Cardiac Amyloidosis – An Underdiagnosed Cause of Heart Failure with Preserved Ejection Fraction – Updated Diagnosis and Treatment Options

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ABSTRACT
Cardiac amyloidosis (CA) still represents a frequently missed cause of heart failure with preserved ejection fraction (HFpEF). In the light of many new and effective therapies for immunoglobulin light chain amyloidosis (AL) and for transthyretin amyloidosis (ATTR), screening for amyloidosis as an important and potentially treatable diagnosis under the HFpEF becomes mandatory. A step-by-step algorithm for CA in HF patients was already provided by the guidelines. This review summarizes the role of all imaging modalities and biomarkers in the diagnosis and prognosis of both subtypes, the algorithm for diagnosis of CA, and new therapeutic options. It is the first Romanian publication which intends to bring altogether the current recommendations in the diagnosis and management of CA.

Keywords: heart failure, amyloidosis, speckle tracking echocardiography, cardiac magnetic resonance, scintigraphy.

INTRODUCTION
Heart failure with preserved ejection fraction (HFpEF), as defined by ESC 2016 guideline and new 2019 scoring system, is still a major healthcare problem1,2. HF guidelines and recent studies provides us a large body of therapeutic options for patients with HF with reduced left ventricular ejection fraction (LVEF) (HFrEF). However, specific treatments to improve the outcome of patients with HFpEF are still lacking1,2. One of the most important factors that might explain this paradox, is that HFpEF comprises a large variety of underlying etiologies, such as hypertension, obesity, diabetes, sleep apnea syndrome, and also infiltrative cardiomyopathies like amyloidosis3.

Amyloidosis still represents a frequently missed cause of HF1,3. Cardiac involvement is the most important factor influencing the prognosis in this multisystem disease4. The prevalence of cardiac amyloidosis (CA) among patients with HFpEF is reported to be 13% to 17%, and approximately 14-16% of patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) have occult cardiac amyloidosis6, and a higher prevalence than 6% seen in surgical aortic valve replacement cohorts7. In the light of many new and effective therapies for immunoglobulin light chain amyloidosis (AL) and for transthyretin amyloidosis (ATTR), screening for amyloidosis as an important and potentially treatable diagnosis under
the HFpEF becomes mandatory. The prognosis of CA at the time of diagnosis can vary widely, dependent on subtype and the extent of cardiac and extracardiac involvement. The ATTR subtype has a more favorable prognosis by comparison with AL subtype. Currently, 25% of patients with AL amyloidosis die within 6 to 12 months from diagnosis, and 25% of patients with TTR amyloidosis die within 24 months from diagnosis. This suggest that early identification of affected individuals and prompt therapy before cardiac dysfunction manifest is essential and can prolong life.

Optimum diagnosis and treatment strategy requires multidisciplinary team (cardiology, neurology, nephrology, gastroenterology, and hematology), but amyloidosis teams are relatively rare. Histopathological diagnosis is the current gold standard diagnostic method. However, there is an emerging role for non-invasive diagnostic imaging modalities in the diagnosis of CA, with large body of evidence supporting the utility of 2D speckle tracking echocardiography (STE), cardiac magnetic resonance imaging (CMR), and bone tracer cardiac scintigraphy.

This review summarizes the role of all imaging modalities and biomarkers in the diagnosis and prognosis of both subtypes, the algorithm for diagnosis of CA, and new therapeutic options.

**PATHOPHYSIOLOGY**

Depending on the type of infiltrating protein, amyloidosis can be divided into three main groups: AL, TTR, and AA amyloidosis, but there are also another rare types reported. Isolated atrial amyloidosis and secondary systemic amyloidosis are also seen. Approximately 5% of elderly patients with HFpEF have at least moderate amyloid infiltration in their LV. Organ damage results from the deposition of misfolded proteins in the interstitium of affected organs. Amyloid deposits generate organ dysfunction due to pro-apoptotic and direct cardiotoxicity effects of circulating precursors, mechanical disruption and oxidative stress in affected organs. Organ tropism is not yet completely understood. Cardiac involvement is predominantly found in AL (75%) and TTR wild type amyloidosis (96%), but may occur also in other types of amyloidosis. Table I summarizes all types of amyloidosis reported till now, responsible protein, organs affected, and important general information about each type.

**DIAGNOSTIC METHODS**

**CLINICAL SUSPICION.** The first critical step in the diagnosis of CA is clinical suspicion. CA is characterized by a clinical heterogeneity resulting in a delayed diagnosis and an inappropriately high mortality risk. The diagnosis of CA often requires a comprehensive integration of data from a number of imaging modalities with clinical status and serum biomarkers. Once the diagnosis of CA is established, data from clinical status (cardiac and extracardiac manifestations), serum biomarkers, and imaging (2DE and CMR) are used for risk stratification, prognosis, and for monitoring cardiac disease progression and response to therapy.

**Extracardiac manifestation.** CA typically is preceded by extracardiac symptoms, which can be significant clinical clues for diagnosis. Ophthalmologic, orthopedic, neurologic, and gastrointestinal abnormalities may be warning signs, particularly in patients with ATTR. Bilateral carpal tunnel syndrome is the most common noncardiac manifestation of ATTR, and it can precede clinical HFpEF symptoms by 5 to 10 years. However, it may be present in all types of CA. Lumbar spinal stenosis may be associated mainly with ATTR-wt, generated by the thickening of the ligamentum flavum, causing compression of the spinal canal. Initial symptoms of polyneuropathy range from sensory abnormalities such as pain, paresthesia, numbness in the feet or a sensation of “walking on rolled up socks” to autonomic dysfunction such as digestive disorders and erectile dysfunction. More advance disease may include motor polyneuropathy such as loss of reflexes and muscle weakness. Macroglossia and periorbital bruising can be present in AL amyloidosis. Hepatic infiltration may occurs generating a hard and non-pulsatile liver on physical exam.

**Cardiac manifestations.** CA results from biventricular wall thickness and stiffness, inducing a restrictive cardiomyopathy, and presents with symptoms of biventricular HF, arrhythmia, or sudden death. The diagnosis of both types of amyloidosis is frequently challenging, particularly in the absence of systemic disease, when a patient presents only with nonspecific cardiac signs and symptoms, such as dyspnea, fatigue, and oedema. AL amyloidosis affects the heart in 74% of the patients, with 47% of them developing HF. Dyspnea is due to LV diastolic dysfunction and increased atrial stiffness. Peripheral edema, ascites, hepatomegaly, and raised jugular venous pressure are often observed. These findings are caused by reduced ventricular filling. Some patients present...
### Table 1. Types of amyloidosis and affected organs \(^{16,20-33}\)

| Type of Amyloidosis | Organs Affected | Responsible Protein | Cardiac involvement Frequency | Important additional info amyloidosis |
|--------------------|-----------------|---------------------|------------------------------|--------------------------------------|
| Primary (AL)       | Heart, kidneys, liver, peripheral and autonomic nervous system, GI tract | Monoclonal light chains (clonal or frankly malignant plasma cells) | 49% | • death within 6-12 months of symptom onset  
• multiple myeloma  
• non-Hodgkin’s lymphoma  
• Waldenstrom’s macroglobulinemia  
• diagnostic sensitivity of fat aspiration 84%  |
| Senile systemic (ATTRwt) | Heart, peripheral and autonomic nervous system | Wild-type transthyretin | 40% | • without underlying diseases  
• diagnostic sensitivity of fat aspiration 15% (11–20%) |
| Hereditary (ATTRv) | Heart, peripheral and autonomic nervous system, GI tract | Mutant transthyretin (more than 120 mutations) | 10% | • death within 5-15 years of symptom onset  
• without underlying diseases  
• inherited in an autosomal dominant fashion  
• diagnostic sensitivity of fat aspiration 45% (36–54%), but dependent on mutation (Val122Ile 33%, Thr60Ala 67%)  |
| Secondary (AA) | Kidneys, GI tract, heart | Serum amyloid A | <1% | • infectious, inflammatory, or neoplastic insults  
• rheumatoid arthritis  
• ankylosing spondylitis  
• severe gout  
• tuberculosis, bronchiectasis  
• osteomyelitis  
• inflammatory bowel disease  
• Hodgkin’s disease  
• renal-cell carcinoma  
• diagnostic sensitivity of fat aspiration - not analyzed |
| Dialysis-related (Aβ2M) | Osteoarticular tissue, GI tract, circulatory system, heart | β2-microglobulin | unknown | • renal failure with dialysis  
• effective treatment is renal transplantation |
| Isolated atrial (AANF) | Heart, atrium | Atrial natriuretic factor | unknown | • abnormal heart rhythms |
| Hereditary (ALys) | Kidneys, liver | Lysozyme | unknown | • without underlying diseases |
| Hereditary (AFib) | Kidneys, liver | Mutant fibrinogen A α | unknown | • without underlying diseases |
| Hereditary (AApoA1, 2) | Heart, kidneys, liver, peripheral nervous system, skin | Principal component of high-density lipoprotein- | <1% | • without underlying diseases |

### Table 2. Red Flag clinical findings for diagnosis of amyloidosis \(^{39-49}\)

| Cardiac amyloidosis | Systemic involvement |
|--------------------|---------------------|
| Biventricular HF especially with HFpEF | Macroglossia and periorbital purpura (AL type) |
| Newly diagnosed HCMP in elderly patients | Carpal tunnel syndrome, particularly if bilateral |
| HFpEF associated with nephrotic syndromes | Spinal stenosis (mainly ATTR wt) |
| Low normal blood pressure with previous history of hypertension | Autonomic signs and symptoms (orthostatic hypotension, alternating constipation/diarrhea, sweating abnormalities) associated with peripheral neuropathy (both types) |
| Intolerance to beta blocker, ACEI, or ARB, ARNI | Spontaneous biceps tendon rupture |
| Unexplained conduction block needing pacemaker AV block + increased LV wall thickness | Nephrotic syndrome/ non-diabetic proteinuria (mainly AL type) |
| Newly diagnosed low flow, low gradient aortic stenosis in elderly patients | Hepatic alteration/hepatomegaly disproportionated to HF status (mainly AL type) |
with exertional syncope or pre-syncope due to low stroke volume which is associated with poor prognosis. However, in most of the patients syncope is caused by hypotension due to autonomic dysfunction. The reduced ventricular filling limits stroke volume and can progress to low-output heart failure. Atrial involvement may cause thrombus formation, even in patients with sinus rhythm, which may cause systemic embolism. Microvascular angina due to perivascular infiltration is also frequently observed.

Typical angina may occur leading to misdiagnosis as CAD. Moreover, persistent elevated troponin levels are frequently found in patients with amyloidosis, but do not show a crescendo-decrescendo pattern. This is particularly relevant in clinical practice, since patients with cardiac amyloidosis, often undergo unnecessary coronary angiography, which usually shows no significant atherosclerotic epicardial coronary disease.

Patients with CA often are diagnosed with HfPEF, which can appear phenotypically as hypertrophic cardiomyopathy. The high level of suspicion for CA comes in patients without longstanding hypertension or ischemia. ATTR subtype might be present in older persons who have been hospitalized for HF, elevated troponin levels, or NT-proBNP that are out of proportion. It is significant that in addition to symptoms of cardiomyopathy, other systemic phenotypes such as polyneuropathy and gastrointestinal or renal disorders may be present. Table 2 summarizes red flag clinical findings suggestive for amyloidosis, with systemic and cardiac infiltration.

**Electrocardiography.** Electrocardiography (ECG) is the simplest and common adjunctive diagnostic tool for CA. The low voltage on limb leads is the most common finding, followed by pseudo-infarct pattern and atrioventricular blocks. In biopsy-proven primary CA the low voltage on ECG was present in 46 to 56% of patients, and a pseudo-infarct pattern in 47-60% of all patients. The pseudo-infarct patterns were anterior (36%), inferior (12%), and lateral (14%). Concomitant low voltage and pseudo-infarct pattern were present in 25% of patients. Atrial arrhythmias are also very common in CA patients. Atrial fibrillation and flutter are the most common arrhythmias. The presence of the above-mentioned findings on ECG or the reverse relationship between the thickness of LV walls and voltages of limb leads strongly supported the diagnosis of CA. It has been reported that the low voltage on limb leads associated with IVS thickness >19.8 mm, has a sensitivity of 72% and a specificity of 91% to diagnose CA. In AL CA low voltage is seen in the majority of cases, whereas only 25% of patients with ATTR subtype (even less depending on the mutation) have low-voltage. However, the presence of low voltage is associated with worse outcome. A corrected QT duration >440 msec and a Sokolow-Lyon index <1.5 mm were found to have a sensitivity and specificity of 85% and 100%, respectively.

Other ECG features of CA include intraventricular conduction delays and blocks. These features were seen more in ATTR as compared to AL subtype. The presence of intraventricular conduction blocks, particularly as they progress over time, reflect a worsening of the disease and higher mortality especially in AL subtype. Decreased heart rate variability is particularly found in AL CA, and in some mutations of the ATTR subtypes, associated with autonomic dysfunction. Fragmented QRS is also seen in CA and was associated with worse prognosis.

**Transthoracic Echocardiography.** As in all cardiomyopathy, 2D TTE is the first line imaging modality that provides two-dimensional measure of cardiac structure and function. It may add a high index of suspicion for CA in patient with HfPEF, non-obstructive hypertrophic cardiomyopathy, disproportionated hypertrophy to the degree of hypertension, and restrictive cardiomyopathy. Although echocardiographic signs are not always present, classic findings suggestive for CA include LV wall thickening, small LV cavity size, bi-atrial enlargement, thickened valves, elevated right pulmonary pressure, atrial septum thickness, restrictive trans mitral pattern, and pericardial effusion (Figure 1). The appearance of the LV walls has been classically described as “sparkling”. In addition, there is thickening of the right ventricular (RV) wall. In patients with HfPEF, presence of severe LV thickening should trigger consideration of CA, especially if there is a discordance between wall thickness and QRS voltage on ECG. Diastolic dysfunction is attributed to increased stiffness as a result of amyloid deposition, and progresses with the degree of myocardial infiltration, ranging from impaired relaxation to a restrictive pattern in patients with advanced disease.

Recently, evaluation of myocardial deformation indices, by 2D STE have been shown to be sensitive in...
the detection of subclinical impairment of LV systolic function in amyloidosis, without CAD. Global longitudinal strain (GLS) in CA presents a pathognomonic sign named “apical sparing pattern” or ‘cherry-on-top’ pattern on the bull’s eye plot (Figure 2 and Figure 3). This is a sensitive and specific finding that can be used to distinguish amyloidosis from other causes of LV hypertrophy. Pagourelas et al. found that the LVEF to GLS ratio has the best accuracy to detect CA in patients with LV hypertrophy, with a sensitivity of 89.7% and specificity of 91.7%, independent of disease subtype.

Moreover, identifying patients with poor prognosis is fundamental to ensure adequate treatment and timely referral to specialized centers. Multiple echocardiographic parameters have shown prognostic value. Conventional measurements such as greater wall thickness, decreased LVEF, restrictive diastolic pattern, increased E/E' ratio and RV involvement had all prognostic value. Recently, there is an increased level of evidence that GLS, left atrial (LA) dysfunction and RV dysfunction are independent and powerful prognostic markers in patients with CA. GLS has been validated to provide additional information beyond the well-validated cardiac biomarkers (NT-proBNP and troponin) for survival among patients treated with stem cell transplantation (SCT). A cut off of -17% was identified as the value that best discriminated survivors from non survivors. GLS has been shown to predict all-cause mortality, especially with values less than -14.8%, and provide incremental value beyond standard clinical and echocardiographic parameters among patients with AL amyloidosis.

Data in ATTR are scarce regarding myocardial deformation analysis and prognosis. Recently, Nocioka et al. showed that all LA strain functions were severely impaired in CA and correlated with a greater LV systolic and diastolic dysfunction. Moreover, current evidence reported that absent atrial contractility in AL patients leads to a high incidence of thrombus formation even in sinus rhythm patients. Recognition of this complication is crucial for timely initiation of anticoagulant therapy.

Lastly, abnormal RV strain is also an independent predictor of death beyond diastolic filling pattern. However, all of the cohorts consisted mainly of patients with AL subtype, with limited data on ATTR.

There is now emerging evidence highlighting a potential role for new myocardial work (MW) analysis,
CARDIAC MAGNETIC RESONANCE. CMR is considered as a “gold standard” for accurate assessment of the LVEF, chamber volumes, myocardial fibrosis and oedema, prior to the onset of LV dysfunction. Regardless of the type of amyloidosis, CMR has emerged as a useful tool in the diagnosis, risk stratification, and prognosis of CA, because of its superior spatial resolution and tissue characterization capabilities.74

Cine CMR imaging is considered the gold standard for measurement of LV and RV, structure as well as global and regional function.61 Typical CMR findings in CA include LV hypertrophy, restrictive LV pattern (preserved LVEF, non-dilated ventricles, enlarged atria, restrictive filling pattern), atrial septal hypertrophy, and mild pericardial effusions.35 It has been reported that LV hypertrophy is more prominent in ATTR than in AL amyloidosis.80 Recently, several CMR findings have been observed in CA, such as RV involvement with a novel STE measures of LV systolic function, derived from LV pressure-strain loop analysis, which may be more sensitive than GLS in the diagnosis and prognosis of CA (Figure 2 and Figure 3). By integration of afterload, MW might have a superior benefit in the evaluation of the prognosis of patients. In CA, the progressive infiltration of the myocardium explains the development of a restrictive cardiomyopathy, with decreased cardiac output and a progressive drop in blood pressure76-79. Global work index and efficiency, derived by MW analysis, showed both a good correlation with NT-proBNP, eGFR and troponin, and peak oxygen consumption76,79. Furthermore, MW indices seem to predict all-cause mortality in CA better than LVEF, even among patients with atrial fibrillation. These indexes might be better used to assess efficiency of the treatment, than GLS or LVEF, because loading conditions are variable over time76-79.

Figure 2. 2D Speckle tracking echocardiographic images
Panel A: Bull’s eye plot by 2D STE in a 42 years old patient with ATTR amyloidosis showing significantly reduced global longitudinal strain (GLS) (-10%) with severe altered deformation mainly at the basal and midventricular segments and relatively preserved at the apex, with a typical “apical sparing” strain or “cherry-on-top” pattern. Panel B: Myocardial work analysis plot of the global work index (GWI) showing severe reduction of the GWI, with a similar “apical sparing” pattern, and an important reduction of the global work efficiency (GWE). Panel C: Myocardial work analysis with low global constructive work (CW) (green bars), also with even lower CW at the basal level, and higher wasted work (blue bars); Panel D: Strain – pressure loops representing GWI (red curve) and a comparative lower WI curve in a basal segment (green curve).
hypertrophy and a typically reduced LV indexed stroke volume, as a better measurement of systolic function than LVEF and concentric remodelling.\textsuperscript{81}

The unique advantage of CMR in the diagnosis of CA arise from its ability to give information about myocardial tissue composition, using late-gadolinium enhancement (LGE) technique, T1 and T2 mapping, and extracellular volume (ECV) using gadolinium enhancement T1 mapping.\textsuperscript{82} Moreover, with phase-sensitive inversion recovery (PSIR) imaging, the tissue with the least gadolinium will always be nulled and thus PSIR reconstruction images are more reliable and should always be used to assess LGE in CA.\textsuperscript{75} The mechanism of LGE in CA is due to infiltration of the amyloid protein and fibrosis caused by ischemia due to capillary obstruction by amyloid deposits.\textsuperscript{35} In amyloidosis, LGE can occur in 3 possible patterns: no LGE, sub-endocardial enhancement, and transmural enhancement.

Figure 3. Comparative STE evaluation in HFpEF patients. Panel A and C: Bull’s eye plot by 2D STE (A) in a 56-year-old patient with HFpEF and AL amyloidosis showing significantly reduced global longitudinal strain (GLS) (-7%) with typical “apical sparing” strain pattern, by comparison with a 62-year-old patient with risk factors and HFpEF without amyloidosis (C), with reduced GLS (-14%) and a coronary distribution of the decreased deformation, affecting mainly septum, and postero-lateral walls, mainly at the apical level. Panel B and D: Myocardial work analysis plot of the global work index (GWI) showing severe reduction of the GWI, with a similar “apical sparing” pattern in HFpEF with amyloidosis patient, by comparison with a GWI plot with important reduction of the GWI, mainly generated by mid and apical segments, in HFpEF patient without amyloidosis.
cement, which can be identified as the amyloid starts to accumulate. Moreover, atrial LGE is a strong clue to the presence of CA, and is associated with atrial contractile dysfunction.

Several studies have suggested that the LGE pattern may help in differentiating the two subtypes of CA, with transmural LGE being more prevalent in TTR amyloidosis as opposed to sub-endocardial LGE, which appears to be more prevalent in AL amyloidosis. In addition, RV LGE and atrial LGE was found to be more present in patients with ATTR compared to AL amyloidosis, underlining the global effect in ATTR amyloid. However, current recommendations draw attention that this technique cannot reliably differentiate subtype. Patterns of LGE have also been associated with prognosis, transmural LGE in AL amyloidosis patients being associated with the poorest prognosis. Moreover, the Query Amyloid Late Enhancement (QALE) score was recently validated as a prognostic score in patients with AL amyloidosis. QALE score was based on patterns of LGE in the LV at 3 levels (base, mid ventricle, and apex) and in the RV free wall. The maximum LV LGE score at each level is 4 (maximum LV LGE score 12), plus 6 if RV LGE is present and ranged from 0 (no LGE in the left or right ventricle) to 18 (global transmural LV LGE with RV involvement). A cut-off of 9 was proved to differentiate prognosis in AL amyloidosis patients with a subendocardial LGE pattern. Patients with a subendocardial LGE-QALE score <9 have a better prognosis, similar to the patients with no apparent cardiac involvement and no LGE, whereas a value ≥9 implies a worse prognosis, similar to the transmural LGE. The use of LGE is relatively contraindicated in patients with severe renal failure.

Native T1 mapping can overcome these limitations as it measures direct quantitative signal from the myocardium, particularly through assessment of the degree of fibrosis. Furthermore, contrast-enhanced T1 mapping enables calculation of the ECV fraction. Patients with CA (both AL and ATTR) have a significantly increased native T1 relaxation time and ECV compared with other cardiac causes such as LV hypertrophy or phenotypically similar Anderson Fabry disease and have shown high diagnostic precision for the detection of both amyloidosis subtypes. Moreover, native T1 and ECV are significantly elevated even in patients with amyloidosis without cardiac involvement on conventional or LGE imaging, emphasizing their utility as early disease markers (Figure 4). ECV was found to correlate strongly with the presence of LGE, and therefore may be an independent predictor of mortality.

Figure 4. Cardiac magnetic resonance in amyloidosis.
CMR images in a 42-year-old patient with TTR-CA. Panel A. short axis view showing LV hypertrophy (IVS = 14mm, AWT= 13 mm, LWT= 15 mm, PWT= 14 mm); Panel B and C: Native T1 mapping short view (B) and 4-chamber view (C) increase in LV native T1 (region of interest IVS) consistent with amyloidosis; Panel D and E: contrast-enhanced T1 mapping short view (D) and 4- chamber view (E) showing significantly elevated ECV (region of interest IVS) compatible with amyloidosis; IVS: interventricular septum; AWT: anterior wall thickness; LWT: lateral wall thickness; PWT: posterior wall thickness; ROI: region of interest; ECV: extracellular volume.
Nevertheless, native T1 mapping and ECV have shown to add incremental value in risk-stratification of patients with CA and for disease surveillance monitoring.\textsuperscript{34}

**BONE TRACER CARDIAC SCINTIGRAPHY.** Bone scintigraphy with $^{99m}$Tc-pyrophosphate ($^{99m}$Tc-PYP) or $^{99m}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD), have a high level of diagnostic accuracy in differentiation of CA subtypes (AL and ATTR).\textsuperscript{34} To note that even there is no direct comparison between these tracers, bone scintigraphy with or $^{99m}$Tc-hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP) has a lowest sensibility in detecting CA.\textsuperscript{34}

TTR amyloidosis has been shown to have avidity for these radiotracers, whilst AL amyloidosis has at most minimal avidity\textsuperscript{86} (Figure 5). Moreover, $^{99m}$Tc-PYP scanning may be of additional help in the 20% of patients with ATTR who have an unrelated monoclonal gammopathy of unknown significance (MGUS), a condition known as wild-type transthyretin amyloidosis (ATTRwt), because the presence of MGUS may lead to an incorrect diagnosis of AL amyloidosis.\textsuperscript{87} On planar images, cardiac retention can be evaluated using a visual scoring method that compares the degree of cardiac uptake with bone uptake (0=absent cardiac uptake; 1=mild uptake less than that of bone; 2=moderate uptake equal to that of bone; and 3=high uptake greater than that of bone).\textsuperscript{35} A positive result is defined as grade 2 or higher, and is highly specific for the diagnosis of TTR-CA, without the need for tissue biopsy, but after monoclonal protein has been excluded.\textsuperscript{34}

**BIOPSY - GOLD STANDARD FOR DIAGNOSIS.** Presence of monoclonal protein is an important differential diagnostic clue for AL and TTR-CA. However, up to 40% of TTR-CA patients have monoclonal gammopathy of unknown significance\textsuperscript{88}. In such cases, a definitive diagnosis should be made by tissue biopsy. The sensitivity of abdominal fat pad aspiration is around 85%, rectal biopsy is 75-85%, and bone marrow biopsy about 50% in detecting systemic amyloidosis\textsuperscript{89,90}. Amyloid, using the Congo red stain, looks pink with normal lighting, and demonstrates apple-green birefringence under polarized light (Figure 6). The various types of amyloid are indistinguishable using light microscopy. It is therefore essential to perform additional studies to identify the type of protein involved, since the prognosis and treatment of amyloidosis is completely different\textsuperscript{25,91}. Amyloid can be specified using light microscopy or immunogold electron microscopy after reacting the specimen with specific antiserum. Mass spectroscopy is considered the current reference standard of classification of amyloid\textsuperscript{90}. If suspicion is high and the preceding tests are not definitive, biopsy of the affected organs can be considered, but the risks need to be weighed carefully in light of the tendency of amyloidosis patients to suffer hemorrhagic complications. It is usually best to proceed with

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**Figure 5.** Bone scintigraphy with $^{99m}$Tc-pyrophosphate in cardiac amyloidosis. Panel A. Negative result defined as no cardiac uptake of the radiotracer in a 55-year-old patient with AL amyloidosis. Panel B. Positive result defined as grade 3= high uptake greater than the bone in an 82-year-old patient with ATTR wt.
the least invasive procedures first. Endo-myocardial biopsy is the current gold standard diagnostic method for CA, which may not be feasible and indicated in all cases, because of the associated risk.

**BIOMARKERS.** Although the first step is clinical suspicion, typical diagnostic algorithms begin with determining whether the patient has a plasma cell dyscrasia. For AL amyloidosis serum protein electrophoresis with immunofixation electrophoresis (SPEP/IFE) is a frequently used screening test. However, it can be normal in 25% of those with CA because either the pathogenic light chains are produced in small amounts or they are completely filtered by the kidneys and therefore not detected in the serum. When used in combination with SPEP/IFE, a 24-hour urine collection with urine protein electrophoresis and IFE can detect 90% of those affected by amyloidosis. The immunofixation studies determine whether abnormal proteins are present, and the serum free light chain assay quantify the number of abnormal proteins. Biopsy is mandatory for a confirmatory diagnosis of AL amyloidosis.

Serum cardiac biomarkers like troponin and BNP/NTproBNP are often persistently elevated in patients with CA, disproportionally to the degree of HF signs. Moreover, these biomarkers are frequently used in patients with CA for risk stratification, to better discriminate between groups with different outcomes, enabling better prognostic classification.

Survival decrease with higher levels of troponin and NTproBNP, and patients with advanced CA (elevated both troponin and NTproBNP levels) are often not considered for SCT, because of high risk for transplantation-related mortality and poor overall survival.

The most recent guidelines for staging patients with systemic AL amyloidosis suggest that overall mortality correlates with three serum assays: plasma free light chain difference (dFLC) greater than 18 mg/dL, NTproBNP >332 ng/L or BNP >100 ng/l, and cardiac troponin-T >0.035 ng/mL. All patients should have their cardiac biomarker risk calculated at diagnosis. This system allows determination of patients as low risk (stage I) (eligible for aggressive therapies such as autologous SCT), intermediate risk (stage II) and high risk (stage III) (often die early before any chance of response to therapy). In the Stage III group, a very high NTproBNP (>8500ng/L) or BNP (>800ng/L) have a very poor prognosis, with a median survival rate of 3.5 months.

These biomarkers are also useful for the quantification of organ response to treatment. Decrease in NTproBNP with more than 30% and >300ng/l decrease in patients with baseline NTproBNP ≥650ng/l, or clinical improvement, is considered a positive response to treatment, whereas an increase of NTproBNP (>30% and >300ng/l), or cTn increase ≥33%, or LVEF decrease ≥10% is considered a progression of CA.

If there is clinical suspicion for CA and no plasma cell dyscrasia is found on laboratory results, should consider a workup for ATTR. No plasma or urinary biomarker is available for the diagnosis of ATTR. NTproBNP is elevated early in ATTR amyloidosis before cardiac symptoms appear, especially among asymptomatic carriers of a TTR gene mutation or in patients with neurological symptoms only. Three staging system are available for ATTR, however their clinical
utility has not been tested prospectively. They use NTproBNP level >3000 pg/ml as a negative prognostic marker, one adds TpT >0.05 ng/ml, and the other one eGFR <45 ml/min. If both parameters are normal Stage 1, if one is abnormal stage 2, and of both are abnormal stage 3. Median survival from diagnosis in untreated patients with TTR-CA is under 4 years. In patients with NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m², survival was <2 years. All staging systems are vulnerable to renal impairment, drugs, and atrial fibrillation as cardiac biomarkers are elevated under these conditions. BNP should be preferred in patients with end-stage renal failure. As levels of cardiac biomarkers are increased by immunomodulation in patients with end-stage renal failure, used under these conditions. BNP should be preferred in patients with end-stage renal failure. As levels of cardiac biomarkers are increased by immunomodulatory drugs, their interpretation requires caution. Staging systems for other forms of cardiac amyloidosis, especially AA and ApoAI/II amyloidosis, are not available, yet.

Beyond cardiac involvement, staging systems have only been defined for renal involvement in AL amyloidosis that typically is characterized by proteinuria and impaired renal function. A reduced eGFR (<50 ml/min/1.73 m²) and proteinuria (>5 g/d) were shown to predict the 2-year risk for the onset of dialysis in AL amyloidosis for stages I, II, and III with 0–3% (both criteria are not fulfilled), 11–25% (one criterion fulfilled), and 60–75% (both criteria fulfilled)49,64,65.

If TTR-CA is identified, then genetic sequencing of the TTR gene is required to define ATTRv versus ATTRwt disease. Differentiating ATTRv from ATTR wt is critical because confirmation of ATTRv should trigger genetic counseling and potential screening of family members. The identification of the Val122Ile mutation suggests aggressive progression and a need for closer follow-up. In Romania, up to this date, the most prevalent mutation in hereditary ATTR is Glu54Gln mutation. Patients with the Glu54Gln mutation present with a mixed phenotype, with clinical onset in the fourth decade. Distal paresthesia and carpal tunnel syndrome are initial manifestations, with significant cardiac involvement and autonomic dysfunction occurring after diagnosis.98

**PET/SPECT QUANTIFICATION.** To date, few published studies have used quantitative SPECT TTR-CA. In a small single-center study using quantitative SPECT, it was demonstrated that SPECT accurately differentiated CA from other cardiac diseases. Caobelli et al. found that quantitative cardiac SPECT is practical, can make the diagnosis of TTR-CA, and provides information that is not identical to visual score from scintigraphy, in grade 2 and 3 patients.99

**CARDIAC AMYLOIDOSIS ALGORITHM FOR DIAGNOSIS.** AL amyloidosis carries the worst prognosis, with a median survival time of 4 to 6 months after a patient is diagnosed with heart failure. ATTR is characterized by years of relative stability despite progressing disease, for 3 to 10 years after diagnosis, depending on their therapeutic options.34,37,49. In this light, it is essential to differentiate both subtypes. Multiple algorithms have been proposed over time, using clinical suspicion, imaging modalities, and organ biopsy. Figure 7 summaries an adapted and modified algorithm based on the most recently published guidelines.16,34,35,49.

**MODERN TREATMENT OF CARDIAC AMYLOIDOSIS**

Management of CA comprises of general therapeutic principles targeting HF and cardiac-associated complications, as well as mechanisms modifying therapies aiming at repressing the underlying pathological substrate, amyloid formation and deposition (Table 3).

**HEART FAILURE AND SUPPORTIVE TREATMENT.** Diuretic agents are considered to play a key role in HFpEF with CA due to their effect in relieving congestive symptoms. Increased reduction in preload by an irrational utilization of diuretic therapy, may lead to decreased cardiac output, systolic blood pressure, and orthostasis.34 Early anticoagulation could be beneficial in high-risk CA patients, due to the higher incidence of mortality-associated intra-cardiac thrombosis and thromboembolic events, observed in these patients. However, at present, there are no guideline recommendations for anticoagulation in patients with CA. Atrial fibrillation, intracardiac thrombosis and thromboembolic events are indications for anticoagulation, irrespective of the CHA2DS2-VASC score. The selection of anticoagulation type must be guideline-driven, according to benefit-risk assessment. Direct oral anticoagulants are recommended over vitamin K antagonists, in the absence of contraindications. Currently, there is no evidence supporting the use of conventional HF medications in the setting of HFpEF with CA. Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor-neprilysin inhibitors are poorly tolerated in patients with CA, and should be used with caution.101
Their use is limited, since they have not been demonstrated to improve outcomes\textsuperscript{101}. In the setting of CA and HFrEF, therapeutic approach with drugs interfering the neurohormonal system, can be taken into account, based on an individualized management\textsuperscript{101}. Recommendations for digoxin use in CA are limited because of the narrow therapeutic window\textsuperscript{104}.

LV assist device placement, as a bridge to heart transplantation or as a destination therapy, represents a therapeutic approach in ATTR cardiomyopathy-related advanced HF, in patients with no extracardiac involvement\textsuperscript{104}. However, the advanced CA, leading to small LV dimension, poses additional challenges to the implantation technique, and it has been shown to be less responsive to assist device support\textsuperscript{105}. Moreover, data provided by the United Network for Organ Sharing registry show an inferior 1-year survival rate in subjects undergoing heart transplant for CA (subjects with both AL and ATTR types), compared to those undergoing heart transplant for other etiologies of restrictive cardiomyopathy\textsuperscript{104,106}.

Patients with CA are at risk of developing atrial and ventricular rhythm disorders, as well as conductance disturbances\textsuperscript{106}. Permanent pacemaker placement is indicated in patients with CA and symptomatic bradycardia, certain types of atrio-ventricular blocks, or history of syncope of undetermined origin\textsuperscript{101,104}. In a retrospective study, conducted by Algalarrondo et al, in asymptomatic patients with familial amyloid polyneuropathy, who developed conduction disorders in the course of the disease, prophylactic cardiac pacing prevented major cardiac events in 25% of the studied subjects\textsuperscript{106}. The study highlights specific electrophysiological criteria for proper patient selection, and suggests the potential benefit of prophylactic pacemaker implantation in high-risk population\textsuperscript{106}.

General guideline recommendations for cardiac resynchronization therapy (CRT) also apply to patients with CA. Patients with indication of pacemaker placement, for whom a high rate of the RV stimulation fraction is anticipated, or who already exhibit reduced LVEF and intraventricular conduction disturbances according to the established guideline criteria, are candidates for CRT system implantation\textsuperscript{101,107}.

Regarding primary prevention implantable cardioverter defibrillator (ICD) implantation, a small retrospective cohort study, on 19 patients with ATTR cardiomyopathy and reduced LVEF\textsuperscript{108}, suggested lack of outcome benefit from ICD placement in these patients. In the paucity of consensus guideline recommendations on the use of primary prevention ICD in CA, routine use of ICD remains controversial\textsuperscript{108}. For secondary prevention, ICD implantation decision is based on the current guidelines for management of ventricular arrhythmias and prevention of sudden cardiac death (IIA/C recommendation)\textsuperscript{109}. In terms of catheter ablation procedures, patients with CA have shown higher relapse rates after catheter ablation compared to control patients\textsuperscript{110}. Ablate-and-pace strategy could represent a therapeutic approach for rate control in patients with atrial arrhythmias, in spite of limited data available on the therapeutic impact in subjects with CA\textsuperscript{101}.

**AMYLOID SPECIFIC THERAPIES**

**AL AMYLOIDOSIS.** The main target of AL amyloidosis therapy is to suppress the abnormal amyloidogenic plasma cell clone, in order to arrest the progressive end-organ deterioration\textsuperscript{111}. Common therapeutic approaches in AL amyloidosis are conventional anti-plasma cell systemic chemotherapy and high-dose chemotherapy followed by autologous SCT\textsuperscript{19}. Their outcome depends on the degree of cardiac involvement at the time of diagnosis, and on the established hematologic and organ response to therapy\textsuperscript{19,100}. Since cardiac involvement is the primary determinant of prognosis

| Table 3. Main therapies for HFpEF in AL and ATTR amyloidosis |
|-------------------------------------------------------------|
| **General therapeutic principles for cardiac symptoms and complications in amyloidosis** | **AL amyloidosis therapies** | **ATTR amyloidosis therapies** |
| • Diuretic therapy | • Conventional chemotherapy: alkylating agents, proteasome inhibitors, immunomodulators, immunotherapy | • Drugs that stabilize the transthyretin tetramer: Tafamidis, Diffusinal |
| • Conventional heart failure treatment (use with caution) | • High-dose chemotherapy and autologous stem cell transplantation | • Drugs that inhibit TTR gene expression: Inotersen, Patisiran |
| • Anticoagulation | | • Drugs that inhibit oligomer aggregation and tetramer dissociation: Epigallocatechin-3-gallate |
| • Devices and ablation therapy | | • Drugs that affect degradation and reabsorption of amyloid fibers: Doxycycline, Tauroursodeoxycholic acid, Miridesap, Dezamizumab |
| • Cardiac assist devices | | • Orthotopic liver transplantation |
| • Heart transplantation | | • Liver-heart transplantation |

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**Figure 7.** Algorithm for diagnosis of cardiac amyloidosis subtype.

HFpEF: heart failure with preserved ejection fraction; CMR: cardiac magnetic resonance; LV: left ventricle; AV: atrio-ventricular; IV: intraventricular; GLS: global longitudinal strain; IFE: immuno-electroforesis; AL: light chain amyloidosis; ATTR: transthyretin amyloidosis.
in AL amyloidosis, cardiologists play a pivotal role in the selection of eligible candidates for SCT, optimal care by guiding cardiac-specific therapies (appropriate diuretic doses), and monitoring of cardiovascular complications. Long-term cardiac follow-up is crucial in the management of patients with AL amyloidosis (assessment of clinical progression of cardiomyopathy by means of increasing cardiac biomarkers values and worsening of LV systolic function parameters). At present, there is no specific cardiac pharmacological agent available for AL cardiomyopathy.

**Chemotherapy drugs.** The vast majority of chemotherapy regimens used in AL amyloidosis have evolved from multiple myeloma treatment schemes. The therapeutic armamentarium has expanded from melphalan-prednisone scheme, as the standard first-line regimen, high-dose dexamethasone-based regimens combined with alkylating agents (melphalan or cyclophosphamide), high-dose melphalan followed by autologous SCT, to the new chemotherapy agents, such as proteasome inhibitors, and novel immunomodulatory drugs. The choice of chemotherapy regimen must be individualized, taking into account the tolerability, efficacy, and the stage of CA, as the main prognostic determinant. Patients with advanced AL cardiomyopathy are restricted from high-dose chemotherapy with autologous SCT.

The specific agents are: bortezomib, carfilzomib, and ixazomib. The most studied proteasome inhibitor in the treatment of AL amyloidosis is bortezomib. It increases overall hematologic response, greater partial response, and enhancement of progression-free and overall survival in the bortezomib-containing chemotherapy regimen. Bortezomib could be a valid option in patients with advanced cardiomyopathy, 67% of patients surviving 2 years after displaying a partial hematologic response. This agent has not been associated with direct cardiovascular toxicity.

**Immunomodulator agents.** Another class of pharmacological agents used in the treatment of AL amyloidosis is represented by immunomodulators: thalidomide, lenalidomide, and pomalidomide. Patients with AL amyloidosis have showed poor tolerability profiles to immunomodulator agents, with a wide range of adverse effects, from cytopenia and infections, to venous thromboembolism and arrhythmias. Considering their toxicity, immunomodulators are reserved for cases of refractory or relapsed AL disease.

**Immunotherapy.** Monoclonal antibodies targeting plasma cells are among the most novel pharmacological strategies for AL amyloidosis. The humanized anti-CD38 monoclonal antibody daratumumab showed positive results in patients with AL amyloidosis and advanced cardiac involvement, who relapsed after high-dose chemotherapy and SCT, or did not respond to the last-administered chemotherapy scheme. Recently, there were published the safety-run in results of ANDROMEDA phase 3 trial which evaluated daratumumab combined with cyclophosphamide and dexamethasone-bortezomib (CyBorD) versus CyBorD alone in newly diagnosed AL amyloidosis. Daratumumab-CyBorD was well tolerated, with no new safety concerns versus the intravenous formulation, and demonstrated robust hematologic and organ response.

Among the newly developed pharmacological agents, a revolutionary approach in reversing organ damage and restoring function could be represented by monoclonal antibodies targeting amyloid deposits. Several ongoing clinical trials are addressing monoclonal antibodies that may enhance phagocytic clearance of amyloid burden. The IgG1 kappa monoclonal antibody, NEOD001, showed favorable results as a single agent, in phase I/II trial (NCT01707264), with good cardiac response, in patients with previously treated AL amyloidosis but biomarker evidence of on-going organ deterioration.

**TTR AMYLOIDOSIS.** Once considered an untreatable pathology, the management approach of TTR amyloidosis evolved from supportive treatment, to orthotopic liver transplant for the specific treatment of ATTRv, and at present, to the development of a series of novel disease-modifying therapeutic strategies. These new targeted medicines, some of them at different stages of clinical studies, can interfere with the production of both amyloidogenic wild-type and mutated transthyretin, or reduce the formation of amyloid fibrils, potentially improving the outcomes of patients with confirmed ATTR amyloidosis. The novel therapeutic options for ATTR amyloidosis include drugs that inhibit TTR gene expression, transthyretin tetramer stabilizers, and molecules that inhibit oligomer aggregation and tetramer dissociation or affect degradation and reabsorption of amyloid fibers.

**Drugs that stabilize the transthyretin tetramer.** Previously published randomized controlled trials documented the efficacy of two orally administered transthyretin tetramer stabilizers in variant ATTR-related neuropathy, diflunisal and tafamidis. Diflunisal is a non-steroidal anti-inflammatory drug that inhibits...
amyloid fibrils formation, by stabilizing wild-type and mutated transthyretin tetramers. Relatively to ATTR cardiomyopathy, at present, Diflunisal has been studied in a small, single-arm trial, that showed no changes in the assessed cardiac structure and function parameters (LVEF and mass index) at 12-month follow-up. However, in a small retrospective cohort of patients with ATTR cardiomyopathy, Diflunisal showed an improvement in cardiac structure and function, evaluated by GLS, and a decrease in troponin I value. Tafamidis acts on reducing transthyretin dissociation into monomers that polymerize into amyloid fibrils, by stabilizing TTR tetrameric architecture. It is the only drug specifically assessed in patients with ATTR cardiomyopathy. In a multicenter, international, double-blind, placebo-controlled, phase 3 randomized study that enrolled 441 patients with HF due to wild-type or variant ATTR cardiomyopathy, Maurer et al identified a lower rate of cardiovascular-related hospitalizations, a lower composite outcome of all-cause mortality, and reduction in the decline of functional capacity and quality of life, in the Tafamidis group, as compared to placebo. Tafamidis has been approved for the treatment of ATTRwt and ATTRv cardiomyopathy. However, the beneficial cardiac effects of Tafamidis were more prevalent in patients with NYHA class I/II heart failure than in those with class III, and the efficacy and safety in patients with NYHA class IV have not been demonstrated. Therefore, the published evidence highlights the importance of timely diagnosis of ATTR-associated cardiac disease, early therapeutic approach and proper medication compliance during follow-up. Moreover, at present, Tafamidis is the only pharmacological agent approved for the therapy of ATTRwt and ATTRv cardiomyopathy.

Drugs that inhibit TTR gene expression. Patisiran, a small interfering ribonucleic acid (siRNA) and Inotersen, an antisense oligonucleotide (ASO), are novel molecules that silence the gene expression of both wild-type and mutated transthyretin, being approved for the specific treatment of variant ATTR-related polyneuropathy. The APOLLO study, a phase 3 placebo-controlled trial, in adults with stage 1-2 hereditary transthyretin amyloidosis with polyneuropathy, with or without cardiomyopathy, showed that Inotersen determines an improvement in the course of neuropathy, compared with placebo. In contrast to Tafamidis, these two gene silencers agents can be administered in patients with ATTRv amyloidosis and advanced stages of neuroopathy. Hitherto, Patisiran and Inotersen have not been approved for the treatment of ATTRwt and isolated cardiac amyloidosis.

Drugs that inhibit oligomer aggregation and tetramer dissociation. Epigallocatechin gallate is a natural polyphenol of green tea that disaggregates amyloid deposits, thus stabilizing the tetrameric structure of wild-type and mutated transthyretin. A small observational report of patients ATTR cardiomyopathy showed positive cardiac results, in terms of significant reduction of LV myocardial mass and interventricular septal thickness.

Drugs that affect degradation and reabsorption of amyloid fibers. Doxycycline and taurourso-deoxycholic acid are two molecules that act as fibril disruptors. The combination of these two agents showed preliminary favorable results in the therapy of both ATTR and AL amyloidosis. The most recent pharmacological agents assessed as fibril disruptors are specific monoclonal antibodies, classified into specific anti-TTR fibrils antibodies and anti-serum amyloid P component (anti-SAP) antibodies. Anti-ATTR antibodies have been studied in vitro, but at present, there are no human trials available. Miridesap and Dezamizumab are anti-SAP antibodies. They bind to serum amyloid P protein, and thus trigger the clearance of amyloid. The clinical trials assessing their therapeutic effect in patients with amyloidosis were terminated due to a change in benefit/risk profile.

In conclusion, Tafamidis is the drug of choice in patients with ATTRwt and ATTRv cardiomyopathy with stage 1 neuropathy or isolated cardiac or neurologic involvement, while Patisiran is indicated in ATTRv cardiomyopathy and advanced neuropathy or isolated neurologic involvement, and Inotersen is recommended in ATTRv with neurologic involvement and stage 1-2 neuropathy.

Regarding the therapeutic management of patients with concomitant aortic stenosis and cardiac amyloidosis, two recently published multicenter studies showed that TAVI improved outcome in patients with AS-amyloid, compared to medical therapy, with indistinguishable results from lone AS patients. Therefore,
TAVI procedure should not be denied from patients with aortic stenosis and cardiac amyloid deposits124.125.

Transplantation
Heart transplant consideration in patients with advanced AL and TTR cardiomyopathy should take into account the extent of extracardiac amyloid organ dysfunction and the risk of immunosuppression complications105. Based on previous published results, isolated heart transplant could represent a therapeutic approach in patients with V122I TTR mutation-associated cardiomyopathy105. In the majority of cases, this particular population exhibits no extracardiac amyloid end-organ involvement105.

Orthotopic liver transplant has been considered the first-line therapeutic option in patients with ATTRv in an attempt to arrest end-organ involvement and amyloid formation, since 95% of circulating TTR protein is developed by the liver48,105. The majority of liver transplants have been performed in patients with Val30Met variant and neuropathic phenotype, with a reported survival of more than 50% at 20 years48. However, orthotopic liver transplantation did not halt progressive cardiac deterioration resulting from the deposition of wild-type TTR protein48,124.

Liver-heart transplantation could represent a therapeutic approach in patients with ATTR v with cardiomyopathy and mutations associated with extracardiac amyloid involvement124. According to published data, combined liver-heart transplantation resulted in a higher survival rate than isolated heart transplantation105.

Autologous stem cell transplantation. High-dose chemotherapy and autologous SCT could be a suitable option for selected patients with AL amyloidosis, age <65, proper performance status, and adequate kidney and cardiac function48. Thus, a tailored approach and a thorough cardiac assessment are mandatory for selecting suitable candidates. However, published data have shown that only 20 to 25% of patients with AL amyloidosis are suitable for SCT based on eligibility criteria19. A series of observational studies revealed an overall survival of 10 years after SCT124.

CONCLUSIONS
Cardiac amyloidosis is an underdiagnosed cause of HFpEF. Evidence of ventricular thickening on echocardiography or a discordance between ECG and echo findings in HFpEF without a clear history of hyperten-

sion should point towards amyloid cardiomyopathy. A step-by-step algorithm for CA in HF patients was already provided by the guidelines. Cardiac magnetic resonance and bone scintigraphy might provide pathognomonic findings and help amyloid typing. Biomarkers such as Troponin and NT-proBNP elevation has a prognostic value in CA. Early diagnosis of cardiac involvement and prompt therapeutic management portends a more favorable outcome in patients with amyloidosis. New treatment opinions are available for both AL and TTR amyloidosis and can slow down the progression of HF. Once considered an incurable disease, CA has become a treatable condition by the development of novel disease-modifying therapeutic agents that target various pathophysiological mechanisms. Referral to hematology in AL amyloidosis is essential, for consideration of chemotherapy or autologous stem cell transplant. Tafamidis and patisiran have been shown to be effective in ATTR, the choice being decided based on ATTR phenotype. Whenever possible, patients should be treated in the setting of clinical studies and ongoing research. Referral to specialized centers is strongly encouraged.

Compliance with ethics requirements:
The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(S), as well as the national law. Informed consent was obtained from all the patients included in the study.

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