




# Practical recommendations for the diagnosis and management of transthyretin cardiac amyloidosis

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## Abstract

Cardiac amyloidosis (CA) is an infiltrative restrictive cardiomyopathy caused by accumulation in the heart interstitium of amyloid fibrils formed by misfolded proteins. Most common CA types are light chain amyloidosis (AL) caused by monoclonal immunoglobulin light chains and transthyretin amyloidosis (ATTR) caused by either mutated or wild-type transthyretin aggregates. Previously considered a rare disease, CA is increasingly recognized among patients who may be misdiagnosed as undifferentiated heart failure with preserved ejection fraction (HFPEF), paradoxical low-flow/low-gradient aortic stenosis, or otherwise unexplained left ventricular hypertrophy. Progress in diagnosis has been due to the refinement of cardiac echocardiographic techniques (speckle tracking imaging) and magnetic resonance (T1 mapping) and mostly due to the advent of bone scintigraphy that has enabled noninvasive diagnosis of ATTR, limiting the need for endomyocardial biopsy. Importantly, proper management of CA starts from early recognition of suspected cases among high prevalence populations, followed by advanced diagnostic evaluation to confirm diagnosis and typing, preferentially in experienced amyloidosis centers. Differentiating ATTR from other types of amyloidosis, especially AL, is critical. Emerging targeted ATTR therapies offer the potential to improve outcomes of these patients previously treated only palliatively.

**Keywords** Cardiac transthyretin amyloidosis · Clinical suspicion · Diagnostic strategy · Treatment

## Introduction

Amyloidosis is a systemic disease caused by the deposition of misfolded protein aggregates that form amyloid fibrils in the interstitial space of various organs [1]. Cardiac amyloidosis (CA) results from infiltration of the heart interstitium by amyloid, which causes stiffening of the heart muscle and progressive cardiac dysfunction. Amyloidoses are classified according to the type of the primary misfolded protein, with over 30 different proteins being etiologically implicated. However, two types of proteins cause the majority of CA cases: monoclonal immunoglobulin light chains, which are produced from a plasma cell clone (light chain amyloidosis, AL), and transthyretin (TTR), a protein synthesized primarily in the liver (causing transthyretin amyloidosis, ATTR). Transthyretin normally serves as a carrier for thyroxine and holo-retinol binding protein and can form amyloid fibrils either when the TTR gene is mutated or if the wild type, nonmutated TTR becomes misfolded [2].

CA was previously considered a rare disease, with AL being the most common type. However, with the recent

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adoption of noninvasive diagnostic techniques that can accurately diagnose ATTR without an absolute need for cardiac biopsy—most importantly myocardial scintigraphy with certain bone-avid tracers—it was realized that ATTR is far more common than previously appreciated, especially among elderly patients [3]. Importantly, it has also been realized that CA is frequently misdiagnosed as HFPEF, low-flow low-gradient aortic stenosis, or otherwise unexplained left ventricular (LV) hypertrophy [4–6]. The introduction of specific therapies for ATTR CA has further increased the need to accurately diagnose these patients, early in the course of the disease. Thus, there is a need to develop appropriate tools to assist clinicians in recognizing possible ATTR cases among populations with high prevalence and then properly evaluate and confirm diagnosis. The present manuscript constitutes a consensus opinion document developed by a panel of CA and hereditary amyloidosis experts in Greece, aiming to provide practical tools for the early recognition and proper diagnostic confirmation of ATTR CA. Moreover, a brief overview of recently approved and emerging ATTR disease-modifying therapies is provided.

## Classification and epidemiology of CA

The two most common types of CA are AL and ATTR. In AL, amyloid fibrils derived from clonal immunoglobulin light chains infiltrate various organs. It is a multisystemic disease with cardiac involvement observed in 50–75% of cases, but the kidneys, liver, lungs, autonomic and peripheral nervous systems and soft tissues are also involved quite commonly [7]. However, isolated cardiac AL is not uncommon, occurring in about 20% of patients (data: Department of Clinical Therapeutics). The prevalence of AL has been reported between 8 and 12 cases per million person-years; it affects slightly more frequently men, and its peak incidence is between the 5th and 7th decades [8]. Treatment of AL consists of cytotoxic chemotherapy aiming to eliminate the clonal plasma cells and therefore the production of the precursor protein [9, 10]. If untreated, prognosis of cardiac AL is dismal, with median survival of approximately 6 months from onset of heart failure (HF) [11]. Even with current therapies, mortality of high-risk patients with elevated cardiac biomarkers exceeds 40% at 1 year after diagnosis [12].

ATTR can be either hereditary or wild type. Hereditary or mutant ATTR (mATTR) is caused by mutations of *TTR* gene that result in TTR protein with an amyloidogenic potential. mATTR is considered a rare disease, with currently estimated prevalence of 50,000 affected individuals worldwide [13]. It has a worldwide distribution

but it is endemic in areas of Portugal, northern Italy, Japan, Sweden and Cyprus [14]. mATTR is inherited in an autosomal-dominant manner with variable penetrance. Over 120 mutations of *TTR* gene have been described with varying phenotypic expression depending on the mutation; not all mutations are amyloidogenic. Most common phenotypes are dominant neuropathic, dominant cardiomyopathic, or mixed. The most common mutation worldwide is V122I, which is detected in approximately 3–4% of African-Americans and is associated with predominantly cardiac manifestations [15, 16]; other cardiomyopathic TTR mutations are L111M and I68L. The most common neuropathic mutation is V30M, which, however, may be associated with a mixed phenotype in late-onset disease. Other less common manifestations of mATTR include ocular abnormalities (including vitreous opacities that can cause gradual visual loss and trabecular obstruction causing chronic open-angle glaucoma), renal involvement (nephrotic syndrome and progressive renal failure), and rarely central nervous system involvement [17]. Prognosis of mATTR varies significantly according to the type of mutation, fibril type, and also within families. However, the main prognostic determinant is the presence of cardiac involvement, as median survival of patients with HF at diagnosis is 2.5–3.5 years versus 8–10 years in patients presenting only with polyneuropathy [18].

Although the cause for misfolding of wild-type TTR (wtATTR) has not been delineated, abnormal protein kinetics and aging-related post-translational modifications have been hypothesized [19]. wtATTR affects predominantly older individuals, usually over the age of 70–75 years, of whom > 90% are men. Although accurate estimates of ATTR prevalence are not available, it appears quite common in certain patient populations. Recent data report rates of wtATTR as high as 13% in patients with HFPEF, 16% in patients with aortic stenosis undergoing transcatheter valve replacement, 5% in those undergoing surgical replacement, and 5% in patients with presumed hypertrophic cardiomyopathy [4–6]. Furthermore, in asymptomatic patients undergoing bone scintigraphy (BS) for other reasons, ATTR has been detected in 1–3% as incidental finding [20, 21]. Cardiac manifestations predominate in wtATTR. However, musculoskeletal involvement may also be observed, that manifests clinically as carpal tunnel syndrome, spinal stenosis, and biceps tendon rupture. In most cases, wtATTR progresses slowly, but symptoms of advanced, refractory HF may develop abruptly after an initial slowly progressing phase. Overall, median survival is approximately 3.5 years after diagnosis, depending on the severity of HF [22–24].

## Diagnostic workup of cardiac ATTR

### Clinical presentation

Clinical manifestations of cardiac ATTR are not specific. Most commonly, patients present with symptoms of HF, including dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, fatigue, exercise intolerance, and peripheral edema that combined with the finding of concentric LV remodeling, usually lead to misdiagnosis of generic, undifferentiated HFPEF. Moreover, diagnosis of ATTR can be concealed in patients with co-existing comorbidities that are associated with ventricular hypertrophy, such as arterial hypertension and aortic stenosis in older individuals [25]. Likewise, in younger individuals with mATTR, LV hypertrophy may be misdiagnosed as hypertrophic cardiomyopathy [26]. However, several clinical clues may raise the suspicion of ATTR in ambiguous cases (Table 1). These may include an apparent “cure” of pre-existing hypertension or a need to down-titrate hypertensive medications such as ACE inhibitors; intolerance of beta-blockers in patients with symptoms of HF; severe aortic stenosis with low-flow, low-gradient pattern, that is attributed to the restrictive physiology of the amyloid-infiltrated LV; and a history of or concurrent conduction system abnormalities necessitating pacemaker implantation. Of note, pacemaker implantation may have preceded HF manifestations by several years [2]. Co-existent extra-cardiac abnormalities that raise suspicion of ATTR include peripheral sensorimotor neuropathy

(lower limb hypo/dysesthesias and motor dysfunction) and dysautonomia (orthostatic hypotension, erectile dysfunction, sweating and alternating bowel pattern), occurring most commonly in mATTR, and orthopedic manifestations due to ligament infiltration, including bilateral carpal tunnel syndrome (50% in wtATTR) [23], biceps tendon rupture (33% in wtATTR) [27], and lumbar spinal stenosis [28]. Interestingly, carpal tunnel syndrome usually precedes development of symptoms of cardiac ATTR by approximately 5–15 years [29].

### Biomarkers

There are no specific biomarkers available for the diagnosis of any type of CA. Serum TTR levels (pre-albumin) have no diagnostic or prognostic value in ATTR. However, certain biomarkers, most importantly natriuretic peptides and troponins, are helpful in the diagnostic workup and as prognostic markers in ATTR. Regarding diagnosis, very high levels of natriuretic peptides that are disproportionate to the severity of cardiac dysfunction, together with persistently increased troponin levels in patients with presumed HFPEF or LV hypertrophy, should alert clinicians towards a possible diagnosis of CA (Table 1) [19, 30]. In addition, the assessment of NT-proBNP may also be of value for the early identification of cardiac involvement in patients with initially neuropathic mATTR [31]. Natriuretic peptides and troponins are incorporated in clinical prognostic scoring systems for cardiac ATTR developed from independent cohorts [24, 32]. According to the Mayo clinic prognostic score, serum NT-proBNP > 3000 pg/ml and troponin T > 0.05 ng/ml can discriminate patients with very high 4-year mortality rate (57% versus 18% in patients with both biomarkers below

**Table 1** Clinical, cardiac imaging, and biomarker tips for the suspicion of cardiac amyloidosis

Males > 65 years, females > 70 years old
History of bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture
Peripheral polyneuropathy and dysautonomia
Unexplained LV hypertrophy (no history of arterial hypertension or absence of hypertensive end-organ damage)
Arterial hypertension “naturally” cured
Thickened RV free wall, valves and atrial septum
Wide QRS complex, low QRS voltages, conduction abnormalities
LV diastolic dysfunction grade II or III
Relative preservation of apical LV myocardial velocities (“apical sparing”)
Co-existence of pericardial effusion
Low-flow, low gradient aortic stenosis
High natriuretic peptide levels
Mildly raised, nonfluctuating troponin levels
Progressive clinical deterioration despite HF therapy
Intolerance to established HF therapies

LV left ventricular, HF heart failure

the cutoffs) [24]. Serum creatinine and eGFR are also of prognostic value in cardiac ATTR (both wtATTR and mATTR), with the poorest outcome observed in patients with eGFR < 45 ml/min, especially when combined with high NT-proBNP (> 3000 pg/ml) [32].

In all cases with suspected CA, laboratory assessment should include detailed assessment for the presence of a monoclonal immunoglobulin, by using serum and urine immunofixation and quantification of serum free kappa and lambda immunoglobulin light chains, which could be suggestive of AL [1, 19]. Immunofixation electrophoresis should be performed instead of simple protein electrophoresis because the concentration of kappa or lambda chains may be too low to be detected by the latter. Free light chain (FLC) assay measures serum concentrations of kappa and lambda light chains. Normal concentrations are 3.3 to 19.4 mg/l for kappa and 5.7 to 26.3 mg/l for lambda chains. Normal range of kappa:lambda ratio is 0.26–1.65. Monoclonal paraprotein testing is considered positive if a monoclonal paraprotein is detected in immunofixation and FLC kappa:lambda ratio is abnormal (if the ratio is < 0.26 a clonal lambda chain is suggested, whereas a ratio > 1.65 is suggestive of a kappa chain) [33]. However, clinicians should be aware that the presence of monoclonal immunoglobulins or abnormally elevated immunoglobulin light chains is not specific for AL, as monoclonal gammopathy of undetermined significance (MGUS) is common among elderly individuals, affecting at least 5% of the general population over 65 years old [34–37]. Another confounding factor is the relatively high incidence of MGUS among patients with ATTRwt, which can be present in up to 25% of cases [38–40]. In addition, serum light chains may be elevated in patients with renal dysfunction who otherwise have no evidence of monoclonal paraprotein or amyloid organ infiltration, since light chains are cleared through the kidneys [41]. Moreover, kappa and lambda chains are differentially cleared by the kidneys, leading to skewed kappa to lambda ratio in renal dysfunction. Thus, a wider normal range of kappa/lambda ratio is used in patients with renal dysfunction compared with normal renal function [41]. Thus, careful evaluation of the tests for monoclonal gammopathy is required, preferentially in experienced referral centers.

### Electrocardiography

The most frequent electrocardiographic (ECG) finding in ATTR is poor R-wave progression (or pseudo-infarction patterns) in precordial/anterior leads, observed in up to 60–70% of cases [6, 42]. This pattern is most common in patients with intermediate or severe LV hypertrophy but less common in normal or mildly hypertrophied LV [43].

Low QRS voltage (QRS amplitude  $\leq$  0.5 mV in limb leads or  $\leq$  1 mV in precordial leads; Sokolow index < 1.5 mV),

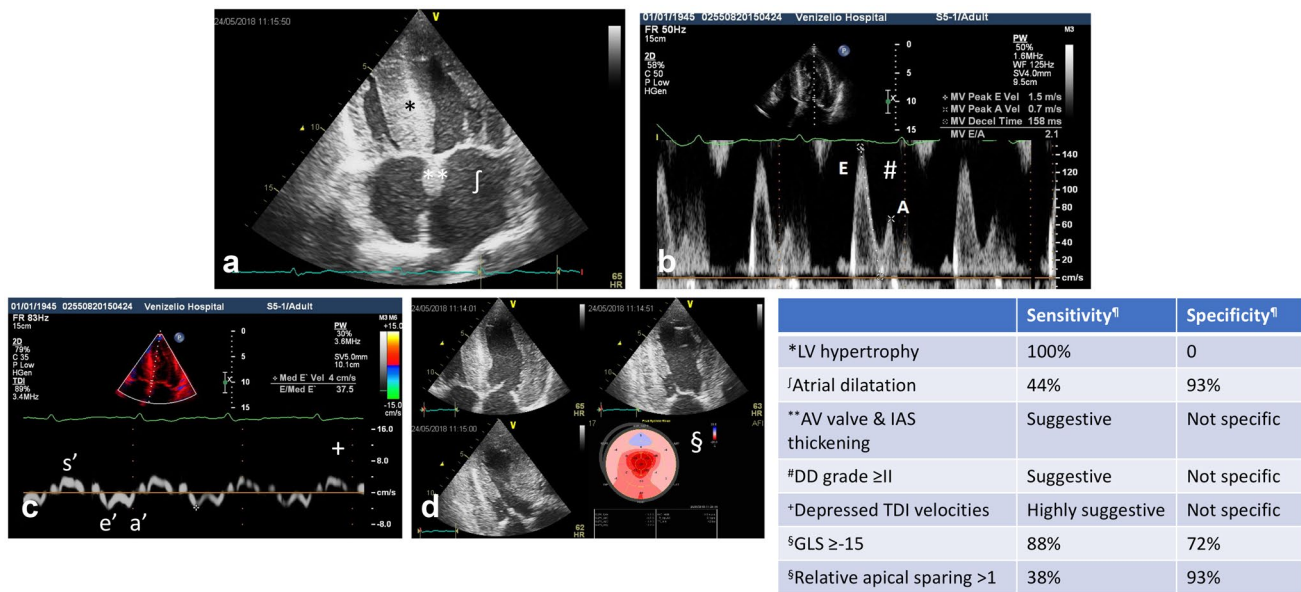
although considered a classic feature of CA, has low sensitivity, especially in ATTR (30% of wtATTR cases and 15–45% in mATTR), although is more common in AL (45% of cases) [22, 23, 25, 42, 44–46]. Recently, markers that correct low QRS voltage by echocardiographically assessed LV mass have been proposed as more sensitive to detect CA, including the ratio of Sokolow index to the cross-sectional area of the LV wall (values < 1.5 indicative of CA) and the ratio of total QRS score (sum of QRS voltages in all leads) to LV mass index [47, 48]. However, it should be noted that up to 20% of patients with wtATTR may show ECG criteria of LV hypertrophy [1, 42].

Arrhythmias are frequent in CA. Most common are conduction abnormalities and atrial fibrillation (AF). Conduction abnormalities include 1st-degree atrioventricular block (up to 33% in mATTR, 45% in wtATTR) and intraventricular blocks (LBBB or RBBB) in 32% of wtATTR [6, 42]. Up to 18–23% of patients with wtATTR have an implanted pacemaker due to conduction abnormalities, which is less commonly seen in AL (5%) or mATTR. AF is reported in up to 55% of wtATTR, but in 17% of mATTR. Lastly, QTc prolongation is present in > 60% in ATTR. Importantly, none of the aforementioned ECG findings is specific to diagnose type of CA.

### Echocardiography

Echocardiography is the most widely used, readily available imaging modality to raise the suspicion of CA in everyday clinical practice. Caveats include a low sensitivity in the early stages of CA and limited discriminatory ability between CA and other causes of LV hypertrophy [49]. Characteristic echocardiographic findings in CA include LV hypertrophy with restrictive LV physiology as well as other structural and functional abnormalities resulting from the indiscriminate interstitial amyloid infiltration. Echocardiographic findings vary according to amyloid disease progression. As such, they range from mild LV hypertrophy with atrioventricular valve thickening and impairment of longitudinal LV function in early/subclinical stages to marked LV hypertrophy with severe diastolic dysfunction (restrictive physiology) and ultimately development of biventricular systolic dysfunction in the advanced stage [50].

Left ventricular hypertrophy is a common morphological finding across all types of CA (Fig. 1a). However, it is more severe in wtATTR compared with other types, even after adjustment for differences in demographics and disease stage [46]. Even so, up to 40% of ATTR patients have no or mild LV hypertrophy [43]. LV hypertrophy is most frequently symmetrical but less commonly may be asymmetrical, affecting preferentially the interventricular septum (IVS). Asymmetric hypertrophy has been reported in up to 23% of wtATTR, while it may be more frequent



**Fig. 1** Typical echocardiographic findings of cardiac amyloidosis and their diagnostic accuracy (sensitivity and specificity). **a** Apical four-chamber view shows severe left ventricular (LV) hypertrophy, dilated left atrium (LA) and thickened interatrial septum (IAS) and atrioventricular (AV) valves. **b** Transmitral pulsed wave inflow velocities showing E/A ratio > 2, suggestive of Grade III diastolic dysfunction (DD). **c** Tissue Doppler imaging (TDI) of the basal interventricular septum, showing depressed systolic (s'), early

diastolic (e'), and late diastolic (a') velocities. **d** Bull's eye map of LV longitudinal strain obtained with speckle-tracking imaging, showing the typical relative sparing of the apical strain compared with basal and mid segments. Data regarding sensitivity and specificity were obtained from ref. [64]. Diagnostic utility of qualitative findings is reported using a descriptive term [84]. Relative apical sparing is calculated as the ratio of apical longitudinal/sum of base and mid longitudinal LV strain [64]. GLS, global longitudinal strain

in late-onset V30M mATTR [6, 43]. In advanced stages, hypertrophy can even affect the papillary muscles [50, 51]. Elderly wtATTR patients with aortic stenosis treated with transcatheter aortic valve replacement (TAVR) show more severe LV hypertrophy and diastolic dysfunction (restrictive pattern), compared with non-ATTR counterparts [4]. Right ventricular (RV) free wall hypertrophy (> 7 mm) is a very frequent finding in ATTR with at least moderate LV hypertrophy (76% of patients with IVS > 14 mm). Ventricular dilatation is uncommon, except for RV dilatation in cases with pulmonary hypertension [46].

With nonharmonic imaging, hypertrophied LV walls may show a “granular sparkling” appearance that is suggestive, but not specific, of CA as a result of the higher echogenicity of the amyloid fibrils compared with the surrounding normal myocardium. Granular sparkling is observed more frequently (up to 65%) in patients with at least moderate hypertrophy [43]. In harmonic imaging, hypertrophied LV shows a speckled appearance [50].

Amyloid infiltration of atrial and valvular tissue appears as thickening of interatrial septum and atrioventricular valves, respectively, with associated valvular regurgitation (Fig. 1a) [52]. Combination of AV valve thickening, RV hypertrophy, and sparkling myocardium should raise suspicion of ATTR in patients with increased IVS thickness [43]. Small pericardial effusions are common in CA (> 40%

in ATTR). However, larger effusions and tamponade are relatively rare [53].

As an archetypic restrictive cardiomyopathy, CA is characterized by LV diastolic dysfunction (DD), the severity of which parallels disease stage. Pseudonormal pattern is most common (43% of ATTR), while restrictive pattern is found in 35% of ATTR (Fig. 1b) [54]. Abnormal relaxation or no DD can be seen in early stage (4.5% of wtATTR and 29% with mATTR) [49]. Early mitral annular diastolic velocity (E') decreases early in AL (even without overt hypertrophy), worsens as hypertrophy progresses, and becomes severely depressed in the advanced stage (Fig. 1c) [49, 54]. Atrial dilatation with low or absent atrial transmitral velocity classically co-exists, due to the elevated ventricular filling pressure and atrial amyloid infiltration (Fig. 1a). Overall, no differences are observed as to the severity of DD between different CA etiologies [46].

Left ventricular ejection fraction is usually preserved up to the advanced stages. However, subtle systolic dysfunction is documented using myocardial deformation imaging (tissue Doppler-TDI or speckle tracking-STE) early in the disease course, even in the asymptomatic stage [55–58]. Deformation imaging has been shown to allow differentiation of CA from other causes of LV hypertrophy. Compared with hypertensive and hypertrophic cardiomyopathy, longitudinal, radial, and circumferential strains are reduced in CA. However, in CA, there is a typical

sparing of longitudinal strain in the apex compared with mid and basal LV segments (apical sparing, Fig. 1d) [50]. Deformation abnormalities are similarly observed in AL and ATTR and are proportional to the severity of LV hypertrophy and amyloid infiltration [59]. However, this association is less prominent in AL than in ATTR, underscoring the importance of other contributors to the pathophysiology of LV systolic dysfunction in AL, including direct myocardial toxicity by the circulating immunoglobulin light chains [60, 61]. Quantitative indexes of deformation abnormalities have been proposed to discriminate CA from other causes of LV hypertrophy. Relative apical longitudinal strain (RALS) index is calculated as average apical LS/(average basal LS + average mid-LS) [62]. RALS index > 2.1 showed high discriminative capacity for the identification of CA among other hypertrophic etiologies [63]. Ejection fraction strain ratio (EFSR) is calculated as LVEF/global LS and was higher in CA compared with hypertrophic cardiomyopathy and hypertensive heart disease. EFSR > 4.1 had 89.7% sensitivity and 91.7% specificity to discriminate CA in a mixed population of 25 AL/15 ATTR patients [64]. Besides its diagnostic utility, STE strain is an independent predictor of clinical outcomes in CA, both ATTR and AL, with worse strain values associated with poorer outcomes [59, 65]. Deformation abnormalities of the atria and RV are also observed [66]. A similar pattern of apical sparing is observed by STE in the RV, which may also assist in the differential diagnosis of CA [67]. Table 2 summarizes the most common echocardiographic findings in cardiac amyloidosis.

### Cardiac magnetic resonance

In addition to anatomic assessment of cardiac walls/chambers, cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) and newer extracellular volume (ECV) techniques allows characterization of tissue composition, in particular amyloid infiltration. The two most typical LGE patterns in CA are either a diffuse subendocardial enhancement in a noncoronary artery territory distribution or transmural enhancement [1, 68]. However, atypical patterns might be observed,

especially in early disease stages [69]. T1 mapping allows the quantification of myocardial extracellular volume either before (native T1) or after injection of contrast medium. Native T1 time is increased in CA and correlates with amyloid burden [70] and is higher in AL than ATTR, whereas post-contrast ECV is higher in ATTR than AL. Diagnostic accuracy of T1 mapping for CA of any subtype has been examined in a recently published study that included 436 patients with histologically confirmed CA among 800 suspected cases [71]. It was shown that native T1 time had 98% negative prognostic value at a cutoff < 1.036 ms and 98% positive predictive value at a cutoff > 1.164 ms to correctly identify CA among suspected cases. At intermediate native T1 values (1.036–1.164 ms), post-contrast ECV had a very high diagnostic accuracy at a cutoff > 0.37. However, T1 technique could not differentiate between CA subtypes. Advantages of native T1 mapping include no need for contrast injection, allowing its use in patients with renal dysfunction as well as serial evaluations. Limitations include platform-dependent variation of normal ranges, confounding by other pathologies such as tissue edema, inability to discriminate between amyloid subtypes or other infiltrative cardiac disorders, relative contraindication in patients with implanted pacemakers/defibrillators, and contraindication in patients with claustrophobia [1].

### Myocardial scintigraphy with bone-seeking radiotracers

The observation in the 1980s that certain  $^{99m}\text{Tc}$ Technetium ( $^{99m}\text{Tc}$ )-phosphate derivative radionuclide tracers originally developed for bone scintigraphy (BS) accumulated in the amyloid-infiltrated heart has led to an extensive evaluation of the role of BS in diagnosing CA, although several decades later [72–74]. Originally applied for the detection of acute myocardial necrosis,  $^{99m}\text{Tc}$ -pyrophosphate ( $^{99m}\text{Tc}$ -PYP) was the first radiotracer shown to be of diagnostic potential in CA. Subsequently, several studies have shown that bone tracers including  $^{99m}\text{Tc}$ -PYP,  $^{99m}\text{Tc}$ -3,3-dicarboxypropane-2,1-diphosphate ( $^{99m}\text{Tc}$ -DPD), and  $^{99m}\text{Tc}$ -hydroxymethylene

**Table 2** Main echocardiographic findings in cardiac amyloidosis

Increased LV wall thickness in the absence of secondary causes

“Granular sparkling” appearance of myocardial walls in nonharmonic imaging

Bi-atrial dilatation and normal or reduced LV cavity dimensions

RV free wall hypertrophy, atrial septum and valve thickening

LV longitudinal systolic dysfunction and diastolic dysfunction are frequent findings but not specific signs of CA

Apical sparing in 2D-STE is an easily recognizable, early and specific sign of CA and can distinguish CA from other cardiomyopathies with LV hypertrophy

CA Cardiac amyloidosis, LV left ventricle, 2D-STE 2-dimensional speckle tracking echocardiography, HCM hypertrophic cardiomyopathy

diphosphonate ( $^{99m}\text{Tc}$ -HMDP) bind with high specificity to ATTR amyloid fibrils. In AL CA, there is usually limited or no uptake of the tracer, but in up to 10% of patients with advanced AL CA, there may be significant uptake of the tracer [40, 75–79]. Importantly, not all bone radiotracers are suitable for detection of ATTR CA [80]. In 2005, Perugini and colleagues published their seminal study, which demonstrated the clinical utility of  $^{99m}\text{Tc}$ -DPD BS to discriminate ATTR from AL or negative controls [80]. Researchers introduced a visual semi-quantitative 4-point score to evaluate cardiac radiotracer uptake: score 0, absent cardiac uptake and normal bone uptake; score 1, mild cardiac uptake, that is less than bone uptake; score 2, moderate cardiac uptake equal to bone uptake that appears to be attenuated; and score 3, strong cardiac uptake with mild or absent bone uptake. In this study, all ATTR patients showed cardiac uptake of at least Perugini score 2 (in 20%) or score 3 (in 80%), while all AL and negative controls showed no bone tracer cardiac uptake (score 0). A large multi-institutional study further evaluated the role of BS for the diagnosis of ATTR [40]. In this study by Gillmore et al., 718 patients with histologically confirmed CA out of 1217 cases with suspected CA were included. Confirmed cases consisted of 181 (25%) AL and 530 (74%) ATTR patients. Bone tracers that were used included  $^{99m}\text{Tc}$ -DPD in 72% of patients,  $^{99m}\text{Tc}$ -PYP in 16%, and  $^{99m}\text{Tc}$ -HMDP in 12%. Monoclonal paraprotein was investigated with serum and urine immunofixation and serum free light chain assay in all patients. This study showed that positive BS (Perugini grade 1–3) was > 99% sensitive and 86% specific in correctly diagnosing ATTR but when Perugini grade 2 or 3 scans were considered, then the sensitivity was 90% with a specificity of 97%. The majority of false positive scans were seen in patients with AL and were graded as Perugini grade 1 on  $^{99m}\text{Tc}$ -DPD. When combined with negative monoclonal paraprotein testing, Perugini grade 2 or 3 scans had 100% specificity and positive predictive value for ATTR. However, in cases with either positive paraprotein testing or grade 0 or 1 scans, the diagnostic yield of BS was low [38–40]. Therefore, it was concluded that biopsy is required to differentiate between AL and ATTR in patients with a detected monoclonal immunoglobulin. A recent bivariate meta-analysis with 529 patients reported a pooled sensitivity and specificity of  $^{99m}\text{Tc}$ -PYP,  $^{99m}\text{Tc}$ -DPD, or  $^{99m}\text{Tc}$ -HMDP BS of 92.2% (95% CI 89–95%) and 95.4% (95% CI 77–99%), respectively, for ATTR [81]. Based on the above data, diagnosis of ATTR CA is established in patients with a grade 2 or 3 positive BS in the absence of a monoclonal immunoglobulin assessed by serum and urine investigations that include immunofixation and serum free light chains assay.

However, careful evaluation of BS for the diagnosis of ATTR CA is required, preferentially in an experienced center. The pattern of myocardial uptake, i.e., diffuse

versus focal/multifocal/regional, should guide the diagnosis towards ATTR versus other underlying cardiac pathologies such as myocardial infarction [82]. Regarding intensity of uptake, other diagnostic parameters have been evaluated to assess bone radiotracer retention in ATTR, including heart-to-contralateral hemithorax (H/CL) uptake ratio and heart-to-whole-body (H/WB) retention ratio [78, 79]. For H/CL, a region of interest (ROI) is drawn over the heart which is corrected for background and ribs by a mirror ROI over the contralateral chest [78, 82]. H/CL ratio presents the fraction of mean uptake in the heart ROI to contralateral chest ROI. An H/CL ratio  $\geq 1.5$  (corresponding to Perugini grade 2 or 3) had a 97% sensitivity and 100% specificity for diagnosing ATTR [78]. The H/WB ratio is positively correlated with LV wall thickness, being higher in patients with LV wall  $\geq 1.2$  cm compared with no hypertrophy [83].

BS protocol for CA requires no specific patient preparation or fasting and is also applicable in patients reluctant or unable to undergo a CMR study [84]. A standard dose of 10–25 mCi (370–925 MBq) of  $^{99m}\text{Tc}$ -PYP,  $^{99m}\text{Tc}$ -DPD, or  $^{99m}\text{Tc}$ -HMDP is injected intravenously at rest. Image acquisition is performed at 1 h and is preferentially repeated at 3 h post-injection for  $^{99m}\text{Tc}$ -PYP and at 2 or 3 h for  $^{99m}\text{Tc}$ -DPD or  $^{99m}\text{Tc}$ -HMDP. Planar, anterior, and left anterior oblique/left lateral imaging is conducted in the supine position using low-energy, high-resolution collimators for a total of 500,000 counts on a  $128 \times 128$  or  $256 \times 256$  matrix, with the heart centered in the field of view and photopeak at 140 keV, with a symmetric 10% window, and allows for direct visual assessment and quantification of the degree of myocardial uptake by optical comparison with rib uptake. Single photon emission tomographic (SPET) imaging in a  $64 \times 64$  matrix, 32 frames at 20 s/frame, is necessary in all cases, especially with positive planar scintigraphy, to avoid overlap of bone uptake and assess the regional distribution of myocardial radiotracer retention, including uptake in the IVS that is commonly affected by amyloidosis. To summarize, ATTR is scintigraphically confirmed by diffuse, intense myocardial radiopharmaceutical retention, specifically grade  $\geq 2$  upon optical assessment and/or H/CL  $\geq 1.5$  on semi-quantitative analysis in conjunction with diffusely intense depiction upon SPET processing.

Iodine-123-metaiodobenzylguanidine ( $^{123}\text{I}$ -MIBG) scintigraphy that assesses myocardial autonomic sympathetic innervation may allow early detection of cardiac involvement in mixed mATTR with late-onset cardiac involvement (such as late onset V30M) or cardiomyopathic phenotype (V122I) [85–87] (Table 3). In a series of 142 individuals with confirmed V30M of whom 53% had polyneuropathy, reduced  $^{123}\text{I}$ -MIBG cardiac uptake was an independent predictor of 5-year mortality [87].

**Table 3** Characteristics of cardiac light chain (AL), mutant (mATTR), and wild-type (wtATTR) transthyretin amyloidosis

Type of cardiac amyloidosis	AL	mATTR	wtATTR
Deposited protein	Immunoglobulin light chains	Mutated transthyretin	Wild-type transthyretin
Epidemiology	Prevalence 8–12 cases/10 <sup>6</sup> person-years	Prevalence 50,000 patients worldwide; endemic in Portugal, northern Italy, Japan, Sweden and Cyprus	General prevalence not available; Highly prevalent in populations with certain cardiac diseases (13% in HFPEF, 16% in TAVR; 5% in SAVR)
Clinical manifestations	More frequently men, peak incidence 5th–7th decade Multisystemic involvement (heart, kidneys, liver, lungs, autonomic and peripheral nervous systems and soft tissues)	Inherited, autosomal-dominant Cardiomyopathic, neuropathic or mixed manifestations depending on specific mutation V122I most common cardiomyopathic mutation (3–4% in African-Americans); V30M most common neuropathic mutation with mixed phenotype in late-onset cases	> 90% men, aged > 70–75 years Predominantly cardiac involvement May involve musculoskeletal system with bone ligament infiltration (carpal tunnel syndrome, spinal stenosis and biceps tendon rupture)
Echocardiographic features [46]			
LV hypertrophy	Moderate	Moderate/severe	Severe
LV ejection fraction	Preserved	Preserved	Preserved (lower than AL, mATTR)
Diastolic dysfunction grade II-III	≈ 75%	≈ 70%	≈ 80%
LV deformation			
Global longitudinal strain	↓↓↓	↓↓	↓↓↓
Apical sparing	Present	Present	Present
Magnetic resonance mapping [70, 143]			
Native T1 time	↑↑↑	↑↑	↑↑
Extracellular volume post-contrast	↑↑	↑↑↑	↑↑↑
T2 time	↑↑↑	↑↑	↑↑
Bone scintigraphy ( <sup>99m</sup> Tc-PYP/DPD/HMDP)	No/mild uptake	Moderate/severe uptake	Moderate/severe uptake
Prognosis	1-year mortality > 40%	Median survival 2.5–3.5 years after diagnosis	Median survival 3.5 years after diagnosis
Treatment	Chemotherapy Proteasome inhibitors	Tafamidis Patisiran Inotersen Diflunisal Heart/heart-liver transplantation	Tafamidis Heart transplantation

## Positron emission tomography

Positron emission tomography (PET) may potentially allow direct tagging of amyloid fibrils by PET radiotracers including <sup>18</sup>F-florbetapir [88, 89], <sup>18</sup>F-florbetaben [90], and <sup>11</sup>C-PiB (Pittsburgh B compound) [91, 92] and has given promising results for early diagnosis and quantification of the cardiac and extracardiac amyloid burden [88, 90]. In pilot studies, PET with the aforementioned compounds correctly identified CA patients from patients with hypertensive heart disease or healthy controls [90, 93]. However, it could not differentiate between CA subtypes.

## Biopsy

The gold standard for diagnosis of amyloidosis is tissue biopsy. The presence of amyloid fibrils is confirmed by positive Congo red staining, which produces a pathognomonic green birefringence when viewed under cross-polarized light. A specialized pathology laboratory that performs high volumes of Congo red testing, by an experienced pathologist, is required for accurate diagnosis. Tissue is obtained either from the affected organ (heart, kidney, liver) or from peripheral tissue, such as abdominal fat pad, salivary glands, gingiva, skin, or gastrointestinal tract, which is a less invasive alternative. Although



abdominal fat aspirate is the preferred peripheral tissue in most cases with suspected AL amyloidosis, with 69–88% sensitivity and 97% specificity for AL [94], it has low sensitivity for ATTR (below 30%); therefore, its role in the diagnostic assessment of patients with suspected CA and negative serum and urine paraprotein testing is limited [60, 95].

Tissue biopsy allows for the typing of amyloid fibrils. Immunohistochemistry (IHC) is the most widely available method for fibril typing, but has low sensitivity and specificity in fat tissue. In EMB, its diagnostic accuracy for ATTR is higher but still limited for AL, due to the nonspecific binding of multiple antisera (usually for ATTR and kappa/lambda chains) to circulating proteins that are present in histopathological samples [96]. Immunoelectron microscopy can be very helpful as it identified the amyloid fibrils and also uses specific gold-labeled antibodies to stain the fibrils.

The gold standard for amyloid fibril typing is mass spectrometry (MS), which detects peptides derived from amyloid abundant regions and after comparisons to reference databases, confirms amyloid subtype with high specificity [97]. However, MS is not widely available and only very few centers in the world can perform MS routinely. In our clinical practice, mass spectrometric analysis is considered in cases where amyloid typing cannot be established with first-line assays (IFE/FLC and BS) and includes patients with (a) confirmed CA with no other organ involvement, clonal immunoglobulin present and indeterminate or positive BS (i.e., grades 1–3) and (b) confirmed CA of no obvious type (negative paraprotein analyses, negative BS and negative genetic testing).

With the advent of BS for noninvasive diagnosis of ATTR, histologic evaluation is reserved for cases with suspected CA that fall within the following scenarios: (a) abnormal monoclonal paraprotein tests, irrespective of scintigraphic results. Here, initial preferred tissue source is abdominal fat. If fat biopsy is negative but clinical suspicion remains high, either another peripheral tissue or endomyocardial biopsy (EMB) is recommended; (b) high clinical and/or echocardiographic/CMR suspicion of CA, no evidence of plasma cell dyscrasia and indeterminate scintigraphic results (Perugini grade 0 or 1), where EMB is recommended; (c) high suspicion of AL despite a negative abdominal fat biopsy result, where EMB should be considered; and (d) negative paraprotein testing, if myocardial scintigraphy with  $^{99m}\text{Tc}$ -PYP/ $^{99m}\text{Tc}$ -DPD is not available.

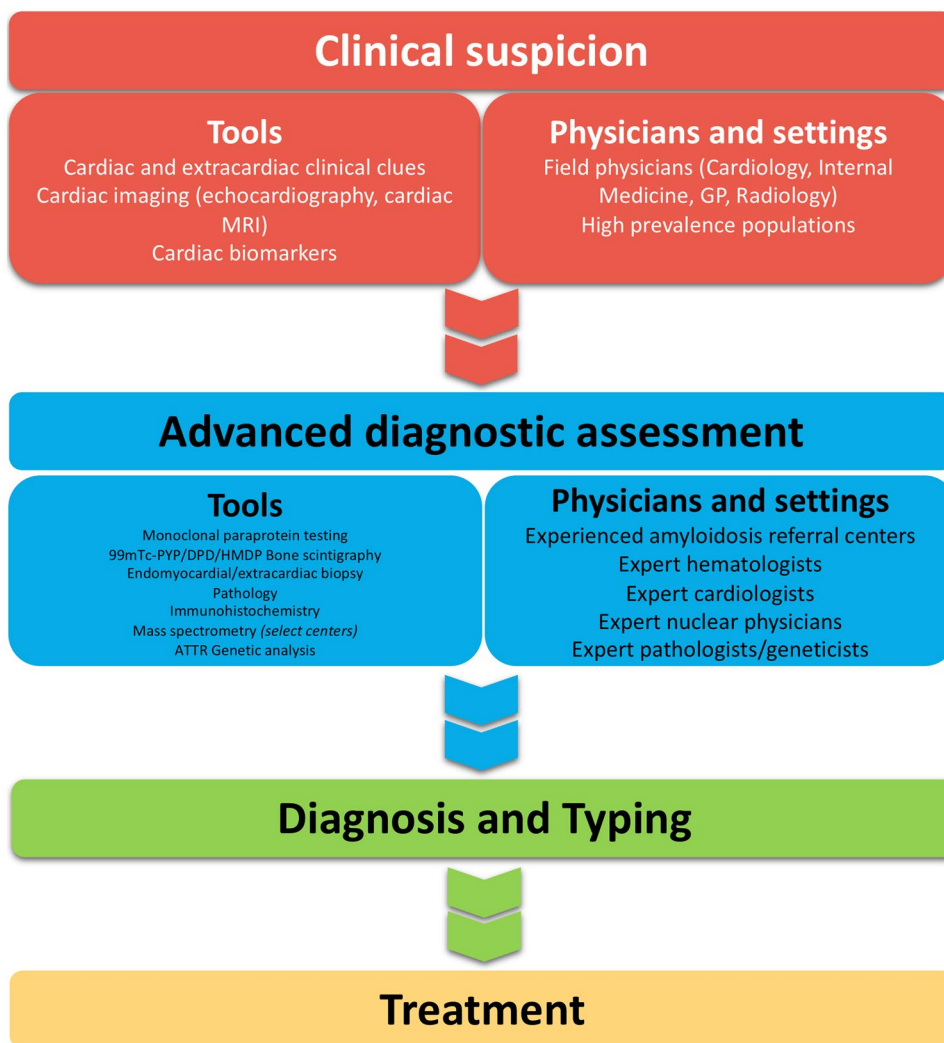
### Genetic analysis (wtATTR versus mATTR)

All cases with confirmed ATTR should undergo genetic testing to differentiate between wtATTR and mATTR, even if no family history of amyloidosis or polyneuropathy is present, because the penetrance of mATTR is variable among mutations, within families and country of origin. There is no age limit for genetic testing and some mutations may cause symptoms for the first time well over the age of 70. In our experience (Department of Clinical Therapeutics), 4% of ATTR patients > 70 years old carried a *TTR* mutation. If mATTR is diagnosed, genetic counseling and screening of relatives for identification and follow-up of asymptomatic carriers are indicated. Identification of ATTR subtype may impact therapeutic options. Currently, approved therapies for cardiac ATTR, mutant and wild type, include only amyloid stabilizers, while in mATTR with polyneuropathy (with or without cardiomyopathy) TTR silencers (patisiran and inotersen) are also approved.

### Diagnostic management of cardiac amyloidosis

The basis for effective diagnostic and therapeutic management of CA patients is the early recognition and suspicion of possible cases based on clinical red flags, cardiac imaging, and biomarkers. We propose that all patients with suspected CA should then be referred for further diagnostic workup to experienced centers in amyloidosis so as to avoid common diagnostic pitfalls, such as misinterpretation/misuse of BS and incomplete/misinterpreted immunoglobulin testing (Fig. 2). Moreover, based on previous literature and our centers' experience, we propose an algorithm for the advanced diagnostic evaluation of patients with suspected CA. In all patients, diagnostic workup should start with serum and urine immunofixation and free light chain assays. If monoclonal paraprotein is detected, further hematologic workup should be performed to confirm or exclude AL. If no monoclonal immunoglobulin is detected, the next step is to perform BS with  $^{99m}\text{Tc}$ -PYP/DPD/HMDP. If BS is strongly positive (Perugini grade 2 or 3); then, ATTR is confirmed. If BS is indeterminate, EMB is required to exclude or confirm CA and its type. In all confirmed ATTR cases, genetic testing should follow to establish ATTR subtype (wild type or mutant) (Fig. 3).

**Fig. 2** Proposed integrated diagnostic management strategy of patients with cardiac amyloidosis



### Current and emerging therapies for cardiac ATTR

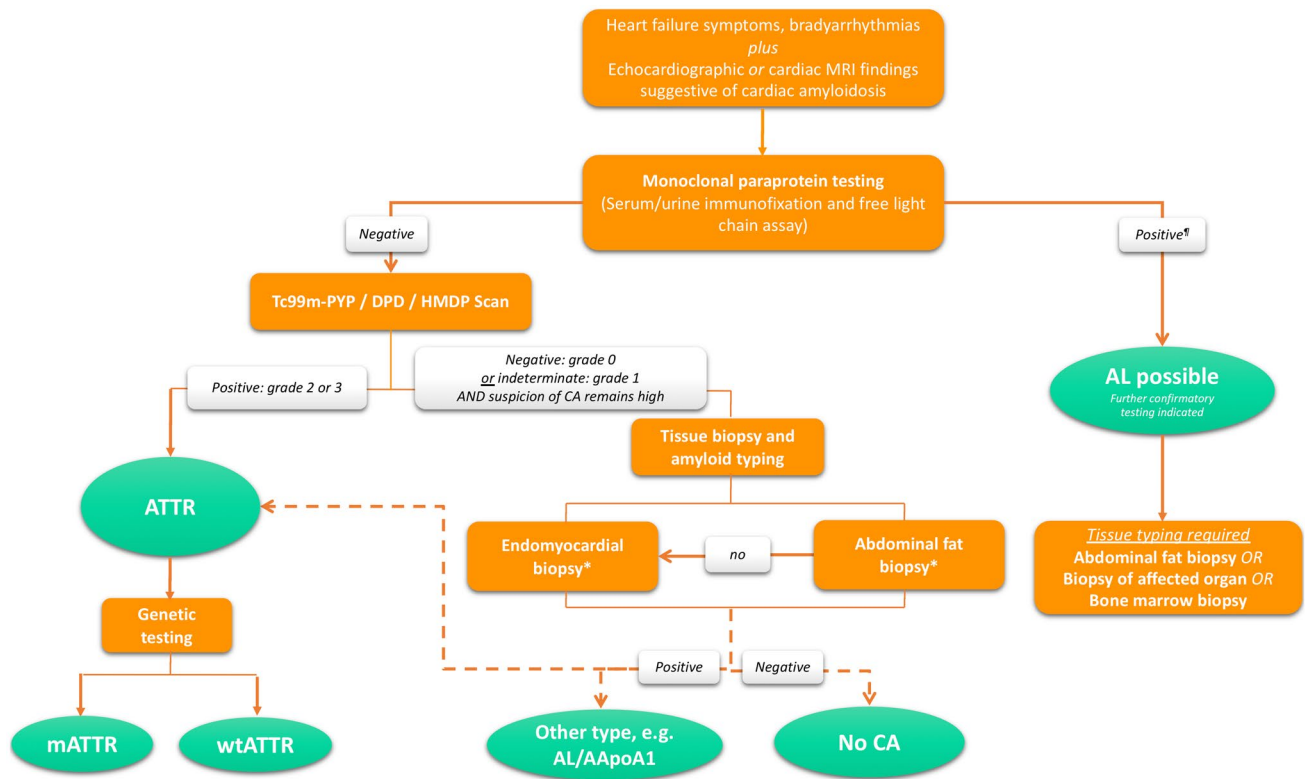
Treatment of cardiac ATTR consists of symptomatic cardiovascular management and disease-modifying therapies, including pharmacologic agents targeting the TTR amyloidogenic pathway and liver transplantation.

### Management of cardiovascular manifestations of CA

Loop diuretics are prescribed to alleviate congestion, frequently combined with mineralocorticoid receptor antagonists, especially in patients with RV dysfunction and peripheral edema. However, aggressive use of diuretics is discouraged and a stepwise approach is preferred, as these patients depend heavily on preload. Other HF recommended therapies are generally not well tolerated by CA patients. Vasodilators including angiotensin converting enzyme inhibitors and angiotensin receptor antagonists may cause

hypotension. Beta-blockers may aggravate HF symptoms due to the dependence of cardiac output on heart rate because of an essentially fixed stroke volume due to restrictive physiology. Patients with amyloidosis may also exhibit autonomic dysfunction, further reducing tolerance to common HF drugs. The use of oral vasopressor/antihypotensive therapies, such as midodrine (an  $\alpha$ 1-receptor agonist) may be helpful, especially in mixed phenotype mATTR.

In patients with AF, ventricular rate is usually naturally controlled due to amyloid infiltrated atrioventricular conduction system. However, rapid ventricular rates may occur, which are poorly tolerated due to shortening of the diastolic period that reduces stroke volume. Rate control drugs in CA are problematic. Apart from previously discussed beta-blockers, nondihydropyridine calcium channel blockers are contraindicated because they can cause atrioventricular heart block and worsening HF and even cardiogenic shock due to their negative inotropic effect. Digoxin has been controversial due to hypothesized increased susceptibility to toxicity because of digoxin binding to amyloid fibrils, although this has not been



**Fig. 3** Proposed algorithm for the diagnostic workup of patients with suspected cardiac amyloidosis

confirmed in a recent series [98]. In two recent case series, significant arrhythmias occurred in up to 12% of CA patients treated with digoxin, however not clearly linked to digoxin toxicity [98, 99]. Expert opinion recommends that if digoxin is trialed for rate control or advanced HF, it should be started in low doses, with frequent monitoring of hemodynamics, renal function, electrolytes and drug plasma levels [100]. Rhythm control is considered if ventricular rate is poorly controlled with pharmacologic agents [101]. Pharmacologic cardioversion is performed with amiodarone, which may also be used for rate control. Direct electric cardioversion may be used, with acute success rate similar to non-CA AF (up to 90–94% of patients) [102]. However, it is associated with higher complication rates, including ventricular arrhythmias, bradyarrhythmias requiring pacemaker implantation, and thromboembolic events. Cardiac amyloidosis is associated with increased thrombogenicity, even without AF [103]. In AF particularly, there is increased incidence of LA thrombi even in low-risk patients such as those with recent onset AF (< 48 h) and anticoagulation for > 3 weeks before AF onset [102]. Therefore, transesophageal echocardiogram should be strongly considered in all CA patients before AF cardioversion, while therapeutic anticoagulation should be commenced in all patients with AF irrespective of CHADS-VASc score. The choice between warfarin and novel oral anticoagulants (NOACs) should be based on specific patient

characteristics as there are no relevant data from randomized studies. However, in a recent retrospective analysis, thrombotic and bleeding event rates were comparable between patients who received warfarin or NOACs, although labile INRs were detected in up to half of warfarin-treated patients, predisposing to increased thrombotic and hemorrhagic risk [104].

Complex ventricular arrhythmias are frequent in CA [100]. Nonsustained ventricular tachycardia (NSVT) has been reported in 18–74%, sustained VT or ventricular fibrillation (VF) in 8–19% and appropriate implantable cardioverter-defibrillator (ICD) shocks in 6.5–32% in small patient series. Sudden death occurs in up to half of CA patients. However, underlying rhythm may not be VT/VF and, indeed, historically electro-mechanical dissociation was thought to be implicated in most cases. Currently, the use of ICDs in CA remains controversial, due to lack of data showing mortality benefit with ICDs, combined with the previously considered dismal disease prognosis. European guidelines recommend ICD implantation for secondary prevention in cardiac AL or mATTR patients with ventricular arrhythmia causing hemodynamic instability who are expected to survive > 1 year with good functional status (Class IIa, Level of Evidence C) [105]. However, with the recent introduction of disease-modifying targeted therapies, recommendations for ICD implantation in CA will probably need to be re-examined.

There is limited experience regarding the safety and efficacy of cardiac resynchronization therapy (CRT) in patients with CA. RV pacing, which is frequently indicated in CA patients, may aggravate their functional class and left ventricular function [106]. Data from single-center retrospective studies have suggested that CRT may be associated with improved NYHA class, LVEF and severity of MR in CA patients with indication of RV pacing or reduced LVEF and wide QRS complex [106, 107]. No data are available yet regarding cardiac contractility modulation therapy in patients with CA, reduced LVEF and narrow QRS, although this therapy has been shown to improve functional status and quality of life in patients with HF and reduced LVEF of common etiologies.

### Disease-modifying therapies

During the past decade, ATTR-specific therapies that target several checkpoints of amyloid formation have been developed, including TTR tetramer stabilization and liver TTR RNA silencing. Therapies aiming towards TTR amyloid fibril-specific extraction from tissues are currently under investigation.

## Currently available therapies

### Stabilizers

Stabilizers act by binding to the TTR tetramer, inhibiting their dissociation and not allowing amyloid formation by misfolded, amyloidogenic, TTR monomers [108]. Tafamidis is a selective TTR stabilizer, a benzoxazole derivative that lacks nonsteroidal anti-inflammatory activity. It binds specifically to the thyroxine binding site of TTR tetramer, stabilizing kinetically wtTTR, and several TTR variants in vitro [109]. It is administered orally and is available in two formulations, tafamidis meglumine (20 mg tablets) and tafamidis free salt (61 mg tablets), which are not substitutable on a per mg basis. Evidence from randomized clinical studies, and subsequent open-label extension studies showed that tafamidis slowed deterioration of neurological function, and maintained health-related quality of life in patients with early-stage V30M polyneuropathy [110–113]. Tafamidis has been approved for the treatment of stage 1 familial amyloid polyneuropathy in Europe and Japan (but not in US). Efficacy and safety of tafamidis in cardiac ATTR were examined in a large phase 3, randomized, placebo-controlled trial (ATTR-ACT), in which 441 cardiac ATTR (mutant or wild-type) patients were randomized in a 2:1:2 ratio to receive tafamidis 80 mg, tafamidis 20 mg, or placebo for 30 months

[114]. Overall mortality at 30 months was reduced in the two tafamidis arms combined by 30% (29.5% vs 42.9%, an absolute decrease of 13.4%). Moreover, cardiovascular hospitalizations were reduced by 32% with tafamidis. In addition, tafamidis reduced the rate of decline in exercise capacity and quality of life compared with placebo. Adverse events did not differ between pooled tafamidis and placebo arms. Tafamidis is currently the only approved disease-modifying specific therapy for cardiac ATTR in Europe and the USA, based on evidence from ATTR-ACT trial.

Diflunisal, a nonsteroidal anti-inflammatory drug, binds in vitro to the thyroxine binding site of TTR, kinetically stabilizing TTR tetramers [115], and has been evaluated in a small randomized, placebo-controlled trial in patients with neuropathic mATTR [116]. However, as a nonsteroidal anti-inflammatory drug, it is associated with side effects [117], while there is no data from randomized clinical trials in cardiac ATTR [118–121]. Diflunisal may be considered for off-label use only in very selected patients with cardiac ATTR.

### Doxycycline and tauroursodeoxycholic acid

Doxycycline and tauroursodeoxycholic acid (TUDCA) are used “off-label” in CA, due to their suggested disruption of deposited TTR fibrils, both mutant and wild type, according to in vitro data [122–124]. The combination of doxycycline (100 mg BID) and TUDCA (250 mg TID) administered for up to 12 months has been examined in a phase II study in a mixed mATTR and wtATTR cohort, where it stabilized cardiac and neurological disease progression with an acceptable toxicity profile [125].

## Emerging therapies for cardiac ATTR

TTR gene silencers are antisense oligonucleotides or small RNA interference molecules that inhibit expression of TTR gene by deactivating its messenger RNA (mRNA). Currently approved silencers include patisiran, a small-interfering RNA molecule (siRNA) and inotersen, an antisense oligonucleotide. Both patisiran and inotersen have been approved for their use only in patients with stage 1 or 2 mATTR polyneuropathy; however, some improvement in parameters of cardiac function and natriuretic peptides was also noted with both drugs in patients with mATTR and cardiac involvement [126–132]. Vutrisiran is an investigational siRNA that is administered subcutaneously every 3 months and is currently being tested in phase 3 trials in mATTR. Currently, the use of these drugs in wtATTR is not approved and studies evaluating their role in this population are ongoing.

## Investigational therapies

PRX004 is a monoclonal antibody that has been designed to specifically bind to and extract TTR amyloid fibrils from affected organs [133]. Tolerability and pharmacological properties of PRX004 are currently being investigated in a phase 1 clinical trial in mATTR (NCT03336580).

AG10 is an investigational TTR stabilizer that mimics the effect of a stabilizing variant, T139M, on TTR tetramers [134, 135]. Safety and TTR stabilizing effect of AG10 in cardiac ATTR were examined in a phase 2, placebo-controlled study, where it demonstrated effective, dose-dependent TTR stabilization, with acceptable safety profile [136]. AG10 has entered phase 3 clinical testing in cardiac ATTR (ATTRIBUTE-CM trial, NCT03860935).

## Liver and heart transplantation

Liver transplantation (LT) has been considered a potentially curative therapy for mATTR, as the liver is the main source of amyloidogenic TTR [137]. It may be considered in patients with early onset neuropathic Val30Met mATTR, in whom it has been shown to prevent progression of polyneuropathy [138]. However, cardiac amyloidosis has been observed after LT, possibly resulting from deposition of wild-type TTR upon pre-existing variant fibrils that serve as matrix for newly deposited ones [139]. Combined heart and liver transplantation (CHLT) could be considered in young patients with advanced mATTR neuropathy and end-stage heart failure [140]. Prognosis after CHLT does not differ significantly from patients who received heart transplants for other etiologies, with 75.8% 5-year survival in a series from Mayo Clinic, comparable with single heart transplantation [141]. Single heart transplantation (HT) has been less commonly performed in mATTR patients with isolated cardiac involvement. In wtATTR, single heart transplantation may be considered in appropriate individuals with advanced heart failure due to CA [140]. However, as wtATTR affects quite elderly persons, they are often ineligible for HT. In a small series of 7 relatively young wtATTR patients (mean age  $66 \pm 9$  years) who underwent HT, 3-year survival was 100%, although subsequent amyloid involvement of the gastrointestinal tract and peripheral nerves was observed in 2/7 patients [142].

## Conclusions

Cardiac amyloidosis is a previously under-recognized entity. Phenotypically, it is characterized by LV hypertrophy with advanced diastolic dysfunction and preserved systolic function. It may commonly be misdiagnosed as undifferentiated HFPEF, low-flow low-gradient aortic stenosis, and hypertensive heart disease in elderly patients or hypertrophic cardiomyopathy

in younger individuals. Several clinical and cardiac imaging findings can assist in raising field physicians' suspicion for CA, prompting patient referral to experienced centers for further diagnostic workup to establish diagnosis and subtyping. Etiologic confirmation is of crucial importance for prognostic assessment and proper therapeutic management, as AL is a malignant disease requiring urgent therapy while ATTR is a more benign entity albeit limiting longevity and impairing quality of life. Recent advent of specific therapies could improve outcomes of ATTR patients, previously managed only palliatively.

## Compliance with ethical standards

**Conflict of interest** Dr. Bistola reports honoraria for lectures from Novartis, Pfizer, and Servier. Dr. Parisis reports honoraria for lectures and advisory boards from Novartis, Pfizer, Servier, Orion Pharma, and Roche Diagnostics. Dr. Kastritis has received honoraria for lectures and advisory boards from Amgen, Genesis Pharma, Janssen, Takeda, Pfizer, and research funding from Amgen and Janssen. Dr. Foukarakis reports honoraria for lectures and advisory boards from Pfizer, Menarini and Bayer. G. Koutsis has received research grants from Genesis Pharma and Teva, consultation fees, advisory boards, and honoraria from Genzyme, Genesis Pharma, Teva, and Novartis. Drs. Valsamaki, Anastasakis, and Efthimiadis report honoraria from Pfizer.

**Consent for publication** All authors agree to publish the present manuscript in its current form.

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