Diagnosis and treatment of transthyretin amyloidosis cardiomyopathy: A position statement of the Polish Cardiac Society

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ABSTRACT

Considering the rare incidence of transthyretin amyloidosis cardiomyopathy (ATTR-CM) in Poland, patients encounter difficulties at the stages of diagnosis and treatment. For successful diagnosis, it is vital to raise the suspicion of ATTR-CM, that is, to identify typical clinical scenarios such as heart failure with preserved ejection fraction or the red flags of amyloidosis. In most cases, it is possible to establish the diagnosis on the basis of noninvasive tests. This article presents the recommended diagnostic algorithms including laboratory workup, imaging tests (in particular, isotope scanning), and genetic tests. Since ATTR-CM should be differentiated from light chain amyloidosis, we also discuss aspects related to hematological manifestations and invasive diagnosis. We describe neurological signs and symptoms in patients with amyloidosis and present therapeutic options, including the causative treatment of ATTR-CM with the only currently approved drug, tafamidis. We also discuss drugs that are being assessed in ongoing clinical trials. We outline differences in the symptomatic treatment of heart failure in ATTR-CM and recommendations for nonpharmacological treatment and monitoring of the disease. Finally, we underline the need for providing access to the causative treatment with tafamidis as part of a drug program, as in other rare diseases, so that patients with ATTR-CM can be treated according to the European Society of Cardiology guidelines on heart failure and cardiomyopathies.

Key words: amyloidosis cardiomyopathy, heart failure with preserved ejection fraction, light chain amyloidosis, tafamidis, transthyretin amyloidosis

INTRODUCTION

This article represents the position statement of the experts of the Amyloidosis Cardiomyopathy Section of the Polish Cardiac Society (PTK, *Polskie Towarzystwo Kardiologiczne*). It presents issues related to transthyretin amyloidosis cardiomyopathy (ATTR-CM) but in a wider context. This is because transthyretin amyloidosis (ATTR), which predominantly affects the heart leading to ATTR-CM, also

involves other organs and thus presents with noncardiac signs and symptoms. Another aspect discussed in this article refers to the differential diagnosis of ATTR, especially when it comes to differentiating it from light chain amyloidosis (AL amyloidosis), as in most patients, AL amyloidosis is also associated with cardiac involvement. Although AL amyloidosis is treated by hematologists, usually, it is initially diagnosed by cardiologists. Therefore, basic information on AL amyloidosis is also presented briefly.

ATTR-CM is classified as a rare disease. A delay in the diagnosis of ATTR-CM results in delayed treatment and early complications. Since 2018, specific treatment with tafamidis has been available for patients with ATTR-CM. Tafamidis reduces mortality and improves the quality of life provided that it is started at the early stage of the disease before advanced cardiac involvement occurs.

According to the strategy for an early diagnosis of amyloidosis, the clinician who first suspects cardiac amyloidosis (CA) should aim at establishing the final diagnosis [1]. In clinical practice, this is usually the cardiologist because the major manifestation of the disease is cardiac involvement. Since access to specialist care in Poland is characterized by regional differences, the National Plan for Rare Diseases (*Narodowy Plan dla Chorób Rzadkich*) has been adopted. According to the plan, it is necessary to create specialist centers providing comprehensive diagnosis and treatment of ATTR-CM [2].

The aim of this expert opinion of the PTK's Amyloidosis Cardiomyopathy Section is to summarize the current knowledge on ATTR-CM, discuss advances in the diagnosis and treatment of the disease, and present the known diagnostic and treatment algorithms for this population of patients.

Amyloidosis: Definition and epidemiology

Amyloidosis is an infiltrative disease characterized by the extracellular deposition of structurally abnormal proteins. CA refers to cases when amyloid deposition occurs in the heart. So far, more than 30 proteins leading to amyloidosis have been identified. However, in more than 98% of cases, CA is caused by 2 types of deposits: light chains of immunoglobulins and transthyretin (TTR) [3].

In the course of multiple myeloma or other plasma cell dyscrasias, a pathogenic clone of plasma cells produces abnormal lambda or kappa free light chains, which are deposited in the form of amyloid, leading to systemic amyloidosis (AL amyloidosis). This type of amyloidosis is severe and is associated with poor prognosis.

Transthyretin is a transport protein that transports the thyroid hormone thyroxine (T4) and retinol. In normal conditions, transthyretin is a tetramer produced mainly in the liver. However, in patients with an abnormal *TTR* gene variant, the abnormal TTR protein is less stable, does not form tetramers, and tends to deposit as amyloid fibrils, for example, in the heart, leading to ATTR-CM [3]. ATTR associated with the abnormal *TTR* gene variant is known as variant ATTR (ATTRv). On the other hand, in patients with the normal *TTR* gene in whom TTR loses stability (usually with aging), the tetramers disrupt, and amyloid deposition occurs, amyloidosis is known as wild-type ATTR (ATTRwt) [3].

Early research shows that ATTR-CM can cause various heart diseases. It accounts for 13% of cases of hospital admissions for heart failure with preserved ejection fraction (HFpEF), 16% of cases of severe aortic stenosis, and 5% of cases of hypertrophic cardiomyopathy [4–7].

Clinical presentation of cardiac amyloidosis

Myocardial amyloid deposition leads both to hypertrophic and restrictive cardiomyopathy. In the early stages, cardiomyopathy may present with no clinical symptoms, but later, it may lead to gradual development of fully symptomatic HFpEF syndrome. Thus, at the level of imaging diagnosis — morphology and function — CA is a cardiomyopathy. On the other hand, in the symptomatic stage, at the clinical level, it is HFpEF syndrome. These are the 2 clinical scenarios to establish CA diagnosis. Nevertheless, as the disease progresses, left ventricular (LV) ejection fraction may gradually reduce.

Almost all ATTR patients show signs and symptoms of cardiac involvement. Cardiac involvement and symptoms of heart failure (HF) are also seen in most patients with AL amyloidosis. At the same time, patients with AL amyloidosis seldom show hematological abnormalities. Therefore, cardiologists are often the first specialists that these patients consult. The subsequent patient pathway will thus depend on awareness of amyloidosis features among the cardiologists [8].

As the clinical presentation of amyloidosis is nonspecific, the initial diagnostic workup to raise suspicion of CA must include clinical examination, additional tests such as electrocardiography (ECG), echocardiography, and laboratory tests, as discussed below. Next, depending on the center's experience and the availability of diagnostic tools, the patient is referred for cardiac magnetic resonance (CMR) imaging or is immediately scheduled for scintigraphy [3].

Cardiac amyloidosis presents with a wide range of various clinical symptoms depending on disease severity. In the early stages, the patient is usually asymptomatic, but amyloid deposition in the myocardium may already result in some ECG and echocardiographic abnormalities that may indicate the need for a more extensive diagnostic workup. It is important to pay attention to the characteristic discrepancy between LV hypertrophy on echocardiography and no corresponding signs of hypertrophy on ECG. At this stage, the diagnosis can be established provided that the consulting physician is aware of cardiac amyloidosis and has adequate knowledge to identify features that may indicate the disease.

It is also important to be familiar with the wide clinical spectrum of amyloidosis. For educational purposes, this article uses a simple diagnostic algorithm that classifies

Table 1. Red flags for cardiac amyloidosis

Cardiac signs and symptoms				
Clinical symptoms	**ECG**	**Echocardiography**	**Cardiac magnetic resonance**	**Biomarkers**
Progressive fatigue HF symptoms Syncope, orthostatic hypotension Resolution of hypertension, intolerance of the previously used antihypertensive drugs Family history of HF, PM, ICD	Symptoms of pseudo myocardial infarction Low-voltage QRS complex or no signs of hypertrophy on ECG despite increased wall thickness on echocardiography Conductions disorders, indications for PM implantation Atrial fibrillation	Increased LV and RV wall thickness LV diastolic dysfunction RA enlargement Valve leaflet thickening IAS thickening Increased echogenicity Aortic stenosis Apical sparing strain pattern	Diffuse LGE pattern Increased T1 and T2 relaxation times Difficulties in setting the inversion time	Chronically increased hs-TnT levels Increased NT-proBNP levels
Noncardiac signs and symptoms				
Musculoskeletal	**Polyneuropathy**	**Gastrointestinal**	**Urogenital**	
Bilateral carpal tunnel syndrome Trigger finger Lumbar spinal stenosis Biceps tendon rupture, Popeye sign Knee or hip pain/previous knee or hip replacement	Burning pain sensation in the hands and feet Reduced muscle strength Family history of polyneuropathy	Chronic diarrhea or constipation Early satiety Unintentional weight loss	Urinary retention or incontinence Erectile dysfunction Proteinuria	

Abbreviations: ECG, electrocardiography; HF, heart failure; hs-TnT, high-sensitive troponin T; IAS, interatrial septum; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker; RA, right atrium; RV, right ventricle

the characteristic red flag signs and symptoms into 2 categories: cardiac and noncardiac (Table 1).

Cardiac signs and symptoms

The simplest sign of early disease is an unclear cardiac hypertrophy (typically LV hypertrophy), on echocardiography in a patient without a history of hypertension if there are no signs of LV hypertrophy on ECG. On the other hand, patients with hypertension may show spontaneous resolution of hypertension (due to autonomic neuropathy caused by amyloidosis) and will need a reduction of antihypertensive medication. This may indicate the development of ATTR or AL amyloidosis.

The clinical presentation of the symptomatic stage includes a gradual reduction of physical capacity manifesting with weakness and dyspnea, with progression to congestive HF. These signs and symptoms are not specific to amyloidosis and require further diagnostic imaging, which may raise suspicion of CA as the underlying cause.

Arrhythmia is another early clinical presentation, both supraventricular (particularly atrial fibrillation [AF]) and ventricular arrhythmia; sometimes as an early symptom in a patient without symptoms of HF. At a later stage, rhythm and conduction disorders are often present in fully symptomatic HF. This is when most patients have already developed permanent AF.

In late disease stages, patients present with congestive HF with the predominating symptoms of right HF such as ascites and lower extremity edema. At this stage, specific treatment options are very limited; hence, it is very important to aim at an early diagnosis of the disease.

Noncardiac signs and symptoms

Noncardiac symptoms of ATTR are usually nonspecific and should be considered in the context of the entire clinical presentation. However, based on these symptoms, suspicion of amyloidosis can be raised in patients with unclear features of cardiac involvement. Therefore, it is helpful to have adequate knowledge of these noncardiac manifestations. The most typical noncardiac symptoms of ATTR include

- a history of bilateral carpal tunnel syndrome, usually a few years before the onset of CA symptoms;
- spinal stenosis, or spontaneous biceps tendon rupture (biceps muscle). A history of hip or knee replacement is an ever more nonspecific finding in patients with ATTR;
- polyneuropathy, characteristic of some forms of ATTRv (see Neurological aspects of amyloidosis).

It is important to note that the clinical presentation is similar in all types of amyloidosis. Some more specific clinical features may only suggest certain types of amyloidosis. However, this is of no particular significance because complete differential diagnosis is required in all patients anyway, with laboratory workup as the first step.

DIAGNOSTIC WORKUP FOR AMYLOIDOSIS

Laboratory tests

Laboratory workup for amyloidosis is the basis of the current noninvasive diagnostic algorithm for CA. AL amyloidosis may be excluded based on negative results of the free light chain (FLC) test as well as serum and urine protein immunofixation with electrophoresis (SPIE and UPIE, respectively) [9]. Negative results of all 3 tests exclude AL

amyloidosis with sensitivity of 99% [10]. For the laboratory diagnostic workup to be reliable, it is necessary to select appropriate tests, that is, protein immunofixation (SPIE) rather than electrophoresis and FLC assay rather than light chain assay. It happens in cardiac centers that wrong diagnostic tests are ordered, which may lead to inappropriate diagnosis. Importantly, the choice of the noninvasive diagnostic algorithm with omission of organ biopsy is possible only on the basis of the negative results of the proper laboratory tests (SPIE + UPIE + FLC).

Another challenge is interpretation of the low monoclonal protein levels or mildly increased serum free-kappa-lambda light chain ratio (FLC ratio). These findings may be seen in patients with chronic kidney disease (CKD) or monoclonal gammopathy of unknown significance (MGUS). In CKD patients, as the glomerular filtration rate (GFR) decreases, the renal clearance of polyclonal FLC decreases, while their serum levels increase [11]. The FLC ratio also changes along with a reduction in the GFR, but this depends on the type of the available FLC assays: Freelite (Binding Site) or N Latex (Siemens). In the N Latex FLC assay, the FLC ratio decreases with the lowering GFR. However, so far no reference range has been proposed for the CKD population. On the other hand, in the most commonly used FLC assay – Freelite – the FLC ratio increases as the GFR decreases, and the FLC ratio of 0.37 to 3.1 is considered a reference for CKD patients. The reference values depending on CKD severity have not been established. However, in patients with moderate CKD (estimated GFR [eGFR] <45 ml/min/1.73 m^2 calculated with the CKD-EPI formula) and normal SPIE/UPIE, the FLC ratio of up to 2.0 (or 3.1 in patients on dialysis) may usually be considered as a reference. If the FLC ratio is higher, consultation with a hematologist is indicated.

A laboratory approach to the diagnosis of amyloidosis with possible biopsy or gene sequencing, based on the algorithm proposed by the Mayo Clinic, is presented in Figure 1 [12].

In CA patients, natriuretic peptide and troponin levels are usually increased in a way that is disproportionate to LV systolic function (usually normal) and HF severity. Frequently, the levels of both cardiac markers, N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin T may be already significantly increased at the early stage of the disease before the onset of congestive HF symptoms. This is one of the important red flags for the diagnosis of amyloidosis.

The novel promising biomarkers for identifying patients at risk of ATTR include TTR, retinol-binding protein-4 (RBP4), TTR kinetic stability, and peptide-based probes that label misfolded TTR oligomers. However, the clinical usefulness of these biomarkers should be tested in future studies.

Echocardiography

Echocardiographic assessment is an indispensable component of the diagnostic algorithm and treatment outcome monitoring in patients suspected of having ATTR-CM [13, 14]. All available echocardiographic techniques should be used: 2-dimensional, M-mode, Doppler, tissue Doppler (TDI), and strain imaging. The echocardiography protocol should include assessment of morphology, left and right ventricular systolic and diastolic function and volume, large vessels, valvular apparatus of the heart, estimated pulmonary pressure, and the endocardium [15].

The characteristic finding in ATTR-CM is increased left and/or right ventricular wall thickness after exclusion of any secondary causes. Left ventricular morphology with concentric wall thickness usually without LV outflow stenosis is an important feature that differentiates ATTR-CM from hypertrophic cardiomyopathy [16]. It is extremely important to measure the wall thickness in individual LV segments as well as to assess LV mass and calculate the LV mass index by body surface area. All markers of LV diastolic dysfunction should also be assessed. In a more advanced stage of the disease, there is a reduction in LV systolic function.

The classic presentation of ATTR-CM mimics the pathophysiology of restrictive cardiomyopathy with normal LV volume, atrial enlargement, and signs of increased filling pressure [7]. The following signs are typical of ATTR-CM:

- granular sparkling myocardium;
- pericardial effusion;
- interatrial septal thickening;
- heart valve thickening;
- intracardiac thrombus [17].

In patients with suspicion of ATTR-CM, echocardiographic examination must include longitudinal strain assessment [15]. It allows evaluation of the myocardium, including the left and right ventricles as well as atrial function by 2-dimensional speckle tracking imaging. Using speckle-tracking echocardiography, it is possible to evaluate global and regional longitudinal strain as well as identify the relative apical sparing pattern of LV longitudinal strain, which is a very sensitive marker of cardiac amyloidosis (Figure 2) [18]. In addition to global longitudinal strain, other clinically useful parameters assessed by speckle-tracking echocardiography include transverse and circumferential strain as well as strain velocity. Notably, global longitudinal strain has the highest prognostic value in these patients. Numerous studies showed that disease progression is associated with the worsening of global longitudinal strain, both in ATTR and AL amyloidosis [15].

In selected cases, a more precise assessment of heart function and morphology can be performed with 3-dimensional echocardiography. This technique is an important addition to standard measurements, especially for assessing left and right ventricular systolic volumes and function, assessing the impact of heart valve disease, and for exercise and transesophageal echocardiography. Three-dimensional echocardiography is useful when there is a need to determine eligibility for surgical and percutaneous valve interventions.

Contrast-enhanced echocardiography helps identify intracardiac thrombi or improve insufficient acoustic window.

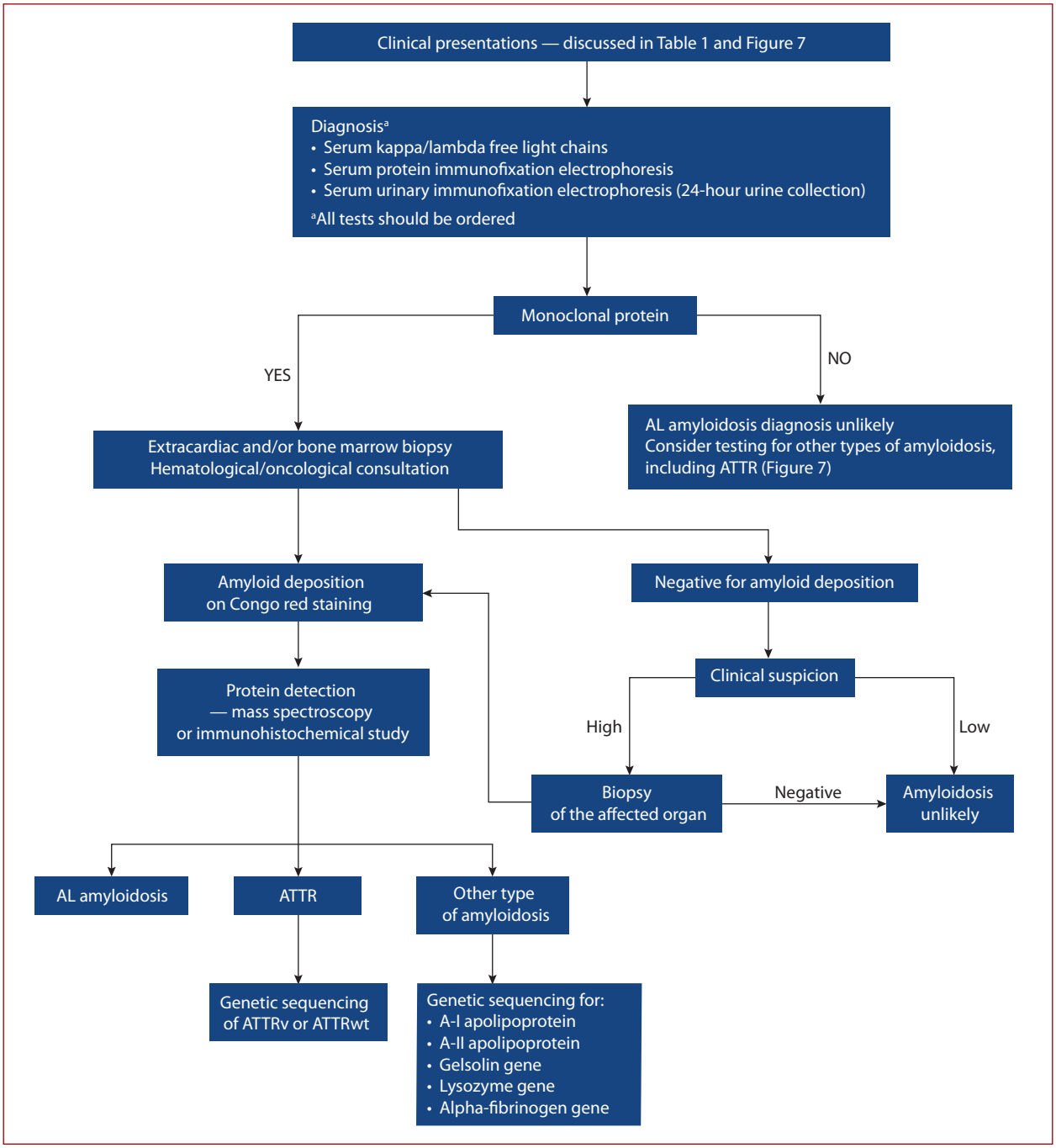

Figure 1. Diagnostic algorithm for amyloidosis based on laboratory testing (based on the Mayo Clinic [12])
Abbreviations: AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRv, variant ATTR; ATTRwt, wild-type ATTR

Lung ultrasound is extremely useful in assessment of fluid overload and constitutes an important addition to the above imaging techniques.

Echocardiographic criteria for CA diagnosis are presented in Table 2. It is important to note that not all echocardiographic abnormalities may be present at early disease stages, while at later stages, the diagnosis based on echocardiography seems to be rather straightforward [3, 13, 19, 20].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance is an important imaging tool in patients with CA: it provides detailed information on the morphology, function, and tissue characteristics of the heart at the ultrastructural level even when lesions are very subtle. The typical abnormalities seen on CMR in advanced disease include massive left and right ventricular hypertrophy, interatrial septal thickening, and heart valve thickening (Figure 3) [21].

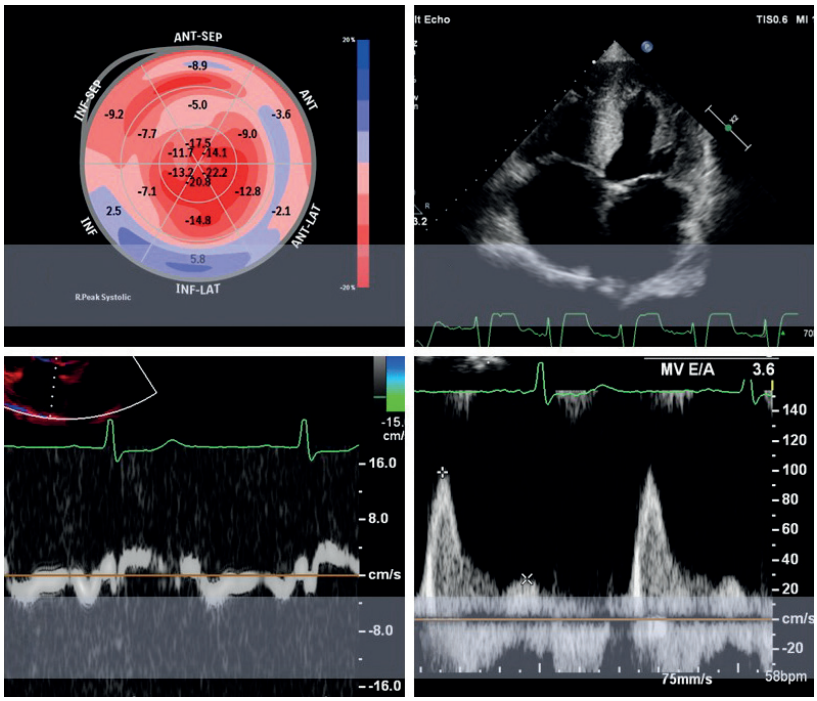

Figure 2. Echocardiographic findings in transthyretin amyloidosis cardiomyopathy. **A.** Speckle-tracking echocardiography showing the apical sparing pattern with preserved longitudinal strain in the left ventricular apical segments and impaired longitudinal strain in the basal segments. **B.** 4-chamber apical view: atrial enlargement as well as concentric thickening and granular structure of the left ventricle. **C.** Tissue Doppler imaging: reduced septal mitral annular velocity. **D.** Mitral inflow on pulsed-wave Doppler: grade 3 left ventricular diastolic dysfunction (source: Echocardiography Laboratory, John Paul II Hospital, Kraków, Poland)

Table 2. Echocardiographic criteria for the diagnosis of cardiac amyloidosis (modified on the basis of the European Society of Cardiology Working Group and multiparametric echocardiography approach [3, 13]

	Unexplained LV thickness ≥12 mm plus fulfilling the criteria listed in I or II:	
I. Echocardiographic findings (≥2)	1. LV diastolic dysfunction (grade 2 or 3)[a] 2. Reduced tissue Doppler s′, e′, and a′ waves velocities (<5 cm/s) 3. Decreased global longitudinal LV strain (<–15%)	
	[a]Criteria for grade 2 or 3 LV diastolic dysfunction: • Grade 2 LV diastolic dysfunction: E/A >0.8 and <2; E/e′ 10–14; TRV > 2.8 m/s; increased LAVI • Grade 3 LV diastolic dysfunction: E/A >2; E/e′> 14; TRV > 2.8 m/s; increased LAVI	
II. Multiparametric echocardiographic score (≥8 points)	Relative LV wall thickness (IVS + PWT)/LVEDD >0.6	3
	Doppler E wave/e′ wave velocities >11	1
	TAPSE ≤19 mm	2
	LV global longitudinal strain absolute value ≤–13%	1
	Systolic longitudinal strain apex to base ratio >2.9	3

Abbreviations: IVS, intraventricular septum; LAVI, left atrial volume index; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; PWT, posterior wall thickness; TAPSE, tricuspid annulus plane systolic excursion; TDI, tissue Doppler imaging; TRV, tricuspid regurgitation velocity

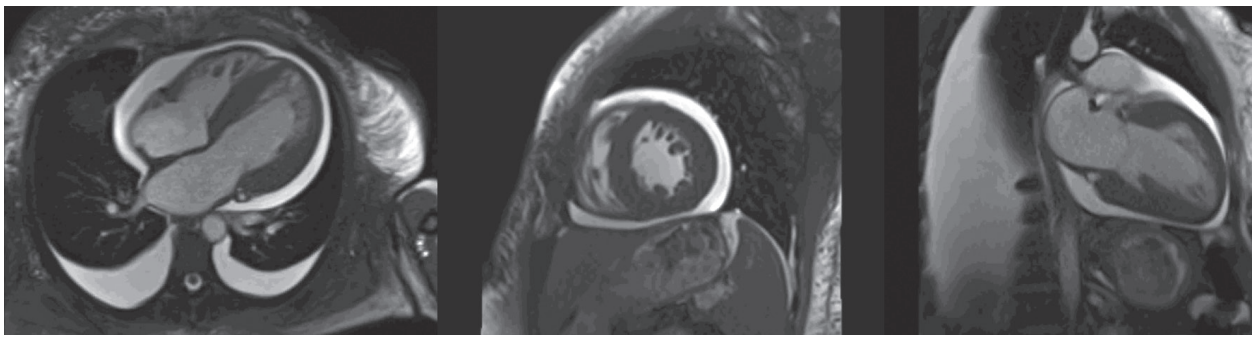

Figure 3. Typical cardiac magnetic resonance findings in a patient with ATTR-CM: hypertrophy, atrial enlargement, and interatrial septal thickening (source: Cardiac Magnetic Resonance Laboratory, National Institute of Cardiology)

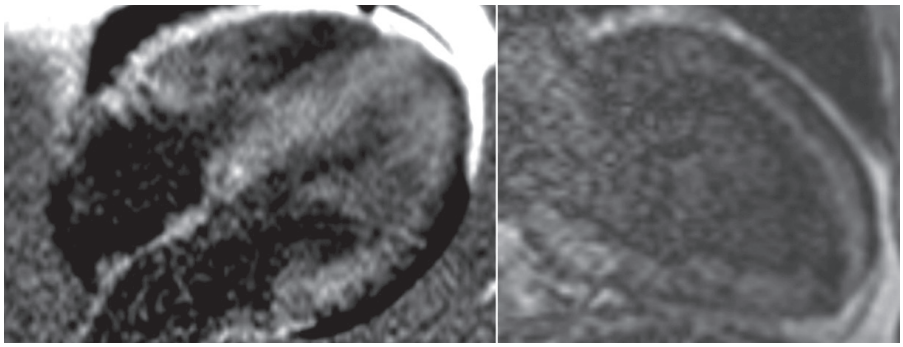

Figure 4. Global subendocardial late gadolinium enhancement in a patient with ATTR-CM (source: Cardiac Magnetic Resonance Laboratory, National Institute of Cardiology)

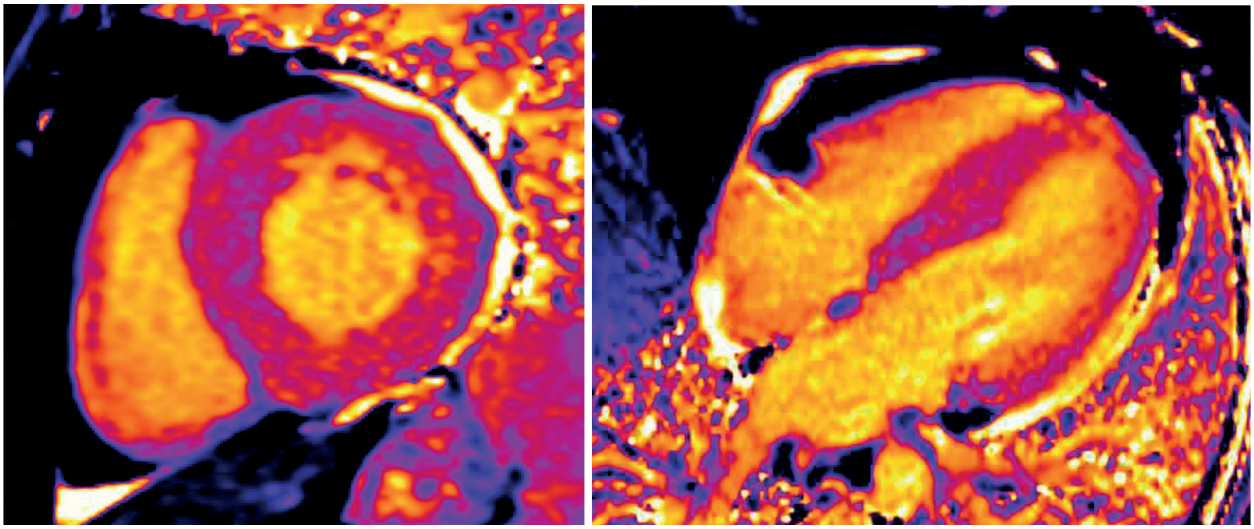

Figure 5. T1 mapping in a patient with ATTR-CM without contrast enhancement (native) T1 >1200 ms (reference ≤1000 ms) (source: Cardiac Magnetic Resonance Laboratory, National Institute of Cardiology)

So far, the concentric remodeling pattern has been considered to be one of the hallmarks of CA. However, most recent studies showed that the majority of patients present with asymmetric hypertrophy found mainly in the interventricular septum. Ventricular contraction is largely associated with disease severity. It can be normal at early stages and deteriorate as amyloid accumulation increases. The impairment of longitudinal contraction is a characteristic feature of CA [22].

In CA patients, CMR shows the characteristic pattern of global subendocardial or transmural late-gadolinium enhancement (LGE) after contrast administration (Figure 4) [23]. Another typical feature is the difficulty in optimizing acquisition parameters and, especially, in setting the inversion time for LGE imaging [24].

Modern CMR techniques, such as T1 mapping, facilitate detailed quantitative assessment of myocardial tissue remodeling (Figure 5). These imaging sequences enable non-contrast assessment (native T1 mapping) of abnormal myocytes. T1 mapping before and after gadolinium contrast administration allows extracellular volume quantification. T1 and the extracellular volume are widely studied markers of amyloid infiltration in patients with amyloidosis [25]. They correlate with disease severity and serve as early markers and prognostic factors for ATTR [26].

In early disease, the characteristic CMR features may not be as evident as at later stages. Initially, the patient may show mild hypertrophy and small LGE areas.

Cardiac magnetic resonance is a valuable tool for differentiating between amyloid infiltration and other types of cardiomyopathy. However, as CMR technology is limited, it is not possible to differentiate between the types of amyloidosis or distinguish ATTR from AL amyloidosis. In the early stages, less experienced clinicians may find it difficult to identify CMR findings as typical of the disease. Therefore, it is not possible to exclude early amyloidosis on the basis of CMR.

Nuclear imaging

Planar scintigraphy and single-photon emission computed tomography (SPECT) have become the key modalities for identification of ATTR-CM patients.

The radiotracers used in nuclear imaging for ATTR-CM include ^{99m}TcDPD (diphosphono-1,2 propanodicarboxylic

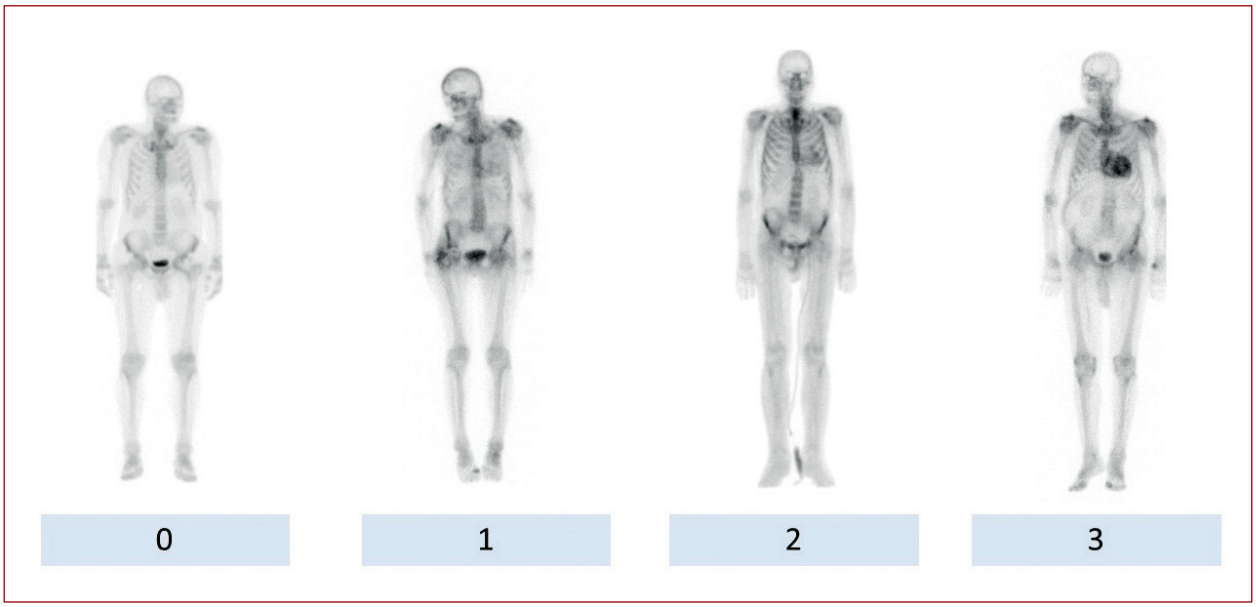

Figure 6. ^{99m}TcDPD scintigraphy: radiotracer uptake graded according to the Perugini score [29] (source: Nuclear Medicine Laboratory, John Paul II Hospital, Kraków, Poland)

acid), ^{99m}Tc HMDP (hydroxymethylene diphosphonate), and ^{99m}TcPYP (pyrophosphate). These markers are currently considered to be specific for diagnosing ATTR-CM [15, 27].

The mechanism underlying the cardiac uptake of radiotracers has not been clarified. It was hypothesized that radiopharmaceuticals bind to microcalcifications, and the areas of microcalcifications are larger in ATTR than in AL amyloidosis. However, this theory does not fully explain radiotracer uptake because, in some cases, there is no uptake in the heart despite confirmed ATTR-CM. This may be attributed to the structure of amyloid fibrils, which contain a mixture of C-terminal TTR fragments and full-length TTR (type A) or only full-length TTR (type B). The type of fibrils (A or B) that form amyloid depositions depends on complex and unknown genetic or environmental factors. Recent studies showed that almost all patients with type A amyloid fibrils showed significant ^{99m}Tc-DPD uptake on scintigraphy, while no uptake was seen in patients with type B fibrils [7, 28].

Planar ^{99m}TcPYP, ^{99m}TcDPD, and ^{99m}Tc HMDP scintigraphy images are assessed by qualitative and semi-quantitative analysis. Quantitative analysis is used to identify amyloid deposits in the heart, while semiquantitative analysis is used to score cardiac uptake after 2 to 3 hours following radiotracer injection. Currently, the Perugini grading scale is recommended for the semi-quantitative analysis. The score is interpreted as follows (Figure 6) [29]:

- 0 — no cardiac uptake and normal bone uptake;
- 1 — mild cardiac uptake, inferior to bone uptake;
- 2 — moderate cardiac uptake and attenuated bone uptake;
- 3 — strong cardiac uptake and mild/no bone uptake.

Score 2 or 3 has very high sensitivity and specificity for diagnosing ATTR-CM. In all patients suspected of having ATTR-CM, also SPECT/CT should be performed to assess myocardial radiotracer distribution, which indirectly reflects amyloid distribution. Preliminary studies showed that ^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMDP SPECT have sensitivity of more than 90% for differentiating ATTR-CM [9, 30, 31]. However, cardiac uptake may be present also in 1 in 5 patients with AL amyloidosis [32]. The diagnosis of ATTR-CM can be established on the basis of the above 3 radioisotopes (^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMDP) without the need for histological examination provided that the patient fulfills all of the following criteria:

- HF with echocardiographic and/or CMR findings is typical of amyloidosis;
- The score for cardiac ^{99m}TcPYP/DPD/HMDP uptake is 2 or 3;
- The are no abnormal serum FLC levels and no monoclonal proteins in serum and urine immunofixation with electrophoresis.

Nuclear imaging plays a pivotal role in ATTR-CM diagnosis, assessment of disease severity, and selection of appropriate treatment. Ongoing studies indicate that the semi-quantitative and qualitative amyloid assessment on SPECT/CT may be a promising tool for predicting and evaluating response to ATTR-CM treatment. However, further studies are needed to guide the selection of appropriate imaging methods for treatment monitoring.

The use of positron emission tomography (PET) with positron-emitting radionuclides for CA diagnosis is currently being investigated [33, 34]. Studies conducted to date demonstrate that ^{18}F-sodium fluoride PET may provide similar data as SPECT but additionally enables quantification of TTR amyloid burden in the heart and other organs. However, this method is not currently recommended for routine use in CA diagnosis.

Table 3. Recommended biopsy sites in the diagnosis of amyloidosis

Recommended biopsy sites	Sensitivity in the diagnosis of AL amyloidosis/ATTR, % [35]	Clinical comment
Salivary glands in the oral vestibule	90/91[b]	Low invasiveness; low sensitivity if there is absence of salivary gland tissue in the sample
Stomach and duodenum	70-90/40	Low invasiveness; high sensitivity in patients with gastrointestinal symptoms on excision of deeper tissue sections; risk of gastrointestinal bleeding after biopsy
Heart	100/100	High invasiveness (risk of severe complications <1% in experienced centers), very high sensitivity even in early stages of disease
Kidney	99/92–100	Indicated only in patients with suspicion of renal amyloidosis; increased bleeding risk; required to confirm MGRS
Bone marrow trephine biopsy	50–60/30[a]–41[b]	For the diagnosis of plasma cell dyscrasias; low sensitivity for detecting amyloid deposition (up to 15%–60% in patients with confirmed AL amyloidosis)

[a]Sensitivity for ATTRwt; [b]Sensitivity for ATTRv

Abbreviations: MGRS, monoclonal gammapathy of renal significance; other — see Figure 1

Invasive diagnosis

Every patient with suspected CA who tests positive for monoclonal protein in serum or urine or has an abnormal serum FLC ratio should undergo an extracardiac biopsy of easily accessible tissue or an endomyocardial biopsy (Figure 7).

Histological examination with Congo red staining shows red positivity in areas of amyloid deposition with yellow, red, or apple-green birefringence under cross-polarized light [35]. Currently, the reference method for amyloid typing is mass spectrometry [3, 36]. In Poland, steps have been taken to make this tool available for the diagnosis of amyloidosis (STARLIGHT study [37]). Immunohistochemical amyloid typing with commercially available antibodies is acceptable provided that the testing is done in an experienced pathological laboratory [3, 36]. The selection of a biopsy site is often guided by the center's experience and the availability of diagnostic tools (Table 3).

We do not recommend gingival, cheek, or abdominal subcutaneous fat pad aspiration biopsy owing to insufficient sensitivity. Rectal biopsy is associated with discomfort for the patient and requires patient preparation. Therefore, it is not routinely recommended [38]. To speed up the diagnosis and increase the sensitivity of biopsy specimens, it is recommended to:

- urgently test biopsies that were obtained previously for other indications, for example, during recent gastroscopy or colonoscopy (histopathological staining for amyloidosis — Congo and Sirius red stain are not routinely done in practice);
- start with a biopsy of easily accessible tissues other than cardiac tissue; if these biopsies are inconclusive and the probability of amyloidosis is high, urgently perform the biopsy of the involved organ, e.g., heart;
- simultaneously obtain samples from several less invasive biopsy sites without waiting for the results, e.g., salivary gland biopsy and gastroduodenoscopy;
- send the biopsy specimens to the pathological laboratory experienced in the diagnosis of amyloidosis;
- in cases of doubt, consult another laboratory in Poland or abroad (results of immunohistochemical amyloid typing are reliable only in 75% of cases).

Genetic testing

TTR gene sequencing is required for the diagnosis of ATTR in patients:

- with suspected ATTR-CM;
- with symptoms of familial amyloid polyneuropathy;
- in first-degree relatives of ATTRv patients (so-called cascade genetic testing).

ATTRv should be diagnosed in patients with ATTR-CM or polyneuropathy in whom the pathogenic or likely pathogenic variant in the *TTR* gene was identified. The identification of a gene variant with unknown significance should not prompt ATTRv diagnosis or further diagnostic workup in first-degree relatives [36]. Genetic testing of ATTR-CM patients, that is, differentiation between ATTRv and ATTRwt, has important implications for first-degree relatives. Some *TTR* mutations may manifest at older age. Therefore, genetic testing should be offered to all ATTR-CM patients, irrespective of age at first symptoms [36]. In cases where the first symptoms occurred at an older age, cascade testing may be more useful in the proband's siblings at similar age than the proband's children who are younger by several decades. The cascade genetic tests may identify asymptomatic carriers of *TTR* mutations. Clinical assessment of these individuals should start about 10 years before the expected age of onset for a given mutation [36].

TTR gene sequencing has also prognostic significance. The *TTR* gene mutation is inherited in an autosomal dominant manner, but due to variable expressivity and incomplete penetrance of gene mutations, clinical presentation can vary between patients with the same gene variant. Despite this, knowing the type of mutation has a prognostic value because it helps predict expected disease progression, dominant phenotype, and age of onset of first symptoms. So far, 130 pathological variants of the *TTR* gene have been described [39]. The distribution and incidence of individual mutations differ depending on ethnicity and geographical region. In Polish patients, quite rare *TTR* mutations were described, mostly associated with a combination of the cardiac and neurological phenotypes: p.Val91Ala, p.Ile93Val, p.Phe53Leu, p.Glu109Lys, p.Ala101Val, and p.Asp58Val. The most common TTR mutation, p.Val50Met, was also reported. It seems that

the p.Phe53Leu mutation may be endemic to southern Poland [19, 40].

Genetic testing for ATTR may influence the choice of an appropriate treatment strategy. Some ATTRv patients with rapid disease progression may benefit from a liver transplant or combined heart and liver transplant. Some disease-modifying drugs such as patisiran, vutrisiran, and inotersen are currently approved for use but only in patients with ATTRv and polyneuropathy (see Symptomatic and specific treatment).

Diagnostic algorithm

In the 2021 position paper, the European Society of Cardiology (ESC) proposed invasive and noninvasive diagnostic criteria for ATTR-CM [3]. It is important to stress that AL amyloidosis should be diagnosed as early as possible, within the first 1–2 weeks of diagnostic workup to promptly start hematological treatment.

Invasive diagnosis requires histological confirmation by a cardiac or other organ biopsy (see Invasive diagnosis). In patients with positive results of extracardiac biopsy, other echocardiographic and/or CMR criteria have to be met for CA diagnosis (see Echocardiography and Cardiac magnetic resonance imaging).

As cardiac biopsy is invasive and may lead to complications, it is currently performed only in selected cases where noninvasive diagnosis is not possible. Thus, if ATTR-CM is suspected, it is not necessary to perform routine cardiac or extracardiac biopsies. Invasive diagnostic tests were replaced by scintigraphy [9, 41]. ATTR-CM can be diagnosed on the basis of positive scintigraphy findings (see Nuclear imaging) and normal SPIE, UPIE, and serum FLC ratio. Scintigraphy and SPECT are recommended especially for early disease detection. The uptake level correlates with disease severity and LV wall thickness assessed by echocardiography [42, 43].

According to the 2021 ESC guidelines, all echocardiographic and CMR criteria have to be fulfilled to diagnose ATTR-CM. However, this recommendation is currently widely debated, and major concerns relate to patients with early disease. In clinical studies, published to date, the only echocardiographic criterion in addition to positive scintigraphy was the LV wall thickness above 12 mm [44].

The most important components of the diagnostic algorithm for CA (Figure 7) include clinical presentation, laboratory tests, imaging tests (echocardiography, scintigraphy, magnetic resonance imaging), and in selected cases, invasive tests (biopsy). They were discussed in detail in the relevant section of this article.

HEMATOLOGICAL ASPECTS OF AL AMYLOIDOSIS

Light chain amyloidosis remains the most common type of CA diagnosed in Poland. The disease cannot be diagnosed using the noninvasive approach. The diagnostic criteria for AL amyloidosis are as follows [45]:

- organ damage due to amyloid accumulation;
- histopathological evidence of amyloid fibrils;
- amyloid fibrils formed from FLC;
- presence of plasma cell dyscrasia (monoclonal protein in serum or urine; abnormal FLC ratio <0.26 or >1.65; clonal plasma cells in the bone marrow).

Monoclonal gammopathy of undetermined significance is a precancerous stage of multiple myeloma, which does not require medical treatment. The incidence of MGUS in the general population is up to 5% of individuals older than 70 years [46], approximately 19% of patients with ATTR [9], and even up to 40% of patients with ATTRwt [47]. MGUS is defined as serum monoclonal protein levels lower than 30 g/l, less than 10% of clonal plasma cells in the bone marrow, absence of the signs of multiple myeloma (so-called CRAB symptoms including hypercalcemia, renal insufficiency, anemia, and osteolytic lesions), and absence of clinical features of amyloidosis [45]. Therefore, patients with serum or urine monoclonal protein or abnormal FLC ratio identified during diagnostic workup for CA should be immediately consulted by a hematologist with experience in the diagnosis and treatment of AL amyloidosis (ICD10 code, D47.2).

On the other hand, low levels of monoclonal protein in patients with MGUS should not cause any major symptoms. Therefore, if a patient with MGUS reports progressive fatigue and presents with increased cardiac marker levels (NT-proBNP and troponin T) or cardiac abnormalities on echocardiography, a consultation with a cardiologist experienced in the diagnosis of CA should be considered.

The most common hematological abnormalities in patients with positive results of ^{99m}Tc-DPD scintigraphy and confirmed ATTR-CM are the FLC ratio between 1.65 and 3.1 (increased FLC kappa levels often seen in kidney disease) and absence of monoclonal protein [48]. In such patients, a noninvasive approach to the diagnosis of ATTR proposed by Gillmore et al. [9] is still indicated. However, if the patient simultaneously presents with signs and symptoms of AL amyloidosis, such as advanced HF, worsening kidney function of unknown etiology, significant reduction in body mass, early satiety, meat disgust, cachexia, periorbital hemorrhage, macroglossia, and onycholysis, a biopsy of an easily accessible tissue/organ should be considered (e.g., salivary glands in the oral vestibule or upper gastrointestinal endoscopy).

As patients with AL amyloidosis are managed mainly by hematologists, this article does not discuss treatment and monitoring of this condition. However, it is important to note that each patient should be consulted by a multidisciplinary team, especially in the case of advanced disease [8].

NEUROLOGICAL ASPECTS OF AMYLOIDOSIS

Polyneuropathy in ATTRv

Polyneuropathy and cardiomyopathy are the 2 most common phenotypes of ATTRv. The predominant clinical pres-

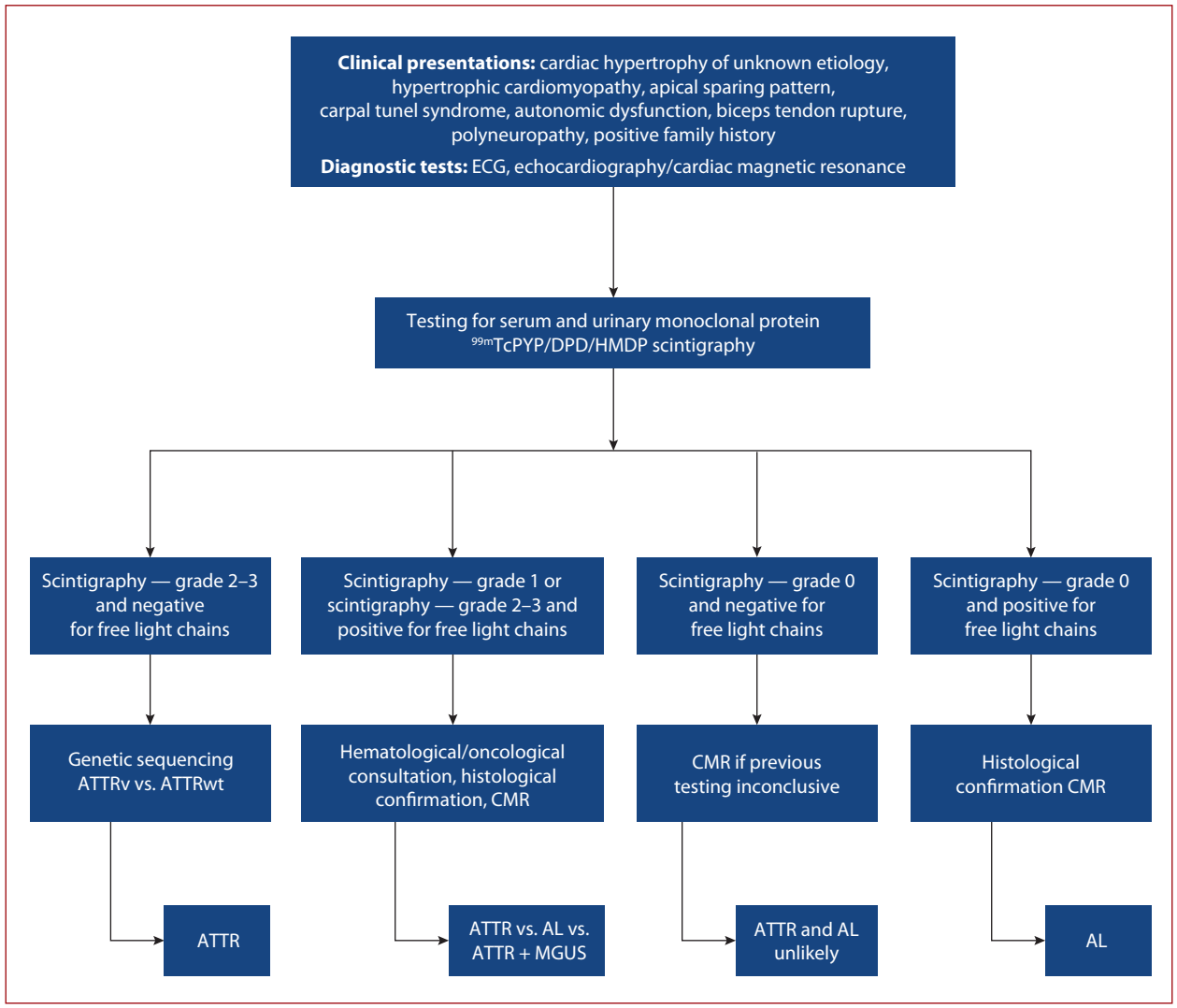

Figure 7. Diagnostic algorithm for cardiac amyloidosis (modified, based on [3])

Abbreviations: ^{99m}Tc, technetium-99m; DPD, diphosphono-1,2 propanodicarboxylic acid; ECG, electrocardiogram; HMDP, hydroxymethylene diphosphonate; MGUS, monoclonal gammopathy of undetermined significance; PYP, pyrophosphate; other — see Figure 1

entation may be either polyneuropathy or cardiomyopathy depending on various factors such as the type of mutation, geographic region, or sex. In Poland, patients most often present with a combination of these 2 phenotypes [40].

The signs and symptoms of polyneuropathy in ATTRv may develop first or at a later stage. Symptoms usually occur in the adult age between the third and the ninth decade of life, with progression over time [49]. The clinical onset of the disease is usually seen within months or several years. Untreated polyneuropathy leads to immobilization and death within 7 to 12 years due to cachexia caused by muscle loss and autonomic dysfunction. The simultaneous development of ATTR-CM is associated with a significantly worse prognosis. The prognosis improves after introducing specific treatment [50].

The typical clinical presentation is symmetric polyneuropathy that involves sensory, autonomic, and motor nerves. The characteristic feature is the predominant involvement of thin fibers, which results in impairment of pain and temperature sensations as well as autonomic symptoms. Symptoms of thin nerve fiber involvement are usually first to appear but may also occur at later stages. With disease progression, the remaining fibers of peripheral nerves become affected. Symptoms of ATTRv polyneuropathy usually occur in the following order:

- damage to thin sensory nerve fibers: impairment of pain and temperature sensations;
- damage to thin autonomic nerve fibers:
  - gastrointestinal: diarrhea and severe constipation,
  - cardiovascular: orthostatic hypotension,
  - sphincter and sexual dysfunction;
- damage to thick sensory nerve fibers: impairment of the sense of touch and proprioception;
- damage to motor nerve fibers.

Sensory nerve involvement usually has distal distribution, with symptoms occurring first in the feet and then in the hands and with decreased sensation following the

Table 4. Questionnaire for autonomic function assessment using the Compound Autonomic Dysfunction Test score (based on [49])

Symptom	Score				
	4	3	2	1	0
Orthostatic hypotension	Absent	Asymptomatic	Syncope	Postural syncope	Immobility
Nausea/vomiting	Absent	Nausea/malabsorption	Vomiting: <1×/week	Vomiting: <1×/week	Vomiting every day
Diarrhea/constipation	Absent	Once a month	1×/week	>2×/week	Every day
Sphincter symptoms	Absent	Dysuria	Dysuria + urinary incontinence episodes	Periodic need for urinary catheterization	Continued need for urinary catheterization

Table 5. Staging the severity of polyneuropathy in ATTRv

Clinical stages (based on [51])	Clinical symptoms
0	No symptoms — carriers
I	Presence of symptoms but preserved walking capability without stick or crutches
II	Walking capability with the help of 1 or 2 sticks or crutches or a walker
III	Confined to a wheelchair or bedridden

"stocking-glove" pattern. With disease progression, nerve involvement is distributed more proximally and may affect the entire extremities if left untreated.

Autonomic function assessment in daily clinical practice

The Compound Autonomic Dysfunction Test (CADT) was developed to assess autonomic dysfunction in polyneuropathy in the course of ATTR (Table 4). Except for asymptomatic orthostatic hypotension, autonomic dysfunction is assessed on the basis of medical history. A reduction in the CADT score (the reference is 20 points for men and 16 points for women), after exclusion of other causes, indicates clinical autonomic dysfunction [49].

The simplest score for the assessment of ATTRv polyneuropathy severity is presented in Table 5. A discussion of more complex scores used by neurologists in daily practice is beyond the scope of this article.

Confirmation of polyneuropathy

In routine clinical practice, polyneuropathy is confirmed by peripheral nerve conduction study and electromyography. These tests usually reveal findings typical of symmetrical sensorimotor axonal polyneuropathy. It is important to note that, initially, polyneuropathy affects only thin and/or autonomic nerve fibers. At this stage, nerve conduction studies show no abnormalities.

The diagnosis of thin fiber neuropathy is complex, and additional tests for assessing damage to autonomic fibers as well as damage to thin fibers that carry information related to pain and temperature are currently unavailable for routine diagnosis.

Other signs and symptoms of nervous system damage in ATTRv

- Carpal tunnel syndrome (CTS) is associated with amyloid deposition in the transverse carpal ligament. CTS should not be considered a symptom of polyneuropathy because it is caused by median nerve compression. Neuropathic pain first affects the hands or radiates to the upper extremities, especially at night. This gradually progresses to sensorimotor deficits in the median nerve innervating fingers 1–3 of the wrist. Importantly, CTS may develop even more than 10 years before the onset of polyneuropathy and/or ATTR-CM.
- Leptomeningeal manifestations of ATTRv are extremely rare and are caused by amyloid deposition in the central nervous system because TTR is also produced in the ventricular choroid plexus.

Neurological manifestations of ATTRwt

- CTS is the most common neurological manifestation of ATTRwt.
- Not all patients with ATTRwt have polyneuropathy, and if they do, it is usually mild. In most cases, thin fibers are involved, resulting in impaired sensations of pain and temperature as well as autonomic dysfunction.
- Lumbar spinal stenosis with nerve root compression has been rarely described. It is caused by amyloid deposition in spinal ligaments [52]. Patients with lumbar spinal stenosis receive specific and symptomatic treatment or undergo spinal surgery depending on the severity of neurological symptoms and individual indications for surgery.

Treatment of neurological symptoms in amyloidosis

Stage 1–2 polyneuropathy in the course of ATTRv is an indication for specific treatment (see Disease-specific treatment). In addition, symptomatic treatment is used depending on symptoms: mobility rehabilitation, treatment for neuropathic pain and autonomic dysfunction, and surgery for CTS or lumbar spinal stenosis.

Cardiomyopathy and neurological manifestations

- Polyneuropathy in a patient with cardiac hypertrophy is one of the red flags that should prompt a diagnostic workup for amyloidosis [53]. It is not possible to determine the type of amyloidosis based on polyneuropathy alone because polyneuropathy can be seen in patients with ATTRv, AL amyloidosis, and — in a milder form — also in ATTRwt.
- Another red flag is CTS, especially when it is bilateral and occurs in men.

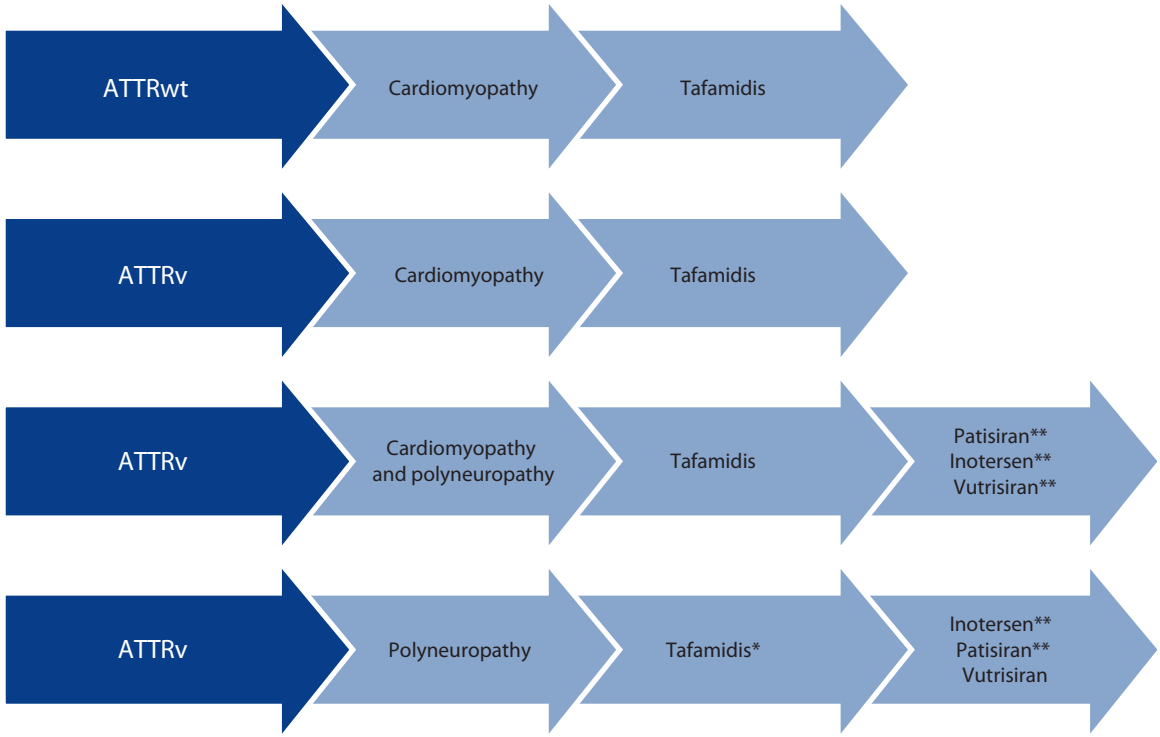

Figure 8. Proposed therapeutic options in patients with ATTR-CM (modified, based on the ESC Working Group on Myocardial and Pericardial Diseases guidelines [3])
*ATTRv polyneuropathy stage 1 in adults; **ATTRv polyneuropathy stage 1–2 in adults
Abbreviations: see Figure 1

- Patients diagnosed with cardiomyopathy in the course of ATTRv should be regularly monitored for the signs and symptoms of progressing neuropathy (approximately every 6 months). Increased severity of polyneuropathy, even in ATTR-CM patients with stable disease, may indicate the need to change the specific treatment of ATTRv [54].
- Carriers of *TTR* gene mutations should be monitored by a neurologist who can recognize the clinical presentation of ATTRv in cooperation with a multidisciplinary amyloidosis team.

TREATMENT

Disease-specific treatment

There are 3 potential therapeutic options in ATTR-CM, guided by the pathophysiology of the disease. This includes inhibition of TTR synthesis in the liver, stabilization of circulating TTR tetramers, and degradation of amyloid protein fibrils in the heart. Most molecules with a potentially therapeutic action are at different stages of clinical research. The only drug approved for use in ATTR-CM in the European Union is tafamidis, which stabilizes TTR tetramers by inhibiting their dissociation to amyloidogenic monomers and extracellular deposition in the extracellular matrix of the heart.

Tafamidis

Tafamidis is currently the only disease-specific treatment with confirmed efficacy in reducing mortality rates and the risk of hospitalization for HF exacerbation in patients with ATTR-CM. At present, this is the only drug approved for use in this indication in the EU at a dose of 61 mg (free acid) or the equivalent dose of 80 mg (tafamidis meglumine) administered orally once daily. Tafamidis is a benzoxazole derivative that acts by binding to the thyroxine-binding site of TTR, thereby inhibiting its dissociation to monomers. According to the ESC guidelines and the ESC Working Group on Myocardial and Pericardial Diseases, tafamidis is recommended as the first-line treatment in ATTRv and ATTRwt in ATTR-CM patients with and without polyneuropathy (Figure 8) [3, 55, 56]. This recommendation was reiterated in the 2021 ESC guidelines, where tafamidis is described as a therapeutic option (class of recommendation I, level of evidence B) for patients with ATTRv and ATTRwt with HF (New York Heart Association [NYHA] class I and II) [3], and in the 2023 ESC guidelines for the management of cardiomyopathies [57].

The evidence for tafamidis efficacy in ATTR-CM was provided by a multicenter international placebo-controlled randomized clinical trial (ATTR-ACT), which included 441 patients with ATTR-CM followed for 30 months. Patients on tafamidis treatment showed a significant reduction

in all-cause mortality and urgent hospital admissions for disease exacerbations as well as improvement in exercise capacity and quality of life. The main study findings were published in 2018 [44]. The long-term extension to the pivotal ATTR-ACT study confirmed tafamidis efficacy in reducing mortality during the 58 months of treatment. Additionally, it showed survival benefits in patients who received placebo in the ATTR-ACT and were transitioned to tafamidis at 30 months in the extension study [14]. Subsequent analyses of ATTR-ACT findings confirmed significant improvement in the clinical condition of patients in the tafamidis vs. placebo arm, as reflected by improved quality-of-life scores and improved distance in the 6-minute walk test [58].

At the same time, studies showed that tafamidis is very well tolerated by patients, with the rates of adverse events (genitourinary infections, diarrhea, epigastric pain) comparable to placebo [14, 44].

Drugs with no proven efficacy currently in clinical trials

A drug that shows a similar mechanism of action to tafamidis is diflunisal. It is a nonsteroidal anti-inflammatory drug that can stabilize the TTR tetramer *in vitro* [59]. However, so far, it has not been shown to offer benefits in the treatment of patients with ATTR-CM. Potential adverse effects such as renal and gastrointestinal damage as well as fluid retention remain a significant problem in patients with symptomatic ATTR-CM. Currently, diflunisal has no marketing authorization in Poland, but it is directly imported from abroad for patients with polyneuropathy.

Acoramidis (AG10), currently in clinical trials, is a highly selective stabilizer of TTR. It prevents its dissociation by selectively binding to the TTR tetramer because it has a similar motif to the thyroxine-binding site as the Thr119Met variant that shows protective anti-amyloidogenic effects [60]. A phase II randomized clinical trial (NCT03458130) confirmed the safety and efficacy of AG10 in patients with CA in the course of ATTRwt and ATTRv. The phase III trial is currently ongoing [61].

Transthyretin amyloid fibril inhibitors

Inotersen is an antisense oligonucleotide that inhibits TTR synthesis. It is recommended in patients with concomitant CA and ATTRv polyneuropathy or in those with ATTRv polyneuropathy stage 1–2 [3]. The safety and efficacy of inotersen in patients with ATTR-CM have to be confirmed in the future. A clinical trial assessing these endpoints is currently ongoing.

Patisiran is a liposomal small interfering RNA therapeutic indicated for the treatment of patients with CA and ATTRv polyneuropathy or adult patients with ATTRv polyneuropathy stage 1–2 [3]. The efficacy and safety of patisiran in patients with ATTR-CM is yet to be confirmed [62].

Vutisiran (siRNA) reduces TTR synthesis in patients with ATTRv polyneuropathy. It is also approved for use in adult patients with ATTRv polyneuropathy stage 1–2, while its efficacy and safety in patients with ATTR-CM require confirmation [3].

Therapies targeting amyloid disruption

Doxycycline and tauroursodeoxycholic acid (TUDCA) act as TTR amyloid disruptors. Experimental studies showed that these therapeutics may slow ATTR progression [63, 64]. However, this effect was not confirmed in clinical trials, and the treatment is not included in the ESC Working Group guidelines [3].

Immune therapy in amyloidosis involves administration of antibodies that target amyloid deposits in the key organs. The therapy is currently in early clinical trials. A phase I trial on the use of a human recombinant antibody (NI006) in the treatment of patients with symptomatic ATTR did not show any drug-related adverse events [65].

Symptomatic treatment

Angiotensin-converting-enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and angiotensin receptor-neprilysin inhibitors are associated with risk of worsening hypotension in patients with HF in the course of ATTR due to autonomic dysfunction. Therefore, these drugs are not recommended in patients with amyloidosis. Beta-blockers may also exert negative effects and should be avoided. When discussing the symptomatic treatment of CA, the 2021 ESC position statement clearly underlines: "Deprescribe beta-blockers. Avoid ACE/ARB" [3]. This recommendation was confirmed in the 2022 ESC guidelines [55]. The key therapeutics for managing congestive HF symptoms in ATTR-CM patients are diuretics and mineralocorticoid receptor antagonists [3]. Calcium channel blockers are not indicated because they irreversibly bind to amyloid fibrils and because they show unfavorable toxicity and adverse event profiles [66]. Currently, data are lacking on the use of sodium-glucose co-transporter-2 inhibitors in ATTR-CM patients.

To reduce arrhythmia in AF, low doses of beta-blockers may be considered. However, CA patients who receive beta-blockers should be closely monitored [36]. In symptomatic AF or tachycardia-bradycardia syndrome, atrioventricular node ablation and pacemaker implantation may be unavoidable. Amiodarone should be the first-line treatment to maintain sinus rhythm [55].

Considering that these patients often develop rhythm and conduction disorders, they should be closely monitored for indications for pacemaker implantation. Implantable cardioverter-defibrillator (ICD) implantation is not recommended for primary prevention. However, ventricular tachycardia in patients with hemodynamic instability constitutes an indication for ICD implantation [67]. Electroanatomical mapping may be useful for determining patients' eligibility for the ICD procedure [68].

Indications for heart transplant or combined heart and liver transplant should be assessed on a case-by-case

basis. In the experience of the National Institute of Cardiology in Warsaw, before the tafamidis era, good long-term outcomes with combined heart and liver transplants were achieved in 2 patients with ATTRv cardiomyopathy. However, the procedure is not indicated in patients with symptomatic gastrointestinal involvement, advanced autonomic neuropathy, or peripheral polyneuropathy.

Anticoagulant treatment

There is evidence of an increased risk of thromboembolic events in ATTR-CM patients even while in sinus rhythm [69, 70]. The standard scores for routine assessment of thrombotic and bleeding risk in AF patients are not recommended [71]. Treatment options include oral non-vitamin K antagonist oral anticoagulants (dabigatran, apixaban, rivaroxaban), vitamin K antagonists (acenocoumarin, warfarin), as well as low-molecular-weight and unfractionated heparin.

Nonpharmacological treatment

Nonpharmacological treatment options for ATTR aim at relieving symptoms and improving the quality of life.

Diet

In patients with CA, it is important to tailor the diet to individual needs depending on the medical conditions or food intolerances present, but also to reduce sodium intake (as it decreases fluid retention and prevents edema) [72] and saturated fats [9]. On the other hand, vitamin D supplementation may be beneficial, because CA patients often have vitamin D deficiency [73].

Physical activity and rehabilitation

Before patients are advised to start physical activity, they should be assessed for exercise capacity. CA patients will benefit from physical activity that is tailored to their individual needs and capabilities. It was shown that cardiac rehabilitation with controlled physical exercise improves exercise tolerance, quality of life, and physical capacity [74].

Social and psychological care

Progressive deterioration of functional autonomy in CA patients negatively affects the quality of life and requires increasing daily support provided by the family and caregivers. Research showed that almost 50% of CA patients experience anxiety, depression, or both [75]. Therefore, patients need psychological support that will increase their ability to adapt to the disease as well as family support and help in everyday disease-related challenges. It is also recommended to seek support in self-help groups and associations for patients and their families.

Palliative care

Patients with end-stage HF or those incapable of walking without assistance require geriatric and palliative care. At this stage, apart from treatment that relieves neuropathic pain, it is necessary to modify the medical treatment (to avoid the simultaneous use of multiple drugs), assess cognitive function, handle social isolation, and address the emotional and spiritual needs of the patient [36].

MONITORING DISEASE PROGRESSION

N-terminal pro-B-type natriuretic peptide is a reference biomarker for predicting HF. Moreover, due to its low cost and ease of use, the NT-proBNP assessment is useful in routine clinical practice.

NT-proBNP results should be read with caution because increased levels are seen in kidney failure and AF, and this may affect the interpretation of abnormalities as signs of ATTR-CM progression. Thus, it should be noted that the association between NT-proBNP and eGFR is complex and reflects the interplay of cardiac and renal factors. Considering that the precision of NT-proBNP is affected by analytical and biological variability, the experts recommend using both relative (30%) and absolute (300 pg/ml) increases in NT-proBNP as a marker of disease progression, so that it can be detected both in patients with early and advanced disease. The proposed thresholds reflecting variability in NT-proBNP levels may be updated when more data become available. The experts emphasize that biomarker tests should be interpreted after 30 days of clinically stable condition, without changes in diuretic doses, and with the same heart rhythm (i.e., sinus rhythm or AF) as on previous testing.

Currently, there are two severity staging systems for ATTR-CM, based on biomarkers measured at diagnosis. The Mayo Clinic system is suitable for ATTRwt and includes NT-proBNP (cutoff value — 3000 pg/ml) and troponin T (0.05 ng/ml) [73]. On the other hand, the UK National Amyloidosis Center Staging System can be used both in ATTRwt and ATTRv. This system uses NT-proBNP levels (cutoff value — 3000 pg/ml) and renal function based on eGFR <45 ml/min/1.73 m^2. Stage I is defined as NT-proBNP ≤3000 pg/ml and eGFR ≥45 ml/min/1.73 m^2, stage II as NT-proBNP >3000 pg/ml or eGFR <45 ml/min/1.73 m^2, and stage III as NT-proBNP >3000 pg/ml and eGFR <45 ml/min/1.73 m^2. Median overall survival in patients with ATTR-CM classified according to the UK National Amyloidosis Center Staging System was determined at 69, 47, and 24 months for stages I, II, and III, respectively [76].

The above staging systems were developed using biomarker levels obtained on initial assessment and do not reflect changes that occur during subsequent follow-up of the patient. Therefore, additional studies are needed to clarify the effect of changes in severity scores during follow-up on disease prognosis.

A consensus document developed by an international panel of experts provides recommendations for long-term monitoring of patients with ATTR-CM [77]. To identify dis-

ease progression, it is recommended to use a minimal set of parameters that should be measured in a relatively short time (6–12 months) from diagnosis or start of treatment. These parameters should include:

- quantification of functional decline (clinical and functional endpoints);
- quantification of disease severity using biomarkers and laboratory markers;
- quantification of disease severity using imaging and electrocardiographic parameters.

Consistently elevated troponin levels indicate myocardial damage and may have prognostic value in ATTR-CM. However, standardization of cardiac troponin measurement remains a challenge, as troponin tests were developed by various manufacturers, resulting in different centers preferring different tests. Moreover, the link between absolute changes in troponin and changes in disease course may not be consistent.

CAUSATIVE TREATMENT OF ATTR-CM IN POLAND AND EUROPE

At present, tafamidis is reimbursed in 19 countries of the European Union/EFTA, including Germany, France, Italy, Belgium, Luxemburg, Austria, Finland, Sweden, Iceland, Switzerland, Portugal, the Netherlands, Norway, Slovenia, Romania, Latvia, Greece, and Croatia. Further 10 countries are, currently, in the process of obtaining reimbursement. Tafamidis is also reimbursed in countries outside the EU such as Canada, Japan, and Israel.

The most important reference centers for patients with amyloidosis in Europe are the National Amyloidosis Centre in London (University College London, UK), Amyloidosis Research and Treatment Center in Pavia (University of Pavia, Italy), Hospital Universitario Puerta de Hierro and CNIC (Madrid, Spain) and Amyloidose Zentrum at the Heidelberg University. The centers in the US include the Cardiac Amyloidosis Clinic at the Mayo Clinic, Amyloidosis Center at the Cleveland Clinic, Stanford Amyloid Center, and Amyloidosis Center at the Boston University School of Medicine. These centers cooperate as part of the International Society of Amyloidosis [78].

In Poland, tafamidis treatment has been provided since 2018 in selected reference centers as part of the early access treatment program financed by the drug's manufacturer (Pfizer). According to the manufacturer's data, currently, there are 71 patients treated with tafamidis in 10 reference centers (Table 6).

Tafamidis used as part of early access to ATTR-CM treatment in adults with HF classified as NYHA class I–III is administered at a dose given in the Summary of Product Characteristics, that is, 61 mg (equivalent to 80 mg of tafamidis meglumine), 1 tablet per day. Eligible patients are those in whom ATTR-CM was confirmed by scintigraphy and the type of ATTR was determined by *TTR* gene sequencing.

Table 6. The list of centers providing tafamidis treatment as part of the Pfizer Cares program

1.	WARSZAWA, Department of Cardiomyopathy, Cardinal Wyszynski National Institute of Cardiology Head: Prof. Jacek Grzybowski, MD, PhD
2.	KRAKÓW, Department of Cardiovascular Disease, Jagiellonian University Medical College; Centre for Rare Cardiovascular Diseases, John Paul II Hospital Head: Prof. Piotr Podolec, MD, PHD
3.	GDAŃSK, 2nd Department of Cardiology and Electrotherapy, Clinical Hospital of the Medical University of Gdansk Head: Prof. Ludmiła Daniłowicz-Szymanowicz, MD, PhD Treating physician: Prof. Alicja Dąbrowska-Kugacka, MD, PhD
4.	SZCZECIN, Independent Nonivasive Cardiac Diagnosis Laboratory for Children and Adults, Public Hospital, Medical University Head: Piotr Gościniak, MD, PhD
5.	KATOWICE, Department of Cardiology, Medical University of Silesia; 2nd Department of Cardiology, Upper-Silesian Medical Center Head: Prof. Zbigniew Gąsior Treating physician: Prof. of SUM Maciej Haberka, MD, PhD
6.	POZNAŃ, 1st Department of Cardiology, University Hospital Head: Prof. Maciej Lesiak, MD, PhD Treating physician: Prof. Ewa Straburzyńska-Migaj, MD, PhD
7.	KRAKÓW, Department of Cardiology and Cardiovascular Interventions, University Hospital Head: Prof. Stanisław Bartuś Treating physician: Renata Rajtar-Salwa, MD, PhD
8.	WROCŁAW, Department of Translational Cardiology and Clinical Registries, Wroclaw Medical University Head: Prof. Ewa Jankowska, MD, PhD
9.	ŁÓDŹ, 1st Department of Cardiology, Medical University of Lodz, Bieganski Hospital Head: Prof. Jarosław D. Kasprzak, MD, PhD
10.	ŁÓDŹ, Department of Electrocardiology, Central Clinical Hospital, Medical University of Lodz Head: Prof. Jerzy Krzysztof Wranicz, MD, PhD

The main contraindication to tafamidis treatment as part of the program is AL amyloidosis.

Currently, there are no systemic solutions that would provide access to causative ATTR-CM treatment in Poland. Therefore, it seems justified to provide such access within the framework of guaranteed healthcare benefits, such as drug programs, which are model solutions for other rare diseases.

CONCLUSIONS

Cardiac amyloidosis is a serious condition that affects not only the heart but also other organs. The 2 main types of CA are AL amyloidosis and ATTR. It is an ultrarare disease that has not been widely studied. Therefore, it is underdiagnosed and poses diagnostic challenges. The diagnosis of CA often requires cooperation between cardiologists, hematologists, radiologists, neurologists, and other specialists to ensure comprehensive assessment of the patient. In ATTR, a noninvasive approach to diagnosis is currently preferred, which improves the diagnostic process and allows identification of the disease at early stages. With the reference method of mass spectrometry unavailable in Poland, invasive diagnosis based on biopsy is burdened with a risk of incorrect amyloid typing even in an experienced referral center. Moreover, due to its invasive character, it is not suitable for large-scale use.

Cardiac amyloidosis treatment requires a multidisciplinary approach and should be tailored to individual patient's needs. Disease-specific treatment with tafamidis has constituted a major breakthrough in recent years. Importantly, this is the first drug with confirmed efficacy as a causative treatment of HFpEF of this etiology. This is important because the use of classic HF medication is not possible in these patients. Early diagnosis, before severe cardiac involvement, followed by disease-specific tafamidis treatment, is of major importance to provide optimal care and improve the quality of life and prognosis for these patients. The key step in the management of this rare and life-threatening disease is to ensure access to tafamidis treatment. Tafamidis improves the quality of life, delays the onset of HFpEF symptoms, prevents hospitalization for HFpEF exacerbations, and improves prognosis. In ATTRv, tafamidis may additionally prevent combined heart and liver transplant. The PTK experts emphasize the need to ensure access to effective causative treatment of ATTR for all patients in Poland. At present, as the disease is rare and the patient population is small and limited to a few reference centers, a drug program modeled on the programs for other rare diseases, would provide optimal access to treatment.

Article information

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