“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 characterised by the extracellular deposition of misfolded proteins in the heart with the pathognomonic histological property of green birefringence when viewed under cross polarised light after staining with Congo red[1].

Although considered a rare disease, recent data suggest that cardiac amyloidosis is underappreciated as a cause of common cardiac diseases or syndromes[2]. Recent advances in cardiac imaging, diagnostic strategies and therapies have improved the recognition and treatment of cardiac amyloidosis[1,2].

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

Definitions and classifications

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 to cause significant cardiac disease[3].

Nevertheless, some forms (AApoAI, AApoAII, AApoAIV, Aβ2M, AFib, AGel) are very rare and cardiac amyloidosis secondary to chronic inflammatory and infectious diseases (AA), although still encountered, is now much less frequent. Accordingly, >98% of currently diagnosed cardiac amyloidosis results from fibrils composed of 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.

Definition of cardiac amyloidosis. Diagnostic criteria.

Cardiac amyloidosis is diagnosed when amyloid fibrils are found within cardiac tissue. Both invasive and non-invasive diagnostic criteria have been proposed. Invasive diagnostic criteria apply to all forms of cardiac amyloidosis whereas non-invasive criteria are accepted only for ATTR (Figure 1).

Invasive diagnostic criteria

Cardiac amyloidosis is confirmed when an endomyocardial biopsy demonstrates amyloid deposits after Congo red staining irrespective of the degree of left ventricle (LV) wall thickness. Identification of amyloid should be followed by classification of the amyloid fibril protein. Although the gold standard for defining the type of amyloid remains mass spectrometry, immunohistochemistry or immunoelectron microscopy are routinely employed for amyloid typing in specialised centres.[4]

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 2).

A recent multicentre study has proposed an echocardiographic score to facilitate echocardiographic diagnosis of AL or ATTR amyloidosis in the presence of increased LV wall thickness.[5] Although not yet externally validated, 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 could also be considered diagnostic of cardiac amyloidosis (Table 2).

Non-invasive diagnostic criteria

Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when ^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or ^{99m}Tc-hydroxymethylene diphosphonate (HMDP) scintigraphy shows grade 2 or 3 myocardial uptake of radiotracer (Figure 2) and clonal dyscrasia is excluded by all the following tests: serum free light chain (FLC) assay, serum free light chain (FLC) assay, serum (SPIE) and urine (UPIE) protein electrophoresis with immunofixation).[6] The combination of SPIE, UPIE and quantification of serum FLC has a sensitivity of 99% for identifying abnormal proamyloidotic precursor in AL amyloidosis.[7] 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 monoclonal proteins (Table 3). Interpretation of low-level monoclonal protein or mild elevations in the kappa:lambda ratio (FLC ratio) could be challenging. These findings can be encountered in patients with chronic kidney disease (CKD) or with monoclonal gammopathy of undetermined

significance (MGUS). In patients with CKD, as the glomerular filtration rate (GFR) declines, the renal clearance of polyclonal FLC decreases and serum concentrations rise.[8] The FLC ratio also varies as the GFR declines, but this depends on the FLC assay available (Freelite assay [Binding Site] or N Latex assay [Siemens]).[8] With the N Latex assay, the FLC ratio decreases as GFR declines but no reference range in CKD has yet been proposed. By contrast, with the most frequently used Freelite assay, FLC ratio increases as GFR declines and a ratio of 0.37 to 3.1 has been proposed to be normal in patients with CKD. No reference values are available according to the severity of CKD, but in patients with moderate CKD (eGFR < 45 mL/min/1.73 m^2 by CKD-EPI formula) in the setting of a normal SPIE/UPIE, a FLC ratio up to 2.0 (or 3.1 if in dialysis) can typically be considered normal (Table 3). Otherwise, consultation with a haematologist is warranted.

In the absence of a detectable monoclonal protein and/or an abnormal serum FLC 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%[6]. Please note, however, that scintigraphy should always include SPECT to confirm that cardiac uptake corresponds to myocardium uptake and not from cardiac chambers (Table 4). Nevertheless, recent reports have shown that rare situations can also lead to positive cardiac uptake.[9] These situations should always be considered when interpreting scintigraphy results (Table 4). Once cardiac ATTR amyloidosis is confirmed, genetic counselling and 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.[10]

Essential concepts

- Although 9 types of cardiac amyloidosis are known, AL and ATTR currently account for the vast majority of cardiac amyloidosis.
- Both invasive and non-invasive diagnostic criteria are accepted to diagnose cardiac amyloidosis. While invasive diagnostic criteria apply to all forms of cardiac amyloidosis, non-invasive criteria are accepted only for ATTR.

Diagnosis of cardiac amyloidosis

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

When to suspect cardiac amyloidosis

Red flags

Cardiac amyloidosis typically 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 are termed "red flags" and include proteinuria (even mild), macroglossia, skin bruises and carpal tunnel syndrome, among others (Table 5). There are also various red flags at the cardiac level, such as heart failure (including disproportionately high NT-proBNP) that appears to be in disproportion to "objective" findings on echocardiogram, "unexplained" right heart failure in the presence of ostensibly "normal" ventricular and valvular function, or "idiopathic" pericardial effusion. Persistent troponin elevation, disproportionally low QRS voltage or early conduction system disease are also signs that could evoke cardiac amyloidosis (Table 5).

Clinical scenarios

In addition to cardiac and extracardiac 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 a chronic systemic inflammatory condition should prompt consideration of amyloidosis, particularly if compatible cardiac imaging findings are present.

Increased wall thickness in a nondilated LV is a prominent characteristic of cardiac amyloidosis and should trigger further evaluation when found in elderly patients with common cardiac syndromes like heart failure with preserved ejection fraction, hypertrophic cardiomyopathy or severe aortic stenosis, particularly among those undergoing transcatheter aortic valve replacement[11-13].

As ATTR has been found in a significant number of patients (up to 7 to 19%) in the abovementioned clinical scenarios, and with the possibility of non-invasive diagnosis, we recommend ascertainment of cardiac amyloidosis in individuals with increased wall thickness with either heart failure, aortic stenosis or red flag signs/symptoms, particularly if older than 65 years (Figure 3).

Diagnostic algorithm

Once cardiac amyloidosis is suspected, a timely, definitive diagnosis should be obtained as patient outcomes depend largely on early initiation of therapy (particularly in AL).

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 ^{99m}Tc-PYP, DPD or HMDP scintigraphy coupled to assessment for monoclonal proteins by SPIE, UPIE and quantification of serum FLC (Figure 4).

The results of these tests could lead to 4 scenarios:

1. *Scintigraphy does not show cardiac uptake and assessments for monoclonal proteins are negative*. There is a very low probability of cardiac amyloidosis and ATTR and AL amyloidosis are unlikely. An alternative diagnosis should be considered. Nevertheless, if suspicion persists, consider CMR followed by cardiac or extracardiac biopsy as bone scintigraphy could be negative in some ATTRv mutations (tracer uptake depends on TTR fibril composition) and in rare subtypes of cardiac amyloidosis (Table 5).

2. *Scintigraphy shows cardiac uptake and assessments 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 the case that cardiac uptake is grade 1, non-invasive diagnosis is not possible and histological confirmation of amyloid deposits (could be extracardiac) is required.

3. *Scintigraphy does not show cardiac uptake and at least one of the monoclonal protein tests is abnormal*. AL amyloidosis has to be ruled-out promptly and CMR can be used to confirm cardiac involvement. If CMR findings do not support cardiac amyloidosis, the diagnosis is very unlikely. In the case that CMR findings

are supportive or inconclusive, cardiac or extracardiac histological demonstration of amyloid deposits is required to diagnose AL cardiac amyloidosis. Cardiac or other clinically-affected organ biopsy is recommended to avoid time delay to diagnosis and consultation with a haematologist is warranted.[14] If CMR cannot be performed promptly, consider performing biopsy directly.

4. *Scintigraphy shows cardiac uptake and at least one of the monoclonal protein tests is abnormal*. ATTR amyloidosis with concomitant MGUS (or any haematological disorder that produces FLC), AL amyloidosis or coexistence of both AL and ATTR amyloidosis are possible in this scenario. Diagnosis of cardiac amyloidosis in this case requires histology with amyloid typing, usually via endomyocardial biopsy.

Essential concepts

- Cardiac amyloidosis should be considered in patients with increased wall thickness in the presence of cardiac or extracardiac red flags and/or in specific clinical situations.
- A diagnostic algorithm based initially on the use of bone scintigraphy coupled to assessment for monoclonal proteins allows appropriate diagnosis in patients with suggestive signs/symptoms.

Outcome and prognosis

Prognosis in cardiac amyloidosis

Although different methods to prognosticate in cardiac amyloidosis have been proposed, the focus has moved to multiparametric biomarker-based prognostic scores, and biomarker-based staging systems have been developed for AL and ATTR cardiac amyloidosis (Table 6).[15-19]

Available scoring systems have been constructed using parameters obtained "at presentation" and provide an initial prognostic stratification. The prognostic impact of any change of the scores during follow-up has not yet been validated, even though recent studies have shown promising results.[20]

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[21], there is a dearth of published data on longitudinal aspects of disease progression and none that are population based without referral and ascertainment biases. In the era of emerging effective therapies, this is a major unmet need.

Follow-up of patients with cardiac amyloidosis

Although no studies have yet addressed the optimal follow-up scheme in patients with cardiac amyloidosis, a common scheme consists of 6-month visits with ECG and complete blood tests (including NT-proBNP and troponin) and yearly echocardiogram and 24-h Holter ECG. A summary of recommended follow-up tests can be found in Table 7.

Follow-up of mutation carriers and genetic counselling

Genetic testing is recommended for relatives of patients with an inheritable form of cardiac amyloidosis. 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.

As age of onset, clinical penetrance, and progression depend upon the variant, assessment of penetrance in allele carriers 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 amyloidosis develop (Table 7).[22]

Essential concepts

- While several staging systems are available to facilitate prognosis, there are limited data on how to assess progression. In the era of emerging effective specific therapies, this is a major unmet need.
- Follow-up of patients with cardiac amyloidosis and mutation carriers should be conducted following a structured protocol.

Treatment

Treatment of cardiac amyloidosis involves two areas: 1) Treatment and prevention of complications; and 2) Stopping or delaying amyloid deposition by specific treatment.

Treatment of complications and comorbidities

Supportive care of patients with cardiac amyloidosis encompasses different clinical aspects including treatment of heart failure, arrhythmias, conduction disturbances, thromboembolism and concomitant presence of severe aortic stenosis (Figure 5).[23-25]

Specific (disease-modifying) treatment

Treating the process of amyloid deposition should target the production of amyloid precursor protein or the assembly of amyloid fibrils.

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 specialised centres.[26]

Patients with AL amyloidosis not only have a haematologic malignancy, but also their multiorgan involvement makes them particularly fragile and susceptible to treatment toxicity. Therapeutic approaches depend on risk assessment that are defined in many circumstances by the degree of cardiac involvement (Supplemental material Figure 1S) and cardiac response depends also on haematological response (Supplemental material Table 1S).[23,24] The role of the cardiologist in the specific treatment includes: 1. Cardiac assessment for initial haematologic strategies, including consideration of autologous stem cell transplantation (Supplemental material Table 2S), 2. Heart transplant evaluation 3. Cardiac monitoring during chemotherapy.

ATTR amyloidosis

There is an increasing availability of novel, effective, targeted therapeutic options for ATTRwt and ATTRv. A prompt diagnosis is essential to enable the timely treatment of neurological, cardiac and other systemic manifestations, as therapy is more effective in the early stages of the disease.[27-28] Effective therapies reduce the production of

mutated (liver transplantation) and overall TTR (genetic silencers) or stabilise circulating TTR molecules (stabilisers), preventing their dissociation or cleavage into amyloidogenic fragments (Figure 6). Several new compounds are under investigation, including agents directed to remove amyloid fibrils (Supplemental material).

Current therapeutic alternatives distinguish between ATTRv and ATTRwt and, in the case of ATTRv, according to the presence of cardiomyopathy, polyneuropathy or both (Figure 7). A detailed description of ATTR therapies that are either available or are being tested in phase III trials can be found in Supplemental material. Tafamidis should be generally considered the agent of choice in ATTR cardiac patients with reasonable expected survival while patisiran could be considered in ATTRv patients with cardiac involvement in whom gene silencers are prescribed due to symptomatic neurological disease.

Essential concepts

- Management of cardiac amyloidosis involves treatment and prevention of complications, and halting or delaying amyloid deposition by specific treatments.
- Specific pharmacologic treatments available for ATTR amyloidosis include stabilising molecules (tafamidis) and genetic silencers (patisiran and inotersen).
- Tafamidis is currently the only drug that has shown efficacy in a randomised trial in patients with ATTRwt and ATTRv with cardiomyopathy, and should be considered in patients with reasonable expected survival.

Organisation of patient care

Collaboration between centres remains essential because not all centres can perform complex diagnostic techniques (such as endomyocardial biopsy and mass spectrometry) or prescribe disease-modifying therapies, and interaction between cardiologists, haematologists, transplant surgeons, neurologists, and other specialists could be needed. The best strategy for the management of patients with amyloidosis is not the *"hub-and-spoke"* model, but rather a *network* where centres can do at least some parts of the diagnostic workup, exchange opinions and information, and refer patients to

regional or national referral centres for selected procedures or particularly complex decisions.

Summary and future directions

As knowledge evolves and new therapeutic alternatives to treat cardiac amyloidosis emerge, new areas of research and unsolved questions arise. Some of the grey zones and areas of active research are summarised in Table 8.

It is expected that advances in the field will change the way we diagnose, prognosticate and treat cardiac amyloidosis in the next few years. Meanwhile, in this paper the Working Group on Myocardial and Pericardial Disease proposes an invasive and non-invasive definition of cardiac amyloidosis, addresses clinical scenarios and situations to suspect the condition and proposes a diagnostic algorithm to aid diagnosis. Furthermore, we also review how to monitor and treat cardiac amyloidosis, in an attempt to bridge the gap between the latest advances in the field and clinical practice.

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Tables:

Figures

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

Figure 2. Cardiac uptake grading in biphosponate 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 3. Screening for cardiac amyloidosis.

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 and comorbidities in cardiac amyloidosis. AA: antiarrhythmic; ACEI: angiotensin converting enzyme inhibitors; AF: atrial fibrillation; ARB: Angiotensin receptor blockers; AS: aortic stenosis; CV: cardioversion; ICD: implantable cardiac defibrillator; LVAD: left ventricular assist device; PPM: Permanent pacemaker.

Figure 6. Available and future disease modifying therapies in ATTR amyloidosis.

Figure 7. Proposed therapeutic alternatives in ATTR patients.

Graphical abstract