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Review Article

Cardiac amyloidosis: An underdiagnosed/underappreciated disease

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ABSTRACT

Cardiac amyloidosis or amyloid cardiomyopathy (ACM), commonly resulting from extracellular deposition of amyloid fibrils consisted of misfolded immunoglobulin light chain (AL) or transthyretin (TTR) protein, is an underestimated cause of heart failure and cardiac arrhythmias. Among the three types of cardiac amyloidosis (wild-type or familial TTR and light-chain), the wild-type (Wt) TTR-related amyloidosis (ATTR) is an increasingly recognized cause of heart failure with preserved ejection fraction (HFpEF), and amyloidosis should be considered in the differential diagnosis of this heart failure group of patients. Recent advances in the diagnosis and drug treatment of ACM have ushered in a new era in early disease detection and better management of these patients. Certain clues in cardiac and extracardiac manifestations of ACM may heighten clinical suspicion and guide further confirmatory testing. Newer noninvasive imaging methods (strain echocardiography, cardiac magnetic resonance and bone scintigraphy) may obviate the need for endomyocardial biopsy in ATTR patients, while newer targeted therapies may alter the adverse prognosis in these patients. Early recognition of ACM is crucial in halting the disease process before irreversible organ damage occurs. Chemotherapy and stem-cell transplantation combined with immunomodulatory therapy may also favorably affect the course and prognosis of light chain ACM. Finally, in select patients with end-stage disease, heart transplantation may render results comparable to non-ACM patients. All these issues are herein reviewed.

1. Introduction

Cardiac amyloidosis or amyloid cardiomyopathy (ACM), commonly resulting from extracellular deposition of misfolded immunoglobulin light chain (AL) or transthyretin (TTR) protein, is an underestimated cause of heart failure [1,2]. Until recently, ACM was considered a rare condition, often only diagnosed at autopsy, deemed untreatable when finally diagnosed. Tremendous advances in both diagnosis and treatment of cardiac amyloidosis have been made over the last decade, while it has been recognized that the condition is more common than previously thought [3–8]. Transthyretin amyloidosis (ATTR), divided into a mutant or hereditary or variant type (ATTRm) and a wild-type (ATTRwt), has gained increasing attention in recent years as non-invasive techniques for specific diagnosis have become available [9]. ATTRwt is an underlying condition that is being increasingly recognized in patients with heart failure with preserved ejection fraction (HFpEF) and often accompanied by atrial fibrillation (AF) [10,11]. In patients with HFpEF, moderate or severe interstitial amyloid (TTRwt) deposition has been reported to be present in 5–13% of the cases, while mild interstitial and/or variable severity of intramural coronary vascular deposition may be present in 12% [11,12].

Amyloidosis is a protein-folding disorder with involvement of various organs which are infiltrated by amyloid, a proteinaceous material that is forming insoluble fibril deposits and is derived from amyloidogenic precursor proteins. These amyloid fibrils, composed of low molecular weight subunits (5–25 kD) of a variety (> 30) of structurally unrelated serum proteins, adopt a beta-pleated sheet configuration that leads to characteristic histologic changes. This amyloid material takes on apple-green birefringence under a polarized light microscope with Congo red staining [13].

Abbreviations: ACM, amyloid cardiomyopathy; AL CM, light chain amyloid cardiomyopathy; AF, atrial fibrillation; ATTR, transthyretin amyloidosis; BNP, brain natriuretic peptide; CM, cardiomyopathy; CMR, cardiac magnetic resonance (imaging); ECG, electrocardiogram; FLC, free light chain (assay); HFpEF, heart failure with preserved ejection fraction; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventric-le(−ular); LVH, left ventricular hypertrophy; TTR, transthyretin

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Table 1
Types of cardiac amyloidosis.

Pathophysiological substrates
Immunoglobulin light-chain (AL or primary) amyloidosis (amyloid fibrils composed of immunoglobulin light-chains, produced by plasma cell clone in the *bone marrow*)/worst prognosis
Transthyretin (TTR)-related amyloidosis (ATTR)/TTR secreted predominantly by the *liver*
Familial (hereditary or mutant) type ATTR (autosomal dominant)
Wild-type (senile) ATTR (older men)

AL = light chain amyloidosis; ATTR = TTR-related amyloidosis; TTR = transthyretin (**trans**porting **thy**roxine and **retin**ol protein).

Involvement of the heart (cardiac amyloidosis) carries a serious prognosis and needs to be diagnosed early for the best outcome of therapy. The most frequent forms of amyloid-producing precursor proteins comprise immunoglobulin-derived light chains and transthyretin (TTR; previously called prealbumin), leading to light chain (AL) amyloidosis and ATTR, respectively (Table 1). TTR is a transport protein of thyroid hormone and retinol (vitamin A). TTR-derived amyloid may be formed from wild-type (normal) TTR or from a mutant form, of which > 120 amyloidogenic mutations have been identified. Amyloidosis is usually not an isolated disease but rather with multi-organ involvement (Table 2). In *AL amyloidosis*, apart from heart disease, there is also renal, neural, and/or dermatologic involvement; less commonly the gastrointestinal tract and the liver may be involved as well [14]. *Transthyretin amyloidosis* (*ATTR*) is a potentially fatal disorder that is characterized primarily by progressive neuropathy and cardiomyopathy and it occurs in both a mutant form with autosomal dominant inheritance (ATTRm) and a wild-type form (ATTRwt) with predominant cardiac involvement [15]. ATTRwt is relatively common in the elderly, often reported as senile amyloidosis. There is also *secondary (AA) amyloidosis*, wherein fragments of serum amyloid A protein, an acute phase reactant, are responsible for this type of amyloidosis, which is associated with various chronic inflammatory disorders. However, rarely does AA amyloidosis produce ACM. Finally, there is another form of senile amyloidosis, an *isolated atrial amyloidosis*, wherein the amyloid fibril protein that is deposited in the atria is atrial natriuretic peptide; this form of cardiac amyloidosis, with a reported incidence reaching > 90% in the ninth decade, has been considered an established cause of AF [10].

AL amyloidosis is the most common clinically significant cardiac amyloidosis, accounting for ~80% of all cases, invariably associated with an underlying plasma cell dyscrasia and almost exclusively seen in individuals older than 40 years [16]. The second most common cause of ACM is ATTRm accounting for ~18% of all cases, while ATTRwt is a significant sporadic cause of cardiac amyloidosis in the older population with ~30% of the population older than 80 years of age being at risk to develop a slowly progressive, infiltrative ACM [9].

All these issues are herein discussed by reviewing old and contemporary literature on the topic of cardiac amyloidosis or amyloid cardiomyopathy by identifying relevant articles in the Medline, Scopus and Google Scholar.

2. Clinical manifestations

Amyloid cardiomyopathy (ACM) is a restrictive form of cardiomyopathy (CM) characterized by diastolic dysfunction and should be suspected in any patient presenting with HFpEF (Table 2) [11]. At later stages, ACM may produce deterioration of systolic function, arrhythmias, and heart failure with reduced ejection fraction. Findings of right ventricular (RV) failure predominate (~85%) with jugular venous distention, hepatomegaly, ascites and peripheral edema. In addition to heart failure signs and symptoms, patients may present with atrial arrhythmias (AF; more common in ATTRwt) [17] or conduction system disease with bradycardia and heart block [18,19] or ventricular arrhythmias [20] due to infiltration of the myocardium by amyloid leading to syncopal episodes and sudden cardiac death. Other manifestations may comprise angina pectoris (from small vessel disease) and pericardial effusion (from amyloid deposits in the pericardium). Infiltration of the myocardium by amyloid produces left ventricular (LV) hypertrophy (LVH) in the absence of hypertension or aortic valve disease or hereditary hypertrophic CM. Due to the insulative properties of the amyloid deposits, the electrocardiogram (ECG) usually displays *low-voltage QRS*. A pseudo-infarct pattern with poor R wave progression and/or pathologic Q waves may also be noted. The amyloid disease most commonly (70–99%) affects males of older age. A frequent association with severe calcific aortic stenosis has also been reported [21].

Amyloidosis may produce small vessel disease that may manifest as angina (microvascular angina), intermittent (leg or jaw) claudication or purpura. Epicardial coronary vessels at coronary angiography are usually normal [22]. Coughing, sneezing, straining or minor trauma may cause periorbital purpura (raccoon eyes), suggestive of capillary involvement and may present a strong clue for AL amyloidosis in a patient with unexplained heart failure. Patients with ACM, particularly those with amyloid atrial myopathy and/or atrial fibrillation, are at risk for cardiac thromboembolism [23–25].

Extracardiac signs pointing to a diagnosis of cardiac amyloidosis may include manifestations of *peripheral neuropathy*, such as the carpal tunnel syndrome [8]. Amyloid neuropathy is typically a symmetric, distal, ascending length-dependent (beginning in the lower limbs and progressing to the upper limbs and more proximally and to the trunk), sensorimotor, axonal polyneuropathy (affecting all functional classes of nerve fibers). Autonomic neuropathy may be present, manifesting as hypotension, sweat abnormalities, urinary incontinence, erectile dysfunction, alternating diarrhea and constipation, and orthostatic

Table 2
Organ involvement and symptoms of amyloidosis.

	Light Chain (AL) Amyloidosis	Mutant ATTR	Wild-type ATTR
Skin/Soft tissue	Purpura/macroglossia/back pain		Back pain/tendon rupture
Cardiac (HFpEF)	Fatigue/SOB/hepatomegaly/ascites/peripheral edema/arrhythmias	Fatigue/SOB/hepatomegaly/ascites/peripheral edema/arrhythmias	Fatigue/SOB/hepatomegaly/ascites/peripheral edema/arrhythmias/syncope
ACM	50–70%	75%	100%
Isolated CM	4%	17%	~60%
Renal	Renal insufficiency/proteinuria/edema (renal involvement 70%)	Renal insufficiency/proteinuria/edema	
GI	Early satiety/nausea/diarrhea/constipation (GI involvement 10%)	Early satiety/nausea/diarrhea/constipation/ weight loss	
Neuro	Peripheral/autonomic neuropathy	Sensory/motor/autonomic neuropathy	Carpal tunnel syndrome/lumbar spinal stenosis
Ocular		Vitreous opacities/glaucoma/keratitis/tortuous retinal vessels	

ACM = amyloid cardiomyopathy; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; CM = cardiomyopathy; GI = gastrointestinal; HFpEF = heart failure with preserved ejection fraction; SOB = shortness of breath.

symptoms and syncope. Neuropathy has an onset typically at the end of the second decade of life or later and progresses a lot during the subsequent 1 or 2 decades. A family history of a similar polyneuropathy is usually present when sought. Investigators have emphasized the need for cardiac screening via cardiac imaging (e.g. cardiac magnetic resonance-CMR) in all patients with familial peripheral neuropathy due to amyloid, even those without clinical signs of cardiac involvement [26]. Of note, neurological symptoms are more severe in ATTRm than ATTRwt, whereas cardiac symptoms are of similar intensity. Finally, patients with some forms of mutant ATTR may also develop proteinuria and renal dysfunction (nephropathic variants) [27], as well as ocular manifestations, such as vitreous opacities, keratitis, glaucoma, tortuous retinal vessels (ophthalmic variants) [28].

3. AL amyloidosis

Light chain (AL) (primary systemic) amyloidosis is a hematologic disorder of plasma cells (plasma cell dyscrasia) related to, albeit different from, multiple myeloma. It is caused by the proliferation of an abnormal clone of plasma cells that overproduce lambda (80%), or less commonly kappa (20%) light chains [14]. In multiple myeloma, there is serum monoclonal protein (IgG or IgA) > 3 g/dl and/or clonal bone marrow plasma cells > 10% [29]. There may be an overlap between these two plasma-cell dyscrasias in the range of ~10–20% when plasma cell count in the bone marrow exceeds 30% and there are associated bony lesions or other manifestations of multiple myeloma.

Cardiac involvement is frequent (70%) in AL amyloidosis in association with other organ involvement and rare (< 5%) as isolated cardiac amyloidosis. In early stages, ACM in AL amyloidosis is characterized by the presence of HFpEF; however, systolic dysfunction commonly ensues which can be unmasked by newer echo imaging techniques that measure LV longitudinal and radial strain [30,31]. Furthermore, *relative apical sparing of longitudinal strain* has been suggested as both sensitive and specific for the diagnosis of ACM, differentiating it from other causes of LVH (e.g. hypertensive CM, hypertrophic CM, Fabry disease, etc) [30]. However, this echocardiographic pattern can also be found in other cardiomyopathies and its absence should not suggest a different diagnosis in patients with high clinical suspicion for ACM, while with progression of the disease and deterioration in systolic LV function, apical sparing becomes less apparent (see further discussion below).

In addition to structural myocardial changes that culminate in diastolic and systolic dysfunction in ACM, circulating light chains also cause direct cardiac toxicity responsible for the apparent additional LV dysfunction noted in AL amyloidosis compared to ATTR [32,33]. In keeping with this notion, when abolition of light chains is achieved with chemotherapy, marked resolution of congestive heart failure and evidence for remission of disease activity has been reported, indirectly suggesting that direct light-chain toxicity may play a role in the genesis of heart failure in patients with AL amyloidosis [34].

4. Transthyretin amyloidosis

Transthyretin (TTR) is a circulating homotetramer carrier protein that functions as a transporter of thyroxine and retinol, synthesized mainly by the liver, with < 5% produced in the choroid plexus of the brain and the retinal pigment epithelium. Transthyretin has a half-life of ~48 h. Single-point mutations raise the likelihood of TTR misfolding into an insoluble β-pleated sheet, which deposits in the heart, nerves, and elsewhere, causing *familial cardiac amyloidosis*, amyloid polyneuropathy, and leptomeningeal amyloidosis. The TTR (or preablumin gene) is located on the long arm of chromosome 18 [35]. Over 120 TTR mutations have been described, with the Val30M being the most frequent mutation reported globally, and Val122I the most frequent cause of ATTRm in the U.S. (prevalence of 3–3.9% in African Americans) [36,37]. A positive family history is important for ATTRm and should be sought, but it may be difficult to extract because of the delayed and incomplete penetrance of the mutations responsible for the forms with prevalent cardiac phenotype.

Wild-type (wt) TTR can also misfold into the amyloid form and be responsible for the acquired *wt TTR amyloidosis (ATTRwt)*, previously called senile cardiac or systemic amyloidosis. ATTRwt is sporadic, with no known biomarkers. Deposition of the wt protein occurs mostly (90%), albeit not exclusively, in men > 60 years of age [38].

The prevalence of mutant ATTR has been estimated at 0.4 per million/year. According to a prospective French study, age-standardized estimated incidence of amyloidosis was at 14 cases per million person-years [39]; of these patients, 60% had ATTRwt and 20% had AL amyloidosis. Autopsies suggest that the prevalence of ATTRwt is much greater than previously reported. In 1 autopsy study of people > 85 years of age, ATTRwt was present in 25% [40]. In a consecutive series of surgical pathology specimens with ATTR (n = 33), ATTRwt was more common (64%) than mutant ATTR (36%) [41]. Endomyocardial biopsies from 101 patients with amyloid showed AL in 54 and ATTR in 42; only 5 of 42 patients with ATTR had mutant TTR [42].

ATTRwt is an underdiagnosed disease that accounts for a significant number (13%) of HFpEF cases [11]. TTR ACM has been reported in 16% of patients with severe calcific aortic stenosis undergoing transcatheter aortic valve implantation [21]. On the other hand, 5% of patients diagnosed with hypertrophic CM have ATTRm [43]. Isolated or exclusive ACM has been reported in < 5% of AL amyloidosis and in 17% of ATTRm [44].

There is considerable phenotypic heterogeneity for neurological and cardiac manifestations in patients with ATTRm and ATTRwt [45]. Indeed, the clinical spectrum of ATTRwt is heterogeneous and differs from the classic phenotype; women have been reported to be affected in a significant proportion (~20%); asymmetric LVH (~20%) and impaired LV ejection fraction (LVEF) (~40%) may not be rare and only a minority (~25%) have low QRS voltages [46]. Transthyretin amyloidosis, either mutant or wild-type, has a more favorable survival rate compared with that of AL or other types of amyloidosis. The natural history of ATTRwt CM is better than other forms of amyloid CM. Death in most patients is due to cardiac causes, including sudden cardiac death and heart failure [38,47].

According to the THAOS registry, among 1411 symptomatic subjects from 9 Western European countries (1286 ATTRm, 125 ATTRwt), 4 mutations (Val122Ile, Leu111Met, Thr60Ala, and Ile68Leu) and ATTRwt were associated with a mainly cardiac phenotype, mimicking hypertrophic CM, showing symmetric LVH, normal diastolic LV dimensions and volume, and mildly depressed LVEF [48]. Subjects with cardiac mutations or ATTRwt (cardiac or mixed phenotype) had a lower survival rate than subjects in other genotype (or the neurologic phenotype) categories (P < .0001, for both).

It has been observed that the cause of heart failure depends on ethnicity. The fourth most common cause of heart failure in Afro-Caribbeans has been reported to be ACM (11.4%), after non-ischemic, ischemic and hypertensive CM; patients with ATTRm Val122I had the worst prognosis compared with other causes of Afro-Caribbean heart failure and white patients [49]. Such data indicate that ATTR is an underdiagnosed disease and far commoner than recognized. On the other hand, today, ATTRwt appears to be the most commonly recognized form of ACM [50]. With more widespread use of diagnostic imaging comprising CMR imaging for diagnosis of unexplained heart failure, and the adoption of bone scintigraphy with ^{99m}Tc-MDP/PYP as a highly sensitive and specific tool for non-biopsy diagnosis of ATTR, it is possible that more cases of ACM could be detected among patients with HFpEF [51].

5. Diagnostic tools

A heightened index of clinical suspicion may help in seeking a diagnosis of ACM in patients presenting with HFpEF, who also have LVH

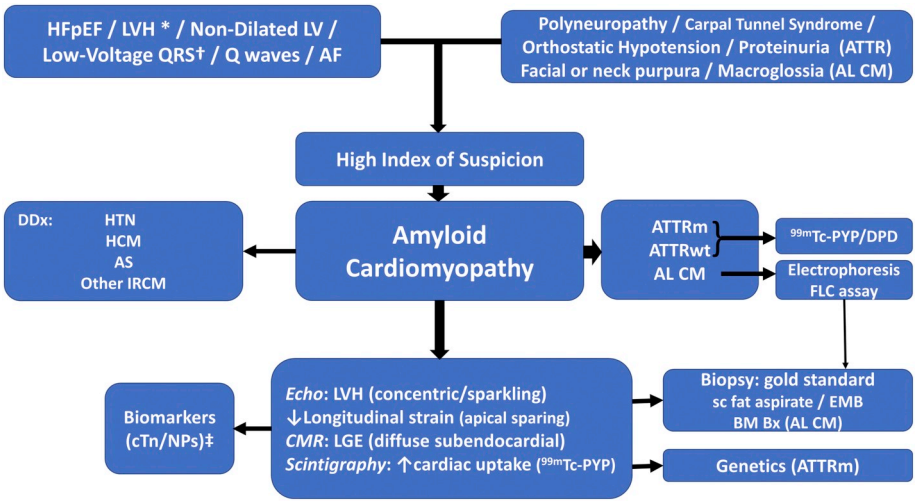

Fig. 1. The schema illustrates a diagnostic algorithm starting with the clinical cardiac and extracardiac clues that may heighten clinical suspicion of amyloid cardiomyopathy, aid the differential diagnosis and lead to further confirmatory testing (see text for discussion). AF = atrial fibrillation; AL CM = light chain amyloid cardiomyopathy; AS = aortic stenosis; ATTR = transthyretin amyloidosis; ATTRm = mutant (hereditary) transthyretin amyloidosis; ATTRwt = wild-type transthyretin amyloidosis; BM Bx = bone marrow biopsy; CMR = cardiac magnetic resonance (imaging); cTn = cardiac troponin; DPD = 3,3-diphosphono-1,2 propanodicarboxylic acid; Echo = echocardiography; EMB = endomyocardial biopsy; FLC = free light chain (assay); HCM = hypertrophic cardiomyopathy; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; IRCM = infiltrative restrictive cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricle; LVH left ventricular hypertrophy; NPs = natriuretic peptides; PYP = pyrophosphate; sc = subcutaneous.

on echocardiography but low voltage QRS on ECG that may also show a pseudo-infarction pattern (poor R wave progression or Q waves) and at the same time a good history taking reveals extracardiac symptoms suggestive of peripheral neuropathy and/or orthostatic hypotension (Fig. 1). In the case of AL CM, serum and/or urine electrophoresis and a free light chain (FLC) assay will lead to a correct diagnosis, while in ATTR, imaging studies, particularly bone scintigraphy, may confirm the diagnosis and even obviate the need for endomyocardial biopsy.

5.1. Differential diagnosis

The differential diagnosis of ACM patients presenting with HFpEF and LVH may include hypertensive heart disease, hypertrophic CM, aortic stenosis and other types of infiltrative restrictive CM (e.g. Fabry disease) (Fig. 1) [52]. As mentioned, LVH caused by hypertensive heart disease or hypertrophic CM or Fabry disease is usually associated with increased or normal voltage on ECG in contrast to ACM, which is associated with low ECG voltage, albeit not consistently, as this depends on the type of ACM. Low voltage on ECG is much less common in ATTRwt (~25–33%) than in AL (~45%), despite markedly increased LV wall thickness in ATTRwt, while it varies in ATTRm (16–45%) [46,53]; furthermore, in ~20% of ACM, ECG evidence of LVH may be found [53]. On the other hand, concentric vs asymmetric septal LVH can both be encountered in ACM, thus further perplexing the differential diagnosis between hypertrophic CM and ACM [54]. Nevertheless, several clinical and other imaging clues will assist in making a distinction and rendering a proper diagnosis (see discussion below).

5.2. Laboratory testing

For the diagnosis of AL amyloidosis, *immunofixation electrophoresis* should be performed on the serum and urine, because, in contrast to multiple myeloma, the concentration of the monoclonal light chain often is too low to be detected by simple protein electrophoresis. Furthermore, *serum free light chain (FLC) assay*, a nephelometric immunoassay, has a sensitivity for circulating free light chains that is reportedly > 10-fold that of immunofixation electrophoresis and allows for rapid and accurate classification of ACM [55]. Because the FLC assay is quantitative, it has utility not only in diagnosis but also in following disease progression or response to treatment.

The presence of a serum or urine monoclonal paraprotein in the setting of a typical echocardiogram is suggestive of AL amyloidosis, but it alone does not firmly establish the diagnosis as there is a high prevalence of *monoclonal gammopathy of unclear significance (MGUS)* in ATTRwt posing a diagnostic challenge (MGUS is defined as serum monoclonal protein < 3 g/dl, clonal bone marrow plasma cells < 10% and absence of end-organ damage). About 23 to 50% of patients with ATTRwt have a monoclonal gammopathy in the serum or urine and ~6–10% have a high serum kappa/lambda ratio [56]. Thus, even if a monoclonal Ig light chain is identified in the serum or the urine, a *bone marrow biopsy* is mandatory to assess the plasma cell burden and exclude multiple myeloma and other, less common disorders that can be associated with AL amyloidosis, such as Waldenström's macroglobulinemia [52]. Then, imaging techniques to assess organ involvement may follow (see below).

5.3. Biomarkers

Cardiac biomarkers characterizing ACM may comprise *cardiac troponin* (cTn) and *natriuretic peptides* (NPs); importantly, high levels of these biomarkers out of proportion to the hemodynamic status of the patient may constitute a clue for ACM. Both these markers (cTn and NPs) have a strong negative prognostic value in ACM irrespective of genotype [57–59]. Some investigators have suggested NT-proBNP as a biomarker reflecting the severity of cardiac amyloid infiltration [58]. A retrospective study comprising 360 patients with ATTRwt indicated that an increase above certain cutoffs of both cTnT (> 0.05 ng/ml) and NT-proBNP (> 3000 pg/ml) identified a patient subgroup with the worst prognosis [38]. In another study, a staging tool that included estimated glomerular filtration rate (eGFR) (< 45 ml/min) and NT-proBNP (> 3000 ng/l) showed that both these markers correlate well with overall survival [60].

Serum TTR levels have been shown to be lower in carriers of TTR mutations compared with controls, suggesting a possible conversion of TTR into amyloid [61]. However, measurement of TTR levels is not routinely performed in clinical practice. Retinol binding protein 4 (RBP4) is an endogenous ligand that stabilizes TTR and prevents misfolding and aggregation. A recent study showed reduced levels of RBP4 in ATTRm patients with the Val122I mutation, which is present in 3–4% of elderly African Americans [62]. The same investigator group proposed a clinical score by combining echocardiographic measurements (LVEF, LV thickness) and ECG parameters (mean QRS) with serum RBP4 levels to discriminate ATTR Val122I amyloidosis from nonamyloid heart failure [63].

A diagnosis of AL amyloidosis should be considered in any patient presenting with HFpEF, nephrotic range proteinuria, a mixed axonal

demyelinating peripheral neuropathy with autonomic features or carpal tunnel syndrome, hepatomegaly without imaging abnormalities, or taste alterations or in any patient with a monoclonal gammopathy or atypical multiple myeloma [64]. The diagnosis may be confirmed by immunofixation electrophoresis of the serum and urine and an immunoglobulin FLC assay. Thus, finding of monoclonal light chain gammopathy discriminates AL from ATTR amyloidosis. Of note, as mentioned, incidental MGUS occurs in > 5% of patients over 70 years of age, misleading the diagnosis of ATTR in favor of AL amyloidosis [65].

5.4. ECG

Despite the presence of LVH, the ECG may show low-voltage QRS complexes in variable percentages (~45% in AL CM, ~30% in ATTRwt and 16–45% in ATTRm) [53]; pseudo-infarction pattern with poor R-wave progression and/or pathologic Q waves may be seen in ~two-thirds of cases, and AF in ~one-third of patients [18,65]. As mentioned, *atrial amyloidosis* probably related to atrial natriuretic peptide amyloid fibril deposits has been reported as a frequent histological finding as detected in atrial appendage specimens obtained from patients with AF and rheumatic or other cardiac diseases [66–68].

5.5. Echocardiography

Echocardiography is the principal diagnostic tool for cardiac amyloidosis [69]. It detects LVH which may be misdiagnosed as hypertrophic CM or hypertensive heart disease. Apart from LVH, echocardiography may also detect a 'sparkling' myocardium with granular texture (Fig. 2, left panel), bi-atrial enlargement, thickened valves, right ventricular thickening, restrictive Doppler filling patterns, pericardial effusion, and thickened inter-atrial septum [69].

Infiltration of the myocardium by amyloid affects the physiologic deformation of the left ventricle usually more in the base and mid sections than the apex. As determined by speckle track imaging, indices of LV strain which are considered more specific for cardiac amyloidosis include the relative *apical sparing* ratio, global longitudinal strain (LS), and the ratio of ejection fraction/global LS [30,32,70]. More specifically, a value over 1.0 in the relative *apical sparing* ratio (average apical LS/average basal LS + mid LS) is considered highly sensitive and specific for the diagnosis of ACM when compared with other causes of LVH [30,71]. It has been suggested that this specific relative apical sparing can be easily observed by LS bull's eye mapping in patients with ACM [30,72]. The bull's eye plot in ACM patients with normal LVEF shows a normal or somewhat reduced average LS, a normal LS value at the LV apex (depicted in bright red color) [73], a markedly reduced strain at all basal segments of the entire LV (pale pink to light red color) and in some patients LS may also be reduced at the mid regions (**Fig. 2**, right panel). Importantly, this deformation gradient is significantly higher in ACM than in patients with other causes of LVH, such as hypertensive CM, hypertrophic CM, Fabry disease, etc. [74] However, with the progression of the disease along with a decrease in LVEF, global LS gets decreased over time with gradual deterioration in apical LS as well. As a result, apical sparing tends to become less apparent in the late stage of the disease in ACM [72]. Furthermore, there are important technical challenges and inherent limitations that need to be considered in applying these speckle tracking imaging techniques [75].

As mentioned, longitudinal LV function can be severely depressed despite a normal LVEF in ACM [53]. In a comparative study, ejection fraction/global LS ratio showed the best performance to discriminate cardiac amyloidosis from hypertrophic CM and hypertensive heart disease [76]. Finally, RV involvement has been reported in ATTR with RV apical sparing pattern, which is not seen in patients with hypertrophic CM [77].

5.6. CMR

CMR, a primary imaging modality for myocardial tissue characterization with use of parametric mapping techniques, permits the routine spatial visualization and quantification of changes in myocardial composition based on changes in T1, T2, and T2* relaxation times and extracellular volume (ECV).[78] *T1* (ms) refers to time constant representing the recovery of longitudinal magnetization (spin–lattice relaxation); *native T1* is T1 in the absence of an exogenous contrast agent; *T2* (ms) refers to time constant representing the decay of transverse magnetization (spin-spin relaxation); *T2** (ms) refers to time constant

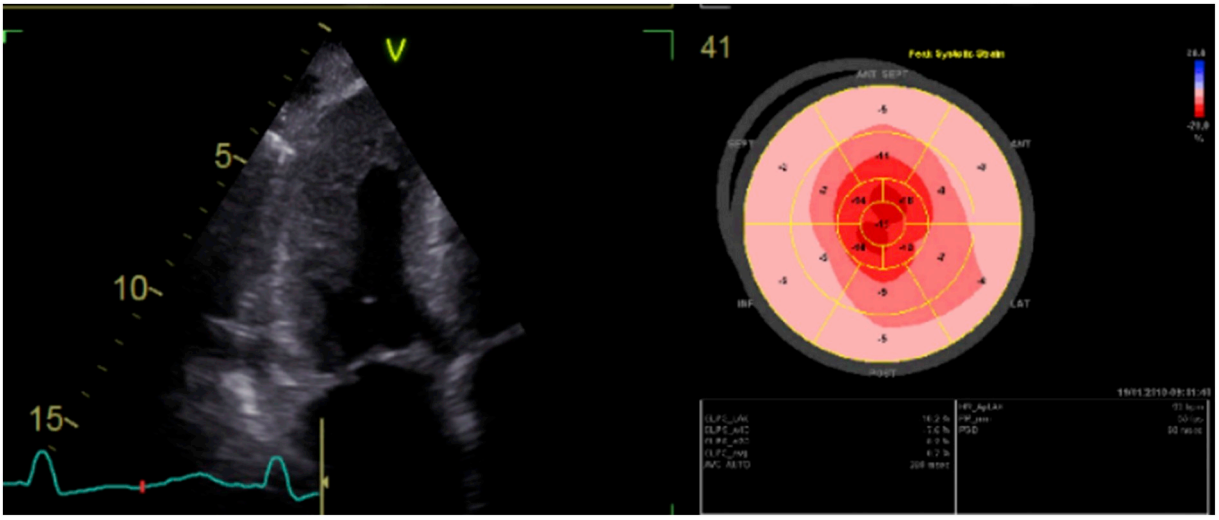

Fig. 2. A sparkling pattern of the thickened myocardium is depicted in this 77-year-old patient with light chain (AL) amyloidosis on the left panel and a bull's eye strain plot in the right panel. In the bull's eye plot, the magnitude and homogeneity of longitudinal strain for each segment are displayed in a color-coded polar map with bright red depicting normal strain values (≤ −16%), light red depicting reduced values (−16 to −11%), light pink (−10 to −6%), and pale pink (−5 to 0%) depicting severely reduced values; the inner ring represents the LV apex, the middle ring represents the mid segments and the outer ring represents the basal segments (blue, not present here, would depict a positive value indicating paradoxical systolic expansion). In a healthy individual, a homogeneously red pattern would be depicted indicating a normal range in strain values (−16 to −22%). Thus, preservation of normal strain values in the central ring (apex) is illustrated in this patient's bull's eye plot (apical sparing) (images courtesy of Dr. George Lazaros). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

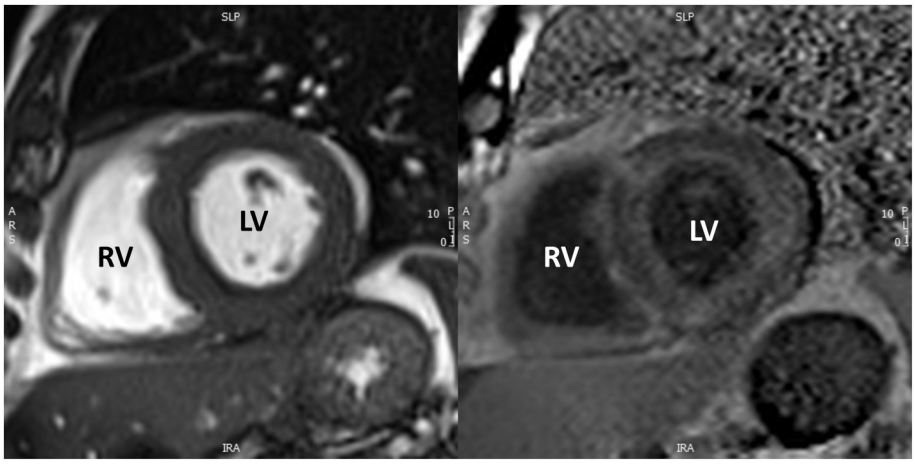

Fig. 3. Cardiac magnetic resonance (CMR) imaging on a patient with light chain (AL) amyloidosis. Left panel is an end-diastolic still frame from a mid-ventricular short-axis cine. Note the concentric thickening of the left ventricle (LV) (dark ring). The right panel is a short-axis late gadolinium enhancement (LGE) image showing diffuse enhancement of both the left and right ventricular walls (contrasted with the dark appearance of normal myocardium, not shown). Also, note the dark blood-pool, a characteristic sign of altered gadolinium kinetics in cardiac amyloidosis (images courtesy of Dr. Theodoros Karamitsos).

representing the decay of transverse magnetization in the presence of local field inhomogeneities. *T1 mapping* can be used to estimate fibrosis or infiltration (e.g. amyloid). *T2 weighted* CMR imaging is commonly used to assess myocardial inflammation and edema. *T2** quantification is currently the method of choice for myocardial tissue iron assessment. *ECV* appears to be a surrogate marker for the amyloid burden and carries prognostic value. T1 mapping can be used to estimate the myocardial ECV, a validated surrogate marker of fibrosis in the absence of confounders (e.g. infiltration) [79]. *Late gadolinium enhancement (LGE)* identifies focal myocardial necrosis/fibrosis.

CMR has enhanced the ability to recognize cardiac amyloidosis because it shows a distinct pattern of LGE over the entire subendocardial or transmural area (**Fig. 3**) [54]. A high diagnostic accuracy of LGE for ACM has been reported by a systematic review and meta-analysis of 7 studies with a sensitivity of 85% and specificity of 92% [80]. CMR is useful when distinguishing cardiac amyloidosis from hypertrophic CM and hypertensive heart disease. Transmural patterns of LGE may distinguish ATTR from AL-CM; a higher percentage (90%) of patients with ATTR demonstrate transmural LGE, compared with patients with AL-CM (37%) [81].

CMR provides detailed information about the presence, location, and distribution of hypertrophy, as well as visualization of cardiac amyloid infiltration with LGE imaging and measurement of cardiac amyloid burden with T1 mapping and ECV [54]. In addition to its ability to detect ACM, CMR may also provide prognostic information beyond that of conventional biomarkers [82]. Myocardial ECV, a non-invasive quantification of the cardiac amyloid burden in the cardiac interstitium, has been shown to predict death and remains an independent predictor of prognosis after adjustment for known prognostic factors [83,84]. Native T1 mapping and ECV have been shown to be good diagnostic techniques for ATTR-CM that are associated with prognosis. Both parameters have been shown to correlate with mortality, but only ECV remains independently predictive of prognosis, suggesting that it is a more robust marker in both ATTR-CM and AL-CM [85,86].

In early disease, native T1 and ECV are elevated before LGE appears [87], although these changes are initially non-specific and thus only clinically useful when the pre-test probability is high [78]. Once subendocardial LGE appears, ECV elevation in remote areas begins to be diagnostic, as diffuse fibrosis rarely increases the ECV > 40%. ECVs of > 55% characterize transmural LGE. Quantification of ECV measures cardiac amyloid deposition in both types (AL and ATTR) of amyloidosis and shows that amyloid deposition is more extensive in patients with ATTR than in those with AL, while ATTR is associated with higher cell volume, which suggests concomitant cell hypertrophy [88]. In the elderly, occult ATTR amyloid may co-exist with other diseases such as heart failure, hypertrophic CM, and aortic stenosis; however, in such patients, bone scintigraphy is more sensitive in rendering a diagnosis as compared with CMR [89]. Importantly, ECV can be used to monitor therapy in amyloid [90], and might be able to track amyloid regression.

CMR might be able to differentiate between the two types of ACM, as myocardial enhancement on LGE sequence is reported to be more intense in ATTR than in AL amyloidosis, with predominant transmural enhancement and frequent RV involvement in ATTR [81]. As mentioned, a study employing ECV quantification reported that ATTR amyloid deposits were larger than AL amyloid deposits and were associated with a ~ 20% increase in cell volume [88], suggesting a concomitant myocyte hypertrophy. AL amyloidosis was associated with a greater elevation of myocardial native T1 and a smaller ECV suggesting myocardial edema. A CMR study in patients with ACM (n = 44) reported a significant raise of myocardial native T2 relaxation time compared to controls (n = 40) suggesting myocardial edema in these patients, which was more pronounced in AL (n = 24) compared to ATTR patients (n = 20) [91]. Myocardial native T2 exhibited higher performances than T1 to differentiate AL and ATTR amyloidosis but was not a predictor of survival. Thus, T2 also separated effectively AL and ATTR patients and could be considered as an additional marker to distinguish these 2 types of ACM.

Finally, one needs to take into consideration several *limitations* and confounding variables of CMR imaging. Some of the limitations are due to patient and patient's physiology, but others may be due to scanner adjustments or field inhomogeneities. CMR is contraindicated in certain patients with standard (non-magnetic resonance conditional) cardiac implantable electronic devices (pacemakers or defibrillators), patients with claustrophobia and patients with impaired renal function [92]. Arrhythmias (atrial fibrillation, frequent extrasystoles) may limit image quality of gated sequences. Patient cooperation is crucial for brief periods of breath holding and for prolonged (≈45-min) scanning. Mapping techniques suffer from major technical limitations limiting their use in clinical practice [78]. The measurement of a parameter of interest such as T1 may depend on other variables such as T2 or patient's heart rate, and many other confounding factors. For example, an elevated T1 might be due to fibrosis, or might be due to confounding effect of elevated T2 arising from edema. In another example, a decrease in T1 might be due to increased iron concentration, or might be due to off-resonance effects in the scanner center frequency. The degree of tissue or infiltrate heterogeneity and size of focal abnormalities is a factor influencing the quantitative measurement and depends on resolution and manner of measurement and reporting [78].

There are also potential limitations of LGE in detecting the diffuse myocardial infiltration that relies on detection of fibrosis which appears late in the disease process. The false negative rate of CMR for ACM is relatively high, at 12%; the false positive rate is at ~10% [93]. The predictive value of LGE has improved with the development of newer

techniques, such as phase-sensitive inversion recovery, which allows the use of different inversion times, corrects some previous technical problems responsible for discrepancies in LGE measurement leading to an underestimation of LGE extent and severity in cases where the majority of cardiac tissue was affected [94]. There seems to be potential additional information provided by quantitative measurement; a technique that attempts to quantify the LGE findings, the Look-Locker post-contrast T1, has been tested and shown to have good diagnostic accuracy in detecting ACM and a correlation with histological amyloid burden [95].

5.7. Radionuclide imaging

ATTR can be diagnosed noninvasively via bone scintigraphy using technetium-labelled radiotracers with very high diagnostic accuracy (92% sensitivity/95% specificity) [96,97]. Bone tracers bind to microcalcifications associated with amyloid deposits in ATTR with high affinity [98]. Myocardial uptake of bone tracers has emerged as a practical diagnostic tool for early detection of ATTR. Technetium-99 m-pyrophosphate (^{99m}Tc-*PYP*), 99mTc-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc-*DPD*) and 99mTc–hydroxymethylene diphosphonate (^{99m}Tc-HDP) have been used as cardiac tracers in both mutant and wt ATTR, as they have a specific avidity for ATTR amyloid deposits [99,100]. Bone tracers can detect ATTR amyloid prior to echocardiographic evidence of cardiac involvement; cardiac uptake of a bone tracer may also correlate with severity of cardiac involvement using echocardiography, ECG and cardiac biomarkers [100]. Radionuclide scanning with ^{99m}Tc-PYP or ^{99m}Tc-DPD can heighten the suspicion of ATTR. A negative result can exclude cardiac involvement or suggest that cardiac amyloid may not be of TTR origin.

Bone scintigraphy enables the diagnosis of ATTR-CM to be made reliably without the need for biopsy in patients who do not have a monoclonal gammopathy. Among 1217 patients with suspected cardiac amyloidosis, of whom 857 patients had histologically proven amyloid (374 with endomyocardial biopsies) and 360 patients were subsequently confirmed to have nonamyloid-CM, myocardial radiotracer uptake on bone scintigraphy was > 99% sensitive and 86% specific for ATTR-CM, with false positives noted almost exclusively from uptake in patients with AL-CM [51]. In the absence of a monoclonal gammopathy, bone scintigraphy had a 100% specificity and positive predictive value for ATTR-CM. Thus, scintigraphy with use of bone-avid compounds is useful for the accurate identification of ATTR-CM (irrespective of genotype), and differentiation from AL amyloidosis or other diseases producing LVH or HFpEF [101].

Thus, bone tracers showing high affinity for ATTR amyloid deposits and minimal affinity with amyloid deposits in AL-CM, allow distinction between the two ACM types with high sensitivity (close to 100%) and specificity (> 85%) [97,102]. Furthermore, quantitative assessment of bone tracer uptake may provide additional prognostic information [102]. It has been shown that increased myocardial retention of the bone tracer is an unfavorable predictor of major adverse cardiac event (MACE)–free survival, and increased acute heart failure and/or death [99,103].

Quantitative assessment of cardiac amyloid burden with use of bone tracers would facilitate monitoring of disease progression and response to novel therapies. However, there are certain limitations in this endeavor. Quantitation of bone tracer uptake in cardiac TTR amyloid deposits is complex and is hindered by competition for radiotracer with amyloid in skeletal muscle [104], although this property may be tracer-specific, with less non-cardiac uptake of Tc-PYP compared with Tc-DPD [102,105,106]. Furthermore, imaging protocols and interpretation criteria are not standardized, while there is a lack of prospective clinical studies [107]. Looking at the myocardial uptake of the bone tracer in the heart over the contralateral (H/CL) chest is thought to normalize for bone and soft tissue uptake, and when this H/CL ratio of uptake is over a certain threshold (e.g. > 1.5), it is considered diagnostic for ATTR CM with a high sensitivity and specificity [102], with the caveat that AL CM and a false positive test have been ruled out [51]. A falsely positive test with elevated H/CL ratio may be encountered in presence of ipsilateral bone fractures, mitral annular calcification, severely calcified aortic stenosis, calcified lung nodules, and/or ipsilateral breast tissue calcifications. In such cases, CMR and/or tissue biopsy may be needed.

With regards to differences among specific bone tracers, one study showed similar diagnostic accuracy using 3 different radiotracers, ^{99m}Tc-DPD, ^{99m}Tc-HMDP, and ^{99m}Tc-PYP [51]. Other investigators have presented cases of ATTR CM in which ^{99m}Tc-methylene diphosphate (^{99m}Tc-MDP) scintigraphy failed to show myocardial uptake, suggesting that ^{99m}TcMDP lacks sensitivity for diagnosis of ATTR CM and thus considered inappropriate for ATTR-CM [106,108,109]. As mentioned, some tracers have greater extra-cardiac uptake than others [108]. The most common ^{99m}Tc bone tracers employed for ACM are the ones already mentioned: ^{99m}Tc-PYP, -DPD, or -HMDP [51]. Diffuse myocardial uptake of ^{99m}Tc radiotracers is graded into 4 grades: 0, no myocardial uptake; 1, myocardial uptake less than bone; 2, myocardial uptake equal to bone; 3, myocardial uptake greater than bone [106,109]. Although this grading has high diagnostic sensitivity and specificity for ATTR CM, it has no prognostic significance [110]. There are many studies on the diagnostic accuracy of the single tracers in detecting ATTR-CM but head-to-head comparisons between tracers are scanty [106,109,111]. A small ($n = 6$) comparative study indicated that ^{99m}Tc-HMDP and ^{99m}Tc-DPD had comparable myocardial uptake intensity on early-phase scintigraphy and may therefore constitute alternative agents for the diagnosis of ATTR-CM [111].

To explain the difference (heterogeneity) of myocardial uptake in the two types of ACM (ATTR vs AL CM) with the ATTR-CM being particularly avid for bone tracers, whereas uptake in AL-CM is absent or mild, it has been suggested that the preferential binding of bone tracers to ATTR may be a result of higher calcium content [106]. Indeed, significantly greater density of small microcalcifications have been found in endomyocardial biopsies of patients with ATTR compared to AL [98]. However, although the amount of calcium within the infiltrated tissue is likely related to the overall amyloid load which in turn is related with the degree of LVH, the correlation between ventricular parietal thickness and semiquantitative measurements of bone tracer uptake remains very weak [99,106]. The specific mutation and the types of amyloid fibrils (type A consisting of C-terminal ATTR fragments and full-length TTR; type B consisting only of full-length TTR) have been suggested as other possible modulators of the binding between amyloid deposits and bone tracer, with the tracer having little if any affinity for type B ATTR deposits [112,113]. Type B fibrils have thus far only been found in predominantly early-onset V30 M and in patients carrying the Y114C mutation, whereas type A is noted in all other mutations currently examined as well as in ATTRwt CM [113]. Thus, bone scintigraphy is probably not reliable in patients with type B ATTR CM and thus, when negative, it does not exclude ACM.

In *summary*, cardiac scintigraphy with bone tracers is changing the diagnostic paradigm of ACM, as the diagnosis of ATTR CM could be achieved non-invasively. Amyloid deposits in the heart are frequently reported in epidemiological studies, especially in older individuals. However, the sole presence of amyloid fibrils in the myocardium should not prevent a complete diagnostic work-up as additional causes of structural heart disease could also be present (i.e. coronary artery disease, aortic valve stenosis). The result of cardiac scintigraphy should therefore be considered according to the whole clinical picture and not in isolation. When scintigraphy is negative, but the clinical picture is suggestive, further testing with use of CMR and/or endomyocardial biopsy should be considered, since ACM of the AL CM type or even ATTR with type B amyloid fibrils could still be present. On the other hand, in individuals with monoclonal gammopathy suggestive of AL CM, cardiac scintigraphy with a bone tracer may still be of great value to evaluate for ATTR CM, since there is a high prevalence of *monoclonal gammopathy of unclear significance (MGUS),* particularly in ATTRwt

(estimated at ~40% in older people). In such ambiguous cases, endomyocardial biopsy may also be needed.

5.8. Tissue biopsy

Endomyocardial biopsy remains the gold standard diagnostic examination for the diagnosis of ACM [2,53]. Similarly, verification of diagnosis for ATTR requires biopsy of the affected organ, abdominal fat, or salivary gland. Biopsy of extracardiac tissues has low sensitivity for the diagnosis of ACM. However, noncardiac biopsy or fat aspiration could be considered as initial testing in patients evaluated for ATTR with characteristic echocardiography findings [114]. Congo red staining is applied to histological specimens to demonstrate the pathognomonic green birefringence under polarized light of amyloid deposits, while typing of amyloid proteins is carried out via laser microdissection with mass spectrometry. However, nowadays other contemporary noninvasive diagnostic techniques with increased diagnostic power, such as multimodality imaging with use of echo, CMR and nuclear imaging, may suffice for the diagnosis of ATTR, having thus reduced the need for biopsy [115]. For AL CM or other ambiguous cases, one must proceed with endomyocardial biopsy (**Fig. 1**). For ATTR CM, as already detailed above, cardiac scintigraphy with a bone tracer can be used if AL amyloid has been excluded when the screening tests for AL amyloidosis are negative.

5.9. Genetic testing

Genetic testing of the ATTR gene is needed to differentiate ATTRwt from ATTRm. > 120 amyloidogenic mutations have been described, which are inherited in autosomal dominant fashion. The most common mutation in the USA is Val122Ile (~45%), responsible for the forms with predominant cardiac phenotype, while Val30Met is the most common mutation in rest of the world, causing the forms with predominant neurologic phenotype and early onset of the disease [2,37]. According with the THAOS registry in the US (n = 390), US patients with ATTR are older (70 vs. 46 years), more often male (85.4% vs. 50.6%), and more often of African descent (25.4% vs. 0.5%) than in other regions of the world [37].

6. Diagnostic algorithm

An algorithm is proposed in Fig. 1 for the diagnostic approach to ACM. For both types of ACM, the algorithm starts with clues obtained from a good history and physical examination which include cardiac and non-cardiac symptoms and signs. In the case of a patient with HFpEF with predominant right-sided symptoms and signs, with or without arrhythmias, low-voltage and/or pseudo-infarct pattern on the ECG, LVH and/or restrictive pattern on echo, in the absence of typical hypertrophic CM or aortic stenosis, a clinical suspicion of ACM may be entertained. Symptoms of carpal tunnel syndrome or spinal stenosis, orthostatic hypotension and polyneuropathy will point to possible ATTR, while facial or neck purpura and/or macroglossia will direct to AL CM.

6.1. AL-CM

Once clinical suspicion of ACM is raised, one has to decide and differentiate between ATTR CM and AL CM. One may start with drawing blood for free light chain (FLC) assay and serum protein electrophoresis with immunofixation to look for monoclonal protein (AL CM). Urine immunofixation electrophoresis may also be performed. If indicated, based on initial tests, bone marrow biopsy may be performed to determine whether plasma cell dyscrasia is present and to determine the percentage and type of λ- or κ-producing plasma cells [116]. Bone marrow biopsy may also provide initial assessment for amyloid; this can also be accomplished from periumbilical fat aspirates or labial salivary gland biopsy specimens as a less invasive approach in patients with suspected AL amyloidosis with relatively high sensitivity (~80%) [116]. Imaging studies (newer echo strain techniques, CMR) and/or biomarkers may then provide evidence for ACM; however, tissue diagnosis via *endomyocardial biopsy* will be required to confirm AL CM, since MGUS is common in patients with ATTRwt, but it is unrelated to amyloid deposition in these patients. In this latter case (MGUS), bone scintigraphy may provide evidence for ATTR-CM in addition to the presence of bystander monoclonal gammopathy. Most importantly, it is crucial to render the correct diagnosis of the ACM type, since treatment for AL CM is sharply different from that of ATTR CM.

6.2. ATTR-CM

If AL amyloid is excluded via above screening tests, then one needs to pursue the diagnosis of ATTR-CM via cardiac scintigraphy with use of a bone tracer. In the case of a positive scan, one may forego the need for endomyocardial biopsy. However, the distinction between ATTRm and ATTRwt will need to be made with the performance of genetic testing.

7. Treatment

Important advances have developed over the recent years in the treatment of all forms of ACM. Particularly, agents that may suppress the synthesis or stabilize TTR and agents that may degrade amyloid fibrils have ushered in a new era in the management of ATTR (Table 3, Fig. 4).

Tafamidis is a drug that functions as a chaperone that stabilizes the correctly folded tetrameric form of the TTR protein by binding in one of the two thyroxine-binding sites of the tetramer, preventing tetramer dissociation and amyloidogenesis. In the *ATTR-ACT* study, a phase 3 trial, 441 patients with ATTR-CM were randomized in a 2:1:2 ratio to receive 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months [47]. In the primary analysis, all-cause mortality and rates of cardiovascular-related hospitalizations were lower in the tafamidis (group (n = 264) compared with the control group (n = 177) (P < .001). Tafamidis was associated with lower mortality than placebo (29.5% vs. 42.9%; hazard ratio, 0.70) and a lower rate of cardiovascular-related hospitalizations, with a relative risk ratio of 0.68. At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-min walk test (P < .001) and a lower rate of decline in quality of life score (P < .001). The incidence and types of adverse events were similar in the two groups. Importantly, only patients classified as NYHA class I and II responded to treatment with tafamidis, while NYHA class III patients did not show any response to therapy [47].

Patisiran, a double-stranded synthetic oligonucleotide interfering with the RNA production of the abnormal TTR thus reducing tissue accumulation of amyloid deposits, was tested in the APOLLO trial, in 148 adult ATTRm patients with polyneuropathy and showed improvement of neuropathy scores, of the 10-min walk test and of nutritional status [117]. In addition, a significant reduction of NT-proBNP and of

Table 3
Treatment of TTR amyloidosis.

TTR suppression (in the liver)
● Liver transplantation
● Silencers of TTR gene (*patisiran*, *inotersen*)
TTR stabilization
● Tafamidis ● NSAID (Diflunisal) ● Green tea ● AG10 (small molecule)
Degradation of amyloid fibrils
● Doxycycline/TUDCA
● Monoclonal antibodies

NSAID = non-steroidal anti-inflammatory drug; TUDCA = tauro-ursodeoxycholic acid; TTR = transthyretin.

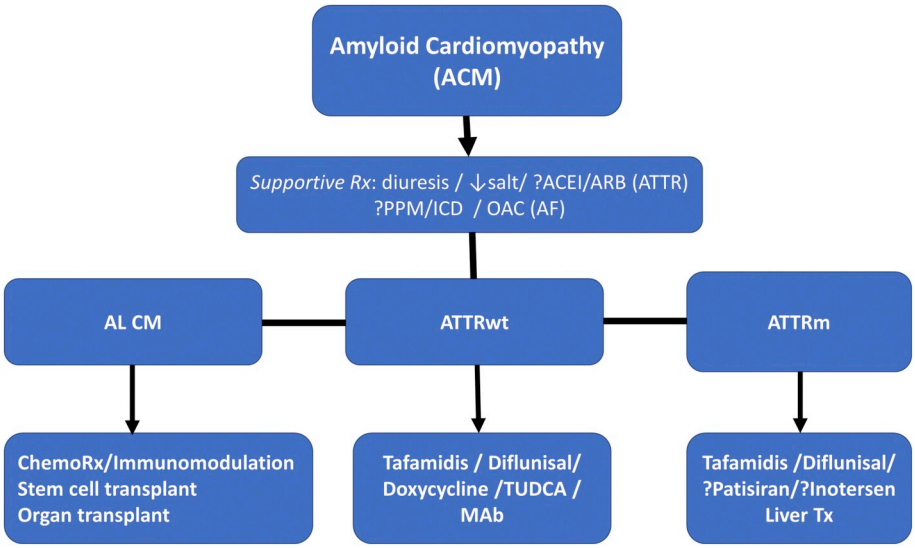

Fig. 4. The schema outlines contemporary management of the three types of amyloid cardiomyopathy (ACM) (see text for discussion). ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AL CM = light chain amyloid cardiomyopathy; ARB = angiotensin receptor blocker; ATTR = transthyretin amyloidosis; ICD = implantable cardioverter defibrillator; m = mutant (hereditary); Mab = monoclonal antibody; OAC = oral anticoagulant; PPM = permanent pacemaker; Rx = treatment/therapy; TUDCA = *tauroursodeoxycholic acid;* Tx = transplant; wt = wild-type.

longitudinal LV strain was demonstrated. This led to FDA and EU approval of patisiran infusion (2018) for patients with ATTRm-related peripheral polyneuropathy [118,119].

In the cardiac subpopulation of the APOLLO study (n = 126; 56% of total population), patisiran reduced mean LVH (P = .017) global longitudinal strain (P = .015), *N*T-proBNP (P < .001), and adverse cardiac outcomes (rates of cardiac hospitalizations and all-cause death; hazard ratio, 0.54), compared with placebo at month 18, suggesting that patisiran may halt or reverse the progression of the cardiac manifestations of ATTRm amyloidosis [120]. Furthermore, in another post-hoc analysis of this trial, patisiran (n = 90) compared to placebo (n = 36) improved the absolute LV global longitudinal strain at 18 months, with the greatest differential increase observed in the basal region (P = .006) and no significant differences in the mid and apical regions among groups [121].

Inotersen, the single-stranded antisense oligonucleotide inhibitor of mutant and wild-type human TTR, selectively binding to TTR mRNA and preventing the synthesis of TTR protein in the liver, thus reducing further amyloid deposition throughout the body, was tested in the NEURO-TTR study in 112 of 172 participants with ATTRm. Inotersen improved the course of neurologic disease and quality of life in these patients [122]. However, the drug caused a higher rate of glomerulonephritis (3%) and thrombocytopenia (3%), with one death associated with grade 4 thrombocytopenia. The authors suggested that these adverse effects of inotersen may be effectively managed with enhanced monitoring. Based on these results, inotersen was recently approved in the EU for the treatment of stage 1 or 2 polyneuropathy in adult patients with ATTRm and is undergoing evaluation in the USA and Canada [123]. No results of the drug effect on ACM are currently available.

AG10 is a selective, oral TTR stabilizer that mimics a protective TTR mutation. A recent phase 2 RCT evaluated AG10 in 49 ATTR-CM patients (mutant or wild-type) with symptomatic (NYHA class II-III), chronic heart failure, randomized 1:1:1 to AG10 400 mg, 800 mg or placebo bid for 28 days [124]. AG10 treatment was well-tolerated, achieved target plasma concentrations and demonstrated near-complete stabilization of TTR. The authors concluded that AG10 is a potentially safe and effective treatment for patients with ATTR-CM.

7.1. AL Amyloidosis

Treatment of *AL amyloidosis* is guided by risk assessment, which is based on levels of cardiac biomarkers [64]. Duration and type of therapy is guided by monitoring of clonal and organ responses. Various regimens comprise several new classes of drugs, such as proteasome inhibitors (bortezomib) and immunomodulatory drugs, together with high - dose chemotherapy and autologous hematopoietic stem cell transplantation. The goal of therapy is rapid elimination of the amyloid precursor and reabsorption of amyloid deposits. Chemotherapy, e.g. with melphalan and dexamethasone, cyclophosphamide or bortezomib, stem cell transplantation and immunotherapy targeting the B cell clone aim at suppressing amyloid light chain synthesis. Immunotherapies (monoclonal antibodies) are being developed to promote reabsorption of amyloid deposits.

7.2. Supportive therapies

In addition to amyloid-specific and targeted therapies, *supportive therapies* are also important for cardiac, renal, neurological and other symptoms. When managing cardiac patients with ACM, one should be aware of certain differences in the response to treatment of these patients compared to other cardiac patients. Patients with ACM do not typically tolerate well conventional cardiac drugs such as β-blockers, calcium channel blockers, angiotensin- converting enzyme inhibitors or angiotensin receptor blockers. The associated sinus tachycardia for many of these patients is a physiologic response to maintain adequate cardiac output, hence its abolition may not be advisable. Furthermore, β- blockers may increase the risk of bradycardia owing to co-existing atrioventricular conduction disease. Loop diuretics (furosemide, torsemide) are important to manage fluid overload and congestive symptoms. However, due to diastolic dysfunction, one should be cautious with over-diuresis using loop diuretics to avoid hypovolemia and its detrimental consequences. Spironolactone and metolazone can be used as adjunctive diuretics. For the management of AF, only amiodarone is relatively safe with less proarrhythmia compared to other antiarrhythmics, albeit with its known organ toxicity. One should be aware of the added toxicity of digoxin in these patients due to its toxic concentration at the tissue level and avoid its use [125]. Invasive therapies to consider may include ablation with either pulmonary vein isolation or even ablation of the atrioventricular node. Complex ventricular arrhythmias have been reported in ~50% of patients with ACM, considered a harbinger of sudden cardiac death [20]. The role of an implantable cardioverter defibrillator (ICD) [126] in ACM may be diminished as pulseless electrical activity is one of the more common preterminal events, rather than ventricular tachyarrhythmias [127], although ICD discharges have been reported in ~1/3 of those bearing an ICD device [128,129].

Patients on β- blockers might have increased risk of bradycardia

owing to conduction block, and in one series, the pre- cardiac arrest rhythm was bradycardia in all 8 patients, including complete heart block in 6 patients [130]. Which patients with AL amyloidosis might benefit from ICD is unclear. Pacemakers may be useful in patients with bradyarrhythmias, however, even in these cases, pulseless electrical activity may not be preventable, especially in AL amyloidosis [130].

7.3. Doxycycline

Doxycycline has demonstrated anti- amyloid activities in vitro and in vivo [64,131]. The addition of doxycycline to standard chemotherapy reduced early mortality in cardiac AL amyloidosis in a retrospective case- matched study of 30 patients with AL-CM and 73 matched controls with a particular impact on patients presenting with a high troponin suggesting that doxycycline may reduce light-chain cardiotoxicity [132]. An international phase III trial is ongoing in newly diagnosed AL CM patients undergoing bortezomib-based therapy comparing doxycycline vs standard supportive therapy (NCT03474458).

7.4. Warning

Amidst all the commotion and excitement about the development of new drugs for the targeted treatment of amyloidosis and possibly ACM, a word of caution has to be uttered emanating from the disappointing results of another RNA-interfering agent (resuviran) which seems to have increased mortality in patients with ACM when tested in a phase 3 trial (ENDEAVOUR; NCT02319005) necessitating the discontinuation of the program [133].

7.5. Heart Transplantation

Orthotopic *heart transplantation* may be used in selected patients [134–137]. For patient selection, certain criteria have been proposed, e.g. applying the DANGER criteria for patient exclusion: **D**iarrhea (weight loss, malabsorption), **A**utonomic nervous system involvement, impaired **N**utritional status, **G**astrointestinal tract involvement, impaired **E**limination (renal dysfunction: nephrotic syndrome, increased creatinine), and **R**espiratory tract involvement [136,137]. Key determinants for the best outcomes include lower tumor burden, organ involvement limited to the heart and effective chemotherapy for AL-CM. However, most patients do not satisfy these criteria and do not survive long enough to receive an orthotopic heart. For patients who do receive transplantation, 5-year overall survival ranges from 18 to 75% [137,138]. Some of the best results have been in AL-CM patients who have high-dose chemotherapy and stem cell transplantation after their cardiac transplant. Use of enhanced chemotherapy regimens for isolated advanced AL-CM is associated with outcomes comparable to non-ACM [137].

8. Therapeutic algorithm

A flow chart of contemporary management of ACM is illustrated in Fig. 4. Supportive therapies for all types of ACM are of paramount importance, including diuresis and low-salt diet, together with electrolyte monitoring and maintenance of electrolyte and fluid balance. Whether angiotensin system inhibitors are of any clinical value remains dubious. Other supportive measures include antiarrhythmic therapies (e.g. for atrial fibrillation), with the caveat of avoiding digoxin and beta-blockers and opting for amiodarone; and cardiac implantable electronic devices for symptomatic brady- and/or tachy-arrhythmias.

8.1. AL-CM

For AL amyloidosis, modified treatment regimens for multiple myeloma are generally used. The goal is to improve organ function; therapies are risk-adapted and individualized, targeting both the clonal plasma cell disorder (to stop production of the precursor protein) and existing myocardial amyloid deposits. These patients are frequently treated with high-dose chemotherapy including alkylating agents, steroids, proteasome inhibitors (bortezomib) and/or immunomodulatory drugs in combination with autologous stem cell transplantation. Several constraints apply to organ transplantation in these patients, however, some patients with isolated cardiac involvement may be eligible for heart transplantation and may experience enhanced survival [139]. Emerging amyloid-directed treatments include immunotherapies with antibodies targeting misfolded light chains or amyloid fibrils, or antibiotic (doxycycline) that inhibits fibrillogenesis [116].

With regards to current approach to patients with AL CM, the recommended strategy involves three steps, which need to be coordinated between cardiology and hematology/oncology services: [138] 1) Induction chemotherapy that generally includes bortezomib-based chemotherapy combinations, aiming to minimize the burden or to eliminate bone marrow plasma cells producing light chains; 2) Heart transplant after a typical 6-month waiting period with the objective to ensure cardiovascular stability for high-dose chemotherapy; 3) High-dose melphalan conditioning chemotherapy followed by autologous hematopoietic stem cell transplant (bone marrow transplant) which is typically scheduled after another approximate 6-month observation period after step 2.

8.2. ATTR-CM

For many years, liver or combined heart and liver transplantation have been the standard available treatments for patients with ATTR, including ATTR-CM. However, tremendous progress has been made over the recent years in the treatment of ATTR-CM with several newer targeted therapies becoming available that suppress TTR production in the liver (patisiran, inotersen), stabilize TTR (tafamidis, diflunisal, AG10), or degrade amyloid fibrils (doxycycline, tauro-ursodeoxy-cholic acid, monoclonal antibodies) (Table 3) [140]. Randomized controlled trials with use of these agents are slowly emerging with encouraging results [47,120,124]. Currently, *tafamidis*, an agent that stabilizes TTR tetramers, seems to be the most promising agent with positive results in a phase 3 trial for patients with ATTR CM, particularly patients in NYHA Class I–II [47]. Other also promising agents are *patisiran* and *inotersen*, which block TTR synthesis, an even better and more promising therapeutic aim [117,122]. With more agents becoming available in the future, one could hope to be able to tailor therapy for each individual patient, based on specific characteristics of each agent; e.g. patisiran could be preferred for a patient with AF receiving anticoagulation, instead for inotersen which may cause thrombocytopenia with its attendant bleeding risk; or for a patient with impaired renal function where inotersen has the potential to cause glomerulonephritis [140].

9. Prognosis

As mentioned, in a retrospective study, 360 patients diagnosed with ATTRwt (median age 75 years, range 47–94 years; 91% male), presenting with dyspnea or heart failure in 67% and atrial arrhythmias in 62%, had a poor natural history [38]. Median overall survival from diagnosis was 3.6 years and did not change over time. Multivariate predictors of mortality included age, LVEF, pericardial effusion, NT-proBNP, and cTnT. A staging system used thresholds of troponin T (0.05 ng/ml) and NT-proBNP (3000 pg/ml). The respective 4-year survival estimates were 57%, 42%, and 18% for stage I (both values below cutoff), stage II (one above), and stage III (both above), respectively. Stage III patients (cTnT > 0.05 ng/ml and NT-proBNP > 3000 pg/ml) had the worst prognosis (hazard ratio: 3.6 compared to stage I; $p < .001$).

Another retrospective analysis of 869 patients with cardiac ATTR

(553 with ATTRwt and 316 with ATTRm) stratified patients into three stages at baseline on the basis of cutoff points in NT-proBNP and estimated glomerular filtration rate (eGFR) [60]. Stage I was defined as NT-proBNP ≤3000 ng/l and eGFR ≥45 ml/min, stage III was defined as NT-proBNP > 3000 ng/l and eGFR < 45 ml/min, and the remainder were stage II. The staging system was validated in a cohort of 318 patients with cardiac ATTR. Median survival for stage I patients (n = 393, 45%) was 69.2 months, for stage II patients (n = 334, 38%) 46.7 months, and for stage III patients (n = 142, 16%) 24.1 months (hazard ratios for death compared with stage I: 2.05 for stage II and 3.80 for stage III; P < .001). Results were similar for both TTR genotypes and were maintained in the validation cohort.

Kappa- and lambda-light chains in AL amyloidosis are toxic to cardiomyocytes, leading to accelerated clinical illness and poor survival, as treatment often remains inadequate due to multiorgan dysfunction and intolerance to chemotherapy. Despite significant advances in the treatment of advanced heart failure, it may not be possible to stabilize end-stage ACM with use of inotropes or mechanical circulatory support, while several restrictions apply to these patients to be considered suitable candidates for heart transplantation.

10. Conclusion

The diagnosis of ACM is challenging, due to various reasons, such as the high heterogeneity of cardiac phenotypes and of systemic involvement. Patients with ACM often present extracardiac symptoms, mainly neurological. Furthermore, ATTR is a late-onset disease and symptoms manifest mostly in elderly patients (> 60 years old) with comorbidities that blur the correct diagnosis. ATTRwt causes most commonly cardiac involvement, and should be suspected in elderly patients presenting with HFpEF and unexplained LVH. Diagnostic clues may comprise neurological manifestations, such as carpal tunnel syndrome and/or spinal stenosis. A positive family history is important for mATTR, but it may be difficult to extract because of the delayed and incomplete penetrance of the mutations responsible for ACM. Peri-orbital purpura and macroglossia combined with proteinuria and peripheral/autonomic neuropathy may be the clues to suspect and seek the diagnosis of AL-CM, again in patients with HFpEF and unexplained LVH. Recent advances in cardiac imaging techniques (strain echocardiography, CMR and bone scintigraphy) may render non-biopsy diagnosis of ATTR-CM feasible. Importantly, tremendous developments in drug therapy with agents that suppress the synthesis of or stabilize TTR and agents that degrade amyloid fibrils have ushered in a new era in the effective management of these patients. Also, chemotherapy combined with stem cell transplant and immunomodulatory therapy have a favorable effect on the course and prognosis of AL-CM. Finally, in select patients with end-stage disease, orthotopic heart transplantation may lead to results comparable to non-ACM patients.

Declaration of Competing Interest

None.

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