

## TASK FORCE OF THE WORKING GROUP ON MYOCARDIAL AND PERICARDIAL DISEASE

ON:

**“Diagnosis and treatment of cardiac amyloidosis. A position statement of the ESC Working Group on Myocardial and Pericardial Disease.”**

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## **Introduction**

Cardiac amyloidosis is characterized by extracellular deposition of misfolded proteins in the heart with the pathognomonic histological property of green birefringence when a tissue specimen is examined under cross polarized light after staining with Congo red<sup>(1)</sup>. Although previously considered a rare disease, recent data suggest that cardiac amyloidosis is underappreciated as cause of common cardiac diseases or syndromes<sup>(2)</sup>. Recent advances in cardiac imaging, diagnostic strategies and therapies have improved recognition and treatment of cardiac amyloidosis<sup>(1,2)</sup>.

The aim of this multidisciplinary position paper by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Disease is to help cardiologists and other physicians in recognizing, diagnosing, and treating patients with cardiac amyloidosis.

## **Types of cardiac amyloidosis:**

While more than 30 proteins are known to be capable of aggregating as amyloid *in vivo*, only 9 amyloidogenic proteins accumulate in the myocardium producing significant cardiac disease<sup>(3)</sup>.

Nevertheless, some forms (AApoAI, AApoAII, AApoAIV, A $\beta$ 2M, AFib, AGel) are very rare and cardiac amyloidosis secondary to chronic inflammatory and infectious diseases (AA), although still encountered, is now much less frequent. Therefore, >98% of currently diagnosed cardiac amyloidosis result from fibrils composed of either monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form. Table 1 describes the main characteristics of each type of cardiac amyloidosis.

## **Pathophysiology**

Two main mechanisms of tissue and organ damage are known: chronic infiltration and acute proteotoxic effect of circulating precursors and nonamyloid aggregates. The latter is particularly evident and documented in AL but has also been shown in ATTRv and ATTRwt. Myocardial infiltration by rigid, space-occupying amyloid fibrils leads to increased stiffness and dysfunction of ventricles and atria. Infiltration is generally diffuse

but can be mainly subendocardial or with patchy areas of transmural involvement<sup>(4)</sup>. A base to apex gradient in left ventricular (LV) myocardial infiltration has been frequently advocated to explain the apex sparing of longitudinal strain abnormalities. Atrial involvement is frequent, leading to poor atrial function and increased rates of atrial fibrillation. While histologic involvement of the epicardial coronary vessels does not appear to be a cause of vascular stenosis, amyloid can deposit in the small intramural coronary arteries could cause myocardial ischemia. The conduction system can be affected both at sinus node level and the A-V node or His bundle causing varying degrees of heart block as well as bundle branch block<sup>(4,5)</sup>. A-V valves are frequently thickened, often with mild to moderate regurgitation. Pericardial involvement can lead to small pericardial effusions (large effusions are rare)<sup>(1,2)</sup>.

Cardiac amyloidosis is commonly considered a form of restrictive cardiomyopathy or to have restrictive physiology in the presence of increased wall thickness. This hemodynamic profile is typical of the fully evolved disease but can be absent or mild in the initial phases. The progressive increasing parietal and chamber stiffness leads to an upward and leftward shift in the end-diastolic pressure–volume relationship with concomitant declines in stroke volume, cardiac output, (and frequently blood pressure)<sup>(6)</sup>. Parallel declines in stroke volume and end-diastolic volume explain why LV ejection fraction (LVEF) remains preserved during the course of the disease until the late phases, whereas myocardial contraction fraction is reduced. LVEF is <50% in about 35% of cases in some types of cardiac amyloidosis when the disease is diagnosed<sup>(7)</sup>. LV systolic function is indeed compromised even in many patients with normal LVEF as documented by the reduction in LV longitudinal function and strain. Furthermore, myocardial contractility and inotropic reserve during exercise are reduced in almost all patients.

### **Diagnosis of cardiac amyloidosis**

Diagnosis of cardiac amyloidosis includes two critical phases: 1) *suspicious phase* and 2) *definite diagnosis phase*. The definite diagnosis phase includes also appropriate typing of the amyloid which is critical to guide specific treatment.

## **When to suspect cardiac amyloidosis**

### *Red-flags*

Cardiac amyloidosis usually appears within a constellation of extracardiac signs and symptoms that are extremely useful to suspect the disease in the presence of compatible cardiac imaging findings. These signs and symptoms receive the name of “red-flags” and include macroglossia, skin bruises and carpal tunnel syndrome among others (Table 2). Furthermore, there are also a variety of red-flags at cardiac level that can also be used to suspect the disease. As such, heart failure (including disproportionately high NT-proBNP) which appears to be in disproportion to “objective” findings on echocardiogram, “unexplained” right heart failure in the presence of what appears to be a “normal” ventricular and valvular function or “idiopathic” pericardial effusion. Persistent troponin elevation, disproportionately low QRS voltage or early conduction system disease are also signs that should evoke a consideration of a unique etiology such as infiltrative myocardial disease. Another “red-flag” should be intolerance to blood pressure or heart failure medications (Table 2).

### *Clinical scenarios*

Further to cardiac and extracardiac specific findings fostering the suspicion, there are several clinical situations in which cardiac amyloidosis should always be considered.

Cardiac disease in the presence of a typical systemic condition such as plasma cell dyscrasia, nephrotic syndrome, peripheral neuropathy or chronic systemic inflammatory condition should evoke consideration of amyloidosis, especially if compatible cardiac imaging findings are present.

Increased wall thickness in a nondilated LV is a prominent characteristic of cardiac amyloidosis and should lead to further evaluation when found in elderly patients with common cardiac syndromes like heart failure with preserved ejection fraction or hypertrophic cardiomyopathy. A relevant proportion (up to 7 to 19%) of elderly heart failure patients with increased LV wall thickness has been described to suffer ATTRwt<sup>(7-12)</sup> and in patients with LV wall thickness  $\geq 15$  mm, ATTRv was found in 11% of patients aged 65 to 84 years<sup>(13)</sup>.



Other studies have reported a significant prevalence of ATTRwt (ranging from 5% to 16%) in elderly individuals with severe aortic stenosis (AS), particularly among those undergoing transcatheter aortic valve replacement (TAVR) with low-flow low-gradient phenotype<sup>(14,15)</sup>.

Based on abovementioned values and with the possibility of non-invasive diagnosis we recommend ascertainment of cardiac amyloidosis in individuals with increased wall thickness and non-dilated LV with either heart failure, aortic stenosis or red flag signs/symptoms, particularly if older than 65 years (Figure 1).

### **Definite and etiologic diagnosis**

Definite diagnosis of cardiac amyloidosis has not been standardized but both invasive and non-invasive diagnostic criteria have been proposed. Invasive diagnostic criteria apply to all forms of cardiac amyloidosis and non-invasive criteria are currently accepted only for ATTR (Figure 2).

#### *Invasive diagnostic criteria*

Cardiac amyloidosis is confirmed when an endomyocardial biopsy demonstrates amyloid deposits on Congo red staining irrespective of the degree of LV wall thickness. Identification of amyloid should be followed by identification of the amyloid fibril protein that can be achieved by referring histological preparations to specialized centers<sup>(16)</sup>. Although the gold standard for defining the type of amyloid remains mass spectrometry, immunohistochemistry or immunoelectron microscopy are routinely employed for amyloid typing in specialized centers<sup>(4)</sup>.

Diagnosis is also confirmed if amyloid deposits within an extra-cardiac biopsy are accompanied either by characteristic features of cardiac amyloidosis by echocardiography in the absence of an alternative cause for increased LV wall thickness or by characteristic features on cardiac magnetic resonance (CMR) (Table 3). CMR is particularly useful to unravel amyloid infiltration when comorbidities such as chronic kidney disease, hypertension, or valvular heart disease are present.

A recent multicentre study has proposed an echocardiographic score to facilitate echocardiographic diagnosis of cardiac amyloidosis in the presence of increased LV wall

thickness<sup>(17)</sup>. Although not externally validated yet, a score  $\geq 8$  points in the presence of LV wall thickness  $\geq 12$  mm in combination with amyloid deposits in an extra-cardiac biopsy should also be considered diagnostic of cardiac amyloidosis (Table 3).

#### *Non-Invasive diagnostic criteria*

Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings, when <sup>99m</sup>Tc-PYP, -DPD or -HMDP scintigraphy shows grade 2 or 3 myocardial uptake of radiotracer (Figure 3) if clonal dyscrasia is excluded by all the following tests: serum free light chain assay, serum immunofixation (SPIE) and urine immunofixation (UPIE)<sup>(18)</sup>. The combination of SPIE, UPIE and quantification of serum free light chains has a 99% sensitivity for identifying abnormal proamyloidotic precursor in AL amyloidosis<sup>(19)</sup>. It is important to stress that serum and urine protein electrophoresis should always be performed with immunofixation to increase the sensitivity of the assays for detecting low-level monoclonal proteins (Supplemental material).

In absence of a detectable monoclonal protein and/or an abnormal serum free light chain ratio, the specificity of grade 2 or 3 bone scintigraphy for cardiac ATTR when the disease is suspected has been proposed to be almost 100%<sup>(19)</sup>. Nevertheless, recent reports have shown that rare situations can also lead to positive cardiac uptake<sup>(20)</sup>. These situations should always be considered when interpreting scintigraphy results (Table 4).

Once cardiac ATTR amyloidosis is confirmed, genetic testing should be performed to assess for the presence of *TTR* mutations in order to differentiate between ATTRwt and ATTRv. Genetic testing should be performed even in elderly patients as a significant number can have *TTR* mutations<sup>(21)</sup>.

#### **Diagnostic algorithm**

Once cardiac amyloidosis is suspected, a timely, definitive diagnosis should be obtained. Patient outcomes depend largely on early initiation of therapy (particularly in AL) and physicians should pursue proper evaluation promptly.

As the large majority of cases of cardiac amyloidosis are AL and ATTR, we propose a diagnostic algorithm focusing on identifying these subtypes by the initial use of <sup>99m</sup>Tc-

PYP, DPD or HMDP scintigraphy coupled with assessment for monoclonal proteins by SPIE, UPIE and quantification of serum free light chains.

The results of these test could lead to 4 scenarios (Figure 4):

- 1. Scintigraphy does not show cardiac uptake and assessment for monoclonal proteins are negative.** There is a very low chance of cardiac amyloidosis. Consider false negative of bone scintigraphy, as tracer uptake depends on TTR fibril composition or rare subtypes of cardiac amyloidosis (Table 4). In case suspicion persists consider CMR followed by cardiac or extracardiac biopsy.
- 2. Scintigraphy shows cardiac uptake and assessment for monoclonal proteins are negative.** If cardiac uptake is grade 2 or 3, ATTR cardiac amyloidosis can be diagnosed. Proceed with genetic testing to differentiate between ATTRv and ATTRwt forms. In case cardiac uptake is Grade 1, non-invasive diagnosis is not possible and histological confirmation of amyloid (could be extracardiac) is required.
- 3. Scintigraphy does not show cardiac uptake and any of the monoclonal protein tests are abnormal.** AL amyloidosis has to be ruled-out. CMR can confirm cardiac involvement. If CMR findings do not support cardiac amyloidosis, the diagnosis is unlikely. In case CMR findings are supportive, cardiac or extracardiac histological demonstration of amyloid would be required to diagnose AL cardiac amyloidosis. A cardiac or other clinically-affected organ biopsy is recommended to avoid time delay until diagnosis<sup>(22)</sup>.
- 4. Scintigraphy shows cardiac uptake and any of the monoclonal protein tests are abnormal.** ATTR, AL and coexistence of both types of amyloidosis are possible in this scenario. Diagnosis of cardiac amyloidosis in this case requires histology with amyloid typing, usually via endomyocardial biopsy.

### **Prognosis in cardiac amyloidosis**

Although diverse ways to prognosticate in cardiac amyloidosis have been proposed and a detailed review of individual prognostic factors can be found at supplemental material, focus has moved to multiparametric biomarker-based prognostic scores.

In 2004, the Mayo clinic reported the first staging system in AL using serum troponin along with NT-proBNP<sup>(23)</sup>. The identification that free light chain burden also affects prognosis in AL led to a revised Mayo biomarker staging system in 2012<sup>(24)</sup>.

Based on the great clinical utility of these staging systems in AL, two biomarker based staging systems were recently developed in ATTR amyloidosis.

One proposed by the Mayo clinic group for ATTRwt cardiac amyloidosis using NT-proBNP concentration and troponin T with cutoff values of 3000 pg/ml and 0.5 ng/ml, respectively<sup>(25)</sup>.

Another staging system, developed at the UK National Amyloid Centre uses NT-proBNP and eGFR (MDRD formula) with cutoff values of 3000 pg/ml and 45 ml/min, respectively<sup>(26)</sup>. This latter score system has the advantage over the previous one that it relies on two parameters widely available and it is not subject to the troponin subtype and its quantification method. Table 5 shows the three prognostic scores with their reported survival.

### **Progression of cardiac amyloidosis**

While there have been multiple studies delineating baseline risk factors associated with adverse outcomes (principally mortality) in AL and ATTR and data is emerging from the placebo arm of therapeutic trials<sup>(27)</sup>, there is a paucity of published data on longitudinal aspects of disease progression and none that are population based without referral and ascertainment bias. In the era of emerging effective therapies, this is a major unmet need.

#### *AL cardiac amyloidosis progression and response*

Given the biologic link between light chain toxicity and NT-proBNP, an NT-proBNP response generally follows lowering of the light chains<sup>(28)</sup>, with a cardiac response defined as a decrease in NT-proBNP  $\geq 30\%$  and  $\geq 300$  pg/ml while cardiac progression is defined as NT-proBNP progression NT-proBNP  $\geq 30\%$  and  $\geq 300$  pg/ml<sup>(29)</sup>. The cardiac response criteria have been shown to be a robust predictor of survival and could serve as a surrogate endpoint for clinical trials<sup>(30)</sup>.

### *ATTR cardiac amyloidosis progression and response*

No formal definition of progression in ATTR cardiac amyloidosis has been accepted. Interpretation of changes in 6MWD in subjects with ATTRv and concomitant neurological disease is complex, but such changes seem to be more associated with the neuropathy than the cardiomyopathy<sup>(31)</sup>.

Response criteria for therapeutic efficacy have not been developed in cardiac ATTR either. Stabilizers have been shown to increase the concentration of tetrameric TTR<sup>(32)</sup>. Silencers, on the contrary, lower TTR levels and the degree of knockdown has been associated with clinical benefits<sup>(33,34)</sup>. Whether following TTR levels during treatment is useful to monitor therapeutic response requires further study.

### **Follow-up of patients with cardiac amyloidosis**

Although there are no studies addressing what is the optimal follow-up scheme in patients with cardiac amyloidosis, a common scheme consists of 6-month time interval visits with ECG and complete blood tests (including NT-proBNP and Troponin) and yearly echocardiogram and 24h Holter ECG.

Atrial and ventricular arrhythmias are common in patients with both AL and ATTR. While episodes of non-sustained ventricular tachycardia are frequently observed<sup>(35)</sup>, their independent association with adverse outcomes has not been consistently reported<sup>(36)</sup>. On the contrary, atrial fibrillation (AF) is associated with serious thromboembolic risk. Given the known benefits of anticoagulation, routine screening for atrial arrhythmias is endorsed.

Furthermore, if feasible, evaluation by 6MWD and Kansas City Questionnaire every 6 months could be of interest given the availability of natural history data from trial's placebo groups<sup>(27)</sup>.

A summary of recommended follow-up tests can be found in Table 6.

### **Follow-up of mutation carriers and genetic counselling**

For relatives of patients with an inheritable form of cardiac amyloidosis, genetic testing is recommended. Such testing should occur along with genetic counselling of patients and their families. As all hereditary amyloidoses have an adult onset, genetic testing of minors is discouraged. Genetic testing could be offered during young adulthood if

genetic information would seem useful to guide professional choices or for reproductive planning.

Among the over 130 mutations in ATTRv, there is significant heterogeneity regarding penetrance which is largely attributable to the specific mutation and is age dependent. Other factors that influence penetrance include sex, region of origin, fibril type (full length or fragmented), maternal inheritance, and/or concomitant inflammation. Specific TTR mutations including Val142Ile, Thr80Ala, Ile88Leu and Leu131Met are diagnosed on average in the 8<sup>th</sup>, 7<sup>th</sup>, 6<sup>th</sup> and 5<sup>th</sup> decade of life. Assessment of penetrance in allele carriers of specific mutations is generally recommended to start ~10 years prior to the age of diagnosis of affected members of the family (or other individuals with the same mutation) or as soon as symptoms compatible with ATTR develop<sup>(37)</sup> (Table 6).

## **Treatment**

Treatment of cardiac amyloidosis involves two areas: 1) Treatment and prevention of complications including heart failure, arrhythmias, conduction disturbances and thromboembolism; and 2) Stopping or delaying amyloid deposition by specific treatment.

### **Treatment of complications**

Supportive care of patients with cardiac amyloidosis encompasses different clinical aspects (Figure 5).

#### *Heart failure*

Avoiding fluid retention is essential in patients with cardiac amyloidosis. A *low-salt diet*, *daily weight monitoring* and *fluid restriction* ( $\leq 1.5$  litres/day) should be strongly recommended.

The mainstay of HF treatment in cardiac amyloidosis is based on *loop diuretics* to control congestion and to reduce HF symptoms. Diuretic dose needs to be adapted frequently to maintain euvolemia. *Mineralocorticoid receptor antagonists* at low doses, might be helpful, in combination with loop diuretics, to prevent hypokalaemia, especially if high doses of diuretics are needed.

However, use of diuretics must be extremely carefully managed because excess diuresis can provoke hypotension and clinical deterioration by reducing preload and LV filling pressures in the presence of a restrictive physiology.

*Midodrine*, a selective and peripheral agonist of  $\alpha$ -adrenergic receptors, and elastic stocking could be used in patients with symptomatic hypotension<sup>(38)</sup>.

There is currently no evidence that patients with cardiac amyloidosis benefit from systolic heart failure therapies, including ACE inhibitors (ACEI), ARBs, sacubitril/valsartan, beta-blockers and ivabradine. In contrast, they could lead to clinical worsening.

Cardiac amyloidosis is frequently associated with hypotension and with a reduced and fixed stroke volume that requires a higher heart rate to maintain adequate cardiac output. Thus, heart failure drugs could be poorly tolerated. In summary, beta-blockers, ivabradine, ACEIs and ARBs should be generally avoided and if needed, they should be used cautiously.

Moreover, non-dihydropyridine calcium channel blockers are contraindicated due to the risk of A-V block and reduced inotropism.

Regarding digoxin, it has been classically contraindicated but a recent retrospective study in AL patients reported significant arrhythmias in only 11% of them, suggesting that *digoxin* might be used if administered at lower doses and with frequent drug concentration monitoring along with close monitoring of electrolytes and renal function<sup>(39)</sup>.

#### *Thromboembolic risk*

Thromboembolism is associated with atrial as well as LV systolic and diastolic dysfunction, right ventricular hypertrophy, high heart rate and low velocities in left atrial appendage, in addition to AF, and contributes to cardiac amyloidosis mortality<sup>(40)</sup>.

Anticoagulation should be started in patients with AF in any form, regardless of CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>(41)</sup>.

Moreover, anticoagulation in sinus rhythm might also be considered on an individual basis as atrial thrombi are present in up to 4.5% of AL and 1.1% of ATTR patients in sinus rhythm possibly due to silent paroxysmal AF and/or atrial myopathy<sup>(42)</sup>. Particularly

consider anticoagulation if atrial standstill is found based on the mitral Doppler flow pattern.

Finally, there is not enough data to recommend direct oral anticoagulants over vitamin K antagonists or vice versa in cardiac amyloidosis and both options are valid.

### *Atrial fibrillation*

Management of AF in cardiac amyloidosis constitutes a challenge and there is little evidence regarding its impact. In ATTRwt for instance, some studies have associated AF with a higher degree of heart failure with no differences in survival in terms of paroxysmal or permanent AF<sup>(43,44)</sup>. In two retrospective studies no survival differences were found between patients with and without AF (but was strongly associated with prevalent and incident heart failure); these differences were maintained when classifying by AL or ATTRwt subtypes<sup>(43,45)</sup>. Therefore, the decision whether to try rhythm or heart rate control should be individualized.

Amiodarone is the preferred antiarrhythmic drug used. Dofetilide could be considered with careful monitoring of QT interval.

Electrical cardioversion should be considered a high-risk procedure with complications including cerebrovascular events, transient AV block, or ventricular arrhythmias<sup>(46)</sup>. As a significant number of patients could have intracardiac thrombi regardless of AF onset or correct anticoagulation, transoesophageal echocardiogram should be recommended before the procedure<sup>(46)</sup>. Initial success rates of electrical cardioversion are similar between cardiac amyloid patients and control patients<sup>(46)</sup>. Recurrences, however, are very frequent. Data regarding the role of AF ablation in cardiac amyloidosis are scarce and controversial and should only be recommended in an individual basis<sup>(47)</sup>.

### *Conduction disorders*

Amyloid infiltration of the conduction system can occur either directly by deposition or by adjacent fibrosis and could be the first manifestation of the disease<sup>(9)</sup>. Conduction disorders can be unpredictable and rates of pacemaker (PM) implantation are quite variable among series<sup>(48,49)</sup>.

In terms of conduction disorders, current PM indications in CA include symptomatic patients with complete AV block, 2<sup>nd</sup> degree AV block or sinus node dysfunction,



according to general guidelines<sup>(50)</sup>. Given the progressive nature of conduction disorders, prophylactic PM implantation could be considered individually in asymptomatic patients presenting with trifascicular block or HV interval >70ms or even with gradual widening of PR interval duration during follow-up.

Although single lead or DDD PPM have been the type of PPM traditionally implanted in patients with cardiac amyloidosis, recent data suggest that cardiac resynchronisation (CRT) devices might be more appropriate if high paced burden (>40%) is required<sup>(51)</sup>.

### *Ventricular arrhythmias*

Although the relation between cardiac amyloidosis and ventricular arrhythmias is known, the usefulness of ICDs in these patients is not well established<sup>(52)</sup>.

SCD in patients with cardiac amyloidosis can occur due to electromechanical dissociation and currently ICD is recommended only for secondary prevention. In case an ICD is implanted, the transvenous ICD is preferred over the subcutaneous ICD as pacing mode could be of interest to avoid low heart rate shown to appear prior to SCD events in some cases<sup>(35)</sup>.

### *Aortic stenosis*

Severe AS is independently associated with worst prognosis in patients with concomitant ATTRwt<sup>(53)</sup>. Moreover, concomitant ATTRwt probably represents a risk factor for AS periprocedural a-v block. Robust data on long term outcome post AS intervention are lacking but recent reports suggest that TAVR significantly improves outcome in amyloid-AS, while periprocedural complications and mortality are similar to lone AS<sup>(54)</sup>.

### *Advanced Heart Failure*

Although LV assist devices (LVAD) appeared not to be suitable for most patients due to small LV end-diastolic volumes, LVAD implantation has been demonstrated to be technically feasible in some patients. Nevertheless, whether this approach has a beneficial role remains uncertain<sup>(55)</sup>.

Heart transplantation could be an option in carefully selected patients with ATTR, predominant heart disease, no significant extra-cardiac amyloidosis and advanced heart failure<sup>(56,57)</sup>.

Combined liver and heart transplantation has been an option in selected ATTRv patients with mixed phenotype with advanced heart failure and mild neurologic involvement but availability of new therapies is challenging the option of combined transplantation.

Finally, cardiac transplantation in AL patients could allow aggressive chemotherapy strategies or Autologous Stem Cell Transplantation (ASCT) to ensure haematological remission as well as a solution for advanced cardiac disease in the presence of stable haematological remission in carefully selected patients with absent or minimal extracardiac amyloid deposition<sup>(56,57)</sup>.

### **Specific (disease modifying) treatment**

In general, treating the process of amyloid deposition should target the production of amyloid precursor protein or the assembly of amyloid fibrils. Future therapies would try disassembling the tissue deposits using small molecules or monoclonal antibodies mobilizing the immune system.

### ***AL amyloidosis***

Specific treatment in cardiac AL amyloidosis should be undertaken by multidisciplinary teams involving oncohaematology and cardiology specialists and whenever possible, patients should be referred to specialized centers<sup>(58)</sup>.

Patients with AL amyloidosis not only have a hematologic malignancy, but their multiorgan involvement makes them particularly fragile and susceptible to treatment toxicity. Therapeutic approaches depend on risk assessment defined in many circumstances by the degree of cardiac involvement (Figure 6). A more detailed state-of-the-art description of therapeutic options and cardiac response probabilities based on the hematological response criteria in AL amyloidosis can be found in supplemental material. Cardiologists' role in AL specific treatment includes: 1. Cardiac assessment for initial hematologic strategy including ASCT consideration (Table 7), 2. Heart transplant evaluation 3. Cardiac monitoring during chemotherapy.

### *Cardiac monitoring during chemotherapy*

A recent ESC position paper has addressed the diagnosis and management of cardiovascular toxicity of chemotherapy. For high-risk patients, such as those with pre-existing LV dysfunction and heart failure, a tailored and detailed plan for cardiac management throughout treatment and beyond should be established<sup>(59)</sup>.

Strategies for screening, detection, and monitoring of cardiotoxicity include biomarkers and cardiac imaging. The choice of modalities depends upon local expertise and availability. Using the same modalities of monitoring with higher reproducibility is recommended<sup>(59)</sup>. The frequency of imaging and biomarker sampling will depend upon the specific chemotherapy, total cumulative dose of cardiotoxic chemotherapy, delivery protocol and duration and the patient's baseline cardiovascular risk. A common scheme includes monthly biomarker evaluation during initial hematological treatment with cardiac imaging every 6 months (table 6).

### ***ATTR amyloidosis***

There is growing availability of novel, effective, targeted therapeutic options for ATTRwt and ATTRv<sup>(60)</sup>. A prompt diagnosis to allow the timely treatment of neurological, cardiac, and other systemic manifestations is essential. In fact, therapy is more effective in the early stages of the disease<sup>(27,33,34)</sup>. Effective therapies reduce the production of mutated (liver transplantation) and overall TTR (gene silencers) or stabilize circulating TTR molecules (stabilizers) preventing its dissociation or cleavage into amyloidogenic fragments. Several new compounds are under investigation including agents directed to remove amyloid fibrils (Figure 7).

### *Liver transplant*

Isolated liver transplant has been indicated in early onset ATTRv patients with mixed phenotype and mild cardiac disease in the early stage of the neurological disease. Clear benefit in terms of quality of life and survival is observed in patients with Val50Met variant, while the benefit is reduced in non-Val50Met variants<sup>(61)</sup>. Despite the suppression of mutated TTR production at the liver, cardiac and neurological progression of the disease might still occur after transplant as a consequence of continued deposition of wild type TTR in pre-existing mutated amyloid aggregates<sup>(62)</sup>.

With the advent of new genetic silencers that suppress production of both wild type and mutated TTR, liver transplantation probably will become an obsolete approach.

### *Tafamidis*

Tafamidis, a kinetic TTR stabilizer, binds to the unoccupied thyroxine binding sites of tetrameric TTR, preventing the amyloidogenic cascade<sup>(63)</sup>. It was approved for treatment of stage I (ambulatory without assistance) symptomatic ATTRv polyneuropathy and is the only therapy that has shown effectivity to treat ATTR cardiomyopathy in a randomized placebo-controlled trial so far. Tafamidis (20 and 80 mg once daily pooled) demonstrated a reduction of around 30% in all-cause mortality and in cardiovascular-related hospitalization and slower decline in QOL in biopsy-proven ATTRwt or ATTRv cardiomyopathy patients with heart failure and NYHA class I to III at 30 months<sup>(27)</sup>. Safety profile of both doses were similar to placebo and the largest benefit was seen in individuals with NYHA class I and II<sup>(27)</sup>. Additional experimental and preliminary data support the use of the higher dose of tafamidis and this has been the basis of the approval by EMA and other regulatory agencies of tafamidis free acid 61 mg (a formulation bioequivalent to tafamidis meglumine 80 mg) for ATTR cardiac amyloidosis. Despite its proven efficacy, concerns about its cost-effectiveness have emerged in the US due to its price<sup>(64)</sup>. Further studies would be needed to address cost-effectiveness of tafamidis outside the US but currently it should be considered the agent of choice in ATTR cardiac patients with reasonable expected survival (Figure 8).

### *Diflunisal*

Diflunisal is a nonsteroidal anti-inflammatory drug with TTR-stabilizing properties. In a randomized, placebo-controlled, double-blinded, study in ATTRv patients, diflunisal at 250mg bid showed decreased neuropathy progression and improved QOL but failed to show statistically significant differences in cardiac parameters among individuals with cardiac disease<sup>(65)</sup>. Although, possible beneficial effects have been reported in small cohorts of ATTR cardiac amyloidosis patients<sup>(66)</sup>, frequent adverse events associated with NSAIDs may preclude its use in patients with heart failure.

## *AG10*

AG10 is a highly selective, small-molecule TTR stabilizer. Phase I and II studies showed a good toxicity profile and stabilization of both mutant and wild-type TTR<sup>(32)</sup>. A phase 3 efficacy and safety study to evaluate AG10 compared to placebo in subjects with symptomatic ATTR cardiomyopathy is ongoing (ClinicalTrials.gov Identifier: NCT03860935).

## *TTR silencers*

Recently, agents capable of silencing the *TTR* gene and substantially reduce the concentration of circulating TTR have entered clinical practice. They specifically degrade *TTR* mRNA at the nucleus (inotersen) or cytoplasm (patisiran)<sup>(33,34)</sup>. Both agents have been approved for treatment of ATTRv polyneuropathy after demonstration of their efficacy in randomized placebo-controlled neurologic trials in patients with stage I or II (ambulatory with assistance) neurologic disease<sup>(33,34)</sup>. Patisiran was effective in secondary analysis of cardiac parameters (NT-proBNP, LV thickness and longitudinal strain) in ATTRv patients with cardiac amyloidosis included in its trial<sup>(34,67)</sup>. In contrast, Inotersen did not show significant difference in echocardiographic variables compared with placebo in ATTRv patients with cardiac disease in its neurological trial<sup>(33)</sup> despite a small open-label study has shown stabilization of cardiac parameters in the majority of both ATTRv and ATTRwt patients followed for up to 3 years<sup>(68)</sup>. While waiting for ongoing prospective cardiac studies, these observations support the use of patisiran in ATTRv patients with cardiac involvement in whom gene silencers are prescribed due to symptomatic neurological disease. (Figure 8). Ongoing Phase III trials in patients with ATTRwt or ATTRv cardiomyopathy of patisiran and new gene silencing molecules (Vutrisiran and AKCEA-TTR-LRx) will definitively address if gene silencing approach is beneficial in ATTR cardiac amyloidosis (ClinicalTrials.gov Identifiers: NCT03997383, NCT04153149 and NCT04136171).

## **AA amyloidosis**

AA amyloidosis is caused by different conditions inducing an increase in the serum concentration of the acute phase protein SAA such as infections, inflammation or malignancies. The kidney is the target organ while significant cardiac involvement is

rare. Nonetheless, an autopsy study in patients with rheumatoid arthritis pointed out that subclinical cardiac involvement may be as frequent as clinical renal involvement, conditioning survival<sup>(69)</sup>. Identifying the underlying disease can be challenging but it is essential since provides an opportunity for targeted therapy, that can result in normalization of SAA levels and halt the progression of amyloidosis and possibly rescue the function of the affected organs<sup>(70)</sup>.

### **Summary**

In this paper the Working Group on Myocardial and Pericardial Disease proposes an invasive and non-invasive definition of cardiac amyloidosis, address clinical scenarios and situations to suspect the condition and proposes a diagnostic algorithm to reach diagnosis. Furthermore, we also provide a detailed review on how to monitor and treat cardiac amyloidosis in an attempt to bridge the gap between latest advances in the field and clinical practice.

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**Tables:**

**Table 1. Main Characteristics of different types of cardiac amyloidosis.**

**Table 2. Cardiac and extracardiac amyloidosis Red-Flags.**

**Table 3. Echocardiographic and CMR criteria for diagnosis of cardiac amyloidosis in the presence of extracardiac biopsy-proven amyloidosis or Grade 2-3 diphosphonate myocardial uptake.**

**Table 4. Possible false positives and false negatives of diphosphonate scintigraphy for detecting ATTR cardiac amyloidosis.**

**Table 5. Prognostic staging scores in AL and ATTR amyloidosis.**

**Table 6. Proposed follow-up schemes in cardiac amyloidosis.**

**Table 7. Autologous Stem Cell transplantation (ASCT) eligibility criteria.**

## Figures

**Figure 1. Invasive and non-invasive diagnosis of cardiac amyloidosis.**

**Figure 2. Screening for cardiac amyloidosis.**

**Figure 3. Cardiac uptake grading in diphosponate scintigraphy.** Grade 0: absence of tracer myocardial uptake and normal bone uptake; Grade 1: Myocardial uptake in a lower degree than at bone level; Grade 2: Similar myocardial and bone uptake; Grade 3: Myocardial uptake greater than bone with reduced/absent bone uptake.

**Figure 4. Diagnostic algorithm for cardiac amyloidosis.** ATTRv: hereditary TTR amyloidosis; ATTRwt: wild-type TTR amyloidosis; AL light chain amyloidosis; CMR: cardiac magnetic resonance.

**Figure 5. Treatment of cardiac complications in cardiac amyloidosis.** AA: antiarrhythmic; ACEI: angiotensin converting enzyme inhibitors; AF: atrial fibrillation; ARB: Angiotensin receptor blockers; CV: cardioversion; ICD: implantable cardiac defibrillator; LVAD: left ventricular assist device; PPM: Permanent pacemaker.

**Figure 6. Proposed approach for therapy in newly diagnosed AL patients.**

<sup>1</sup> Bortezomib-based consolidation

<sup>2</sup> Change in therapy is required early in the treatment course, typically if at least hematological VGPR is not reached within 3-4 cycles.

ASCT: Autologous Stem Cell transplantation; BMDex: Bortezomib, melphalan, dexamethasone; CyBorD: Cyclophosphamide, bortezomib, dexamethasone; CR: Complete response; HDM: High dose Melphalan; VGPR: Very good partial response.

**Figure 7. Available and future specific therapies in ATTR amyloidosis.** Modified from<sup>(60)</sup>.

**Figure 8. Proposed therapeutic alternatives in ATTR patients.**