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Advances in the diagnosis and treatment of transthyretin amyloidosis with cardiac involvement

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Abstract

Amyloidosis is caused by extracellular deposition of insoluble abnormal fibrils constituted by misfolded proteins, which can modify tissue anatomy and hinder the function of multiple organs including the heart. Amyloidosis that can affect the heart includes mostly systemic amyloidosis (amyloid light chain, AL) and transthyretin amyloidosis (ATTR). The latter can be acquired in elderly patients (ATTRwt), or be inherited in younger individuals (ATTRm). The diagnosis is demanding given the high phenotypic heterogeneity of the disease. Therefore, "red flags," which are suggestive features giving support to diagnostic suspicion, are extremely valuable. However, the lack of broad awareness among clinicians represents a major obstacle for early diagnosis and treatment of ATTR. Furthermore, recent implementation of noninvasive diagnostic techniques has revisited the need for endomyocardial biopsy (EMB). In fact, unlike AL amyloidosis, which requires tissue confirmation and typing for diagnosis, ATTR can now be diagnosed noninvasively with the combination of bone scintigraphy and the absence of a monoclonal protein. Securing the correct diagnosis is pivotal for the newly available therapeutic options targeting both ATTRm and ATTRwt, and are directed to either stabilization of the abnormal protein or the reduction of the production of transthyretin. The purpose of this article is to review the contemporary aspects of diagnosis and management of transthyretin amyloidosis with cardiac involvement, summarizing also the recent therapeutic advances with tafamidis, patisiran, and inotersen.

Keywords ATTR · Cardiac amyloidosis · Diagnosis · Transthyretin · Treatment

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Abbreviations

[99mTc]-DPD	Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid
[99mTc]-HMDP	Tc-99m-hydroxymethylene diphosphonate
[99mTc]-PYP	Tc-99m-pyrophosphate
123I-MIBG	123I-Metaiodobenzylguanidine
AL	Light chain amyloidosis
ANP	Atrial natriuretic peptide
AS	Aortic stenosis
ATTR	Transthyretin amyloidosis
ATTRm	Mutant transthyretin amyloidosis
ATTRwt	Wild-type transthyretin amyloidosis
BNP	Brain natriuretic peptide
CA	Cardiac amyloidosis
CMR	Cardiac magnetic resonance
cTnT	Cardiac troponin T
ECG	Electrocardiography

EMB	Endomyocardial biopsy
EF	Ejection fraction
EFSR	Ejection fraction strain ratio
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire-Overall Summary
LFLG	Low-flow low-gradient
LGE	Late gadolinium enhancement
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
Norfolk QOL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NT-proBNP	N-terminal pro-brain natriuretic peptide
PET	Positron emission tomography
RBP4	Retinol binding protein 4
RCM	Restrictive cardiomyopathy
RV	Right ventricular
SCD	Sudden cardiac death
ST	Speckle-tracking
TAVI	Transcatheter aortic valve implantation
TDI	Tissue Doppler imaging
TTR	Transthyretin

Introduction

Amyloidosis is a group of diseases where uncontrolled deposition of structurally abnormal proteins (amyloid fibrils) affects multiple organs, such as the liver, kidney, eyes, nervous system, gastrointestinal tract, and the heart, and eventually increasing the patients' morbidity and mortality. Over 30 different amyloidogenic proteins have been identified. However, the two most common types of amyloidosis are the immunoglobulin light chain amyloidosis (AL) and the transthyretin amyloidosis [ATTR], the latter comprising the mutant transthyretin (ATTR-m), and the "wild-type" transthyretin (ATTRwt) entities [1, 2].

Patients with cardiac amyloidosis (CA) due to AL (AL-CA) have a plasma cell dyscrasia, with amyloidogenic light chains (80% lambda and 20% kappa) exerting toxic effects to cardiac myocytes. Cardiac involvement is frequent in AL (70% of cases). However, exclusive cardiac involvement occurs in < 5% of patients. Furthermore, isolated atrial amyloidosis (IAA) is caused by the deposition of atrial natriuretic peptide (ANP) fibrils in the atria. It is a common form of CA as more than 90% of patients over 90 years old have measurable ANP deposition in their hearts [3] and it bears significance in the pathophysiology of atrial arrhythmias such as atrial fibrillation [4]. Finally, the overproduction of the acute-phase protein serum amyloid A (SAA) in chronic inflammatory conditions can cause secondary amyloidosis. SAA can show heart deposition; however, clinically significant cardiac involvement is rare [5].

Regarding ATTR, transthyretin (TTR) is a circulating homotetramer carrier protein that functions as a transporter of thyroxine and retinol and is produced mainly by the liver, with additional production within the choroid plexus of the brain and the retinal pigment epithelium. It is in equilibrium with its composite monomers, which can unfold and aggregate into fibrils that deposit preferentially in the heart and peripheral nervous system as well as in the skin, and elsewhere, causing ATTR and organ dysfunction [6].

There are two types of ATTR:

1. Wild-type (formally known as senile) amyloidosis (ATTRwt) arises from genetically unaltered TTR and leads to cardiac amyloid deposition in patients usually after their sixth decade of life. Autopsies show that 25% of people older than 80 years have their myocardium infiltrated by TTR amyloid depositions [7, 8].
2. Point mutations within the TTR protein alter dissociation kinetics and thereby promote amyloid formation. Hereditary amyloidosis caused by mutations of the TTR gene (ATTRm) is transmitted in an autosomal dominant inheritance pattern [2, 9, 10].

Deposition of amyloid into the myocardium causes diastolic dysfunction, restrictive physiology with late deterioration of systolic function, arrhythmias, and heart failure (HF) [11, 12]. CA is the primary cause of restrictive cardiomyopathy (RCM) [13, 14]. The presence of CA among HF patients is being increasingly acknowledged, as can be observed from its inclusion in the novel MOGES classification of cardiomyopathies [15]. Non-biopsy-based diagnostic studies of Gillmore et al. [16] and Castano et al. [17] have reported an ATTR prevalence of 13% among patients with HF with preserved ejection fraction (HFpEF) [18, 19]. Furthermore, CA has been reported in 16% among patients undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) [20], and in 5% among patients with the clinical presentation of hypertrophic cardiomyopathy (HCM) [21].

The survival in ATTRm is considerably better than in AL-CA (median 27 vs 5 months). In addition, data on outcomes of African Americans with ATTR-CA compared to Caucasians with ATTRwt, a phenotypically similar condition, reveal that African Americans present with more advanced disease [2, 22]. Death in most patients is due to cardiac causes, including sudden cardiac death (SCD) and heart failure [19, 23].

This review aims to offer insight into the advances in the diagnosis along with the novel treatment options of ATTR with cardiac involvement.

Diagnosis

The diagnosis of CA is challenging, partly due to the high heterogeneity of cardiac phenotypes and of systemic involvement. The patients may present with various nonspecific clinical signs and symptoms that demand a high clinical suspicion for early diagnosis, in combination with laboratory findings, electrocardiography (ECG), multimodality imaging, and eventually biopsy diagnostics and genetic testing (Table 1). Particularly helpful are the so-called diagnostic "red flags," i.e., highly suggestive data that corroborate the diagnostic suspicion [24].

Clinical data

Unique cardiac involvement is rare. Patients with CA often present a variable constellation of non-cardiac symptoms, mainly neurological. Furthermore, ATTR is a late-onset disease and symptoms manifest mostly in elderly patients (predominantly male after the 6th decade) with comorbidities, a factor that further hampers the early correct diagnosis.

The acquired wild-type variant of ATTR (ATTRwt) causes most commonly cardiac involvement, and in the past it was often an unrecognized cause of diastolic HF in elderly patients. Interestingly, it has also been diagnosed in 12% of patients referred for TAVI. A diagnostic red flag is that ATTRwt is often preceded by carpal tunnel syndrome (in 33% of patients and frequently bilateral) or spinal stenosis or both [25]. In 20% of cases, the disease affects female patients, presenting at a later age and with less severe characteristics [26].

The hereditary mutant variant of ATTR (ATTRm) leads to variable phenotypic presentation and can cause polyneuropathy with exclusively neurological involvement, exclusive cardiac manifestations with cardiomyopathy (reported in 17% of ATTR Caucasian patients at presentation) [27], or both with mixed cardiac and neurologic phenotype. Familial history is important, but a manifest family history is very rarely disclosed because of the delayed and incomplete penetrance of the mutations accountable for the forms with prevalent cardiac phenotype [24].

Cardiac involvement by ATTR embraces mostly HF symptoms (predominantly right-sided) in 87% of patients. In particular, it was demonstrated that ATTRwt accounted for 13% of the hospital admissions of elderly HF cases with preserved ejection fraction (HFpEF), even if a role of the high amount of comorbidities could not be precluded [18]. Other manifestations are as follows: cardiac arrhythmias (most commonly atrial fibrillation), syncope, angina pectoris, and SCD. A frequent association with severe calcific AS has also been reported. ATTR was prevalent in 16% of patients with severe calcific AS referred to TAVI and was associated with a severe AS phenotype of low-flow low-gradient (LFLG) with mildly reduced LVEF [20].

Table 1 Diagnostic hallmarks of ATTR amyloidosis

Clinical data	-ATTRwt: late-onset disease with cardiac involvement in elderly, often preceded by carpal tunnel syndrome or spinal stenosis or both
	-ATTRm: causes more severe neurological symptoms
Biomarkers	-High levels of troponin or natriuretic peptides
	-Absence of monoclonal light chain gammopathy
ECG	-Pseudonecrosis pattern is the most common feature
Echocardiography	-LV diastolic dysfunction is the main feature
	-LVH, typically concentric and "sparkling"
	-Preserved LV size and LVEF but early decrease in longitudinal strain with apical sparing pattern
	-Increased thickness of RV wall, IAS, valves
	-Pericardial effusion
	-LFLG AS and new diagnosis of HCM in elderly patients
CMR	-Diffuse subendocardial LGE
	-RV-LGE
	-Increased T1 relaxation time
Bone scintigraphy with bisphosphonates	-Increased cardiac uptake
Biopsy	-Diagnostic gold standard, allows histological evidence of amyloid deposits with typing of amyloid proteins
Genetic test	-Differentiates ATTRwt from ATTRm

Progressive polyneuropathy can affect both the peripheral system (with carpal tunnel syndrome, paresthesia, sensibility deficit) and the autonomic system (orthostatic hypotension, sexual dysfunction, incontinence, diarrhea).

Of note, neurological symptoms are more severe in ATTRm than ATTRwt, whereas cardiac symptoms are similarly intense. Among ATTRm patients, cardiac involvement is more pronounced in patients with exclusive cardiac phenotype [27].

Biomarkers

A red flag for CA is high levels of cardiac biomarkers such as troponin or natriuretic peptides, out of proportion in relation with the hemodynamic burden.

Cardiac troponin T (cTnT) is a marker of cardiomyocyte death and has shown a strong negative prognostic value in AL and ATTR [28]. Also, the brain natriuretic peptide (BNP) and the protein that derives from the N-terminal cleavage of BNP's prohormone (NT-proBNP) have been shown to be reliable prognostic markers for AL and ATTR [29]. According to the Transthyretin Amyloidosis Outcomes Survey (THAOS), patients with elevated BNP and NT-proBNP levels at the time of diagnosis showed poorer prognosis, mainly due to renal insufficiency and worsened functional status [30].

A similar staging system to that used in AL has been proposed for ATTRwt, utilizing cTnT and NT-proBNP values to stratify disease severity in three stages [23].

Furthermore, a recent investigation developed a staging tool to predict median survival in both ATTRwt and ATTRm. This staging tool included eGFR and NT-proBNP, which both correlate well with overall survival [31].

TTR concentration in serum was demonstrated to be lower in carriers of TTR mutations compared with controls, suggesting a possible conversion of TTR into amyloid [32]. However, testing of TTR levels is not routinely performed in clinical practice.

A recent study demonstrated significantly reduced levels of retinol binding protein 4 (RBP4) in ATTRm patients with the V122I mutation, present in 3–4% of elderly African Americans [33]. By combining echocardiographic measurements (LVEF, LV thickness) and ECG parameters (mean QRS) with serum RBP4 levels, the authors proposed a clinical score with significant diagnostic accuracy [34].

Laboratory evaluation can help in discriminating ATTR from AL amyloidosis, the latter being characterized by monoclonal light chain gammopathy. Serum and urine immunofixation electrophoresis can confirm the presence of monoclonal gammopathy. This test is however insensitive and should always be accompanied by quantitative demonstration of light chain proteins increase in serum with serum free light chain assay, which measures free kappa and lambda light chain levels and reports their ratio.

Of note, incidental monoclonal gammopathy of undetermined significance (MGUS) occurs in more than 5% of patients over 70 years of age, misleading the diagnosis of ATTR in favor of AL amyloidosis.

ECG

A discrepancy between no LV hypertrophy (LVH) criteria or low-voltage QRS complexes at ECG and LVH at imaging is a red flag for the diagnosis of CA.

However, absence of low-voltage QRS at ECG does not rule out CA. Low-voltage QRS complexes are more frequent in AL amyloidosis (up to 70% of cases) and less prevalent in ATTR (16% in ATTRm and 29% in ATTRwt). Moreover, low-voltage QRS is a relatively late phase phenomenon and thus an inadequate screening tool.

A pseudonecrosis pattern (mainly in anterior leads) is present in up to 70% of patients and it is the most common ECG feature noticed in ATTRwt (Fig. 1).

Furthermore, atrioventricular block and intraventricular conduction delays are common and more frequently encountered in ATTR than in AL-CA.

In addition, atrial arrhythmias are common, especially atrial fibrillation [35].

Echocardiography

Amyloid infiltration in myocardium causes initially LV diastolic dysfunction, which is an early important feature of CA. Echocardiography can detect progression of diastolic dysfunction from impaired relaxation in early stages to restrictive LV pathophysiology in advanced stages of amyloid infiltration with increased LV filling pressures. Tissue Doppler imaging (TDI) shows low myocardial diastolic velocities, with increased in E/E′ ratio [36]. Peak early diastolic velocity (E′) is reduced in the early stages of the disease and shows a further decrease with the disease progression. This finding helps in the differential diagnosis from other conditions such as constrictive pericarditis or HCM, where E′ is normal or only mildly reduced [37].

Another relevant echocardiographic feature of CA is increased LV thickening, which is due to infiltration of amyloid fibrils and not to myocyte hypertrophy per se, even though it is routinely reported as LVH. Greater degrees of LV wall thickness have been described in ATTR (16–18 mm) than in AL (13–15 mm) [38]. However, a study described normal LV wall thickness in 3% of patients with CA (14% with ATTRwt) confirmed by endomyocardial biopsy (EMB); therefore, normal wall thickness should not rule out the diagnosis [39].

LV thickening is typically concentric. Asymmetric septal hypertrophy is occasional in ATTRwt (25% of cases) [26] and has been seen mainly in early stages. Its prevalence was surprisingly high (up to 69% of cases) in a cardiac magnetic resonance (CMR) study considering several types of CA

[40]. Dynamic LV outflow tract (LVOT) obstruction has been noted in some cases with asymmetric septal hypertrophy and can lead to misdiagnosing obstructive HCM (HOCM).

An increased myocardial echogenicity or the so-called "granular sparkling" myocardial texture due to the increased echogenicity of the amyloid protein [41] has been extensively reported in previous echo-studies on CA, but nowadays (with the employment of harmonic imaging) this feature has lost its specificity and sensitivity in detecting CA as it is highly dependent on machine settings . Echocardiographic findings in a patient with cardiac amyloidosis are shown in Fig. 2.

An important clue to diagnosis is simultaneous thickening of both LV and right ventricular (RV) free wall.

LV dimensions are usually smaller than normal, therefore cardiac output is low (due to decreased LV volumes) despite normal LVEF. A reduction in LVEF is usually a late finding in CA, even though an LVEF < 50% was recently found in 36.8% of ATTRwt [26].

Despite the presence of normal LVEF in early stages, TDI shows low myocardial longitudinal systolic (s′) velocities. Myocardial performance index (MPI or Tei index), which integrates systolic and diastolic time intervals, may not only

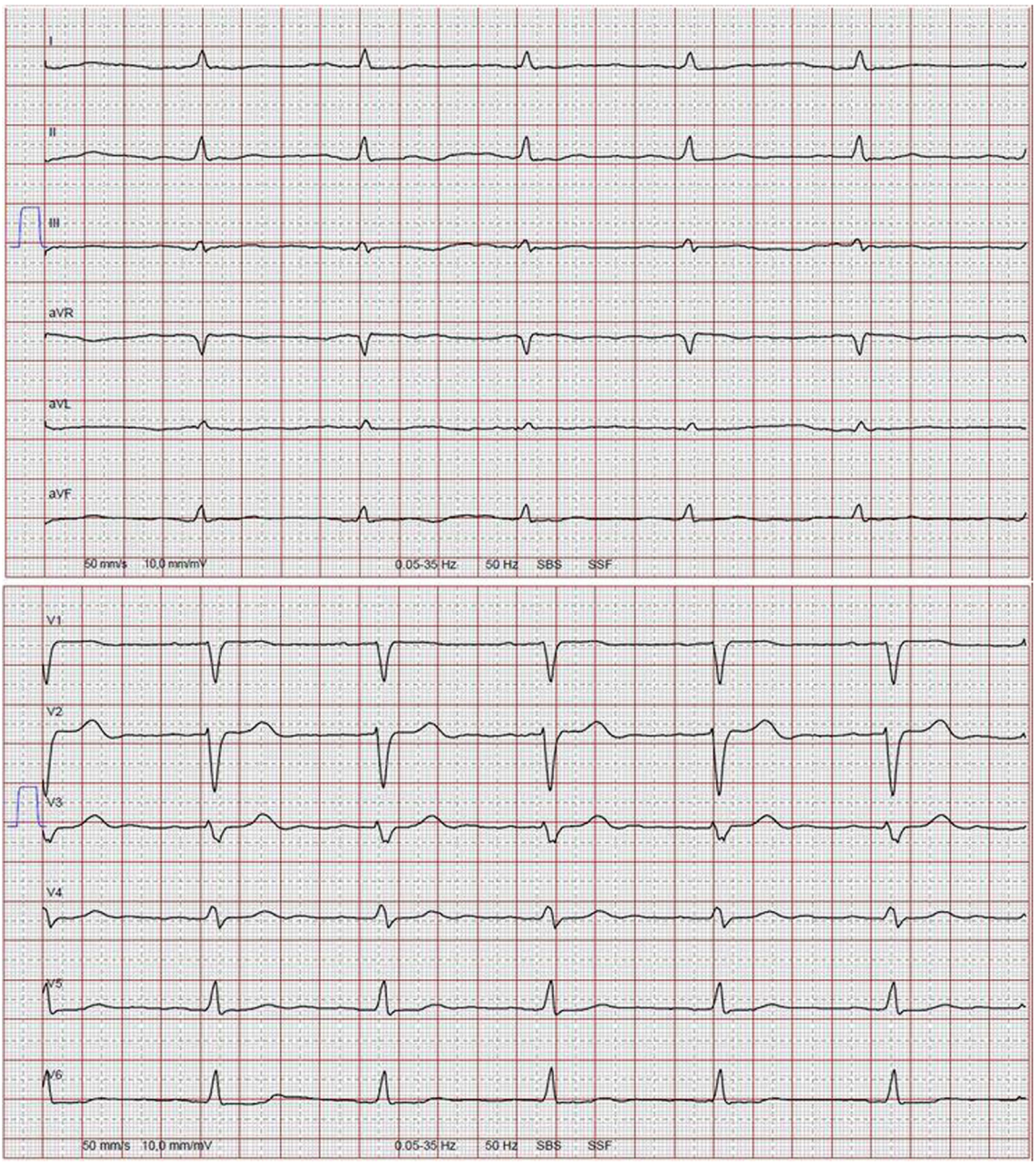

Fig. 1 ECG of a 64-year-old woman with CA, showing a pseudonecrosis pattern in anterior lead (top) and low-voltage QRS complexes in peripheral leads (bottom)

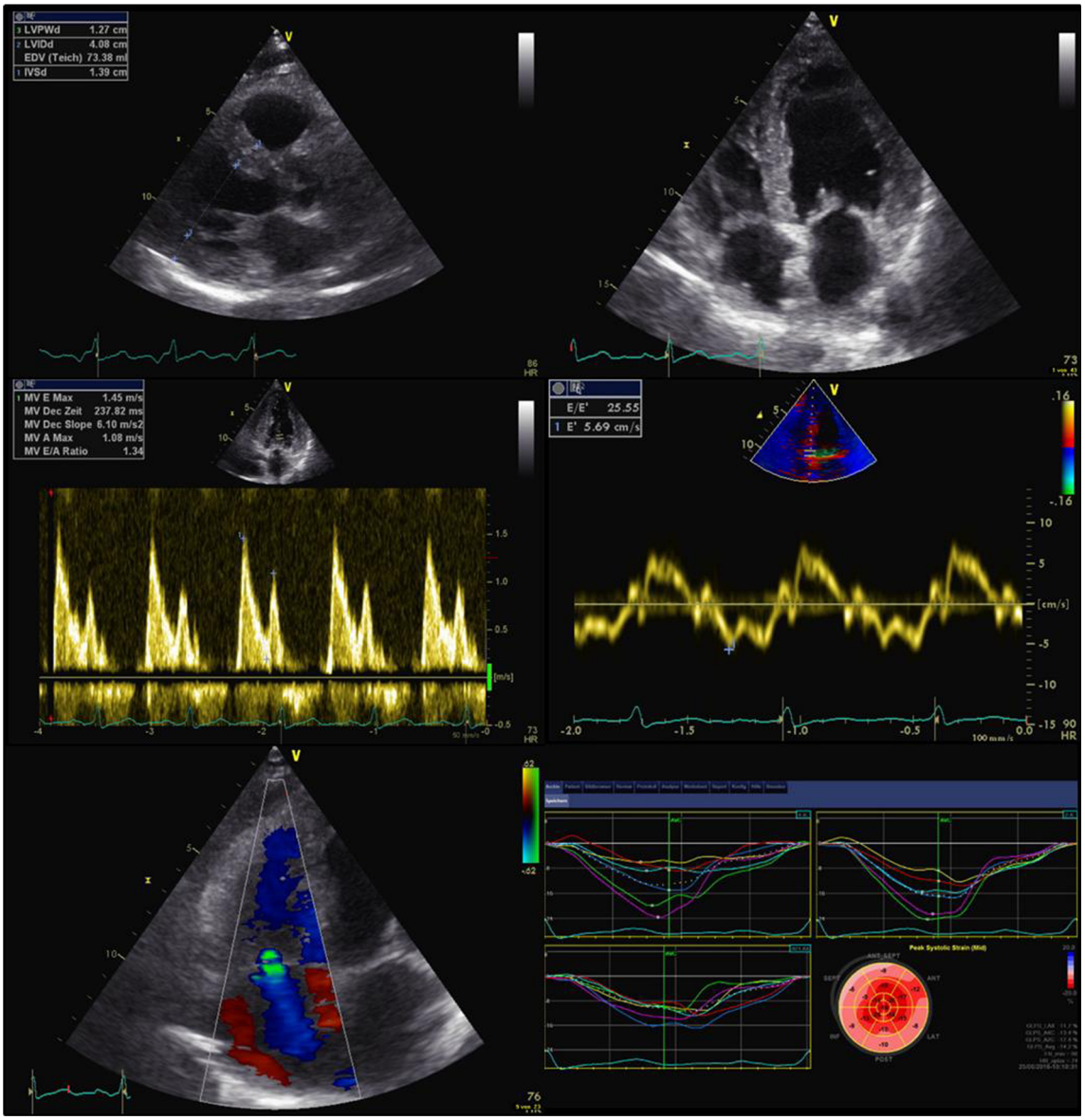

Fig. 2 Echocardiogram of the same patient as in Fig. 1, showing moderate concentric and "sparkling" increase in LV thickness (interventricular septum thickness 14 mm) and normal LV dimensions (top left). Increased thickness of RV wall, IAS, and valves is also present (top right). Transmitral pulsed Doppler and TDI show diastolic dysfunction grade II with increased LV filling pressures (E/E′ = 25, mid panels). Mild valvular regurgitations are seen (TR in bottom left panel). LVEF is preserved (60%) but there is decreased global longitudinal strain (− 14%) with apical sparing pattern (bottom right)

yield significant information on myocardial function of CA patients, but it may also be considered as an index of outcome [42, 43].

In addition, two-dimensional speckle-tracking (ST) strain imaging demonstrates severe longitudinal dysfunction with a so-called pattern of relative apical sparing in longitudinal strain, where preserved strain in the LV apex coexists with reduced strain in mid and basal segments due to predominant deposition of amyloid in basal segments [44]. This feature has been seen in all CA types [45] and it is both sensitive and specific for the diagnosis of CA [46].

Arvidsson et al. [47] detected an RV apical sparing pattern in longitudinal ST strain, similar to what has been described for the LV, in patients with ATTR, but not in HCM patients. Further research is needed to confirm the clinical importance of these findings.

Not only global longitudinal strain (GLS) but also circumferential and radial deformations are significantly reduced in CA patients compared to patients with HCM or hypertensive heart disease [48]. A recent study proposed the ejection fraction strain ratio (EFSR = the ratio of GLS to EF) as a reliable tool to diagnose CA. EFSR is significantly higher in CA compared to other groups [49], and it has proven a very specific

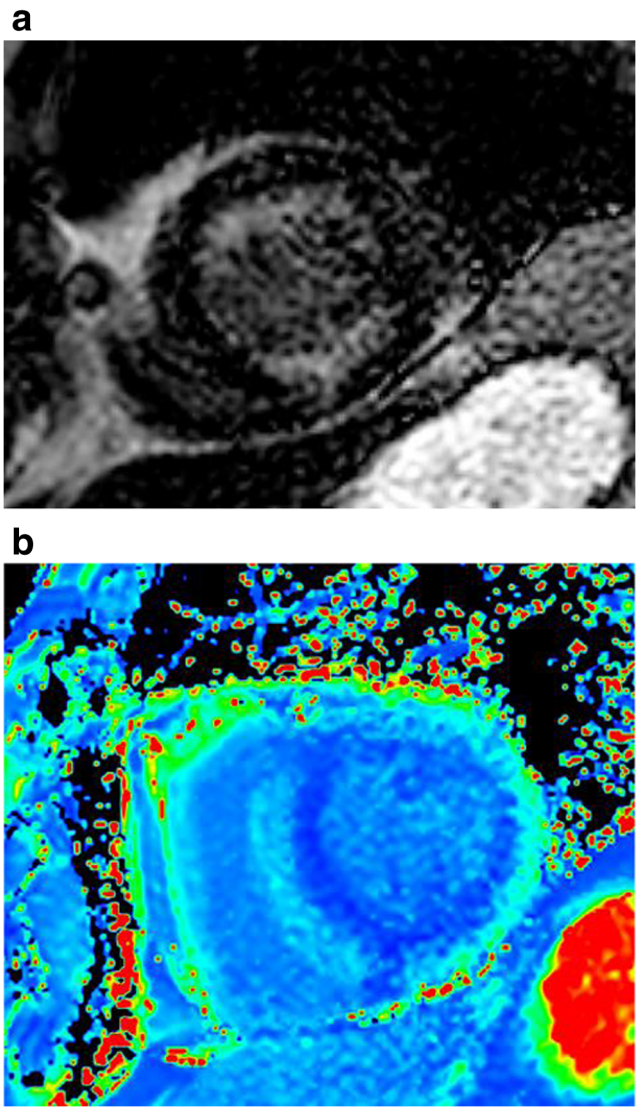

Fig. 3 CMR in a patient with ATTR amyloidosis. **a** Diffuse subendocardial LGE without coronary distribution pattern. **b** Post-contrast T1 mapping showing diffuse subendocardial deposition

(91.7%) and sensitive (89.7%) echocardiographic parameter in diagnosing CA. The study also confirmed that EFSR displays low inter-observer variability and maintains its high diagnostic value in populations with either increased wall thickness or preserved LVEF.

A three-dimensional ST echocardiography has been recently used to differentiate CA from other forms of myocardial hypertrophy. In particular, basal rotational strain in CA was significantly reduced compared to the apical one, in contrast to HCM [50].

Additional frequent echocardiographic features are pericardial effusion, interatrial septum hypertrophy, and biatrial enlargement. The presence of intraatrial thrombus is relatively frequent even in sinus rhythm [46]. Interestingly, a recent study assessed the left atrial (LA) myocardial function employing LA strain, which turned out to be reduced irrespective of the LA cavity size [51].

Valvular thickening (mainly affecting the aortic valve) with mild to moderate regurgitation is also frequent. A recent study demonstrated that CA can be associated with and regarded as a potential explanation for LFLG AS with preserved EF. LFLG AS is therefore suggested as a red flag for CA diagnosis in the elderly [52].

In summary, echocardiographic features can be suggestive for the disease but have limited specificity and sensitivity. Nonetheless, echocardiography is regarded as the first diagnostic tool to identify patients likely to have the disease, thus leading to further assessment. Its sensitivity and specificity has been recently substantially improved by advances in technology, such as TDI and strain imaging.

CMR

CMR has high sensitivity and specificity (> 86%) for the diagnosis of CA. This imaging technique is not only useful to confirm the echocardiographic suspicion showing the same morphological changes, but it also provides also additional information since amyloid deposition in myocardium shows a specific late gadolinium enhancement (LGE) distribution pattern, namely diffuse subendocardial LGE without coronary distribution. However, LGE can also be more localized and patchy with dark mid-wall (zebra pattern). More advanced disease can show transmural LGE. Nevertheless, absence of LGE does not exclude the diagnosis of CA. In addition, RV and interatrial septum may show LGE deposition as well. RV-LGE may differentiate AL (absent in up to one third of cases) from ATTR [38]. Notably, a parameter more sensitive than LGE in detecting early subclinical cardiac involvement is the T1 relaxation time, which is influenced by amyloid deposits [53]. CMR findings in a patient with cardiac amyloidosis are shown in Fig. 3.

CMR can also play an important role in the differential diagnosis between CA and other conditions. For example, while HCM shows a patchy LGE pattern mainly located in the mid-wall, and Fabry's disease shows a LGE pattern localized in the LV basal posterolateral segments, CA shows atypical signal intensity related to the amyloid deposition pattern and faster clearance of gadolinium [54]. Of note, the diminished T1 difference between myocardium and blood pool is due to this faster clearance of gadolinium in CA patients.

The combination of both LGE and the relative apical strain sparing is very reliable in detecting CA [55].

Furthermore, absence of myocardial edema on T2 black blood imaging may help differentiate CA from inflammatory processes.

The Look-Locker magnetic resonance sequence is a technique that aims at quantifying amyloid deposition and has shown good diagnostic accuracy to detect CA and correlation with histological amyloid burden [56].

Finally, non-contrast T1 CMR has demonstrated a 92% accuracy in detecting cardiac involvement in amyloidosis

and it is safe in patients with renal failure, which is commonly present in this population [53, 57].

Nuclear imaging

Radionuclide bone tracers such as technetium-labeled bisphosphonates (99mTc-DPD, 99mTc-PYP and 99mTc-HMDP) have shown high affinity to ATTR amyloid in early stages, even prior to echocardiographic or CMR evidence of cardiac involvement.

The high sensitivity (up to 100%) to detect ATTR amyloid deposits in heart and organs is due to intense cardiac and soft tissue uptake (particularly in the shoulder, gluteal, chest region, and abdominal wall) with obscuring of bone uptake.

99mTc-DPD uptake occurs also in carriers of the TTR mutations before ECG and echocardiographic changes and in asymptomatic elderly patients with ATTRwt. The amount of uptake is related to the severity of amyloid deposition in the heart (i.e., level of LV thickness and grade of LV systolic/diastolic function) [58]. Similar results have been shown by 99mTc-PYP and 99mTc-HMDP [59].

Bone scintigraphy with score 2 or 3 myocardial uptake (= moderate or high) showed > 99% sensitivity for ATTR-CA but a lower specificity of 82–86% due to mild-moderate cardiac uptake in AL-CA [16, 58].

Radionuclide bone scintigraphy can therefore to some extent differentiate ATTR from AL amyloidosis, where cardiac uptake is less frequent and lower in quantity [60], and distinguish other causes of cardiac hypertrophy, as HCM (see paragraph on differential diagnosis).

A recent study [16] has proposed an algorithm to diagnose ATTR-CA noninvasively without the need of histology, but only with echocardiographic or CMR findings suggestive of CA, cardiac uptake at scintigraphy, and absence of monoclonal light chain gammopathy in serum and urine. Bone tracer scintigraphy can give the diagnosis of ATTR without the need of EMB with > 98% certainty when grade 2 or 3 cardiac uptake is present. Thereafter, TTR genotyping is pertinent to distinguish between ATTRwt and ATTRm.

On the other hand, if laboratory analysis detects monoclonal light chain gammopathy in serum and urine, AL-CA should be confirmed by extracardiac biopsy.

Positron emission tomography (PET) is emerging as a potential useful technique for the diagnosis of CA. In particular, PET tracer [18F]-sodium fluoride showed cardiac uptake only in cases with ATTRwt and ATTRm, but not in AL-CA [61].

PET imaging with ^{11}C-Labelled Pittsburgh compound B (^{11}C-PiB) showed promising results in the evaluation of amyloid distribution in patients with AL and ATTR amyloidosis [62]. Further studies are needed to confirm these results, but the ability of ^{11}C-PiB to image amyloidosis would greatly increase PET's accessibility, since this is a relatively common tracer.

Finally, ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy can detect cardiac sympathetic denervation in CA [63]. Specifically in ATTR, ^{123}I-MIBG can identify innervation changes before echocardiographic evidence of disease [64]. Although scarce data are available in the setting of amyloidosis patients, positive (123)I-MIBG findings would indicate an increased likelihood of lethal arrhythmias also in this condition.

Fat ultrasonography

Fat ultrasonography has been recently proposed as a promising tool for screening and diagnosis of ATTR. In the presence of ideal imaging conditions, it has 85% sensitivity and 97% specificity [65]. Further studies are needed to confirm the potential role of the technique in this setting.

Biopsy

Traditionally, verification of diagnosis for ATTR-CA required EMB or biopsy of an affected organ, abdominal fat, or salivary gland. Histological evidence of amyloid deposits in tissue is performed with Congo red staining demonstrating pathognomonic green birefringence under polarized light, and typing of amyloid proteins is achieved by means of laser microdissection with mass spectrometry.

EMB is still the diagnostic gold standard and allows differentiation of CA type with 100% sensitivity. However, as stated above, multimodality imaging alone can nowadays lead to diagnosis of ATTR with good accuracy. Of note, the need for a histological demonstration of amyloid infiltration in heart has delayed the diagnosis in the past as EMB is confined to referral centers with expertise in the technique and demands skilled pathological analysis of samples.

Biopsy of extracardiac tissues has shown low sensitivity for the diagnosis of ATTR-CA [66]. Another study on non-cardiac biopsy or fat aspiration showed that nearly all cases of ATTRm had positive histology, whereas only one third of patients with ATTRwt had positive results [67].

Genetic test

Genetic testing of the ATTR gene is needed to differentiate ATTRwt from ATTRm. The variant and wild-type proteins can also be demonstrated by isoelectric focusing of serum, but should then be confirmed by polymerase chain reaction amplification and DNA sequencing of the transthyretin exons 1 to 4 [68].

More than 120 amyloidogenic mutations have been described, which are inherited in autosomal dominant fashion. The most common mutation in the USA is Val122Ile, responsible for the forms with predominant cardiac phenotype, and, in the rest of the world, Val30Met, causing the forms with

predominant neurologic phenotype and early onset of the disease [69]. Ile68Leu is the most frequent mutation responsible for the forms with exclusive cardiac phenotype in Italy [27].

Differential diagnosis

The differential diagnosis of CA includes firstly other causes of LVH such as hypertensive heart disease, aortic stenosis, and genetic HCM.

Hypertensive heart disease is the most common misdiagnosis. In such patients, ATTR-CA should not be excluded and suspected when patients show normal blood pressure and need dose reduction or discontinuation of antihypertensive drugs.

Furthermore, differential diagnosis of CA should be raised in AS patients with suggestive echocardiographic findings [52]. In particular, LFLG AS in the elderly and new diagnosis of HCM in an elderly patient are red flags for CA.

A study demonstrated that 5% of patients diagnosed with HCM actually has ATTRm CA [70]. Recently, the European Association of Cardiovascular Imaging proposed specific multimodality imaging criteria to differentiate CA from HCM. LVH is moderate, concentric, and "sparkling" in CA as opposed to severe and asymmetric in HCM; LVOT obstruction is frequent in HCM and rare in CA, although it may also exist in the latter in early stages. Frequently encountered in CA are as follows: pericardial effusion, interatrial septum hypertrophy, and apical sparing at strain imaging. LGE by CMR is diffuse, subendocardial global or segmental in CA. At cardiac nuclear imaging, there is ^{99m}Tc-DPD uptake in ATTR: a score 2 or 3 myocardial uptake has 100% sensitivity and specificity in the differential diagnosis with HCM [36]. Furthermore, ischemic abnormalities on ECG are more frequent in HCM than in CA [27].

Other potential differential diagnoses should include idiopathic RCM, storage cardiomyopathies (e.g., Anderson-Fabry disease, hemochromatosis, glycogenosis), sarcoidosis, infiltrative neoplasia, and inflammatory processes.

Treatment

Major therapeutic advances have been achieved for all forms of amyloidosis, including CA, in the past decade. This evolution has rendered the previously hopeless disease to a possibly curable condition. Early diagnosis is critical for the best outcome of therapy.

Traditionally, the clinical management of a patient with symptomatic restrictive amyloid focuses on managing fluid balance using diuretics. Former studies revealed not only that typical HF medications including digitalis, calcium channel blockers, beta-blockers, or angiotensin-converting enzyme inhibitors can have significant adverse effects on amyloid-associated cardiomyopathy, but also that digitalis has a high propensity to bind amyloid fibrils, causing unpredictable and possibly toxic circulating concentrations, thus precluding its employment in CA [71, 72].

It has been described that treatment for patients with AL is risk-adapted and customized on the basis of individual patient characteristics, and significant progresses have been made by chemotherapy [73]. On the other hand, ATTR patients may require ultimately liver transplantation or heart transplantation for survival. Liver transplantation is however not indicated in ATTRwt since TTRwt continues to be produced by the transplanted organ. There are presently no validated curative or disease-modifying treatments for ATTRwt. Nevertheless, there are a few drugs in development to treat ATTRm either by decreasing production of TTR or by stabilizing the abnormal protein. Both methods are being developed to slow progression of the disease.

Further research aims at identifying and refining effective treatments for preventing the deposition of amyloid fibrils. These recently published trials are summarized in Table 2. Tafamidis (Vyndaqel™) is a molecule that is able to bind TTR and to stabilize the tetrameric protein, inhibiting its dissociation into monomers. In Europe, Tafamidis^{TM} is approved for stage I ATTR-familial amyloidotic polyneuropathy (FAP). The recently published ATTR Cardiomyopathy Clinical Trial (ATTR-ACT) showed that tafamidis is superior to placebo in lowering the combination of all-cause mortality and cardiovascular-related hospitalizations in patients with ATTR ($p < 0.001$). A consistent advantage of tafamidis related to mortality and cardiovascular-related hospitalizations was observed in all subgroups, with the exception of those with New York Heart Association (NYHA) class III. Tafamidis was also related to a significant reduction in the decrease in functional capacity (as measured by the 6-min walk test; $p < 0.001$) and in the deterioration of quality of life (as measured by the Kansas City Cardiomyopathy Questionnaire-Overall Summary/KCCQ-OS; $p < 0.001$) at month 30, with differences first detected at 6 months. On the other hand, the impact on overall survival appeared after approximately 18 months [19]. This dissociation between the effect on symptoms and survival has also been observed with other therapies for systolic HF in which LV remodeling takes months to occur [74–76]. Maurer et al. demonstrated a consistent benefit of tafamidis treatment related to mortality in all subgroups [19].

Patisiran is a double-stranded synthetic oligonucleotide interfering with the RNA production of the abnormal TTR. In the APOLLO trial, Adams at al. treated $n = 148$ adult ATTRm patients with polyneuropathy with intravenous (i.v.) administration of patisiran. This RCT showed improvement of neuropathy scores by established

Table 2 Recent therapeutic studies in amyloidosis

Study acronym; first author; reference	Study medication; study protocol	Mechanism of study medication	Patient characterization	Number of verum treated (and total study) patients (*n*=)	Clinical effects
ATTR-ACT; Maurer et al.; [19]	Tafamidis (Vyndaqel™); RCT; tafamidis 80 mg or 20 mg versus placebo for 30 months in a 2:1:2 ratio	Stabilization of TTR; chaperone	Adult patients with cardiac TTR-amyloidosis	264 (441)	Reduction of all-cause mortality and heart failure–related hospitalizations; reduction in the progression of loss of functional capacity and of the progression of deterioration in quality of life
APOLLO; Adams et al.; [77]	Patisiran (Onpattro™); RCT; i.v. patisiran (0.3 mg per kg) once every 3 weeks versus placebo in a 2:1 ratio	Double-stranded antisense oligonucleotide inhibitor of RNA production of abnormal TTR	adult ATTRm patients with polyneuropathy	148 (225)	Improvement of Neuropathy (modified Neuropathy Impairment Score+7/mNIS+7 and of Norfolk Quality of Life-Diabetic Neuropathy/Norfolk QOL-DN) questionnaire; Improvement of 10-m walk test; Improvement of nutritional status (modified BMI)
NEURO-TTR; Benson et al.; [79]	Inotersen (Tegsedi™); RCT; inotersen (300 mg) s.c. versus placebo per week in a 2:1 ratio	Single-stranded antisense oligonucleotide inhibitor of mutant and wild-type human TTR	adult ATTRm patients with polyneuropathy	112 (172)	Improvement of mNIS+7 and of Norfolk QOL-DN scores

RCT: randomized controlled trial

questionnaires (modified Neuropathy Impairment Score+ 7/mNIS+7 and of the Norfolk Quality of Life-Diabetic Neuropathy/Norfolk QOL-DN), furthermore a significant improvement of the 10-m walk test, and finally an improvement of nutritional status (modified BMI). Additionally, this trial also showed significant reduction of NT-proBNP and improvement of longitudinal left ventricular strain [77]. The U.S. Food and Drug Administration approved patisiran (Onpattro™) infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by ATTRm in adult patients in August 2018. By preventing the production of TTR, the drug can reduce the accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients to better manage the condition [78].

Furthermore, the single-stranded antisense oligonucleotide inhibitor of mutant and wild-type human TTR, inotersen (Tegsedi™), has been developed for the treatment of ATTRm. In the NEURO-TTR RCT, a significant Improvement of mNIS+7 and of Norfolk QOL-DN scores were confirmed by the s.c. administered inotersen. However, it should be noted that this trial showed a higher rate of glomerulonephritis (3%) and thrombocytopenia (3%), with one death associated with grade 4 thrombocytopenia in the inotersen group. These adverse effects of inotersen may be effectively managed with enhanced monitoring [79]. Inotersen received its first global approval on July 6, 2018, in Europe for the treatment of stage 1 or 2 polyneuropathy in adult patients with ATTRm, and is under evaluation in the USA and Canada for a similar indication [80].

In future, approaches directed at amyloid fibril clearance in combination with agents that target plasma cells will be needed both to eradicate the malignant clone and to establish beneficial organ responses [73].

Conclusions and future outlook

CA is characterized by significant morbidity and mortality; therefore, recent research aims at early diagnosis, as treatment in the initial stages of the disease is a prerequisite for improved prognosis. Diagnosis frequently is demanding, as symptoms are rarely specific for the disease. Echocardiography is the best tool to “rule in” amyloidosis. CMR and nuclear imaging are employed to confirm and quantify cardiac involvement. An integrated approach involving multimodality diagnostic tools provides nowadays high sensitivity and specificity for the disease. Finally, innovative promising therapies are under development and are believed to be beneficial for prognosis and outcome in patients with ATTR.

Compliance with ethical standards

Conflict of interest MN has received grants by the Deutsche Forschungsgemeinschaft through the Sonderforschungsbereich Transregio 19 "Inflammatory Cardiomyopathy" (SFB TR19) to MN (TP B2) and to CT (TP B5); and by the University Hospital Giessen and Marburg Foundation Grant "T cell functionality" (UKGM 10/2009). MN has been consultant to the IKDT (Institute for Cardiac Diagnosis and Therapy GmbH, Berlin) 2004–2008, and has received honoraria for presentations and/or participated in advisory boards from AstraZeneca, Bayer, Fresenius, Miltenyi Biotech, Novartis, Pfizer, and Zoll. AR has received honoraria for presentations from AstraZeneca. MA has received honoraria for presentations from AstraZeneca.

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