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Review Article

Cardiac Amyloidosis, Something More Common than we Think. Review of the State of the Art.

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Abstract

Cardiac amyloidosis is a condition caused by extracellular deposits of amyloid proteins in the heart muscle. Until a few years ago, it was considered a rare entity. However, the advent of new diagnostic methods and the increasing clinical suspicion have shown that this disease is more common than previously suspected. Its diagnosis and treatment depend on the clinical history, immunohistochemical, imaging and genetic studies, and histopathological identification of amyloid deposits. Risk stratification and identification of the type of circulating or tissue-deposited amyloid protein will determine the appropriate treatment method for each patient. Genetic screening should also be performed on relatives of patients with hereditary forms of the disease. The following review provides a context for the current state of the art of this disease.

Keywords: *cardiac amyloidosis, amyloid protein, immunohistochemical studies.*

Introduction

Amyloidosis is the general term used to refer to the extracellular tissue deposition of highly ordered fibrils composed of low molecular weight subunits of a variety of proteins, many of which, in their native form, circulate as normal constituents of plasma. Amyloid deposits may result in a wide range of clinical manifestations depending upon their type, location, and amount.

At least 38 different human protein precursors of amyloid fibrils are known. Some are produced at the site of amyloid formation (localized amyloid) and some circulate in the blood to deposit in a variety of tissues and organs (systemic amyloidosis)[1,2].

Amyloidosis results from the predominantly extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins, typically in the range of 5 to 25 kD. Genetic factors play an important role in many forms of amyloidosis. Point mutations, deletions, and premature stop codons may result in structural changes predisposing to fibril formation (fibrillogenesis) by these proteins and the development of amyloid. Depending upon the type of amyloidosis, factors affecting protein folding and stability, including molecular chaperones and failure of disaggregating pathways, may be operative[3].

These low molecular weight subunits are derived from soluble precursors and undergo conformational changes that lead to the adoption of a predominantly antiparallel beta-pleated sheet configuration in which state they auto-aggregate in highly ordered fibrils[4-7]. Oligomeric intermediates that are pre-fibrillar may contribute to tissue toxicity and disease pathogenesis in certain amyloid related disorders[8].

Several types of amyloidosis are clearly hereditary, and clinical disease has been linked in most familial forms to missense mutations of the precursor proteins. In some instances, deletions or premature stop codon mutations have been described[4,9].

Virtually all heredofamilial amyloidoses associated with nephropathic, neuropathic, or cardiopathic disease are dominantly inherited heterozygous disorders, and both the wild-type and mutant molecules can be identified in the amyloid deposits. In some instances (eg, transthyretin [TTR], apolipoprotein A-I [ApoAI], Alzheimer APP, and prion protein [PRP]), both the wild-type and mutant molecules are able to form amyloid fibrils under different circumstances, with the wild-type protein implicated in aging-associated diseases. As an example, wild-type TTR; ApoAI; and the beta protein, A-beta, a cleavage product of APPs, may form deposits in association with organ-specific pathology in the aging heart, aorta, and brain, respectively[9-11].

Types of amyloidosis

There are 18 different types of systemic and 22 localized forms of amyloidosis[12]. The principal systemic types seen in tertiary referral centers and inpatient medical services are the primary (immunoglobulin light chain [AL]) and transthyretin (ATTR) types. However, other types of amyloid (eg, secondary [AA]) are clinically important, some of which are common and others rare. A review of more than 11,000 patients seen at a single center from 1987 through 2019 showed that systemic AL amyloidosis accounted for 56 percent, ATTR 21 percent, and AA 8 percent of typed cases[13]; in particular, there has been a substantial increase in the recognition of systemic amyloid due to ATTR in major referral centers. Nomenclature for amyloid subunit proteins includes the letter "A," followed by the abbreviation of the name of the precursor protein. Major forms include:

- AL amyloid: AL amyloid, caused by a plasma cell dyscrasia, is due to deposition of protein derived from immunoglobulin light chain fragments.

- ATTR amyloid: ATTR amyloid may occur as a "wild-type" (ATTRwt) associated with aging or as mutant proteins (ATTRv or hATTR [where v indicates a variant and h indicates hereditary; these were formerly termed ATTRm, to indicate a mutant protein]) associated with familial neuropathy and/or cardiomyopathy[13].

- AA amyloidosis: AA amyloidosis is a potential complication of chronic diseases in which there is ongoing or recurring inflammation that results in sustained high-level production of serum amyloid A protein, an acute phase reactant, which can form amyloid deposits.

- Other types of amyloidosis: Additional forms of amyloid seen clinically include dialysis-related amyloidosis, heritable amyloidosis, organ-specific amyloid, leukocyte cell-derived chemotaxin-2 (LECT2) amyloid, insulin amyloid[14], and others.

In this review, it will be just made reference to AL amyloidosis, ATTRwt, and (ATTRv or hATTR) since these types are the commonest found causing affectation of the cardiovascular system.

AL amyloid cardiomyopathy (AL-CM)

Clinical features

AL amyloidosis is a rare condition associated with plasma cell dyscrasias that has an annual incidence of approximately 1 per 100,000 people in the United States[15].

Patients with AL amyloidosis typically present at age ≥40 years. Systemic AL amyloidosis is a multisystem disorder which commonly affects the liver, kidneys, spleen, the autonomic and peripheral nervous systems, lungs, and heart. Cardiac amyloid infiltration is present in most patients with AL amyloidosis (50 to 70 percent) and it is the main determinant of prognosis[16,17].

Cardiac amyloidosis typically presents with symptoms and signs such as dyspnea, lower extremity edema, elevated jugular venous pressure, hepatic congestion, and ascites, which are caused by restrictive cardiomyopathy with predominantly right ventricular failure; symptoms and signs of low cardiac output (eg, diminished pulse pressure and diminished capillary refill) are features of advanced disease. Angina is uncommon, although microvascular dysfunction is a frequent finding. Amyloidogenic light chains may be toxic to myocardial cells as suggested by in vitro studies[18,19] as well

as clinical observation of worse symptoms in patients with AL amyloidosis compared with patients with ATTR amyloidosis with similar degrees of cardiac involvement.

Patients with cardiac amyloidosis also frequently present with syncope or presyncope[20]. Syncope is frequently caused by bradyarrhythmias or advanced atrioventricular block and is infrequently caused by ventricular arrhythmia.

Other conditions may contribute to the risk of syncope in patients with amyloid cardiomyopathy including postural or exertional hypotension caused by excessive diuresis or autonomic neuropathy.

Patients with AL amyloidosis or atrial fibrillation, are at risk for cardiac thromboembolism. Amyloid deposits in atrial as well as ventricular walls and thus causes atrial dysfunction including atrial electromechanical dissociation during sinus rhythm with associated risk of atrial thrombus formation[21-23].

ATTR amyloid cardiomyopathy (ATTR-CM)

Clinical features

The spectrum of clinical presentations in patients with ATTR amyloidosis obliges all clinicians to be aware of common disease patterns, additional clues, and commonly affected populations.

Patients with ATTR-CM typically present at age ≥60 years, and most commonly >70 years. Various transthyretin mutations are associated with differing ages of onset (ranging from 30 to 70 years) and differing risks of cardiomyopathy. Cardiac amyloidosis is the dominant feature of wild-type ATTR amyloidosis (ATTRwt amyloidosis) and for some ATTR variants (eg, Val122Ile, Thr60Ala, Ile58Leu, and Leu111Met)[15,24-26].

Suspicion of ATTR-CM should be triggered in older persons who have been hospitalized for HF, elevated troponin levels, or levels of NT-proBNP (N-terminal pro-brain natriuretic peptide) that are out of proportion to the clinical context. Other hints of ATTR-CM include hypertension that resolves over time and an intolerance of ACE (angiotensin-converting enzyme) inhibitors, angiotensin receptor blockers, or β blockers. In addition, though not infrequent in the general population, carpal tunnel syndrome occurs particularly frequently among males with ATTR-CM[27]. Lumbar spinal stenosis[28,29], previous orthopedic procedures[30], and spontaneous biceps tendon rupture[31] may also be early indicators

of ATTR-CM.

Patients with ATTR amyloidosis (wild-type or hereditary) often develop progressive conduction system disease and pacemaker implantation is often required. In contrast, patients with AL amyloidosis infrequently develop high-degree atrioventricular block or symptomatic sinus node dysfunction[26].

Patients who develop ATTRwt amyloidosis and aortic stenosis have similar demographic features, and some patients have both cardiac ATTRwt amyloidosis and aortic stenosis[18-20, 32]. Cardiac ATTR amyloidosis has been identified in a substantial minority of patients with severe aortic stenosis undergoing surgical valve replacement (6 to 12 percent[33,34]) or transcatheter aortic valve implantation (TAVI; 16 percent[35]). It has been postulated that ATTR amyloidosis with associated restrictive cardiomyopathy may be a contributing cause of low-flow, low-gradient aortic stenosis[32].

A study carried out by Westin O et al reported that screening for amyloid cardiomyopathy in patients with prior surgery for bilateral carpal tunnel syndrome finds approximately 5% with early-stage ATTR cardiomyopathy[36].

Diagnosis

The following chart depicts some clinical, imaging and electrocardiographic clues in which cardiac amyloidosis should be suspected:

Chart 1. Diagnostic Clues to ATTR-CM

Clinical, Imaging and Electrocardiographic Clues:

- Past familial history of cardiomyopathy with left ventricle hypertrophy and/or sudden cardiac arrest.
- Patients with unexplained left ventricle hypertrophy with or without heart failure.
- Patients with left ventricle hypertrophy and or right ventricle hypertrophy on echocardiogram and low QRS voltage or no signs of left/right ventricle hypertrophy on ECG with or without HF.
- Heart failure with preserved ejection fraction (HFpEF), particularly in men.
- Evidence of right-sided heart failure (eg, hepatomegaly, ascites, and lower extremity edema)
- Patients with presyncope, syncope, angina, or no cardiac symptoms with unexplained left ventricle hypertrophy

- Bilateral carpal tunnel syndrome
- Intolerance to ACEs inhibitors, ARBs or beta blocker
- Lumbar spinal stenosis
- Biceps tendon rupture
- Patients with left ventricle hypertrophy on echocardiogram, granular sparkling pattern of the myocardium and apical sparing pattern on 2D strain rate.
- Unexplained peripheral neuropathy (eg, loss of warm/cold discrimination), particularly if associated with autonomic dysfunction (eg, postural hypotension, alternating bowel pattern)
- Unexplained atrial arrhythmias or conduction system disease/need for a pacemaker
- Patients with aortic stenosis with features associated with cardiac amyloidosis, such as presence of low-flow, low-gradient aortic stenosis and/or echocardiographic detection of impaired longitudinal strain (eg, mitral annular S' ≤6 cm/s)

The initial diagnostic evaluation of the patient with suspected cardiac amyloidosis includes a clinical examination to identify and assess cardiac and extracardiac symptoms and signs, laboratory tests, and an electrocardiogram, as described above.

An ECG and echocardiogram are the initial cardiac tests for patients with suspected cardiac amyloidosis.

ECG findings

A hallmark of cardiac amyloidosis is discordance between increased left ventricular wall thickness (identified by cardiac imaging such as echocardiography) and QRS voltage, which is often reduced. However, this feature of cardiac amyloidosis has low sensitivity and the prevalence of low voltage varies markedly with etiology, with higher frequency in patients with AL-CM (60 percent) than in patients with ATTR-CM (20 percent)[23,37]. Thus, the absence of low QRS voltage does not exclude cardiac amyloidosis, particularly in patients with ATTRwt amyloidosis.

Among patients with ATTRwt amyloidosis, 30 percent have voltage criteria for LV hypertrophy or left bundle branch block, and 70 percent have pseudo-infarction patterns; conduction abnormalities affecting the sinus node and His-Purkinje systems are also common. Thus, the presence of atrioventricular block in an older patient with left ventricle hypertrophy should prompt consideration

of cardiac amyloidosis[38].

Because the thickening of the ventricle in amyloidosis is due to myocardial infiltration rather than cardiomyocyte hypertrophy, the ECG limb lead voltage tends to decrease as the ventricle thickens and is often associated with extreme left axis or right-axis deviation. However, only ~50% of patients with AL-CM and about 25%-40% of patients with ATTR-CM meet true low-voltage criteria (that is, QRS amplitude <5 mm in limb leads or <10 mm in precordial leads[23]). Hence, the absence of low-voltage criteria does not exclude the diagnosis of cardiac amyloidosis.

Other common features present in the ECGs of patients with cardiac amyloidosis include left anterior hemiblock, ischaemic or nonspecific T wave abnormalities, and rhythm disturbances, particularly atrial fibrillation, which has been reported in up to 70% of patients with ATTRwt amyloidsis[57]. Ventricular arrhythmias are also common, although the first clinically apparent evidence of an abnormal ventricular rhythm might be ventricular tachycardia or fibrillation in the setting of a non-resuscitable cardiac arrest.

Figures 1A and 2A show two ECGs of patients with diagnosis AL and ATTRwt cardiomyopathies and the typical ECG findings.

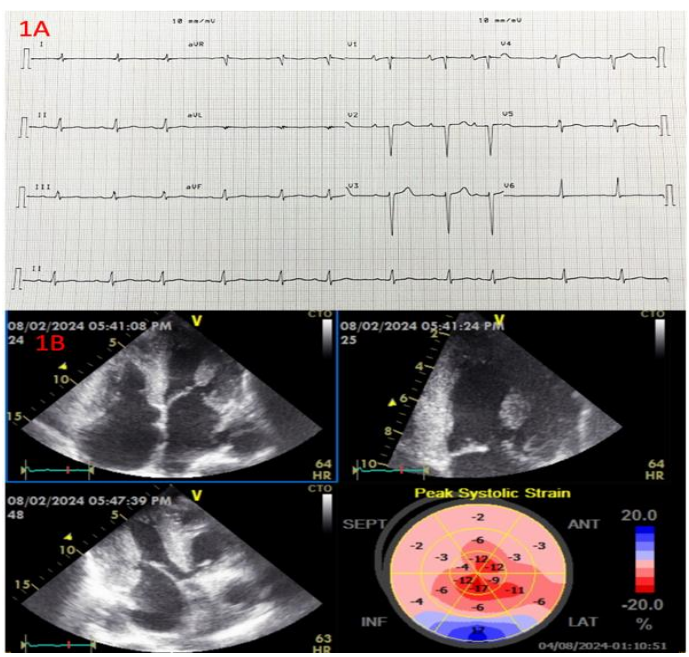
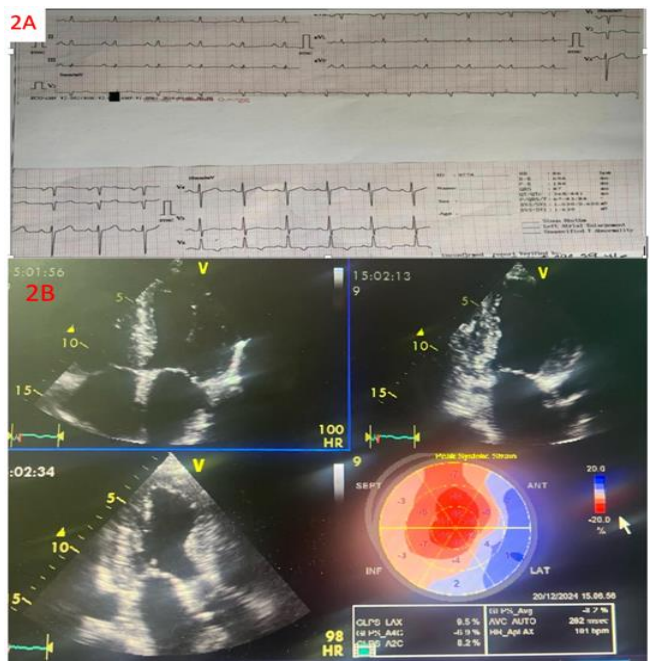


Figure 1A. ECG performed to a 65-year-old patient with multiple myeloma and AL amyloid cardiomyopathy showing sinus rhythm with first degree atrioventricular block, low QRS voltage in

most of limb leads (except lead II), and pseudo anterior infarction pattern with poor R wave progression in precordial leads. 1B. Echocardiographic apical 4 chambers, apical three chambers, apical 2 chambers views with the 2D GLS Bull's eye display depicting left and right ventricular hypertrophy with granular sparkling pattern, biatrial enlargement, small ventricular cavities and thickening of the interatrial septum, very reduced GLS (-4.3%) and the typical relative apical sparing pattern on 2d GLS strain Bull's eye display.



Figures 2A. ECG performed to a 59-year-old patient male with monoclonal gammopathy of unknown significance (MGUS) and ATTRwt amyloid cardiomyopathy what depicts sinus rhythm, low QRS voltage in the horizontal plane, pseudo-infarction pattern in precordial leads with non-specific T wave abnormalities in I-aVL and inferior leads and T wave inversion in V6 lead, left atrial enlargement signs and poor R wave progression in precordial leads. 2B. Echocardiographic apical 4 chambers, apical three chambers, apical 2 chambers views with the 2D GLS Bull's eye display depicting idem findings like figure 1B.

Echocardiogram

Echocardiography is cost-effective, readily available, bedside to perform, and an excellent tool to identify systo-diastolic dysfunction. Although not always present, classic echocardiography findings of infiltrative disease include left ventricle wall thickening, small left ventricle cavity size, biatrial enlargement, thickened valves, elevated right ventricular systolic pressure and atrial septum thickness, granular sparkling appearance of the myocardial wall, pericardial effusion, restrictive transmitral Doppler filling pattern, and reduced ventricular strain, apical-to-basal strain ratio >2.1, left ventricle ejection fraction-to-strain ratio >4[39-41]. (Table 1; Figure 1B and 2B).

The pulmonary artery systolic pressure, as estimated from the peak velocity of the tricuspid valve regurgitant jet, may indicate moderate pulmonary hypertension (estimated pulmonary artery pressure of 40 to 50 mmHg). This is almost invariably secondary to the markedly elevated left ventricle diastolic pressure and does not indicate primary pulmonary hypertension or cor pulmonale. Pericardial and pleural effusions are common findings, especially in AL-CM.

Reduction in global longitudinal strain (a measure of systolic function) is one of the earliest markers of cardiac amyloidosis and presents with a characteristic pattern of relative apical sparing of longitudinal strain (ie, the ratio of apical longitudinal strain/average of mid and basal longitudinal strain >1.0)[41]. This pattern of longitudinal strain alteration has high sensitivity (93 percent) and specificity (82 percent) for cardiac amyloidosis with proven utility in differentiating cardiac amyloidosis from other hypertrophic phenocopies[41,42].

Cardiovascular magnetic resonance (CMR)

CMR is a key test in the diagnosis of cardiac amyloidosis and is generally performed with contrast[43]. CMR provides a detailed assessment of cardiac structure (including identification and quantification of left ventricle hypertrophy) and function as well as unique information on the characteristics of the myocardial tissue. CMR can detect early cardiac amyloidosis before the development of left ventricle hypertrophy. However, CMR cannot distinguish cardiac AL from ATTR cardiac amyloidosis[44,45].

Cardiac amyloidosis has a highly characteristic appearance on CMR imaging performed with late gadolinium enhancement (LGE): Initially, there may be diffuse subendocardial LGE, while later in the course of disease, there is a transmural myocardial LGE pattern[46]. The three progressive LGE patterns

identified in cardiac amyloidosis (none, subendocardial, and transmural) correlate with the degree of myocardial infiltration[47]. In a systematic review of studies comparing LGE with endomyocardial biopsy and/or echocardiography and other clinical features, the pooled sensitivity of LGE for cardiac amyloidosis was 85 percent (95% CI 77-91 percent) and the pooled specificity was 92 percent (95% CI 83-97 percent)[48].

Limitations of LGE include lack of quantitative results (which limits the ability to track changes over time) and limited applicability since gadolinium-based contrast agents are relatively contraindicated in patients with a severe reduction in renal function (which is relatively common in patients with AL-CM).

T1 mapping can overcome some of the limitations of LGE but center-specific reference ranges are required for early disease detection[49]. T1 mapping provides quantitative measures of myocardial T1 relaxation time (precontrast [native] or postcontrast). Native myocardial T1 increases with cardiac amyloid infiltration and correlated with markers of systolic and diastolic dysfunction[50].

Native myocardial T1 elevation is an early disease marker with high diagnostic accuracy for cardiac amyloidosis when the pretest probability is high[51]. In a study of 868 patients with suspected cardiac amyloidosis (222 with cardiac AL-CM, 214 patients with cardiac ATTR-CM, and 427 with no cardiac involvement), T1 mapping diagnosed cardiac amyloidosis with a sensitivity of 85 percent and specificity of 87 percent[52]. T1 mapping may be particularly helpful in patients with severely impaired kidney function, in whom gadolinium contrast is contraindicated. However, native T1 is a composite myocardial signal from both interstitium and myocytes that does not distinguish among the underlying processes (fibrosis, edema, amyloid, myocyte volume) and while the T1 elevation is marked with advanced disease, the lower elevations in early disease can be accurately identified only by referencing the center-specific normal range.

Extracellular volume (ECV) fraction measurement using intravenous gadolinium-based contrast agent is an ancillary method for identification and assessment of cardiac amyloidosis that helps to quantify the amount of cardiac amyloid. ECV elevation may be detected early before the development of left ventricle hypertrophy, LGE or elevation in serum biomarkers[53]. ECV elevation correlates with markers of disease activity, including cardiac function, serum biomarkers, patient functional performance[54], and prognosis[42, 55]. Native T2 mapping is another technique that may be helpful; T2 elevations demonstrate that edema is part of cardiac amyloidosis (particularly AL-CM) and is linked to prognosis[56].

Bone tracer cardiac scintigraphy

Bone tracer cardiac scintigraphy (using 99m technetium [Tc]-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], 99mTc-labeled pyrophosphate [PYP], or 99mTc-labeled hydroxymethylene diphosphonate [HMDP]) is an essential test for identifying ATTR amyloidosis.

The intensity of retention of bone-avid radiotracers in the heart can be interpreted by semi-quantitative visual analysis, by grading myocardial uptake to rib uptake on planar or single-photon emission computerized tomography (SPECT) imaging, and by quantifying radiotracer uptake using a heart-to-contralateral lung (H/CL) ratio[58]. The current diagnostic criteria for patients with ATTR-CM include visual myocardial uptake equal or greater than that in bone (specifically in the ribs) or a H/CL ratio ≥1.5[59]. An H/CL ratio of ≥1.6 is associated with poor survival[60].

Perugini et al classified cardiac amyloid uptake based on a simple visual scoring system of the delayed (3 h) planar image, in which grade of 0 means no cardiac uptake, a grade of 1 means mild cardiac uptake (less than in bone), a grade of 2 means cardiac uptake greater than bone (but uptake in bone remains clearly visible) and a grade of 3 is indicative of substantial cardiac uptake with a weak or no signal evident in bone[61]. Figure 3.

A subsequent multicenter study showed that ATTR-CM is particularly avid for bone tracers (the mechanism is not understood); in contrast, in cardiac AL amyloidosis, there is either absent or only grade 1 uptake (grade 1 being present in approximately 40 percent of patients)[35]. As illustrated by a systematic review, the presence of grade 1, 2, or 3 scintigraphy had high sensitivity (pooled value of 82 percent) and specificity (98.8 percent) for cardiac amyloidosis as compared with tissue biopsy in studies evaluating the diagnostic performance of scintigraphy for cardiac amyloidosis[44]. Presence of grade 2 or 3 positive bone tracer cardiac scintigraphy in a patient without monoclonal protein (ie, free light chain ratio is normal and serum and urine immunofixation results are both normal) is highly specific for ATTR-CM and thus sufficient for diagnosis of this condition without tissue biopsy[35].

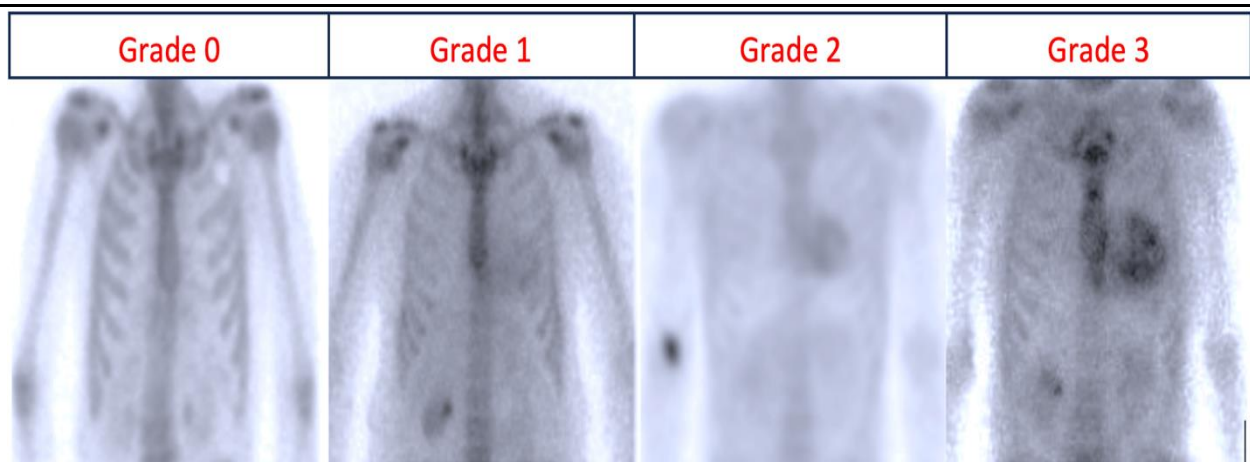


Figure 3. 99mTc-DPD scintigraphy and Perugini visual scoring of cardiac uptake: Grade 0 represents no cardiac uptake, grade 1 represents mild cardiac uptake (less than that in bone), grade 2 represents cardiac uptake greater than that in bone (but bone uptake still remains visible), and grade 3 represents substantial cardiac uptake with only a weak or no signal evident in bone.

Positron emission tomography

Positron emission tomography (PET) is emerging as a useful diagnostic tool for cardiac amyloidosis. Several PET tracers such as ^{18}F-florbetapir, ^{18}F-florbetaben, ^{18}F-flutemetamol and ^{11}C-Pittsburgh B (C-PiB) have been used successfully to diagnose cardiac amyloidosis[62]. These tracers have been shown to bind specifically to brain β-amyloid plaques, allowing diagnosis and follow-up of patients with Alzheimer's disease[63]. These tracers likely bind to the β-pleated structure of amyloid fibril, which facilitates the identification of amyloid deposits independently of the precursor protein.

PET tracers are quantitative tools, permitting the measurement of amyloid burden. Small studies have demonstrated that ^{18}F-florbetapir is taken up in the heart of patients with cardiac amyloidosis, with a trend towards a higher myocardial retention index in patients with AL-CM versus those ATTR-CM, and no significant uptake in the healthy controls[64, 65]. Similar findings have been observed with ^{11}C-PiB[66, 67] and ^{18}F-florbetaben[68]. In another small study ^{18}F-florbetaben was evaluated in patients with AL-CM (n = 5) or ATTR-CM (n = 5) and compared with control patients with hypertension (n = 4).

Myocardial retention was higher in patients with AL-CM and ATTRCM compared with controls, and

myocardial retention inversely correlated with LV global and RV free wall longitudinal strain[68]. However, an onsite cyclotron is required for the production of ^{11}C tracers, given their short half-life of 20 mins. The longer half-life of ^{18}F tracers (110 min) means that it can be distributed and used for research and clinical applications at sites without a cyclotron, making its use more practical compared with ^{11}C-PiB tracers.

Dietemann et al. showed that $1^{8}F$-flutemetamol target to background ratio (TBR) was significantly higher in amyloid subjects compared with control subjects[69]. They suggested that ^{18}F-flutemetamol could be a promising tool in diagnosing and in therapy response assessment for patients with CA[69].

Also, ^{18}F-florbetaben is feasible for diagnosis of CA and might be useful in differentiating CA subtypes[70]. Kircher et al. showed that using semi-quantitative analysis, tracer retention was highest in patients suffering from AL, followed by patients with AA and ATTR, respectively[70].

Monoclonal protein

Identification of monoclonal protein (by serum protein immunofixation, urine protein immunofixation, or serum free light chain ratio analysis) along with echocardiographic or CMR findings consistent with cardiac amyloidosis is suggestive of AL amyloidosis but may also be caused by ATTR amyloidosis (or a rarer cause of cardiac amyloidosis) with an unrelated monoclonal gammopathy of undetermined significance (MGUS)[71].

The M protein in AL amyloidosis is IgG in approximately 35 percent, IgA in 10 percent, IgM in 5 percent, IgD in 1 percent, and light chain (lambda or kappa) in the remaining patients[72]. Most patients with AL amyloidosis have little or no intact monoclonal immunoglobulin, but are characterized by the presence of monoclonal free light chain. The monoclonal light chain type is lambda in approximately 70 percent of cases, kappa in 25 percent, and biclonal in 5 percent[73].

Tissue biopsy

Tissue biopsy is not required when other findings are diagnostic for the presence and type of cardiac amyloidosis. As described above, the presence of grade 2 or 3 positive bone tracer cardiac scintigraphy

in the absence of monoclonal protein is diagnostic for cardiac ATTR-CM, and thus no tissue biopsy is required. The presence of CMR findings consistent with cardiac amyloidosis in a patient with previously confirmed systemic AL amyloidosis is diagnostic for AL-CM, so endomyocardial biopsy is not indicated.

Endomyocardial biopsy is invasive, carries a small risk for serious complications, and requires technical expertise, whereas fat pad biopsy is less invasive and poses little risk but has varying sensitivity in ATTR-CM (with roughly 45% sensitivity for ATTRv and roughly 15% sensitivity for ATTRwt).[74] Given the high false-negative rate from biopsies of nonclinically involved sites (eg, fat pad, bone marrow), further evaluation is warranted even in the presence of a negative biopsy from such sites if clinical suspicion remains elevated. In such cases, biopsy of a clinically affected organ (eg, endomyocardial biopsy) is imperative. Endomyocardial biopsy assessment with Congo red staining has ≈100% specificity and sensitivity for detecting amyloid deposits and is still considered the gold standard in situations with equivocal noninvasive findings.[75]

Diagnostic characteristics of extracellular amyloid deposits include typical apple-green birefringence with Congo red dye under polarized light microscopy and unique cross–β-pleated sheets under electron microscopy. The fibrils also bind thioflavine T (producing an intense yellow-green fluorescence), and sulfated Alcian blue (producing a green color). The type of amyloid fibril may be identified using immunohistochemistry, immunofluorescence or immunoelectron microscopy but laser microdissection with mass spectrometry is considered the gold standard for identifying the precursor protein and amyloidosis type.[76]

Genetic sequencing of the TTR gene

In the context of ATTR-CM is identified, then genetic sequencing of the TTR gene will determine if the patient has a pathological variant (ATTRv) or wild-type (ATTRwt) disease[77].

Differentiating ATTRv from ATTRwt is important because confirmation of ATTRv would trigger genetic counseling and potential screening of family members and some presently approved therapies like inotersen and patisiran can be used only for ATTRv with polyneuropathy[78, 79].

ATTRv is considered rare and is transmitted in an autosomal dominant manner and with variable penetrance. Certain variants typically result in cardiomyopathy, whereas others typically result in polyneuropathy, although cardiomyopathy and polyneuropathy manifestations may overlap. The prevalence of cardiomyopathy among persons with ATTRv is estimated at approximately 40 000 of the 50 000 persons with ATTRv globally[80], but this may be an underestimate.

The most common worldwide TTR variant, Val122Ile (or pV142I), occurs in approximately 3% to 4% of black Americans, with undefined phenotypic penetrance[81, 82]. This Val122Ile TTR variant manifests predominantly as cardiomyopathy,[83] and one estimatation shows 10% of black Americans with HF who are older than 60 are carriers of the Val122Ile TTR variant[84]. Thr60Ala, another common TTR variant, often manifests as a mixed phenotype, including cardiomyopathy, polyneuropathy, and gastrointestinal dysfunction and is present in approximately 1% of persons in northwest Ireland[85]. The Val30Met variant is the most common cause of ATTRv with polyneuropathy; however, late-onset ATTRv in patients of the Val30Met variant typically manifests as cardiomyopathy. Phenotypic penetrance of ATTRv is clearly age dependent; thus, ascertainment of population prevalence varies depending on age.

Laboratory tests

Laboratory test abnormalities in patients with cardiac amyloidosis include proteinuria which may or may not be accompanied by elevations of serum BUN and creatinine in patients with kidney disease and liver biochemical abnormalities (eg, elevation in serum bilirubin) in patients with congestive hepatopathy.

Natriuretic peptides and troponin T and I levels are commonly elevated in patients with cardiac amyloidosis[21,22].

During the clinical assessment, the combination of very high plasma levels of NT-proBNP (disproportionate compared with the degree of HF) and elevated troponin levels in a patient with echocardiographic hypertrophic phenotype is strongly suggestive of amyloid cardiomyopathy and can prompt the diagnostic workup. NT-proBNP is a biomarker that is elevated early in ATTRv amyloidosis before cardiac symptoms appear, especially among asymptomatic carriers of a TTR gene mutation or patients with neurological symptoms only[86]. In addition, the usefulness of circulating retinol binding

protein 4 in conjunction with electrocardiographic and echocardiographic measures to identify patients with HF who have ATTR-CM from the Val122Ile mutation has recently been reported[87].

Staging

The Revised Mayo Stage system is the most acceptable use to staging AL amyloid cardiomyopathy and it is based on serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T, and free light chains[88]. The scoring system assigns 1 point for NT-pro-BNP ≥1800 pg/mL, troponin T ≥0.025 ng/mL, and difference between the kappa and lambda free light chains ≥18 mg/dL. Median survival for stage III patients was 14 months and for stage IV patients was 5.8 months[88]. Within stage III, NT-proBNP >8500 pg/mL combined with a systolic blood pressure <100 mmHg identifies a group of patients with the highest mortality (IIIb). Chart 2.

Chart 2. Prognostic staging systems for AL amyloidosis.

Prognosis Model	Risk Groups		Survival in patients not undergoing stem cell transplantation		Survival in patients undergoing stem cell transplantation	
			Average in Months	5-year Survival rate in (%)	Average in Months	4-year Survival rate (%)
Revised Mayo Stage System	Stage I	NT-pro BNP <1800 ng/L, cardiac troponin T<0.025 mcg/L, and difference between involved and uninvolved serum free light chains <18 mg/dL	55	50	Not reached	87
	Stage II	Presence of an elevated marker	19	35	97	72
	Stage III	Presence of two elevated markers	12	20	58	56
	Stage IV	NT-pro BNP ≥1800 ng/L, cardiac troponin T ≥0.025 mcg/L, and difference between involved and uninvolved serum free light chains ≥18 mg/dL	5	15	22	46

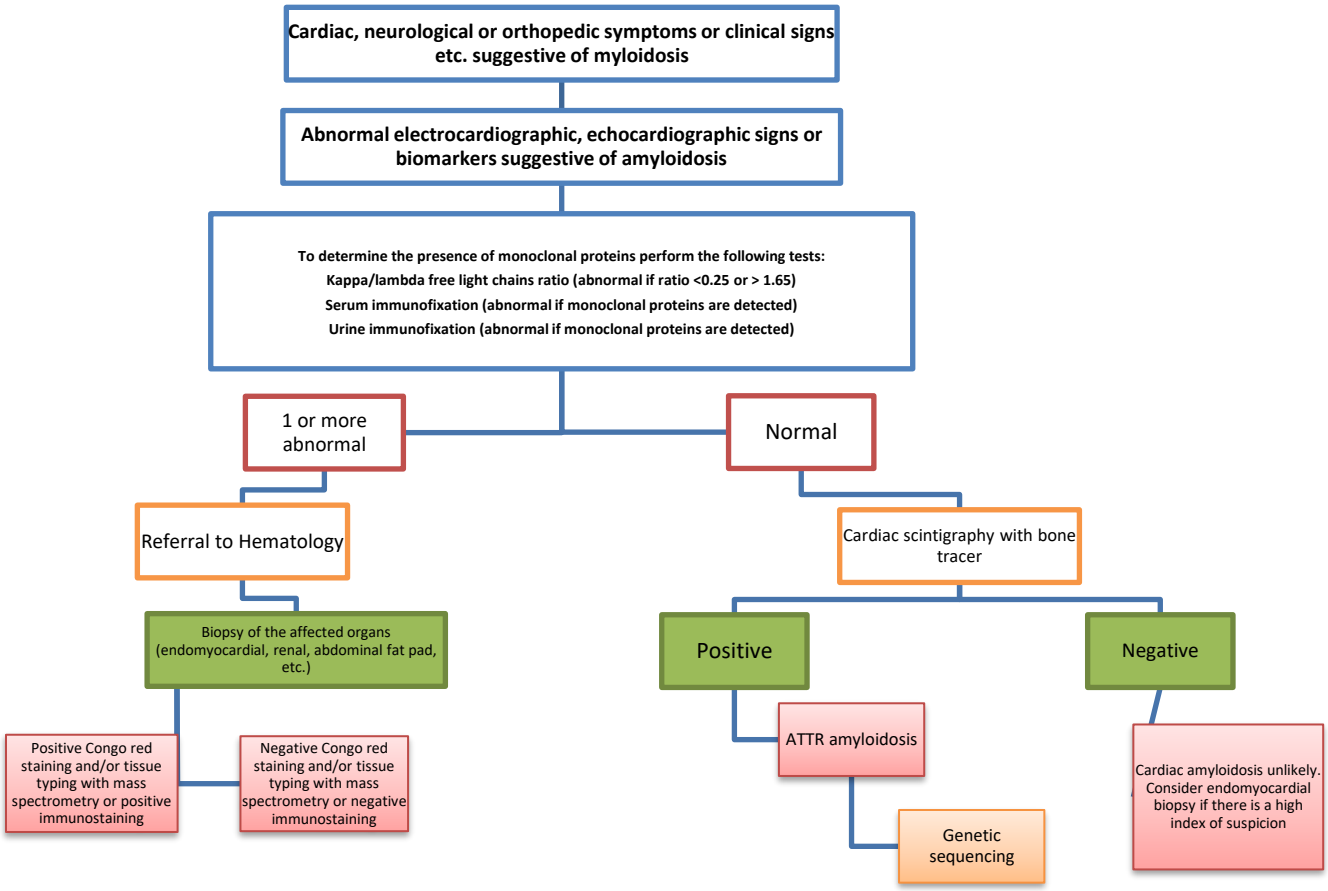
ATTR amyloidosis

Two staging systems have been proposed in patients with ATTR amyloidosis:

The first published staging system for ATTRwt is based on serum levels of NT-proBNP and cardiac troponin T[89]. Thresholds of troponin T (0.05 ng/ml) and NT-proBNP (3000 pg/ml) were used. The respective four-year overall survival estimates were 57, 42, and 18 percent for stage I (both values below cutoff), stage II (one above), and stage III (both above), respectively.

The second staging system, validated in both ATTRwt and ATTRv, is based on serum levels of NT-proBNP and estimated glomerular filtration rate (eGFR)[21]. Stage I is defined as NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min, Stage III is defined as NT-proBNP >3000 ng/L and eGFR <45 mL/min, and the remainder were Stage II. Median survival among Stage I patients was 69.2 months, Stage II patients 46.7 months, and Stage III patients 24.1 months[21].

Diagnostic algorithm for cardiac amyloidosis



Treatment

General perspective

Heart failure in patients with cardiac amyloidosis is secondary to complex pathophysiologic alterations. The pathologic changes that result from extensive amyloid infiltration result in a nondilated normal to small biventricular cavity size, with significant diastolic dysfunction because of decreased compliance. Systolic dysfunction is almost invariably present, and this usually affects first the longitudinal contraction (better assessed with longitudinal strain) and, in later stages, the radial contraction (reduced ejection fraction). In addition, the infiltration of the atria may severely impair atrial contraction, further decreasing ventricular filling. This combination results in a decreased stroke volume and cardiac output and marked elevation of intracardiac pressures with frequent occurrence of functional mitral and tricuspid regurgitation. In addition, there is experimental evidence that excessive circulating free light chains in AL amyloidosis are cardiotoxic, possibly explaining the worse prognosis in cardiac AL amyloidosis compared with ATTR

The management of symptomatic cardiac amyloidosis can be divided into two scopes:

1.Treatment for the heart failure syndrome (medical therapy, device assisted therapy, heart transplantation)

2. Treatment of associated conditions to heart failure (atrial fibrillation, anticoagulation and conduction system disease, ventricular arrhythmia and sudden cardiac arrest prevention)

3. Treatment for the underlying disease (AL, ATTRwt or ATTRv amyloidosis)

Medical therapy for heart failure:

Loop diuretics

Loop diuretics are a mainstay of the management of heart failure. If edema is severe, hospitalization and a course of intravenous diuretics should be strongly considered. This should be accompanied by careful monitoring of blood pressure and renal function, as overvigorous diuresis may result in progressive azotemia. Aldosterone antagonist therapy like spironolactone, in conjunction with loop diuretics is generally tolerated without the development of excessive hypotension.

Beta blockers

Although this group of medications reduce morbidity and mortality in patients with systolic dysfunction HF generally, they have no proven benefit in patients with heart failure due to cardiac amyloidosis. Indeed, they are poorly tolerated in patients with cardiac amyloidosis in whom cardiac output is dependent on heart rate due to presence of a low, fixed stroke volume.

Angiotensin converter enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs)

The safety and efficacy of ACE inhibitors or angiotensin receptor blockers (ARBs) in patients with cardiac amyloidosis is uncertain. There are no clinical trials of ACE inhibitors or ARBs in amyloidosis, but clinical experience has shown that these agents often provoke profound hypotension in AL amyloidosis, possibly by exposing a subclinical autonomic neuropathy. ACE inhibitors and ARBs appear to be better tolerated in patients with ATTRwt amyloidosis, in whom autonomic neuropathy is rare. Tolerability of ACE inhibitors and ARBs in ATTR cardiomyopathy due to a mutant protein depends on the presence or absence of concomitant autonomic dysfunction. If a trial of ACE inhibition is attempted in a patient with AL amyloidosis, initiation should be with a very low dose of captopril with careful blood pressure monitoring and slow, carefully monitored up-titration of the dose if tolerated.

Digoxin

Amyloid fibrils bind to digoxin and this interaction may account for increased susceptibility to digitalis toxicity[90]. Although digoxin has no role in treating heart failure due to amyloid cardiomyopathy, careful use of digoxin may be of value in a patient with atrial fibrillation and a rapid ventricular response, particularly when hypotension makes beta blocker use untenable[91].

Calcium channel blockers (CCB)

Calcium channel blockers such as verapamil or diltiazem that are used to slow heart rate and that may possibly improve ventricular relaxation in diastolic HF (eg, in hypertensive heart disease or hypertrophic cardiomyopathy) have not been proven to be effective in cardiac amyloidosis, and this is

probably related to the different mechanism leading to diastolic dysfunction, as the diastolic dysfunction is due to the amyloid and not to myocardial cellular dysfunction. Indeed, these drugs are contraindicated, as their negative inotropic effects may be profound, possibly because of an abnormal binding to amyloid fibrils, and may depress compensatory heart rate responses to low stroke volume and cardiac output[90,92,93].

SGLT2 inhibitors

In a study of 220 patients with ATTR cardiac amyloidosis treated with SGLT2 inhibitors and 220 propensity-matched controls, SGLT2 inhibitor treatment was associated with less worsening of NYHA functional class, N-terminal pro-B-type natriuretic peptide, and estimated glomerular filtration rate as well as fewer new initiations of loop diuretic agent therapy [30]. After 28 months, SGLT2 inhibitor therapy was associated with a lower rate of all-cause mortality (HR 0.57, 95% CI 0.37-0.89) and a lower rate of hospitalization for HF (HR 0.57, 95% CI 0.36-0.91). Due to the retrospective nature of the trial, these results are hypothesis-generating[156].

ARNI (Sacubitril/Valsartan)

Martin Negreira-Caamaño et al[157] conducted a prospective observational study including consecutive patients referred to the Cardiomyopathy Unit between 2018 and 2021 with ACTTR-CM and impaired ejection fraction (LVEF <50%). ACTTR-CM was diagnosed using current recommendations. ARNI was started at a dose of 12/13 mg twice daily and titrated to maximum tolerated dose in all cases. Laboratory and clinical examinations were carried out before starting ARNI and at one, three and six months, as per the Unit's protocol.

ARNI was promptly started in most patients (4/6 within six months of ATTR-CM diagnosis). Maximum dose was not achieved in any case, but medium dose (49/51 mg twice daily) was tolerated in three out of six patients. Therapy onset was generally well tolerated. One patient needed a temporary withdrawal for one week due to symptoms of hypotension. Blood pressure measurements showed no clinically significant hypotension and renal function remained similar in all cases (estimated glomerular filtration rate improved in 50% of patients). Moderate hyperkalemia was observed in one case but was

successfully controlled with dietary recommendations and medical therapy. No hospitalizations due to acute HF were observed within six months of starting ARNI.

The main result of this research was that, when carefully titrated, ARNI was well tolerated, with only mild deleterious effects on blood pressure or renal function. It was also observed a general improvement in clinical status after ARNI onset as assessed by NYHA class, relief of edema, weight loss and decreased natriuretic peptides. Despite this isolated investigation and some expert criteria in individual cases, more evidence is necessary for a proper recommendation of this therapy.

Device assisted therapy

Cardiac resynchronization therapy (CRT)

CRT is highly effective in dilated cardiomyopathy patients with impaired left ventricle ejection fraction and left bundle branch block. In cardiac amyloidosis patients, left ventricular dysfunction and conduction disorders are common but the potential benefit of CRT in this particular setting is unknown.

A multicentre retrospective study carried out by Fischer et al in cardiac amyloidosis patients implanted with a CRT device, the one-year echocardiographic response was not significantly associated with a reduction of major adverse cardiac events (MACE) at long-term follow up. Thus, the benefit of CRT in cardiac amyloidosis patients appears uncertain[94].

Donnellan et al also evaluated the efficacy of CRT in ATTR-CM and the impact of CRT on survival. Their main findings were: (1) CRT is associated with improved survival among patients with ATTR-CM; and (2) CRT is associated with improvements in heart failure symptoms and left ventricle ejection fraction (LVEF) in ATTR-CM[95].

There is no strong unified or standardized evidence that CRT can be widely implemented in patients with amyloid cardiomyopathy and HFrEF, however, this therapy might be beneficial in specific cases.

Cardiac contractility modulation therapy (CCM)

Cardiac contractility modulation (CCM) signals are biphasic relatively high-voltage signals (7.5V/22ms duration) delivered to the right ventricular septum during the absolute refractory period[96,97].

Clinically, CCM is currently suggested for consideration by the European Society of Cardiology guidelines in patients with symptomatic heart failure on optimal medical therapy and with normal or mildly prolonged QRS duration and reduced EF[98].

CCM has been shown to improve quality of life [Minnesota Living with Heart Failure Questionnaire (MLHFQ)], LVEF,[99,100] indexes of diastolic function,[100] New York Heart Association (NYHA) classification, 6 minutes walk test,[101] and peak oxygen consumption during cardiopulmonary stress testing[102,103] in patients with symptomatic heart failure on optimal medical therapy (including ICD when indicated), with QRS duration <130 ms and EF <45%.

To date there are no published studies or trial demonstrating if this therapy is beneficial for patients with amyloid cardiomyopathy, however, a multicentre observational prospective study named Cardiac Contractility Modulation Therapy in Amyloid Cardiomyopathy Patients With Heart Failure; Unique identifier: NCT05167799 is ongoing and the results are expected to be available soon.

Heart transplantation

The great majority of patients with AL-CM have significant noncardiac amyloidosis and are not suitable candidates for heart transplantation. For example, in one series, only 4 percent of patients had clinically isolated cardiac disease[104]. Early experience with cardiac transplantation in AL-CM did not address the importance of a sustained clonal response and, not surprisingly, when the disease relapsed, the disease progressed in other organs and/or returned in the transplanted heart[105,106]. The few major centers that accept patients with AL-CM for cardiac transplantation accept only those who have disease clinically isolated to the heart. Heart transplantation for AL-CM in these centers is followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation within a 12-month period. Long-term follow-up data in these patients are not yet available, but several appear to have had excellent cardiac results and a durable hematologic response[107-111].

Patients with ATTRwt amyloidosis generally have the disease clinically isolated to the heart and as such would appear to be more suitable candidates. However, most patients are diagnosed in their seventh or eighth decade of life and are excluded based on their age. Nevertheless, successful heart transplantation has been carried out in a few patients with ATTRwt amyloidosis who presented at a younger age[112].

Patients with ATTRv cardiac amyloidosis are often younger than ATTRwt patients, and may be candidates for heart transplantation if amyloid neuropathy is absent or mild. However, since the mutant TTR is produced in the liver, most mutations may need a combined liver and heart transplant to prevent recurrence in the transplanted heart. Fourteen patients in a single center in Italy had combined liver-heart transplantation for familial amyloid cardiomyopathy between 1999 and 2012. Actuarial survival at one and five years was 93 and 82 percent, respectively, and the explanted liver was retransplanted into another (nonamyloid) recipient in 8 of 14 cases. No recurrent amyloid was reported in heart-liver recipients[113]. An exception to the requirement of liver transplantation is probably the Val122Ile mutation, common in African-Americans, in which isolated heart transplantation has been performed without documentation of recurrent disease[114].

Ventricular assist devices

Ventricular assist devices have been used very infrequently in cardiac amyloidosis, owing to technical difficulties when used in a restrictive cardiomyopathy as well as the presence of coexisting noncardiac amyloidosis[115].

In Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), patients with amyloid cardiomyopathy who received mechanic circulatory support (MCS) have more frequent biventricular support, and the cumulative incidence of death was higher for these patients than their counterparts with nonamyloid restrictive cardiomyopathy or dilated cardiomyopathy. Furthermore, amyloid cardiomyopathy was also associated with a higher burden of adverse events early after device implantation in comparison to these other cardiomyopathies. These data question the utility of durable MCS for the management of advanced amyloid cardiomyopathy in the present era[116].

Treatment of atrial fibrillation

If atrial fibrillation with a rapid ventricular response develops in a patient with AL-CM or ATTR-CM, low-dose beta blockade and careful digoxin use may help with rate control (notwithstanding the above concerns about beta blocker and digoxin use in amyloid cardiomyopathy generally). Despite severely impaired atrial contractile function, clinical improvement may occur after restoration of sinus rhythm

in a patient with atrial fibrillation of recent onset, possibly due to a regularization of the heart rate. Amiodarone use to maintain sinus rhythm appears to be well tolerated without specific amyloidosis-related side effects. Experience with catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis is limited. Results in 26 patients over two decades indicate symptomatic improvement but without evidence of change in disease-related mortality[117].

Cardioversion

In patients with AL-CM or ATTR-CM who require cardioversion for symptomatic management, TEE prior to cardioversion is recommended rather than no TEE prior to cardioversion. This recommendation applies regardless of the duration of anticoagulation prior to cardioversion and regardless of the duration of atrial fibrillation or flutter prior to cardioversion. This approach is consistent with professional guidelines[158].

Anticoagulation

Amyloid cardiomyopathy is associated with high risk of intracardiac thrombus, predominantly in the atria[118].

Anticoagulation is indicated if a patient with amyloid develops atrial fibrillation, since the risk of intracardiac thrombus is very high. The role of anticoagulation in patients in sinus rhythm is uncertain. Atrial failure, even in the presence of sinus rhythm, is very common in amyloidosis and is associated with atrial thrombus formation, particularly in patients with AL-CM[119-120].

Although amyloidosis is associated with increased hemorrhagic risk due to amyloid angiopathy, intestinal or bladder amyloid, or coagulopathy, major bleeding in anticoagulated patients does not seem to exceed that seen in other patients with similar nonamyloid degrees of illness, so anticoagulation should not be withheld if indicated unless a clear-cut contraindication exists. There are no controlled data on bleeding risk of oral anticoagulants in cardiac amyloidosis, but bleeding has not been found to be excessive, and warfarin or one of the newer oral anticoagulants have been used (oral direct thrombin inhibitor or direct factor Xa inhibitor) without unanticipated problems.

Intracardiac thrombosis occurs in approximately one- third of patients with cardiac amyloidosis, in some cases in the absence of diagnosed AF[121-123] and regardless of CHA2DS2-VASc score[124]. The use of anticoagulation reduced the risk of intracardiac thrombi in a retrospective study[121]. The choice of direct oral anticoagulants (DOAC) versus warfarin has not been studied in patients with ATTR-CM, nor has the role of left atrial appendage closure devices. The risk of anticoagulation on bleeding risk in patients with ATTR-CM and AF has not been established. However, although patients with AL amyloidosis may have ac- quired hemostatic abnormalities, including coagulation factor deficiencies, hyperfibrinolysis, and platelet dysfunction, ATTR amyloidosis is not associated with hemostatic defects.

Conduction system disease and pacemaker implantation

Despite the high prevalence of conduction disease in cardiac amyloidosis and the predisposition for amyloid to deposit in the atria, sinus node dysfunction in cardiac amyloidosis is not well studied. Most studies investigating conduction system disease in cardiac amyloidosis do not discuss sinus node dysfunction. Available data suggest it is uncommon. In a recent single-institution retrospective study of 369 patients followed over 28 months, sinus node dysfunction occurred in 7% of patients[125]. It was more common in ATTRv-CM than in ATTRwt-CM (8% vs 6%); however, statistical significance was not reached[125].

Atrioventricular conduction disease is common in cardiac amyloidosis. In a single-center retrospective study including 369 patients with ATTR-CM, 9.5% had pacemakers implanted for high-grade atrioventricular block before their diagnosis with cardiac amyloidosis [125]. During a follow-up period of 28 months, a further 11% developed a pacemaker requirement for high-grade atrioventricular block[125]. First-degree atrioventricular block was very common in this population, occurring in 49% of those with ATTRwt-CM and 43% with ATTRv-CM[125]. No significant differences in the development of atrioventricular block were observed across disease stages, and only a QRS duration ≥120 milliseconds was associated with an elevated risk of atrioventricular block[125].

Pacemakers are commonly required in patients with cardiac amyloidosis. Analysis of 145,900 hospitalizations across the United States demonstrated that 3.9% of those with cardiac amyloidosis and documented arrhythmias had pacemakers[126]. One study observed that 10% of patients with ATTRwt-CM and 7% with ATTRv-Cm had pacemakers in situ at the time of cardiac amyloidosis diagnosis[125].

In a 10-year retrospective review of 262 patients with ATTRv, a pacemaker was inserted in 45% of cases[127]. Compared with patients with HFpEF without a diagnosis of cardiac amyloidosis, patients with cardiac amyloidosis and HFpEF require pacemakers far more commonly (43.8% vs 11.5%; P = 0.004)[128]. Most reports agree that pacemakers are most common in ATTRwt-CM, followed by ATTRv-CM and, finally, AL-CM. However, advanced age at the time of diagnosis could confound these results.

Ventricular arrhythmias and implantable cardioverter-defibrillator (ICD)

There are numerous potential mechanisms driving ventricular arrhythmogenicity in amyloid cardiomyopathy. One proposal involves patchy amyloid fibril infiltration within the ventricular myocardium along with microvascular ischemia leading to the development of anatomical re-entrant circuits suitable for ventricular arrhythmias[129]. Other mechanisms include preferential amyloid cytotoxicity to ventricular myocardial cells. This may explain the apparent higher prevalence of VAs in AL-CM over ATTR-CM.

Although ventricular arrhythmias are common in amyloid cardiomyopathy[129], their effect on mortality may not be as significant as expected. In a study of AL-CM patients with presyncope or syncope who had a loop recorder implanted, bradycardia followed by pulseless electrical activity was the terminal rhythm in 62% of deaths, whereas only 1 episode of non-sustained ventricular tachycardia was evident from 272 loop recordings[130]. Bradycardia and complete atrioventricular block were common prior to pulseless electrical activity suggesting prophylactic pacemaker rather than implantable cardioverter defibrillator (ICD) insertion could offer a survival benefit in patients with severe AL-CM.

The efficacy of (ICD) therapy in patients with cardiac amyloidosis is uncertain. Sudden cardiac death is common in patients with cardiac AL-CM and prophylactic ICDs have been suggested as an option to reduce this risk. However, electromechanical dissociation appears to be a significant cause of sudden cardiac death in these patients, so the role of ICD therapy in preventing Sudden cardiac death in this population is unclear.

This issue was illustrated by a study in which 19 AL-CM patients with history of syncope (n = 4) or high-grade ventricular arrhythmias (n = 10), or both (n = 5) received an ICD[131]. Two subsequently underwent cardiac transplant, and one died of an unrelated disease. There were six cardiac deaths, all

sudden despite the ICD. One patient received appropriate shocks but later died of electromechanical dissociation, which was also the cause of death in the other five. Only one patient received appropriate ICD shocks with long-term survival.

Treatment for the underlying disease

Evidence-based therapy for AL amyloidosis

Despite of AL-CM is managed by hematology-oncology specialists, the diagnosis is often made by cardiologists when cardiac amyloid becomes evident. It will briefly be mentioned the up-to-date therapy pillars for this condition in this review.

The therapy involves the administration of chemotherapy and/or autologous stem cell transplantation in an attempt to treat the underlying plasma cell clone responsible for AL amyloid formation. The goal of therapy in patients with cardiac involvement is to achieve a 90 percent or greater reduction in serum free light chain levels, but not all patients may be able to attain this level of response. The intensity and type of therapy chosen is affected by the number and extent of organ involvement. The most common initial chemotherapy regimens used are now bortezomib-based regimens such as daratumumab, cyclophosphamide, bortezomib, dexamethasone (dara-CyBorD) or cyclophosphamide, bortezomib, dexamethasone (CyBorD). For patients who are candidates for stem cell transplantation, autologous stem cell transplantation involves administration of high-dose melphalan followed by stem cell rescue. The risk of treatment-related mortality associated with autologous stem cell transplantation in AL amyloidosis restricts the use of this procedure to a small group of selected patients.

Recent clinical trial data show that among patients with AL amyloidosis (≈71% with cardiac involvement), the addition of daratumumab to conventional therapy led to a dramatic improvement in hematologic and end-organ response compared with conventional therapy alone[132].

In a study of transgenic mice that exhibit a light-chain amyloidosis phenotype, doxycycline had a dose-dependent inhibitory effect on recombinant AL aggregation in vitro and reduced the quantity of AL fibrils ex vivo[133]. Observational data from a single-center cohort (n=103) of patients with AL-CA suggest that doxycycline use in addition to bortezomib-based treatment may be associated with improved survival and greater cardiac response (defined as a larger decrease in aminoterminal NT-proBNP)[134]. Until now, clinical trial data testing the efficacy of doxycycline as a treatment for AL-CA

have been lacking.

Notwithstanding, Shen et al[135] argues against the role of doxycycline among other therapies for AL that target amyloid fibril formation and clearance in comparison with therapies that target plasma cells. These observations highlight a lack of usefulness of doxycycline as an adjunct for AL-CA treatment.

The development of agents that inhibit AL fibril formation and clear deposited AL aggregates is continuing to evolve. The monoclonal antibody birtamimab (NEOD001) is a humanized immunoglobulin G1 engineered to target misfolded light chains promoting phagocytic clearance of AL deposits[136]. Its clinical benefit has not been demonstrated clearly, as shown in the phase 3 trial (Efficacy and Safety Study of NEOD001 Plus Standard of Care Versus Placebo Plus Standard of Care in Subjects With AL Amyloidosis) testing the added effect of birtamimab for AL-CM in addition to usual care was terminated early for lack of benefit.

Another agent, CAEL-101, is an amyloid fibril–reactive chimeric immunoglobulin G1k monoclonal antibody currently under development. When bound to misfolded light chains, CAEL-101 activates neutrophils and launches a proteolytic cascade against AL fibrils. Results from a recent phase 1a/b study of CAEL-101 in patients with relapsed or refractory AL-CA support the hypothesis that it improved target organ function through improved left ventricular global longitudinal strain and lower NT-proBNP after 12 weeks of therapy[137].

Evidence-based therapy for ATTR amyloidosis

Targets for disease-modifying therapies in ATTR-CM include TTR stabilizers, silencing, TTR silencers, and TTR disruption. TTR stabilizers bind to the TTR tetramer and prevent misfolding and thus deposition of amyloid fibrils. TTR silencers target TTR hepatic synthesis. TTR disruptors target the clearance of amyloid fibrils from tissues.

TTR stabilizers

Tafamidis is a TTR stabilizer that binds the thyroxine-binding site of TTR. In the ATTR-ACT randomized trial (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) of patients with ATTRwt-CM or ATTRv-CM, tafamidis was associated with a significantly lower all-

cause mortality (29.5% versus 42.9%) and lower cardiovascular-related hospitalization (0.48 versus 0.70 per year) after 30 months. There was a higher rate of cardiovascular-related hospitalizations in the prespecified subgroup of patients with NYHA class III heart failure, which may have been attributable to longer survival during a more severe period of disease, underscoring the importance of early diagnosis and treatment. Tafamidis was also associated with a lower rate of decline in 6-minute walk distance (P<0.001) and a lower rate of decline in Kansas City Cardiomyopathy Questionnaire-Overall Summary score (P<0.001)[138]. Tafamidis was approved by the US Food and Drug Administration for use in ATTR-CM in May 2019.

Given that tafamidis prevents but does not reverse amyloid deposition, tafamidis is expected to have greater benefit when administered early in the disease course. As the survival curves separate after 18 months, patients for whom noncardiac disease is not expected to limit survival should be selected. Benefit has not been observed in patients with class IV symptoms, severe aortic stenosis, or impaired renal function (eGFR <25 $mL/min^{-1}/1.73\ m^{-2}$ body surface area). Tafamidis is available in 2 formulations: tafamidis meglumine is available in 20 mg capsules; and the FDA-approved dose is 80 mg (4 capsules) once daily. Tafamidis is also available in 61 mg capsules; the FDA-approved dose for this new formulation is 61 mg once daily.

One model-based analyses used the results of the ATTR-ACT study [138] to evaluate the cost-effectiveness of chronic tafamidis compared with no amyloidosis- specific therapy among patients with wild-type or variant transthyretin amyloidosis and NYHA class I to III heart failure[139]. With assumptions that tafamidis remained effective beyond the clinical trial duration, they estimated tafamidis increased average survival by 1.97 years and quality-adjusted life year by 1.29. Despite these large clinical benefits, tafamidis (with an annual cost of $225,000) had an incremental cost-effectiveness ratio >$180,000 per quality-adjusted life year gained, the benchmark used by this guideline for low value. The cost of tafamidis would need to decrease by approximately 80% for it to be intermediate value with a cost per quality-adjusted life year <$180,000.

Diflunisal is a nonsteroidal anti-inflammatory that stabilizes TTR in vitro. In a randomized trial of patients with ATTRv and polyneuropathy, diflunisal was associated with reduced progression of polyneuropathy. There are no controlled trials of diflunisal in patients with ATTR-CM, although single-center retrospective analyses demonstrate safety and tolerability and suggest efficacy[140,141].

AG10 is a TTR stabilizer that binds to the tetramer and mimics coinheritance of the TTR T119M mutation, providing natural stabilization of TTR to prevent amyloid fibril formation and deposition. A phase 2 trial of AG10 demonstrated an acceptable safety profile,[142] and data from the open-label extension indicate that mortality and cardiovascular hospitalization were lower in AG10 open-label extension participants than in placebo-treated ATTR-ACT participants at 15 months[143].

TTR Silencing

TTR protein silencers target the hepatic synthesis of TTR. Patisiran is an intravenously administered siRNA that degrades TTR mRNA, and inotersen is a subcutaneously administered single-stranded antisense oligonucleotide that binds TTR mRNA, leading to degradation. Both therapies result in >85% reduction in circulating TTR protein concentration.

Two randomized trials of TTR silencers in patients with ATTRv amyloidosis and polyneuropathy have been reported: the APOLLO trial (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy; patisiran)[144] and NEURO-TTR (Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy; inotersen)[145]. Both demonstrated slower progression of amyloidosis-related polyneuropathy.

Although not explicitly tested, there is evidence that TTR silencers may have beneficial cardiac effects. Prespecified subgroup analyses of APOLLO trial participants with increased LV wall thickening unrelated to hypertension or aortic stenosis (assumed to be from amyloidosis) demonstrated that patisiran attenuated the deterioration of LV global longitudinal strain,[146] LV wall thickness, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration[147]. Similarly, inotersen demonstrated stabilization of LV wall thickness, 6-minute walk test, and global systolic strain[148]. Trials to assess the efficacy of TTR silencers in ATTR-CM are currently ongoing.

TTR Disruption/Resorption

TTR disruption targets the clearance of amyloidosis fibrils from tissues. Preclinical studies demonstrated that doxycycline plus TUDCA (tauroursodeoxycholic acid) removed amyloid deposits. However, small open-label studies demonstrated a high incidence of side effects with conflicting results

on efficacy[149,150]. EGCG (epigallocatechin-3-gallate), a catechin in green tea, inhibits amyloid fibril formation in vitro, but there is little evidence of benefit[151] from it or turmeric. With the advent of US Food and Drug Administration–approved therapies, the therapeutic roles of these agents are uncertain. Other agents, including monoclonal antibodies such as PRX004, are under investigation[152].

Liver transplantation

In ATTR amyloidosis, the source of the amyloidogenic protein is the liver. Transplantation of the liver removes the mutant amyloidogenic TTR in ATTRv, but in ATTRwt the precursor protein is native TTR, and thus liver transplantation is not indicated. Unfortunately, cardiac disease has progressed after liver transplantation in some patients with familial ATTR, even though deposits elsewhere may stabilize[153]. Examination of the composition of TTR in the heart of patients with progressive cardiomyopathy after liver transplantation reveals that the mechanism is enhanced deposition of wild-type TTR on a template of amyloid derived from variant TTR. Patients with advanced heart disease may be treated with combined heart and liver transplantation[154].

Once a patient with a transthyretin mutation is found to have a positive biopsy for amyloid, he or she should undergo evaluation for liver transplantation, with the goal to receive the transplant as early in the disease as possible. If an amyloid cardiomyopathy is present with significant heart failure, isolated liver transplantation is contraindicated and consideration should be given to a combined liver-heart transplant or just heart alone.

This appears to be particularly true in patients with the Ala60 mutation in whom cardiomyopathy is almost always present and in whom liver transplant alone does not stop progressive cardiomyopathy[155].

Conclusions

Amyloid cardiomyopathy, previously known as a “rare diagnosis”, can now be diagnosed earlier thanks to new imaging and humoral methods, thus offering various therapeutic alternatives to affected patients, according to the type of amyloidosis that predominates. It is a mandatory task for all physicians who manage heart failure to rule out this entity in the context of pump failure with preserved ejection fraction, elements of restrictive cardiomyopathy with thickening of the ventricular walls that do not respond to abnormal load conditions, since conventional management of heart failure in this group can

be deleterious for patients. In cases of AL-CM, regardless of whether their most appropriate management is by hematology-oncology, cardiologists or clinicians are obliged to carry out the diagnosis and timely stratification of these patients, since the main adverse prognostic marker is cardiovascular involvement by this entity.

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