Chapter

Cardiac Amyloidosis

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Abstract

Amyloidosis represents a heterogeneous group of disorders caused by amyloid fibril deposition in the extracellular space in different organs. Among the many types of amyloidosis cardiac involvement occurs almost exclusively with immunoglobulin light chain amyloidosis (AL amyloidosis) or transthyretin amyloidosis (ATTR amyloidosis). When present cardiac amyloidosis (CA) has a significant impact on disease prognosis. The typical clinical presentation in CA is that of a restrictive cardiomyopathy. Clinical suspicion of CA is based on clinical, laboratory and electrocardiographic findings. The diagnosis is confirmed using echocardiography, cardiac magnetic resonance imaging, biopsy, and/or bone scintigraphy. A precise definition of amyloidosis type is essential for choosing the specific treatment for this condition. Treatment of CA has two components: general treatment of congestive HF, and specific treatment of the underlying protein misfolding disorder.

Keywords: cardiomyopathy, amyloidosis, restrictive cardiomyopathy

1. Introduction

All types of amyloidosis involve deposition of amyloidogenic protein, composed of low molecular weight subunits, most of which circulate as plasma components. The amyloid deposits are formed by subunit proteins which originate from soluble precursors. These proteins have undergone conformational changes that generated an antiparallel beta-pleated sheet.

There are more than 30 precursor proteins that can form deposits in the extracellular space and can generate progressive organ dysfunction.

The majority of cases of amyloidosis are caused by 3 subtypes: the most common form, which accounts for approximately 70% of all cases is AL amyloidosis, due to the deposition of misfolded immunoglobulin light chains. The other two forms with increased prevalence are ATTR amyloidosis caused by deposition of transthyretin either as wild-type (ATTRwt) form, or mutated/variant (ATTRv) [1].

CA is a myocardial infiltrative disease due to amyloid fibril deposition in the extracellular space of the heart. The infiltrative process results in increased thickness of the left ventricular wall, diastolic dysfunction and HF.

Until about a decade ago amyloidosis used to be considered a rare condition, managed primarily by hematologists, neurologists and nephrologists. CA used to be

diagnosed late in the evolution of the disease, with negative impact on prognosis of these patients. In the last few years there has been and increased emphasis on early diagnosis on optimization of screening and diagnosis of CA. The reason for this is the advent of targeted therapies, which showed increased efficacy in treating CA if they are applied early in the course of the disease [2].

Systemic forms of amyloidosis affecting the heart, are mainly AL, ATTRwt, and some forms of ATTRv amyloidosis [1].

2. Pathophysiology and epidemiology of CA

The pathophysiology of CA is complex. Amyloid infiltration of the heart leads to a decrease in ventricular compliance. This in turn creates the premises for diastolic dysfunction. The decrease in ventricular compliance is associated with an elevation in ventricular filling pressures. Backward transmission of high filling pressures results in bi-atrial dilatation and stasis.

AL amyloidosis is usually caused by a small clonal B cell or plasma cell population, with about 10% of patients having multiple myeloma [3]. From a pathophysiological standpoint there is interstitial deposition of immunoglobulin light chains, as well as direct toxicity on the myocytes caused by the free light chains. These chains can induce lysosomal dysfunction, oxidative stress, apoptosis, and dysregulation of MAP kinase signaling transduction pathways as well as autophagy [4]. The amount of cardiac involvement independently predicts mortality [4].

Transthyretin (TTR), which is a transport protein for retinol and thyroid hormone synthesized by the liver, can form amyloid fibrils when it dissociates from tetramers into monomers. The destabilization tetramers with accumulation of TTR monomers can result from gene mutations in the TTR gene (ATTRv) or are the result of age-related processes (ATTRwt) [4].

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Detailed information regarding the epidemiology of CA is lacking. Gilstrap et al., in a study published in 2019, found a prevalence rate of CA among Medicare beneficiaries of 8–17 per 100,000 person-years. The incidence rate in the same study was 18–55 per 100,000 person-years [5]. The prevalence of AL amyloidosis has increased 2.6-fold in the United States between from 15.5 cases per million in 2007 to 40.5 in 2015 [6].

Cardiac involvement in AL amyloidosis is a major determinant of prognosis, with mean survival time is only about 6 months without treatment in cases with advanced cardiac disease and HF [7]. The median overall survival is extended to >5 years if modern treatment strategies are used [1].

3. Clinical manifestations

The clinical presentation of patients with amyloidosis is heterogeneous and nonspecific and, varies depending on the degree of organ involvement. The onset of symptoms depends on the type of amyloidosis.

Amyloid infiltration of the heart can generate symptoms and signs that are common in restrictive cardiomyopathy.

Lower extremity edema is a nonspecific clinical manifestation, which is common in different conditions associated with heart failure (HF). It can be associated with the elevation of jugular venous pressure, pleural effusion, ascites, pain in the right hypochondriac region caused by liver congestion, dyspnea at exertion or at rest and orthopnea. These symptoms are related predominantly to right ventricular failure and restrictive cardiomyopathy, which is one of the most common forms of presentation in CA [8].

Another symptom that can occur in CA is presyncope or syncope consequent to bradyarrhythmias or high-degree/complete atrioventricular block. Loss of consciousness is often present in AL amyloidosis and in some cases can have combined etiology [9]. Furthermore, hypotension induced by autonomic neuropathy may lead to syncope in patients with amyloidosis.

Sometimes, patients complain of palpitations which occur in the setting of atrial fibrillation (AF) due to the infiltration of the atrium with amyloid deposits or by the dilated atrium secondary to restrictive cardiomyopathy. This is the most common described arrhythmia, found in 10–15% of the patients [10]. Ventricular tachyarrhythmias can occur in advanced stages of the cardiomyopathy, however sudden cardiac death often due to electromechanical dissociation [9].

In advanced forms of CA with systolic dysfunction, the patient can exhibit signs and symptoms of low cardiac output such as fatigue, dizziness, weakness, hypotension, delayed capillary refill and decreased pressure of pulse wave.

Angina or myocardial infarction, rare manifestations of CA, may develop as a cause of microvascular dysfunction or amyloid deposits in the coronary arteries [8]. However, an in vitro experiment performed by Liao R. et al. showed that amyloidogenic light chains may have a direct toxic effect on cardiac myocytes [11] and it can explain why patients with AL amyloidosis have poorer quality of life than patients with ATTR amyloidosis with the same degree of cardiac involvement.

Extracardiac organ involvement leads to a plethora of other signs and symptoms in amyloidosis. Because of the variety of the manifestations such as nephrotic syndrome, gastrointestinal symptoms, pulmonary disease, bleeding diathesis, macroglossia, purpura, musculoskeletal abnormalities, carpal tunnel syndrome, the diagnosis is often delayed [12].

Due to the multisystemic involvement of this pathology, it is worth to mention that pulmonary disease is seen in about 50% of cases. Pulmonary amyloidosis has different patterns such as diffuse alveolar septal involvement, tracheobronchial and nodular parenchymal amyloidosis. Clinical manifestations of pulmonary amyloidosis could be misinterpreted because of the nonspecific signs and symptoms such as dyspnea at exertion, weight loss or productive cough. Because of the poor prognosis of these patients, as we can see in CA too, pulmonary involvement must be searched during the work-up and specific treatment should be initiated.

Given these clinical considerations, CA should be considered in the differential diagnosis in a patient with HF, unexplained left ventricular hypertrophy and preserved ejection fraction.

4. Laboratory and electrocardiographic findings in CA

There is no specific serum biomarker for the ATTR subtype. In the case of AL amyloidosis however, blood screening tests are available and these include electrophoresis and immunofixation of serum and urine proteins, as well as quantification of immunoglobulin free light chain levels with evaluation of the

kappa - lambda ratio [13]. Due to the possible presence of a monoclonal gammopathy of undetermined significance (MGUS) in up to 5% of the general population aged >65 years, positive laboratory findings need to be carefully evaluated [13]. In the meantime, the cardiac amyloidosis' ATTR subtype may coexist with MGUS and needs to be differentiated from the AL subtype by seeking evidence of amyloid infiltration in affected organs with identification of the precursor protein [13].

Amyloid fibrils deposition in the myocardium is often correlated with the onset of arrhythmias and conduction abnormalities, consequently highlighting the key role of the electrocardiogram (ECG) in the diagnostic assessment [14]. One of the ECG findings is the presence of diffuse low voltage in the limb and/or precordial leads [15]. Even if this ECG finding is not very sensitive and it generally occurs only in late the stages of the disease, it is common, specific and has prognostic signficance in patients with CA [16]. In order to increase the diagnostic sensitivity, a low-voltage-to-mass ratio assessment was suggested (given the discordance between the low voltage on the ECG and the left ventricular hypertrophy on cardiac imaging) (**Figure 1**) [16].

Another important finding on the ECG, which is present in up to 70% of these patients, is the pseudoinfarction pattern which consists of pathologic Q or QS waves in any two consecutive leads, but without any history of infarction and without wall motion abnormalities [16]. As previously mentioned, patients with CA also tend to develop, as the disease progresses, arrhythmias which range from brady- and tachyarrhythmias or sudden cardiac death [17]. The most common arrhythmia noted in CA is AF (up to 70% of patients), but ventricular arrhythmias such as premature ventricular beats or ventricular tachycardia can also occur [18]. Conduction disease is also common and appears to be more frequent in the wtATTR subtype. This last condition can require implant of a pacemaker [18].

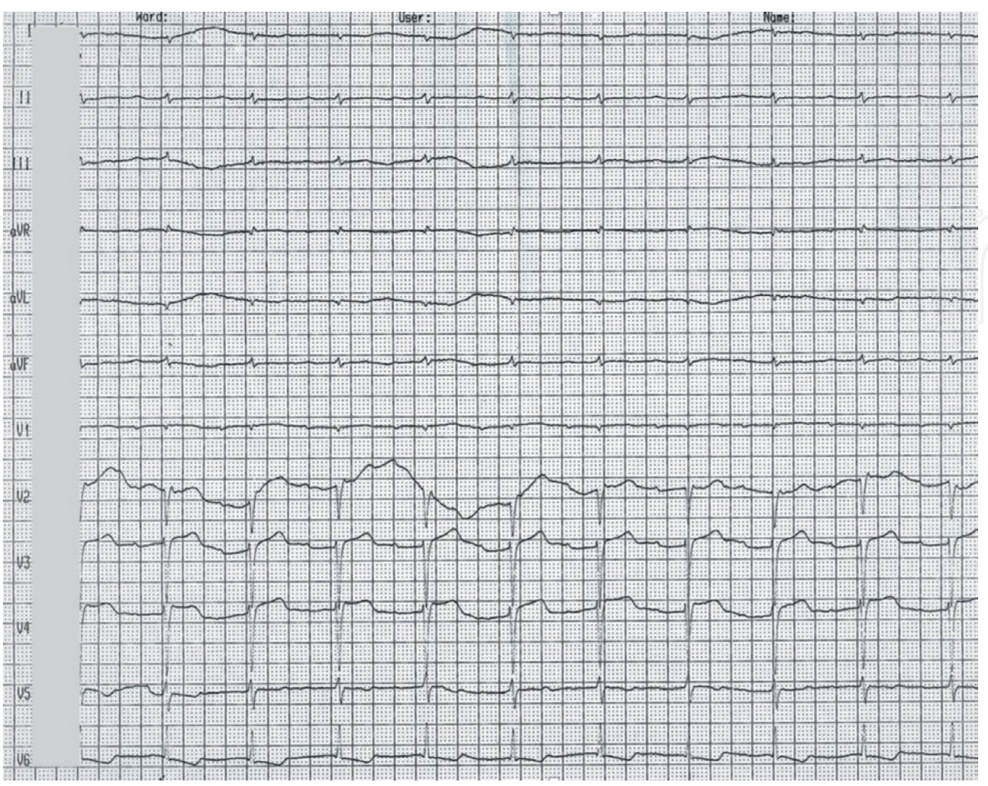

Figure 1.
ECG with low voltage seen in the frontal plane leads in a patient with AL type cardiac amyloidosis.

5. Diagnostic suspicion of CA

In the past CA used to be underdiagnosed, given its nonspecific symptoms and because it was thought to be a rare condition. In order to improve diagnostic specificity and sensitivity different "red flag" signs can be used to raise the clinical suspicion and allow an early diagnosis [16].

ATTR amyloidosis which consequentially determines cardiac amyloid infiltration is usually preceded years before onset by various clinical entities such as: carpal tunnel syndrome, lumbar spinal stenosis, and biceps tendon rupture [16]. Moreover, ATTR is also often associated with sensoriomotor polyneuropathy, autonomic dysfunction as orthostatic hypotension, erectile dysfunction, gastrointestinal motility disorders or urinary retention [16].

Even if not sensitive, macroglossia and periorbital purpura are specific signs for the AL amyloidosis and are rare seen in ATTR subtype. Other "red flags" for AL subtype include hepatomegaly and peripheral neuropathy, but these are neither sensitive, nor specific for this condition. Also, when facing patients with undifferentiated cardiac hypertrophy and nephrotic proteinuria, AL amyloidosis should be considered as a possible diagnosis [16].

6. Echocardiography in CA

Transthoracic echocardiogram is the most common non-invasive imaging tool used in patients with suspected or confirmed amyloidosis. In 1975 Chew et al. described for the first time the echocardiographic appearance of CA, based on M-mode tracings. The features seen were: normal diastolic size of the left ventricle, increased systolic dimension and pericardial effusion; given these findings, the term" stiff heart" was chosen in these patients [19, 20].

Later on more echocardiographic features were added to the amyloid phenotype: symmetric thickness of the left ventricular wall in patients with no history of hypertension or aortic valvular abnormalities, hypokinetic interventricular septum and posterior left ventricular wall with decreased systolic thickening, normal or small left ventricle cavity, increased thickness of the right ventricular anterior wall, dilated left atrium, a decrease of the E-F slope (given reduced ventricular compliance) [19, 21–23].

6.1 Two-dimensional echocardiography

The development of two-dimensional echocardiography offered the posibility to describe further the amyloid phenotype [20]. Some defining features of CA are represented by left ventricular hypertrophy with a normal/reduced cavity volume, increased thickness of the right ventricular wall and the valves (especially aortic and mitral valves), and bi-atrial enlargement (**Figures 2** and **3**) [24, 25].

Concerning the left ventricular wall thickness, it has a different pattern depending on the amyloidosis type: symmetrical in AL and asymmetrical in ATTR [26]. The presence of extracellular amyloid deposits gives the myocardium a„granular sparkling" appearance, better visualized at the interventricular septum [27]. A small pericardial effusion or dilated inferior vena cava are often observed as signs of a restrictive filling pattern [28].

6.2 Doppler

In the 80s, Doppler ultrasound offered new possibilities to characterize the heart's function and structure, providing a more accurate diagnosis, and the

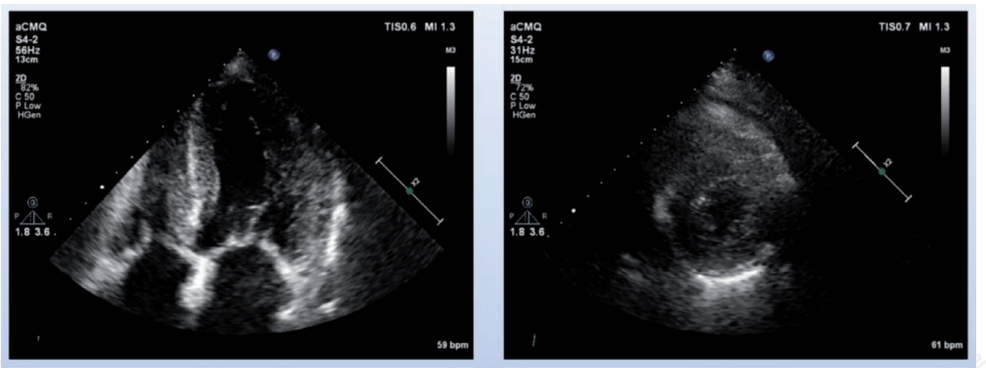

Figure 2.
2D echocardiogram (apical 4 chamber view and parasternal short axis view) in a patient with AL type cardiac amyloidosis revealing increased thickness of the left ventricular walls.

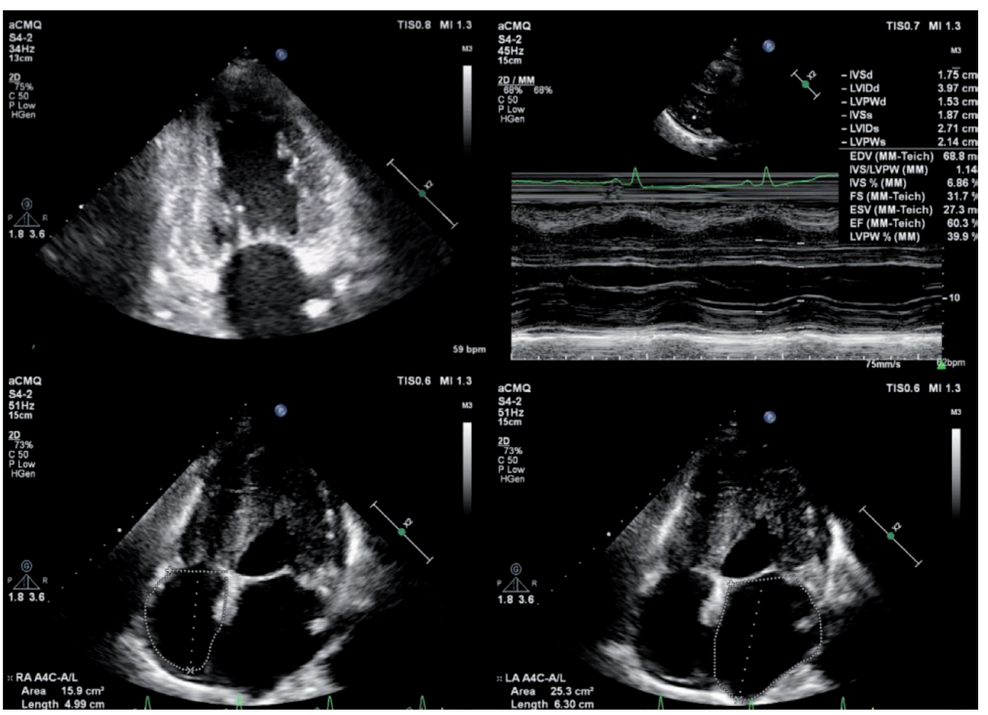

Figure 3.
2D echocardiogram (apical 2 chamber view, M-mode in parasternal long axis view and apical 4 chamber view) in a patient with AL type cardiac amyloidosis revealing increased thickness of the left ventricular walls, biatrial dilatation and hypertrophic interatrial septum.

diastolic dysfunction became a main feature of CA. First studies, performed by Klein et al. revealed that in early stages, when the parietal thickness of the left ventricle is 12-15 mm, there is an abnormal relaxation with a reduced early filling velocity, elevated late velocity, reduced early to late velocitsy ratio and longer isovolumic relaxation time. Contrary to this, in late-stage CA associated with significant ventricular wall thickening (parietal thickness equal to or more than 15 mm) an elevated E/A ratio was observed, suggesting a restrictive cardiomyopathy [19, 27]. In late-stage disease the deceleration time is markedly reduced (restrictive pattern).

The diastolic function is usually severely impaired, with a restrictive pattern defined by a decrease deceleration time on the transmitral pulsed Doppler and low tissue Doppler velocities in the left ventricular wall; E/e' is often higher than 15, which suggests elevated filling pressures (**Figure 4**) [29].

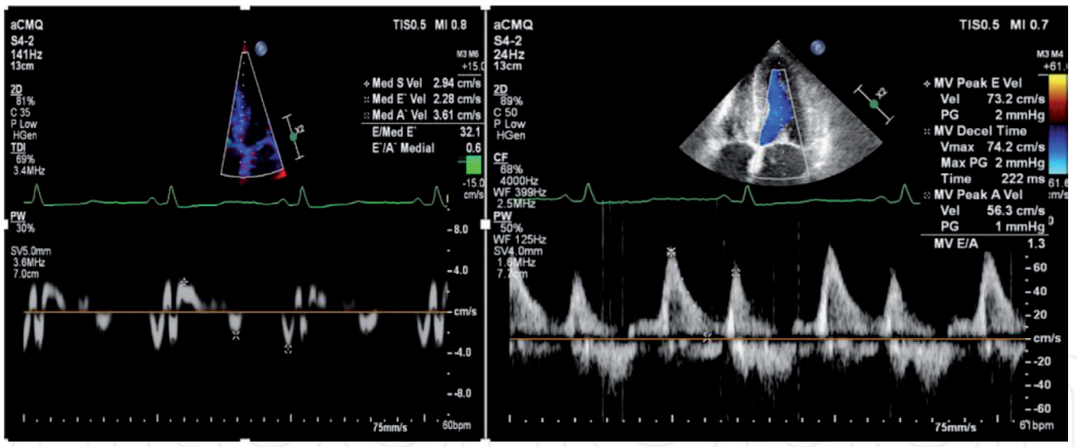

Figure 4.
2D echocardiogram with tissue Doppler sample at base of the interventricular septum and pulsed-wave Doppler at mitral valve inflow in a patient with AL type cardiac amyloidosis revealing impaired relaxation, septal e' of the LV decreased and a pseudonormal pattern.

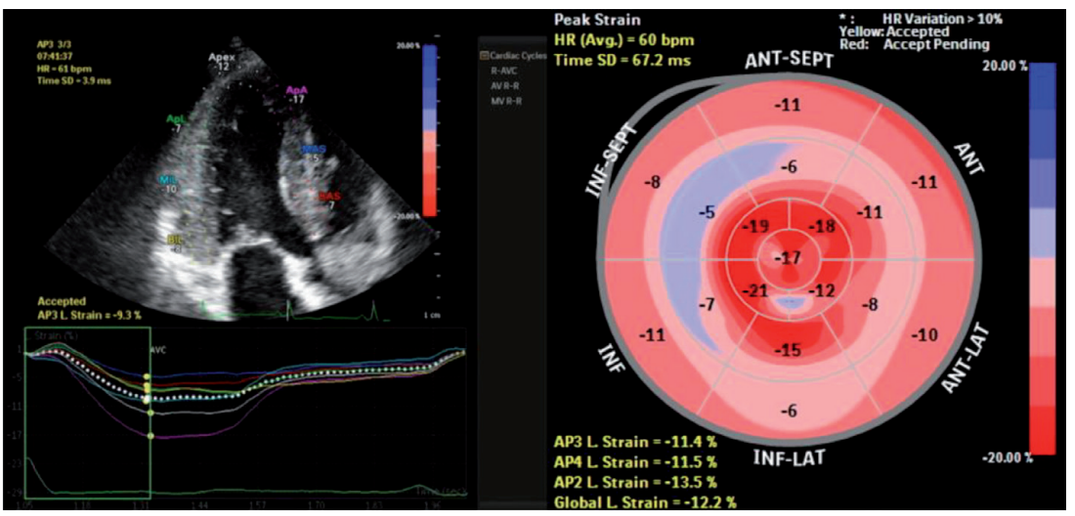

Figure 5.
Left ventricular strain image with impaired longitudinal shortening at basal and mid-ventricular level with preserved longitudinal function at the apex (relative apical sparing) as seen in the bull's eye plot on the right.

6.3 Speckle-tracking echocardiography

The speckle-tracking echocardiography (STE) plays a major role in evaluation of patients with CA, being a sensitive echocardiographic technique which detects cardiac damage due to amyloid infiltration from early stages, even when other classic parameters are still in range [30]. In patients with CA, a reduced global longitudinal strain can be observed when the left ventricular ejection fraction is still preserved [31].

Speckle tracking imagining in CA reveals reduced longitudinal shortening at the basal and mid-ventricular level with preserved longitudinal function at the apex [31]. This pattern, described by Phelan et al. as 'relative apical sparing' is a helpful tool, both sensitive and specific, to make a diagnosis of CA [32]. Longitudinal strain bull's eye plot has a typical pattern that is easy to recognize. The mechanism that determines this pattern is not yet clearly understood. Proposed mechanisms include: 1. a reduced infiltration with amyloid fibrils at the apex, compared to basal segments; 2. an increased tendency towards apoptosis at basal level, as a result of the higher parietal stress [25, 28, 33]. This typical appearance was first described in late-stage CA, but there are studies that suggest its presence in less affected hearts [31, 34].

2D STE is helpful in differentiating the thickness of myocardium caused by amyloidosis from a real left ventricular hypertrophy. In CA a systolic septal longitudinal base-to-apex strain ratio more than 2.1 in association with a low deceleration time is useful to differentiate it from patterns encountered in other types of ventricular thickening, such as true hypertrophy (**Figure 5**) [19, 31].

7. Magnetic resonance imaging in CA

The use of cardiac magnetic resonance (CMR) in patients with CA allows a good definition of cardiac morphology, ventricular and valvular function, and the possibility to analyze the structure of the ventricular wall [35]. However, the main benefit of CMR imaging in this disease remains the evaluation of the ventricular diastolic function and the structure of the ventricular wall.

The gadolinium contrast agents are very useful in characterizing the myocardial wall structure due to the differences in clearance of gadolinium between normal myocardium, edematous or scarred myocardium, and myocardium with amyloid deposits.

The gadolinium contrast agents accumulate in extracellular spaces of both normal myocardium and diseased one, but it is rapidly washed out from the normal areas, remaining in the pathological areas, late after the contrast has washed out from the normal tissue. The late gadolinium enhancement (LGE) of the myocardium has different patterns in different diseases, which, together with the other functional changes that can be evaluated by MRI. The ischemic scars appear as subendocardial LGE in a coronary territory, usually associating the thinning of the myocardial wall. In contrast to this, the amyloid deposits appear as subendocardial LGE that extend beyond a coronary artery territory (the "arch" shaped LGE) and is usually associated with increased wall thickness. In more severe stages the subendocardial LGE can be diffuse (the "annular" shaped LGE) or it can even become a transmural LGE [36]. These aspects can combine in the same patient, as they represent a continuum from no amyloid deposits and no LGE to subendocardial LGE and then to diffuse and transmural, intense LGE [37].

The expansion of the extracellular space due to amyloid deposition can also be measured by the T1 mapping technique allowing monitoring of the treatment response [38]. The extracellular volume (ECV) is below 28% in normal situations and can increase significantly with edema and fibrosis, but also with amyloid deposition. An increase above 40% of ECV is a highly suggestive sign for amyloidosis in patients with high pretest probability; this sign appears early, before LGE

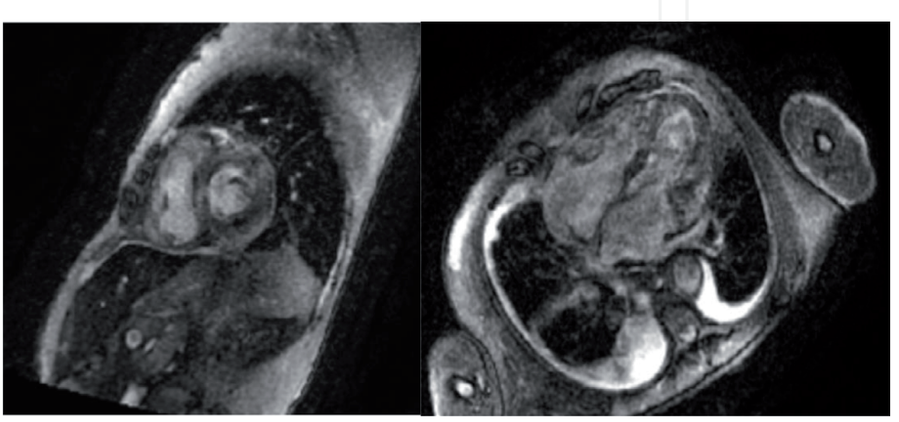

Figure 6.
MRI images: short axis 2D myocardial delayed enhancement (left) and four-chamber 2D myocardial delayed enhancement (right): diffuse, inhomogeneous late gadolinium enhancement, suggestive of cardiac amyloidosis.

appearance [39]. Given the T1 mapping technique which allows objective measurement of the extracellular volume, the response to treatment can be monitored (**Figure 6**) [40].

8. Nuclear medicine: radionuclide scintigraphy

Bone affinity isotope scintigraphy plays an important part in the early diagnosis of ATTR-type CA and in its differentiation from AL amyloidosis and other types of hypertrophic heart disease [41].

The radiotracers recommended in diagnosing ATTR amyloidosis are: 99 mTc - PYP (pyrophosphate), 99mTc - DPD (3,3-diphosphono-1,2-propanodiacarboxylic acid) and 99mTc-labeled hydroxymethylene diphosphonate (HMDP) [42]. They have an increased affinity for calcium. In ATTR-type amyloidosis, the extracellularly deposited amyloid, at the cardiac level, contains a protein that binds amyloid fibers through a calcium-dependent mechanism, which explains the affinity of these radiotracers for this type of amyloid [43]. There are comparative studies on endomyocardial biopsies, which show that patients with ATTR amyloidosis present more frequent microcalcifications in comparison to those with AL amyloidosis. In very few cases, however, patients with AL amyloidosis may have microcalcifications and in these situations scintigraphy with bone affinity radiotracers may be slightly positive [44].

Other radiotracers that can be used to highlight CA and differentiate it from other hypertrophic cardiomyopathies are as follows: 11C-Pittsburgh compound B (11C-GDP), 18F-florbetaben, and 18F-florbetapir. They have affinity for both the AL-type amyloid and ATTR and require further clinical trials for validation [41, 43].

The scintigraphy using the 123I-metaiodobenzylguanidine tracer can also detect the sympathetic denervation of the heart and thus patients at risk of cardiac arrhythmias can be identified [41, 45].

High levels of light serum and urinary chains or of medullary plasma cells are suggestive of AL-type amyloidosis, and biopsy is required to confirm amyloid deposits. In this case, myocardial scintigraphy is performed only to obtain additional information [41].

When monoclonal gammopathy is not present, myocardial scintigraphy with bone avidity radiotracers is required. If it reveals abnormal uptake of the radiotracer at the myocardial level, the diagnosis of ATTR amyloidosis is made with a sensitivity of 100%. Biopsy is not required for detecting amyloid deposits [41].

The myocardial scintigraphy protocol with bone affinity radiotracers involves monoplane imaging (anterior and posterior), 3 hours after the intravenous administration of the isotope, which allows the identification of radioactive tracer uptake and its quantification by visual evaluation of the Perugini score (0- no uptake, 1 - low uptake, of subcostal intensity, 2 - significant uptake, of intensity equal to that of the ribs, 3 - important uptake, of supracostal intensity) [43, 46].

Another way of assessing the uptake of radiotracer at the level of the heart involves performing the ratio between the values measured in a certain region at the level of the heart (H) and at the contralateral level (CL), one hour after the administration of the radiotracer [25, 47].

When the value of the Perugini score is higher than or equal to 2 and/or if the value of the H/CL ratio is higher than or equal to 1.5, the diagnosis of ATTR amyloidosis is made [47].

The H/CL ratio also has a prognostic value. Thus, values higher than 1.5 are associated with the survival reduction to 5 years (together with the echocardiographic characteristics of a more advanced stage of the disease) [43].

9. Diagnostic strategy in CA

Diagnosis of CA can be difficult given the polymorphic and nonspecific clinical manifestations [41] of this systemic disease. CA must be considered in the differential diagnosis in HF with left ventricular hypertrophy and preserved ejection fraction. By the time of the onset of signs and symptoms, it is essential not to delay the diagnosis because it has a negative influence on evolution and prognosis of the patient. Below is an algorithm for an easier approach to the diagnosis CA [41, 48, 49]. Two important steps in this algorithm in patients with clinical suspicion of CA are screening for monoclonal protein (for identification of kappa or lambda free light chains) and, in case this is positive, biopsy, most of the time from fat pad, which has a sensitivity and specificity of 79% and 80% respectively for diagnosing amyloidosis (**Figure 7**) [50].

10. General treatment of heart failure in CA

Therapy of HF along with the treatment of the underlying disease stand for different sides of the same coin in CA. There are several dissimilarities regarding medications used in CA with HF, compared to those used in patients with non-CA HF with reduced ejection fraction (HFrEF). The median survival after the onset of HF is less than 6 months in untreated patients [51].

10.1 Medical treatment of heart failure in CA

General treatment management in patients with CA and HF is challenging due to lack of randomized clinical trials on which to fundament treatment strategies [52]. Therapy should first focus on a sodium restriction diet and daily weight monitoring in conjunction with diuretics, in order to improve congestion and relieve symptoms. Neurohormonal blockade is recommended by current HF guidelines [53, 54] for patients with HFrEF regardless of its etiology, but various concerns have been raised in patients with CA-HF due to potential harmful effects [55].

Thus, diuretics and especially loop diuretics in combined with a mineralocorticoid receptor antagonist, represent the cornerstone of therapeutic strategies in this group of patients [52, 55, 56]. Clinical benefit of other usual HF therapies including beta-blockers (BB), calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACEI) has not yet been proven, moreover these therapies may even be harmful in CA patients [55, 57, 58].

In amyloid cardiomyopathy, CCB and digitalis are contraindicated because they can bind to amyloid fibrils and determine severe adverse effects such as serious hypotension and syncope [58, 59]. Moreover, BB and ACEI can cause marked hypotension due to low cardiac output and fatigue, leading to a limited tolerability among these patients. Orthostatic hypotension caused by autonomic dysfunction can be exacerbated by ACEI or angiotensin receptor blockers, and the coexistence of renal dysfunction can limit their usage [52, 58]. Still, these medications should be cautiously considered in selected cases of severe nephrotic syndrome with marked proteinuria [58].

Beta-blockers with their negative chronotropic and inotropic effects, interfere with contractility and heart rate which help maintain cardiac output, resulting in significant hypotension, extreme bradycardia and even heart block since amyloid patients are already predisposed to electrical conduction anomalies [52, 55, 58]. However, in case of atrial tachyarrhythmias, BB (particularly in low doses) might present real benefits for rate control [52, 55, 58].

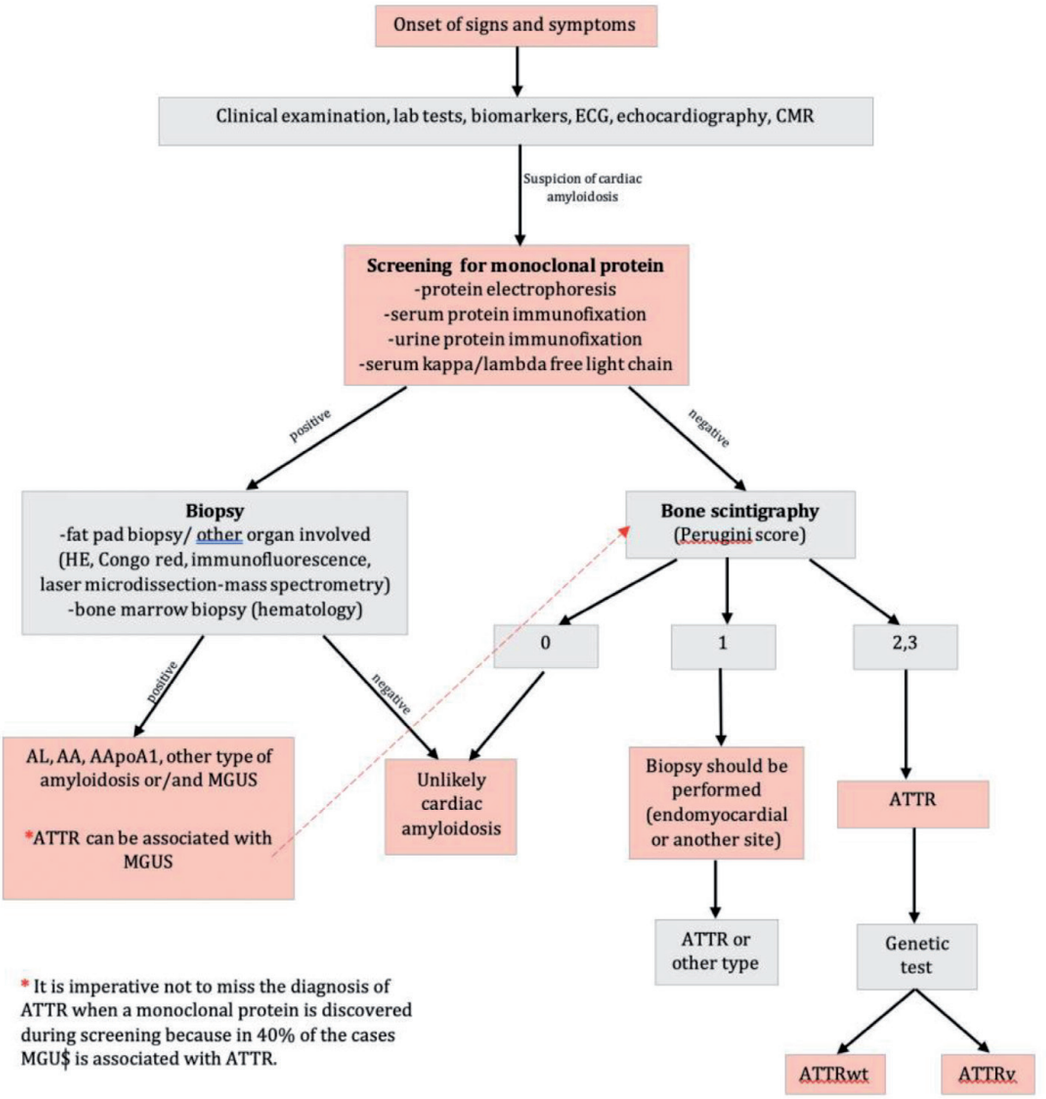

Figure 7.
Diagnostic strategy in CA. (ECG, electrocardiography; CMR, cardiovascular magnetic resonance imaging; HE, hematoxylin eosin staining; AL, amyloid light-chain amyloidosis; AA, amyloid A protein amyloidosis, AApoA1, apolipoprotein AI-derived amyloidosis; MGUS, monoclonal gammopathy of undetermined significance; ATTR, transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ATTRv, mutant transthyretin amyloidosis).

Overall, authors agree that common medications for subjects with non-amyloid-HFrEF, should be carefully considered in those with CA-HFrEF [52, 55, 58]. Furthermore, these therapies should be discouraged in HF with preserved ejection fraction (HFpEF) and CA [56].

10.2 Heart transplantation and ventricular assist devices

Previously, overall heart transplantation in CA was thought to be contraindicated since amyloidosis represents a systemic disease and there is an increased risk of relapse [55, 58, 60]. In transplanted amyloid patients compared to standard heart transplant patients, there was no difference in survival rate, and those with end stage disease continue to have an extremely poor prognosis (50% death on the waiting list) [61, 62].

Many authors focused their attention in the last decade on mechanical circulatory support (MCS) for end-stage CA. Left ventricular assist device (LVAD), biventricular assist device (BiVAD) and total artificial heart (TAH) nowadays

represent either bridge to transplantation (BTT) or destination therapies [63–68]. Some studies reveal that TAH is a feasible bridging therapy, with 82% survival, and should be preferred over LVAD therapy for durable support in selected patients [64]. Accordingly, LVAD is not suitable for CA patients with left ventricular end-diastolic diameter under 46 mm and was even associated with higher mortality post-implantation [64, 66]. Other studies found no significant difference in wait-list and up-to 5-years survival after heart transplantation in subjects sustained by BiVAD or TAH as bridging therapies [65, 66]. Outcomes become acceptable with advances in specific therapies for the underlying disease and heart transplant or heart/liver transplant could even be curative in selected cases, but there is still need for additional studies [57, 60].

10.3 Atrial fibrillation and anticoagulation

While AF is the most frequent arrhythmia in HF patients, in amyloid patients, traditional therapies could lead to severe side effects and in general, are poorly tolerated [18, 53]. Rate and rhythm management among this population continue to be challenging. For rate management the usage of beta-blockers in low doses may be attempted, but their clinical benefit remains unproven in CA. Nondihydropyridine CCB and digoxin are not recommended and may even be toxic for these patients [18, 52, 55]. Options for pharmacologic rhythm control are restricted, but studies support the use of amiodarone as first choice antiarrhythmic therapy, since it tends to be well tolerated [18, 52].

Some experts advise following a rhythm control strategy over a rate control strategy in amyloid patients, but there are no studies to support this strategy until present days.

Last but not least, several studies concluded that chronic oral anticoagulation is recommended in all patients with CA and AF irrespective of CHADS-VASC score due to an increased risk of thromboembolic events [55, 57, 69].

10.4 Cardiac implantable electronic devices

Implantable electronic devices such as pacemaker and/or implantable cardioverter-defibrillator (ICD) have not been shown to prevent sudden cardiac death or improve survival in CA patients [18, 52, 55, 57, 70]. Moreover, since overall mortality after implantation outweighs its benefits, cardiac implantable electronic devices should be used mainly for secondary prevention (hemodynamic instability due to ventricular arrhythmias) in patients with more than a year survival rate [52, 54, 55, 57]. However, permanent pacemakers, especially biventricular pacing, were shown to improve symptoms and should be considered in patients with CA and severe conduction disease [18, 57].

11. Specific treatment of AL amyloidosis cardiomyopathy

The last two decades have brought in a decrease in mortality rates and improved survival in patients with AL amyloidosis, mainly due to early diagnosis and better treatment implementation [71]. During the same period, new treatment options have become available for these complex patients, among which the most notable are new chemotherapy regimens, autologous stem cell transplantation, proteasome inhibitors and monoclonal antibodies [72].

Treatment should be adapted according to the patient's comorbidities and severity of organ involvement in order to achieve the most efficient and safe therapeutic regimen [73].

Apart from patients with monoclonal gammopathies of undetermined significance (MGUS) or smoldering myeloma, in whom initiation of specific therapy could be delayed until the first sign of organ involvement, all patients diagnosed with AL amyloidosis should be initiated on specific therapy as soon as possible [74, 75].

The treatment of these subjects should be decided by a multidisciplinary team, coordinated by a hematologist and with the involvement of other relevant medical specialties: nephrology, cardiology, pneumology, neurology and gastroenterology [76].

In addition to specific HF therapy, which has several peculiarities compared to that of the general population, patients with AL amyloidosis and cardiac involvement require treatment of the underlying disease [77].

The purpose of therapy in cardiac AL amyloidosis is to reduce the serum free light-chain levels and to obtain organ response. This should be done promptly and for as long as possible, in order to obtain a reduction of more than 90 percent in free light-chain levels, therefore preventing further amyloid deposition and fibrillogenesis [75, 78].

The standard treatment includes high-dose chemotherapy in combination with autologous stem cell transplantation (ASCT), alkylating agents, steroids, proteasome inhibitors, and immunomodulatory drugs [76]. An adequate level of response may not be obtainable in all patients. Because of this, treatment efficacy should be assessed at 3 months after ASCT (autologous stem cell transplantation) and 1–2 months after nontransplantation therapies. A decision to shift to other regimens depends on the hematologic response [76]. Patients with important cardiac involvement have a higher mortality despite good initial hematologic response, while a rapid improvement of cardiac biomarkers and left ventricular ejection fraction can be seen in those with mild CA when free light chain can be significantly reduced [73, 75].

Risk stratification is essential when choosing the treatment strategy. Only 20% of the patients newly diagnosed with AL amyloidosis are eligible for ASCT, these being considered low risk patients. Effective up-front therapy may increase this percentage, making certain other patients eligible [78]. Generally, in order to be eligible for ASCT, patients should meet the following criteria: age $\leq$ 70 years, cTnT <0.06 ng/mL, NT-proBNP <5000 ng/L, systolic blood pressure $\geq$ 100 mmHg, LVEF >45%, New York Heart Association (NYHA) functional class I or II, creatinine clearance $\geq$50 mL/min (unless on chronic stable dialysis), Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, DLCO >50%, less than 3 organs significantly involved (heart, liver, kidney, or autonomic nervous system) [76, 77].

Treatment with bortezomib, a proteasome inhibitor, should be considered in low-risk patients prior to ASCT if there are no contraindications, in order to achieve high rates of deep and durable hematologic response. This should be followed by high dose melphalan, an alkylating agent, combined with autologous stem cell transplantion, rather than chemotherapy alone [78]. ASCT allows the administration of high doses of melphalan, with myeloablative effect, thus contributing to the suppression the underlying plasma cell dyscrasia [79].

As mentioned above, the majority of AL amyloidosis patients are not eligible for ASCT, being staged in a class of intermediate or high risk [76]. For these patients, the most common initial chemotherapy regimens used nowadays are bortezomib-based, such as combinations with cyclophosphamide and dexamethasone (CyBorD) or melphalan and dexamethasone (BMDex). These regimens have a significantly higher hematological response rate, a longer progression-free period and increased overall survival compared to the older regimen of dexamethasone and prednisone, which has been the standard of care for many years in these subjects [79, 80].

Daratumumab is an anti-CD38 monoclonal antibody, which has a direct on-tumor and immunomodulatory mechanism of action, with proven activity in AL amyloidosis, which is particularly attractive in case of severe cardiac involvement. High risk patients with important cardiac involvement and NYHA class III or IV and ECOG PS = 4, need a very rapidly acting and safe regimen and supportive therapy during the chemotherapy cycles in order to sustain organ function [81]. Recently, in the phase 3 ANDROMEDA-trial, a combination of daratumumab with CyBorD in patients with newly diagnosed AL amyloidosis resulted in significantly higher hematologic, cardiac, and renal response rates typically within one cycle, and was well tolerated. Therefore, it should be considered a promising novel therapy for AL amyloidosis [82].

In patients in whom a rapid and significant reduction in the serum free light-chain levels is not achieved, a second-line treatment should be considered after hematological response assessment. In responders, maintenance therapy is not indicated [76, 83].

Organ response criteria are essential during treatment follow-up. Cardiac biomarkers, especially NT-pro BNP, have a particular importance for the cardiac response, although they are influenced by therapy related complications, fluid status and supraventricular tachyarrhythmias, very common in CA [84]. A decrease with more than 30% and > 300 ng/l, in NT-pro BNP levels and an improvement of NYHA functional class has been demonstrated to be associated with increased overall survival [83].

In patients resistant to alkylating agents and proteasome inhibitors, immunosuppressive therapy is the only remaining option. Treatment regimens that include immunosuppressant agents (lenalidomide, thalidomide) have demonstrated efficacy among patients with relapsed or resistant AL amyloidosis. These are generally avoided due to significant cardiac and renal toxicity, and are especially useful in patients with contraindications to bortezomib or in subjects with refractory disease.

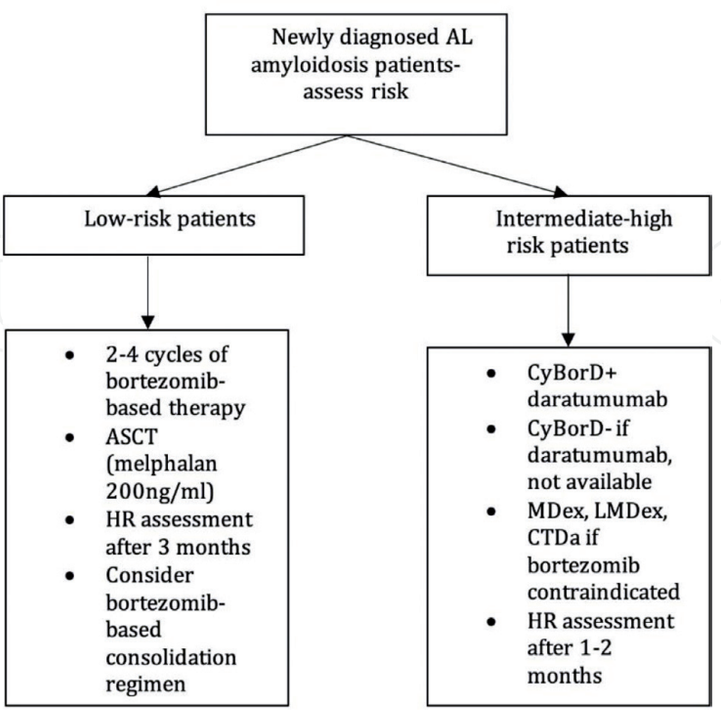

Figure 8.
Treatment algorithm of AL Amyloidosis. CyBorD = cyclophosphamide and dexamethasone; ASCT = autologous stem cell transplantation; MDex = melphalan and dexamethasone; LMDex = lenalidomide, melphalan, and dexamethasone; CTDa = cyclophosphamide and dexamethasone; HR = heart rate.

Treatment with these agents is associated with increased NT-pro BNP levels and affects the assessment of cardiac response, Also, worsening of renal failure and increased proteinuria can be detected [85, 86].

Low dose thalidomide in addition to cyclophosphamide and dexamethasone (CTDa) was demonstrated to have the highest response rates, with acceptable toxicity, but it is not recommended as a routine maintenance therapy due to cumulative neurotoxicity [87]. Lenalidomide in combination with low dose dexamethasone, with or without cyclophosphamide, could be taken into consideration in patients with relapsed AL amyloidosis, but with an increased risk of thrombotic complications (**Figure 8**) [88].

12. Specific treatment of ATTR amyloid cardiomyopathy

Recent findings in the research of molecular pathogenic mechanisms revolutionized the treatment of ATTR amyloidosis. New agents have recently been developed to suppress the production of amyloid in both wild-type and hereditary CA. Current treatment strategies include management of underlying disease process in association with symptomatic relief.

12.1 Disease modifying therapies

1. TTR synthesis inhibitors target by inhibiting the hepatic synthesis of TTR.

   - Patisiran (0.3 mg/kg iv., once daily, every three weeks for 18 months) is a second-generation small interfering RNA (siRNA), which blocks the expression of TTR, leading to reduction in TTR levels [89].

   - Inotersen (200 mg sc., once a week) is a second-generation antisense oligonucleotide, which lowers hepatic production of TTR by bonding to the mRNA [89].

   Both these drugs lead to a reduction of >85% in the concentration of circulating TTR. Two recent randomized trials have demonstrated reduction in the progression of polyneuropathy in patients with ATTRv: the APOLLO trial [90]. (The Study of an Investigational Drug, Patisiran, for the Treatment of TTR Amyloidosis) and the NEURO-TTR [91]. trial (Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy). Even though not explicitly tested, TTR synthesis inhibitors may have beneficial cardiac effects [91, 92]. In order to demonstrate cardiac benefits, two clinical trials assessing the efficacy of TTR synthesis inhibitors in patients with cardiomyopathy are currently ongoing: 24 Month Open Label Study in the Tolerability and Efficacy of Inotersen in TTR Amyloid Cardiomyopathy Patients and the APOLLO-B trial (A Study to Evaluate Patisiran in Participants With TTR Amyloidosis With Cardiomyopathy).

2. TTR stabilizers prevent the misfolding of TTR by binding to TTR tetramer.

   - Tafamidis slows the dissociation of TTR tetramers into monomers by binding to the thyroxine-binding site of the TTR. In the ATTR-ACR randomized trial (Safety and Efficacy of Tafamidis in Patients with TTR Cardiomyopathy), which recruited both patients with ATTRv cardiomyopathy and ATTRwt cardiomyopathy, there was a significant lower all-cause

mortality and cardiovascular-related hospitalization after 30 months after receiving Tafamidis when compared to placebo. Moreover, there was a lower rate of decline in the 6-minute walk test and in the quality of life under both Tafamidis doses (20 and 80 mg orally) [93]. Tafamidis was approved for the use in TTR cardiomyopathy in May 2019.

- Diflunisal is a non-steroidal anti-inflammatory drug, which significantly reduced the progression of polyneuropathy by stabilizing TTR tertramers in a randomized trial [94]. Although no controlled trials evaluated the effect of Diflunisal on TTR cardiomyopathy, two single center studies demonstrated some benefits (250 mg orally twice daily) [95, 96]. However, side effects are not rare (thrombocytopenia and renal dysfunction), administration should be avoided in patients with eGFR<45 mL/min/1.73m^2, thrombocytopenia or signs of hemodynamic or renal instability [97]. Diflunisal is not approved for TTR amyloidosis and can be used off-label.

- AG10 is a synthetic TTR ligand, which acts by binding to the TTR tetramer and therefore prevents amyloid fibril formation and deposition. A phase II randomized multicenter study demonstrated that AG10 (400 mg or 800 mg twice daily for 28 days) induced almost complete stabilization of TTR and patients treated with AG10 showed reduced mortality and cardiovascular hospitalization at 15 months [97].

- Tolcapone is approved for the treatment of Parkinson disease and acts by inhibiting TTR aggregation. It is currently under investigation in patients with TTR amyloidosis [55].

3. TTR disruptors target the clearance of amyloid fibrils from tissue.

- The combination of Doxycycline and TUDCA (tauroursodeoxycholic acid) removed amyloid deposits in preclinical studies, but there was a high incidence of side effects [98, 99]. The role of these therapies is therefore uncertain.

12.2 Symptomatic relief

The control of peripheral and autonomic neuropathy leads to significant improvement in the quality of life. Implantation of a cardiac pacemaker might be beneficial in patients with TTRv and conduction disorders [100]. Implantable cardioverter-defibrillators (ICD) are recommended in patients with significant arrhythmias or aborted sudden cardiac death with expected survival of more than one year. Although reduction in cardiac filling pressures is also necessary, it must be performed with caution, as these patients are dependent of the cardiac output. On the same principle, many drugs used in the treatment of HF might not be beneficial in patients with CA and some agents might have an abnormal distribution by binding to amyloid fibrils (eg. digoxin) [100].

12.3 Management of TTR amyloidosis in patients with aortic stenosis

Recent data demonstrated that the association between CA and aortic stenosis (AS) is more common than previously known and TTR cardiac amyloidosis is the most prevalent type to coexist with AS [101]. Since there are no randomized trials to

evaluate the best therapeutic management in patients with TTR cardiac amyloidosis and AS, the treatment of CA follows the general principles and should be instituted immediately after the diagnosis is confirmed. Regarding the management of AS, the majority of the studies reported a high risk of mortality after surgical aortic valve replacement (SAVR) [101–106].

One study performed on a limited number of patients demonstrated that in patients with CA and AS outcomes might be better with trans-aortic valve replacement (TAVR) than SAVR [102]. Two ongoing prospective trials, ATTRact-AS (The Role of Occult Cardiac Amyloid in the Elderly With Aortic Stenosis) and Amylo-CARTESIAN (Prevalence and Post-surgical Outcomes of CARdiac Wild-type TransthyrEtin amyloidoSIs in Elderly Patients With Aortic stenosis Referred for Valvular Replacement) might lead to better understanding of the prevalence and management of patients who present both pathologies. One recently published sub-study of the ATTRact-AS trial showed that there was no difference in mortality after TAVR between patients with CA and AS or AS alone [107]. Thus, TAVR might be a better option for patients with intermediate to high surgical risk. However, since some patients might be prone to complications during TAVR because of the fragility of the infiltrated myocardium [108]. a multidisciplinary heart team should discuss the optimal therapy.

13. Summary

Amyloidosis represents a heterogeneous group of disorders that present as a multi-organ disease presenting with unspecific symptoms. The diagnosis of amyloidosis often is difficult and can be delayed, and therefore the number of unreported cases is likely quite significant.

Amyloid can infiltrate all structures of the heart including ventricular and atrial walls, the conduction system, the heart valves, and the coronaries. The typical clinical presentation in CA is that of a restrictive cardiomyopathy. When present, cardiac amyloidosis has a significant impact on disease prognosis.

Cardiac biomarkers, echocardiography, and other imaging techniques such as CMR or 99mTc-phosphate scintigraphy are available for the diagnosis of CA as well as determination of the extent of this disease. Endomyocardial biopsy remains the main method used for histopathological confirmation and subtyping of CA.

The main goal of the diagnostic strategy is to detect CA early, to define the extent of CA, and to enable targeted therapy.

14. Conclusion

Until recently, amyloidosis was still considered a rare multi-organ disease. The diagnosis of CA was often missed or only documented at a late stage with negative impact on the prognosis of the patients.

Meanwhile, it has become evident that CA is more prevalent than once thought and can be the only manifestation of amyloidosis so that early diagnosis and subsequent therapy are becoming increasingly important.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

All authors contributed equally to this chapter.

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