assist devices. By the one-year mark, 9 patients had undergone successful transplantation, while 2 had passed away. However, recent INTERMACS data reveal that MCS outcomes in patients with amyloid cardiomyopathy are poorer compared to those with dilated or other restrictive cardiomyopathies, especially when using left ventricular-only support.[150] In summary, while some success has been observed, the optimal role of MCS in this patient group remains unclear and requires further exploration. On the other hand, cardiac transplantation in the context of ATTR-CA also poses a number of critical limitations.[147] For those with wild-type ATTR, cardiac transplantation is often limited by the advanced age of most patients and the presence of comorbidities. In hereditary amyloidosis, the situation is more complex and highly dependent on the specific genotype. For genetic variants that result in a combination of cardiomyopathy and

neuropathy symptoms, heart transplantation alone is insufficient, as it will not stop the progression of debilitating polyneuropathy. In these cases, liver transplantation may be considered as a way to eliminate the production of the abnormal transthyretin protein. However, with the availability of effective pharamcaological treatments like patisiran and inotersen, it is uncertain whether liver transplantation is still necessary, or if a combination of heart transplantation and pharmacological treatment would be a better approach. Prior to performing heart transplantation in patients with gene mutations linked to mixed-phenotype disease, a comprehensive neurological assessment is essential to rule out significant neuropathy. An analysis of three decades of patients with ATTR cardiomyopathy at the UK National Amyloidosis Centre has explored the outcomes of patients who underwent cardiac transplantation.[151] Within the study, eleven patients with ATTR cardiomyopathy underwent cardiac transplantation, of which three had hereditary ATTR. Cardiac transplantation in these patients was moderately well tolerated and it resulted in the enhancemet of functional capacity and the prolongation of survival beyond that expected of patients with ATTR cardiomyopathy. In addition, there was no recurrence of ATTR amyloidosis in the transplanted cardiac allografts. The limitations of cardiac transplanatstion in ATTR-CA coupled with the advent of novel pharmacotherapies renders cardiac transplantation inedffective in a large number of patients. However, a minority of carefully selected patients may benefit from this therapy. Nonetheless, larger cohort studies with longer-follow up periods are required to adequately assess the benefit of cardiac transplantation amomg patients with ATTR-CA.

Regarding targeted medical therapy for AL cardiac amyloidosis, the main therapeutic approach involves plasma-cell directed chemotherapy to reduce the formation and accumulation of toxic light chains.[152] In addition to anti-plasma cell targeted chemotherapy, patients with AL amyloidosis require a multidisciplinary approach to their treatment with a particular focus on cardiorenal multimorbidity.[152] These patients often require frequent monitoring and assessment of treatment response and organ function and the subsequent adjustment of treatment dosing in correlation with clinical improvement or the emergence of significant toxicities. Moreover, younger patients with heart failure as a result of AL-CA and no extracardiac comorbidities may benefit from cardiac transplantation.[153] Nonetheless, cardiac transplantation in this patient group is associated with a high recurrence in allografts consequently resulting in a reduction in survival outcomes.[154] However, the utilization of post-heart transplant haematopoietic stem cell transplantation and plasma-cell directed chemotherapy has been shown to significantly reduce disease recurrence in transplanted allografts.[155,156]

Targeted therapy for ATTR-CA includes medications that either directly inhibit or alter transthyretin deposition. Tafamidis, a transthyretin tetramer stabilizer, has emerged as the first-line drug for ATTR-CA.[125] Mechanistically, Tafamidis binds to the thyroxine-binding site of transthyretin and prevents its misfolding, thereby attenuating the formation of amyloid fibrils.[21] The ATTR-ACT randomized controlled trial demonstrated that patients receiving Tafadimis had significantly lower all-cause mortality (HR, 0,70; 95% CI, 0.51–0.96) and cardiaovascular-related hospitalizations (RR, 0.67; 95% CI, 0.56–0.81) compared to placebo at 30 months of follow-up.[28] Moreover, patients in the Tafamidis arm had a significantly lower rate of decline in functional status and higher quality-of-life measures compared to the placebo arm. Additionally, the drug was shown to be effective in patients with both wild-type or hereditary ATTR-CA. The ATTR-ACT study demonstrated that the clinical efficacy of Tafamidis was evident at 18 months and that it was more effective when utilized in the early stages of disease onset, indicating that Tafamidis likely impedes disease progression but may not cause regression of advanced disease. Therefore, early diagnosis is of critical value in improving patient outcomes with Tafamidis. Despite its clinical efficacy, the financial cost of Tafamidis may hinder access to the drug and limit its utilization around the globe. A secondary analysis of the ATTR-ACT study has found that Tafamidis is estimated to add approximately 1.29 quality-adjusted life years (QALY) in comparison with standard therapy alone.[157] Nonetheless, this comes at a significant financial cost of $100 000/QALY. Nonetheless, Tafamidis remains a critical therapeutic option in the management of ATTR-CA, especially considering its favorable side effect profile and its significant clinical efficacy.

Apart from Tafamidis, a number of novel drugs are currently emerging in targeted therapy for ATTR-CA. Acoramidis, a TTR stabiliser that restricts the dissociation of tetrameric TTR, has shown promising efficacy in the recent phase 3, randomised, double-blinded, placebo-controlled ATTRibute-CM trial of 632 patients with ATTR-CA.[27] The primary endpoint of this trial was a composite of all-cause mortality, cardiovascular-related hospitalization, change in baseline in NT-proBNP level, and change from baseline in the 6-min walk test. Patients randomised to Acoramidis had a significantly higher four-step primary hierarchical outcome when compared to placebo. There were no significant differences in adverse events between the placebo arm and the Acoramidis arm.

On the other hand, RNA silencers that block the synthesis of transthyretin in the liver have demonstrated promising results in the treatment of hereditary transthyretin neuropathy.[158] More recently, the impact of these therapeutics on transthyretin amyloid cardiomyopathy has been explored. For instance, the RNA silencer Eplontersen is being evaluated for treating transthyretin amyloid cardiomyopathy in a phase 3 randomised controlled trial of 1400 participants. The CARDIO-TTRansform study (NCT04136171) will

evaluate the safety and efficacy of Eplontersen in patients with transthyretin amyloid cardiomyopathy following the promising results of the NEURO-TTRansform assessing the efficacy of Eplontersen in patients with hereditary transthyretin neuropathy.[159,160] The HELIOS-B was a double-blind, randomized, placebo-controlled trial of 655 patients with ATTR-CA that randomized patients to receive 25 mg vutrisiran, an RNA interefence agent to decrease expression of the ATTR gene, or placebo every 12 weeks for 36 months.[161] Through a follow-up of 42 months, vutrisiran-treated patients had a significantly lower hazard of the primary endpoint of all-cause mortality and recurrent cardiovascular events (HR, 0.72; 95% CI, 0.56–0.93; P = 0.01). Regarding secondary endpoints, vutrisiran treatment led to less decline in distance covered on the 6-min walk test and patient's subjective assessment of their health status (measured by the Kansas City Cardiomyopathy Questionnaire-Overally Summary (KCCQ-OS) score). The incidence of adverse events were similar between the placebo and treatment groups.[161]

Finally, a phase 1, randomized, placebo-controlled, double-blind trial of 40 patients with WT-ATTR or variant-ATTR cardiac amyloidosis demonstrated the favorable safety profile of NI006, an anti-ATTR IgG antibody that tags ATTR and promotes its removal by phagocytic immune cells.[26] At 12-months, cardiac tracer uptake on scintigraphy, extracellular volume on CMR, NT-proBNP, and troponin-T levels were reduced in patient treated with at least 10 mg/kg doses of NI006; these findings are subject to validation by larger, adequately powered phase III trials.

Management of aortic stenosis in patients with concurrent cardiac amyloidosis

The management of severe AS encompasses aortic valve replacement either surgically (SAVR) or through transcatheter intervention (TAVR). Patients with concurrent AS and CA are often older and frail; therefore, surgical replacement may carry a heightened risk of complications. Indeed, two recent studies comparing SAVR and TAVR among patients with co-existent severe AS and CA have shown improved outcomes along with lower complication rates and hospitalization costs in patients receiving TAVR.[14,162] Moreover, TAVR has been shown to be superior to medical therapy in patients with concurrent severe AS and ATTR-CA. For instance, Scully et al assessed the outcomes of dual AS and cardiac amyloid pathology in 200 patients referred for TAVR and found TAVR to have superior outcomes compared to medical management.[56] Similarly, a recent meta-analysis by Cannata et al found significantly reduced mortality in patients with CA following TAVR compared to medical therapy alone.[61] Interestingly, despite the multimorbid nature of CA patients, Nitsche et al and Elzeneini et al found no difference in outcomes following TAVR between patients with co-existing CA and controls without CA.[55,58] Nonetheless, a number of factors are associated with poor outcomes in patients with CA and futility of aortic valve replacement including: low ejection fraction (<50%), severely depressed global longitudinal strain (≥−10%), moderate-to-severe low-flow state, and low-gradient AS.[20] Therefore, a holistic approach should be initiated to determine the suitability of aortic valve replacement among patients with CA. This approach should incorporate cardiovascular and echocardiographic parameters, frailty and comorbidities, functional status, and expected life-expectancy to determine the most suitable clinical approach. In cases where AVR is likely to be futile, optimization of heart failure therapy in addition to the potential initiation of TTR-targeted therapies is often required.

Conclusions and perspectives

The coexistence of AS and ATTR-CA presents a significant and increasingly recognized clinical issue, particularly as the population ages. This dual pathology often goes undiagnosed, contributing to an underappreciation of its prevalence and impact. Our review underscores the critical need for increased awareness and improved diagnostic strategies to better identify and manage these patients, given the severe prognosis associated with the combined presence of AS and ATTR-CA.

Clinical evaluation and non-invasive tests, including ECG, echocardiography, CMR, and bone scintigraphy of the heart are crucial for early detection and diagnosis of concomitant AS and ATTR-CA. These diagnostic tools aid in identifying patients who would benefit from a multidisciplinary assessment to determine the optimal treatment strategy.

Management of patients with severe AS and concurrent ATTR-CA remains complex. TAVR is often preferred over SAVR due to the higher surgical risk in older patients with amyloid-infiltrated tissues. The development of disease-modifying therapies for ATTR-CA presents new therapeutic opportunities that may significantly alter the treatment landscape and improve outcomes for these patients. However, the optimal timing and integration of valve-specific and amyloid-specific therapies require further investigation.

Future research directions should focus on dedicated randomized trials to assess the benefit of combining TAVR with disease-modifying therapies for CA, as current evidence is lacking. With the availability of non-invasive diagnostic methods and pharmacotherapies, there is an urgent need to determine the best approaches for screening and treating CA in patients with AS. Specific guidelines should be developed to guide the heart team in decision-making regarding the type and timing of treatments, including SAVR, TAVR, and pharmacotherapy. The ongoing Amylo-CARTESIAN (Prevalence and Post-surgical Outcomes of CARdiac Wild-type TransthyrEtin amyloidoSIs in Elderly Patients

With Aortic steNosis Referred for Valvular Replacement) (NCT02260466) study will provide valuable insights into the prevalence, management, and outcomes of CA in AS patients referred for AVR. Additionally, exploring whether patients with CA are at higher risk for structural valve deterioration following biological AVR is essential. The use of artificial intelligence and machine learning could further enhance the systematic screening of CA in patients with AS by automatically detecting red flags, thereby improving diagnosis and management strategies.[163]

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