

Clinical presentation, diagnosis and current treatment options of cardiac amyloidosis

Cardiac amyloidosis

Sofie Brouwers^a, Natallia Laptseva^{a,b}, Bernhard Gerber^c, Rahel Schwotzer^d, Frank Ruschitzka^a,
Andreas J. Flammer^a

on behalf of the Amyloidosis Network Zurich

^a Cardiology, University Heart Centre, University Hospital Zurich, Switzerland; ^b Cantonal Hospital, Baden, Switzerland; ^c Division of Haematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; ^d Haematology, University Hospital Zurich, Switzerland



Cardiac amyloidosis is a prototype of restrictive cardiomyopathy and should be considered in any adult with unexplained heart failure and an echocardiography result suggestive of amyloidosis.

Introduction

Amyloidosis is a rare and complex disease, resulting from extracellular deposition of insoluble misfolded amyloid fibrils. As amyloidosis affects many organ systems, the diagnostic workup and therapeutic strategies should ideally be guided by an interdisciplinary team experienced with this rare disease. Therefore, the *Amyloidosis Network Zurich* was founded at the University Hospital in Zurich 5 years ago.

This short review will focus mainly on the clinical presentation, diagnosis and current treatment options of cardiac amyloidosis. In systemic amyloidosis, cardiac involvement is the leading cause of morbidity and mortality [1, 2] and the most common cause of restrictive cardiomyopathy in nontropical regions. Cardiac amyloidosis can be caused by a variety of different amyloid depositions. The two most common proteins are light chains and transthyretin, leading to “light chain amyloidosis” (AL) and “transthyretin amyloidosis” (ATTR), respectively. Rarely, hereditary AApoA1 amyloidosis, and AA amyloidosis can affect the heart (table 1). Cardiac amyloidosis is characterised by rapid progressive heart failure, arrhythmias, orthostatic dysregulation and conduction abnormalities, and is associated with high mortality. Therefore, suspicion of amyloidosis should be high in any patient with unexplained symptoms of

heart failure and an echocardiography (or magnetic resonance imaging [MRI]) test) typical for the disease.

Types of cardiac amyloidosis

Light chain AL amyloidosis

AL amyloidosis results from the production of light chain antibodies, usually by a small plasma cell clone. The main organs involved are the heart, kidneys, liver, peripheral and autonomic nervous systems, and soft tissues. In 50–70% of patients cardiac involvement is seen – isolated cardiac AL amyloidosis is very rare. A couple of clinical features may raise the suspicion of AL amyloidosis, such as periorbital purpura (“racoon eyes”), macroglossia and nail dystrophy. Other nonspecific symptoms are fatigue and weight loss and signs such as hepato- and splenomegaly, submandibular gland enlargement, albuminuria and renal dysfunction. Peripheral neuropathy may present as para- or dysaesthesia, and often patients have already undergone surgery for a carpal tunnel syndrome.

Transthyretin ATTR amyloidosis

Transthyretin is a transport protein, produced by the liver to transport thyroxine (T4) and retinol (vitamin A). TTR is a homotetramer, in which each monomer con-

Table 1: Types of cardiac amyloidosis.

Type	Precursor protein	Underlying disorder	Organ involvement
Light chain AL amyloidosis	Immunoglobulin light chain	Plasma cell dyscrasia	Heart, kidneys, liver, peripheral neuropathy, soft tissue, gastrointestinal tract
Wild-type transthyretin ATTR amyloidosis	–	Wild-type transthyretin	Heart, carpal tunnel syndrome
Mutant transthyretin ATTR amyloidosis	Mutations in transthyretin (TTR) gene	Abnormal transthyretin	Heart, peripheral neuropathy
Apolipoprotein A1 amyloidosis	Mutations in apolipoprotein A1 gene	Abnormal apolipoprotein A1	Kidneys, liver, peripheral neuropathy, heart, testis
Amyloid A amyloidosis	Serum amyloid A	Inflammatory disorders	Kidneys, liver, heart (rare)
Isolated atrial amyloidosis	Atrial natriuretic factor	Unknown	Heart only

sists of a beta-sheet structure. Two of those monomers form a dimer, and the association of two dimers forms the homotetramer with two thyroxine binding sites. TTR misfolding can lead to amyloid deposition. A distinction is made between acquired and hereditary forms of ATTR amyloidosis. The acquired form is called wild-type ATTR (wtATTR), and typically does not occur until the 7th or 8th decade and therefore was previously called “senile” amyloidosis. However, ATTR amyloidosis has increasingly been recognised in patients with heart failure with preserved ejection fraction (HFpEF) and in younger patients [3]. The main manifestations are cardiac amyloidosis and carpal tunnel syndrome.

The hereditary form of ATTR (hATTR), also called familial or variant transthyretin amyloidosis, is caused by mutations in the *TTR* gene. The two main manifestations are cardiomyopathy and peripheral neuropathy, also known as familial amyloid polyneuropathy or familial amyloid cardiopathy. There are 80 confirmed pathogenic mutations, mainly autosomal dominant. The mutations vary per geographic and ethnic group. The three most common mutations are V122I, V30M and T60A. The V122I mutation mainly occurs in the population with origin in USA, Caribbean and Africa, V30M in patients originating from Portugal, Sweden or Japan and T60A in people from the UK and Ireland [4].

Apolipoprotein A1 amyloidosis

AApoA1 amyloidosis is one of the hereditary forms of amyloidosis, but the only one with possible cardiac involvement. Apolipoprotein A1 is a component of high-density lipoprotein complex unloading cholesterol from the cells back to the liver to increase its excretion and decrease atherosclerosis. AApoA1 amyloidosis is a rare autosomal dominant disease with mainly renal and hepatic manifestations [5].

AA amyloidosis

In this form, amyloidosis is characterised by the deposition of serum amyloid A protein and is also called secondary or reactive systemic amyloidosis. AA amyloidosis is mostly caused by chronic inflammation such as infectious diseases or inflammatory disorders (e.g., familial Mediterranean fever, rheumatoid arthritis). Amyloid deposition occurs most frequently in the thyroid, gastrointestinal tract, liver, spleen and kidney. Cardiac involvement is uncommon [6].

Isolated atrial amyloidosis

Isolated atrial amyloidosis is a rather recently discovered form of cardiac amyloidosis, mainly diagnosed postmortem. Subunits of atrial natriuretic peptide deposit in the atrium and may cause atrial fibrillation [7].

Main clinical issues in cardiac amyloidosis

Heart failure

The key clinical feature of cardiac amyloidosis is heart failure. Formally, the patients fulfil criteria for HFpEF. As a result of amyloid deposition, cardiac and vascular stiffness increases and leads to impairment of both contraction and relaxation of the ventricles and to disturbances in electrical conductance. There is an exaggerated increase or decrease of blood pressure for the same changes of after- or preload, due to the combined ventricular-arterial stiffening. Furthermore, elevated left sided filling pressures due to delayed pressure recovery during relaxation lead to an increase in pulmonary venous pressure causing dyspnoea and exercise limitation. In an early stage of cardiac involvement, progressive shortness of breath and reduced exercise tolerance are seen, whereas signs of right ventricular failure, with elevated jugular venous pressure, oedema and hepatomegaly are present in a more advanced stage [8]. In the presence of heart failure, prognosis of the disease is dismal.

Orthostatic hypotension, syncope and sudden cardiac death

Owing to the common involvement of the peripheral nervous system, adaptation from the supine to the standing position can be altered, leading to orthostatic hypotension. Moreover, syncope is a signum male in cardiac amyloidosis patients, as it may be caused by malignant arrhythmias. Syncope with exertion may also be induced by the inability to increase cardiac output (fixed stroke volume, chronotropic incompetence).

Abnormalities in the conduction system

Particularly in ATTR amyloidosis, amyloid deposits are found in the conduction system with consequent atrio-ventricular and intracardiac blocks, needing pacemaker implantation in many cases.

Increased risk for stroke

Patients with cardiac amyloidosis have a significantly increased risk for stroke and other thromboembolic complications. For a significant proportion of patients, stroke is the first presenting symptom of amyloidosis. As a result of the high filling pressures of the left atrium, atrial fibrillation is commonly triggered, and atrial fibrillation in a stiff left atrium leads to thrombus formation. Amyloid deposits can be found in the vessel walls as well. Therefore microvascular dysfunction in particular can be regularly observed, for example leading to angina pectoris without significant coronary artery disease.

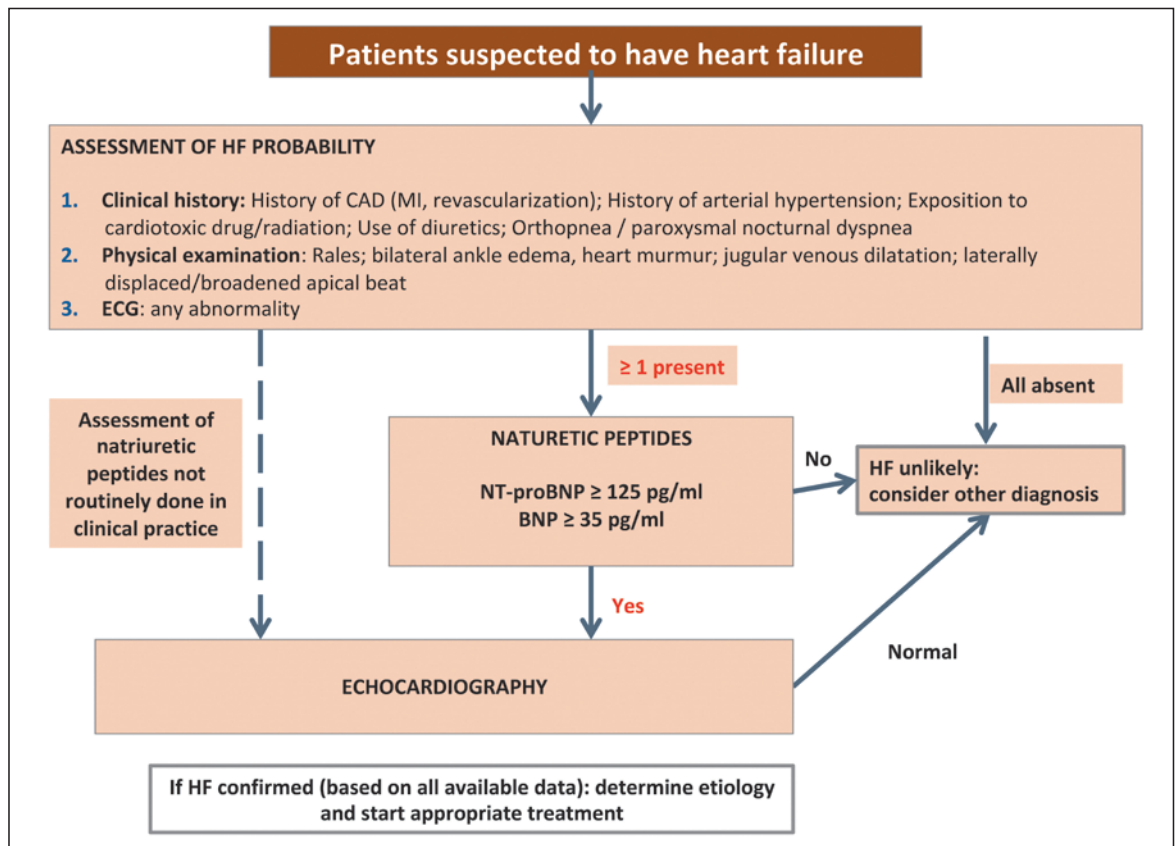


Figure 1: Flow chart for the diagnosis of heart failure (adapted from [19]).

How do we diagnose cardiac amyloidosis?

As outlined above, any patient with clinical signs and symptoms of heart failure with an imaging test suspicious of amyloidosis should be further evaluated. First, signs and symptoms of heart failure will lead the physician to evaluate the patient according to the diagnostic algorithm for the diagnosis of heart failure (fig. 1). On ECG, low peripheral voltage may be present, but this is not so common as initially thought. However, a normal ECG is rarely seen in patients with cardiac amyloidosis. Low levels of N-terminal pro-B-type natriuretic peptide

(NTproBNP) virtually excludes heart failure (and with it cardiac amyloidosis). However, if suspicion of heart failure remains high, echocardiography should be performed in any patient.

Echocardiography is key in detecting cardiac involvement in amyloidosis. Often, a hypertrophic cardiomyopathy is initially suspected on the basis of increased wall thickness and low ventricular volume (fig. 2). Tissue Doppler and strain measurements are especially important to detect diastolic and systolic dysfunction as patients initially present with HFpEF. The ventricle will first show diastolic dysfunction (fig. 3) due to noncom-

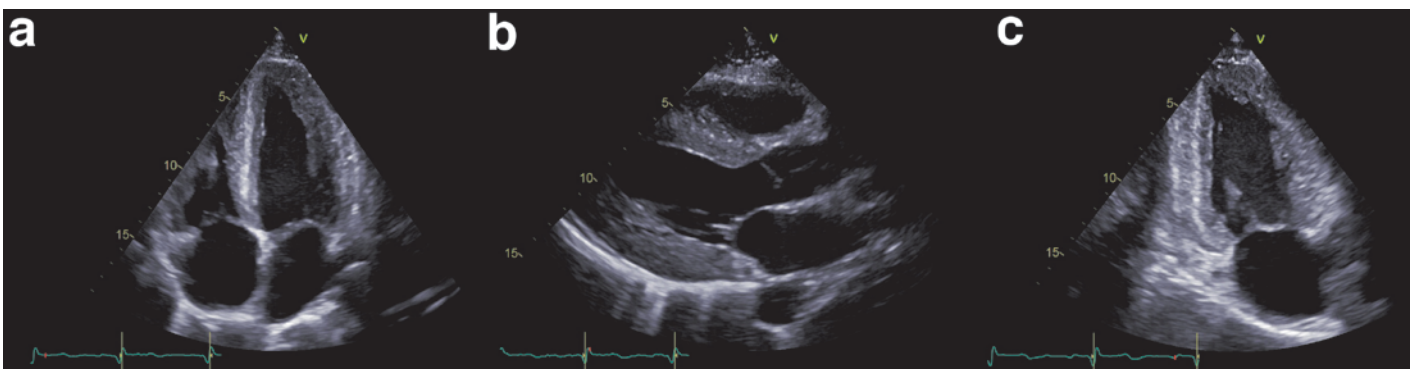


Figure 2: Echocardiographic example of hypertrophic cardiomyopathy caused by amyloidosis.

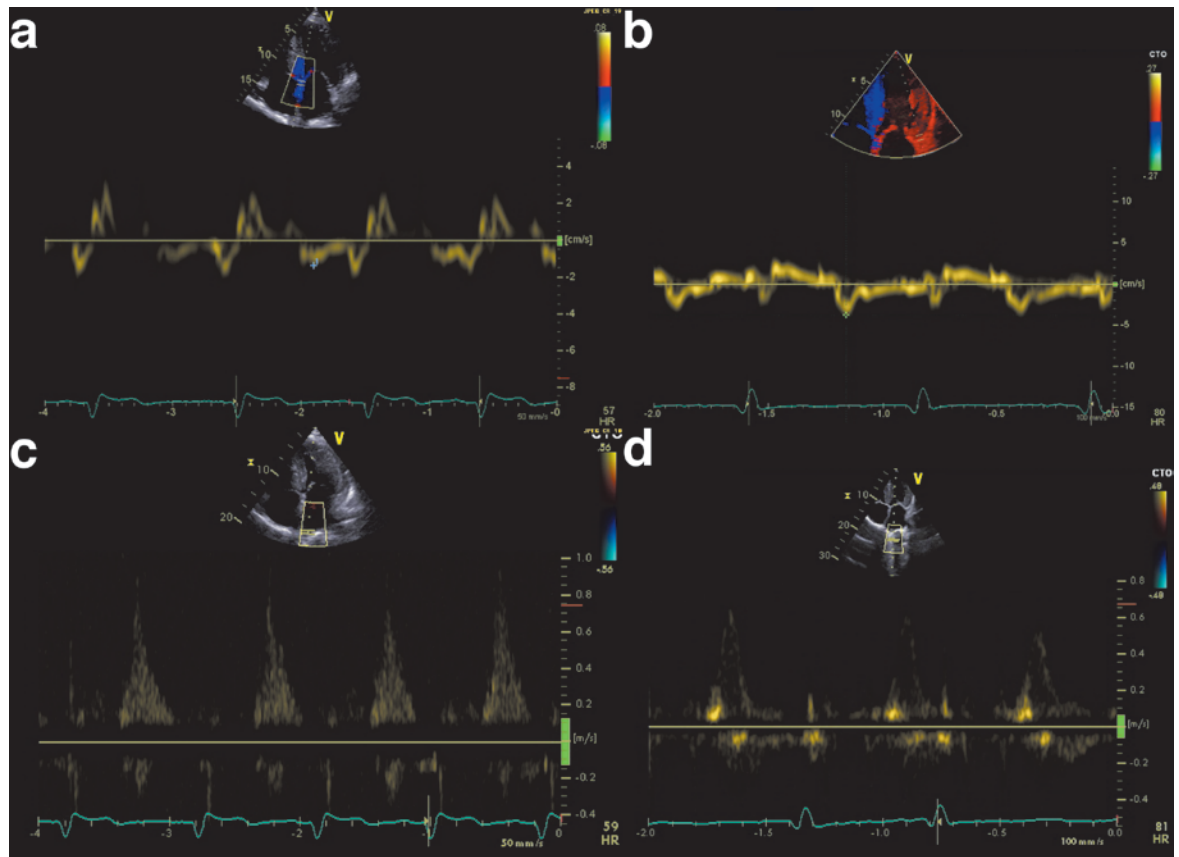


Figure 3: Echocardiographic example of diastolic dysfunction in amyloidosis. Panels a and b show low septal and lateral tissue Doppler e' values, characteristic of high left ventricular end diastolic pressure. Panels c and d show decreased pulmonary vein systolic flow, and increased diastolic flow.

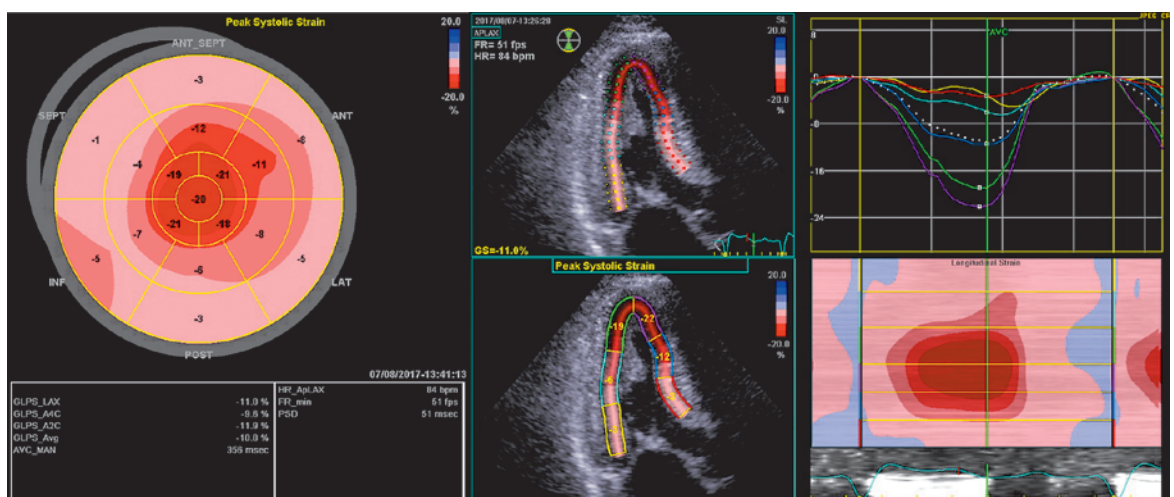


Figure 4: Speckle tracking echocardiographic example of impaired peak systolic strain and the typical 'bull's eye' showing 'apical sparing'.

pliance of the infiltrated myocardium, and in more advanced stages systolic dysfunction. Cardiac amyloidosis is characterised by regional variations in longitudinal strain, typically with apical sparing (fig. 4). Also a “granular sparkling appearance” of the left ventricle is typical (important: switch off second harmonic imaging, as it may produce sparkling appearance in non-amyloidosis

patients). Doppler measurements show restrictive filling patterns with increased left ventricular filling pressures. Additionally the aortic and mitral valves appear thickened (amyloid deposits), as well as the intra-atrial septum and the right ventricle. The atria are typically dilated and quite often a pericardial effusion is found. The combination of echocardiographic signs of hyper-

trophic cardiomyopathy and a normal or low voltage ECG have a high sensitivity and specificity for amyloidosis [9–11].

For all types of cardiac amyloidosis, cardiac MRI offers the possibility to evaluate ventricular wall thickening and mass, and diastolic and systolic function, as well as to detect amyloid depositions, visualised by diffuse late gadolinium enhancement (fig. 5). The slower wash in and wash out of gadolinium is due to expansion of the extracellular space, which is typical for amyloid. Typically, the pattern of late gadolinium enhancement is diffuse and patchy.

If cardiac amyloidosis is suspected, extensive laboratory and urinary testing to assess further organ involvement is crucial. NTproBNP and troponin T (for AL) and estimated glomerular filtration rate (for AL and ATTR) are important prognostic markers [12–14].

To differentiate AL from other types of amyloidosis, serum and urine protein electrophoresis with immune fixation and serum free light chain analysis must be performed. Of note, in 80% of the patients, the AL amyloid fibrils are composed of lambda light chains, and in only 20% of cases are kappa light chain found. This is in contrast to monoclonal gammopathy with unknown significance and multiple myeloma, where the kappa light chains are more common. If plasma cell dyscrasia is suspected, bone marrow biopsy should be performed to assess plasma cell volume and clonality. Cytogenetic studies such as interphase fluorescent *in situ* hybridisation have prognostic value concerning response to therapy or clinical outcome [15]. The diagnosis is confirmed when amyloid is detected in a tissue biopsy. Biopsies can

be taken from almost any organ. Abdominal fat aspirate, or rectum or salivary gland biopsy are usually easily obtained. Furthermore, biopsies (e.g., taken during colonoscopy) performed for other reasons are usually archived by hospitals and can be re-examined in order to establish the diagnosis and determine the precise type of amyloid. In the case of positivity for light chains and negative findings for TTR in immunohistochemical work-up, the diagnosis of AL amyloidosis is confirmed. If tissue results are negative and suspicion remains high, organ biopsy such as endomyocardial biopsy should be performed. In the case of ambiguous results in histological work up, mass spectroscopy should be performed (fig. 6).

In the absence of plasma cell dyscrasia, bone scintigraphy with technetium-labelled bone-seeking radiopharmaceuticals is extremely useful in the diagnosis of ATTR amyloidosis, as the tracer strongly binds to amyloid composed of transthyretin, but much less to amyloid composed of immunoglobulin light chains [16, 17]. In case of typical imaging (cardiac MRI or echocardiography), and strongly positive scintigraphy with no detectable monoclonal gammopathy, TTR amyloidosis can be diagnosed without performing a biopsy (fig. 7). Genetic testing will distinguish between the wild-type and mutant form of TTR amyloidosis. However, in the case of a negative scintigraphy and a persistent high suspicion of amyloidosis, again, endomyocardial biopsy should be performed. Although diagnosing amyloidosis in theory is straightforward, it is still a challenging diagnosis [18].

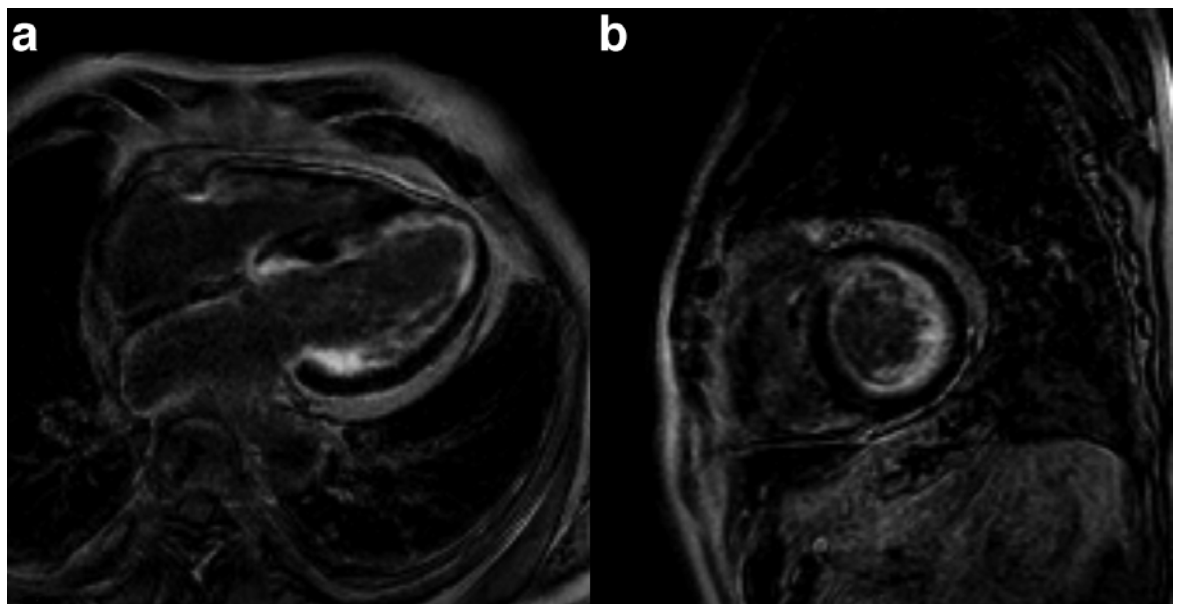


Figure 5: cMRI example of late gadolinium enhanced images demonstrating diffuse late gadolinium enhancement in the left ventricular myocardium and to a lesser extent even in the left atrial myocardium.

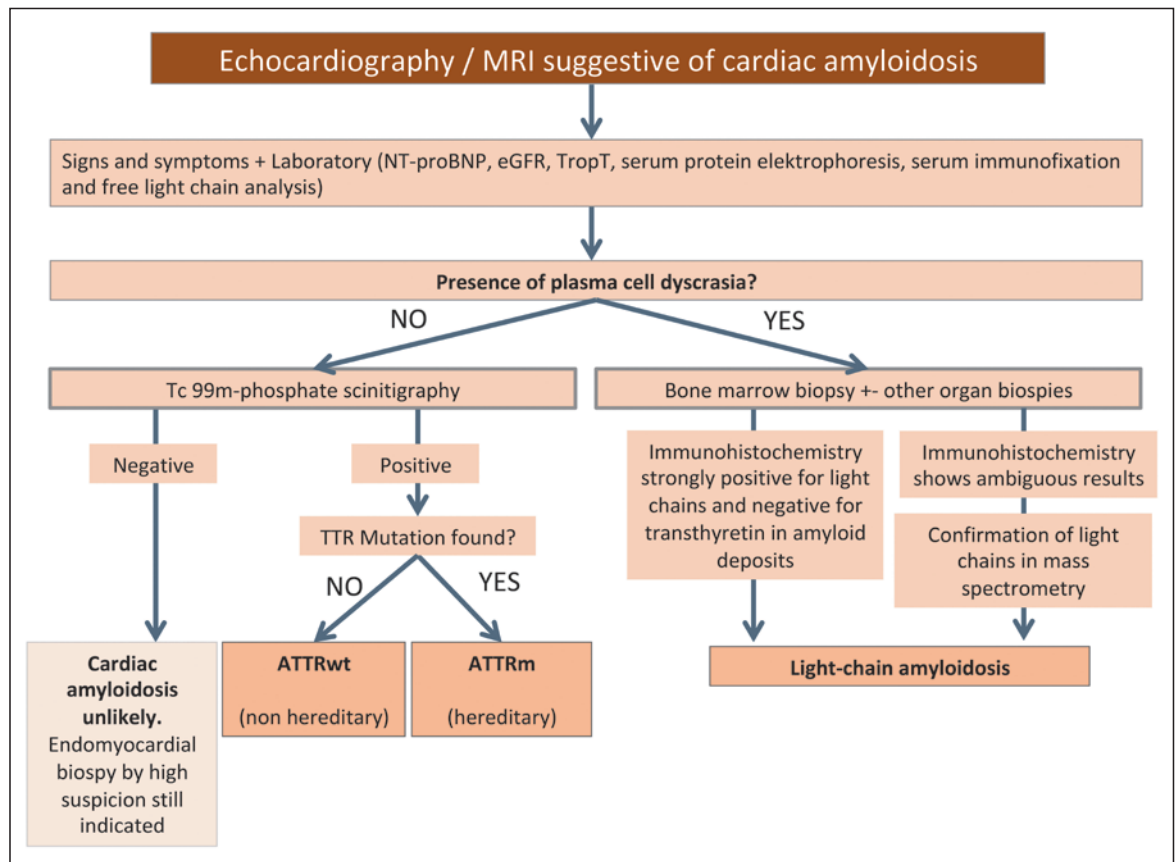


Figure 6: Flow chart for diagnosis of amyloidosis (adapted from [9]).

Treatment

There are two mainstays of the treatment of cardiac amyloidosis: treatment of symptoms and treatment of the underlying disease.

Treatment of the symptoms

For the patient, relief of congestion is the most immediate goal. Therefore, diuretics are the cornerstone of treatment. However, it is important to keep in mind the altered pressure-volume curves of a restrictive cardiomyopathy, and thus diuretics must be titrated very carefully – over-diuresis may induce hypotension and orthostatic syncope, whereas congestion on the other hand may rapidly lead to lung oedema. Treatment of these patients is challenging and regular visits with the physician to adapt diuretic dosages are mandatory. Medications improving prognosis in HFpEF are lacking [19]. This is not different in cardiac amyloidosis. Angiotensin converting-enzyme inhibitors and angiotensin-receptor blockers have no proven benefit, but may induce profound hypotension in patients with cardiac amyloidosis. Similarly, there are no data on the benefit of mineralocorticoid antagonists in cardiac amyloido-

sis. The use of beta-blockade should be especially limited, as it may worsen hypotension and bradycardia. In advanced cardiac amyloidosis, cardiac output (stroke volume \times heart rate) is dependent mainly on heart rate, because stroke volume cannot adapt owing to the extremely stiff ventricle.

Cardiac troponin and NTproBNP serve not only as important biomarkers for staging of AL amyloidosis, but also for follow-up and survival prediction. Patients presenting with symptoms of heart failure have a poor outcome.

One of the most important goals is to prevent the occurrence of stroke. Atrial fibrillation is extremely common in patients with cardiac amyloidosis and should be actively screened for [1]. We recommend performing ambulatory 24-hour monitoring at least every 6 months. In the case of atrial fibrillation, oral anticoagulation is mandatory, irrespective of the CHA2DS2-Vasc score. Because of the high morbidity of atrial fibrillation in cardiac amyloidosis, some groups start oral anticoagulation as soon as absence of atrial expansion during ventricular systole is seen (with strain imaging of the left atrium). Rhythm control can possibly be established with amiodarone, but in most cases this is not success-

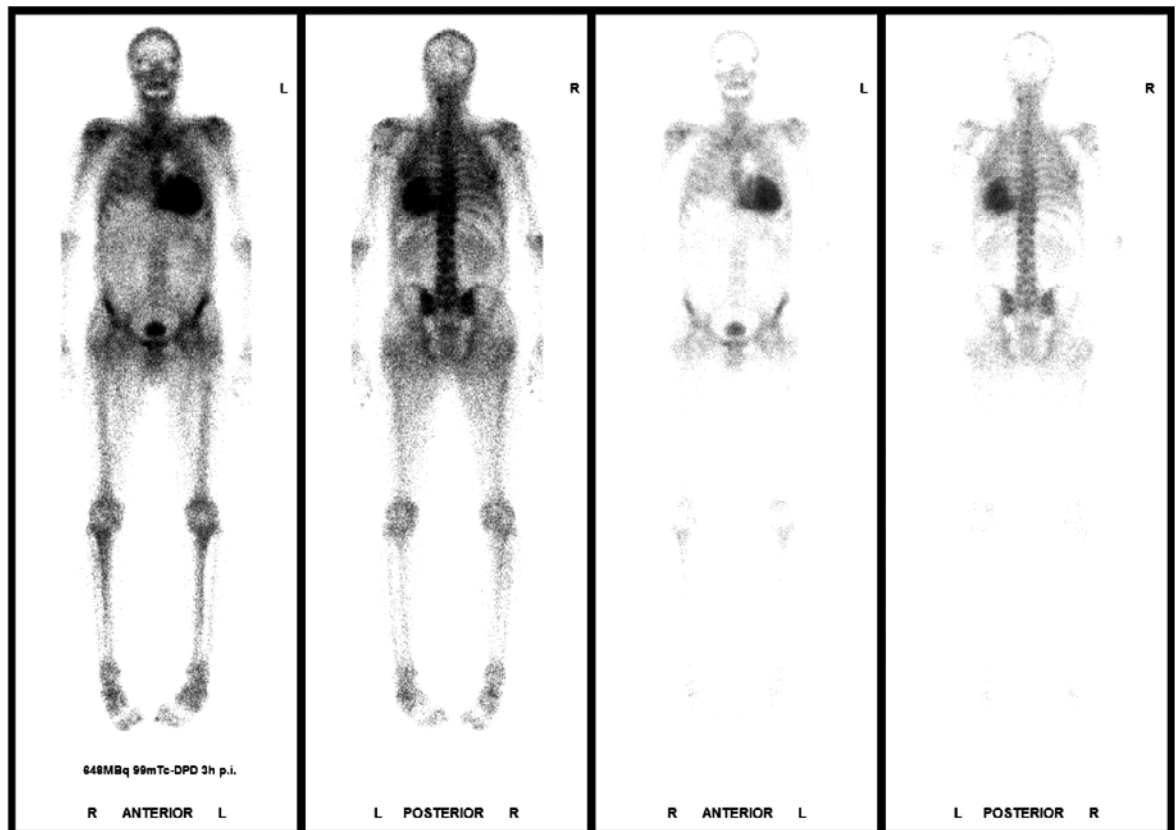


Figure 7: Technetium 99m-phosphate-scintigraphy showing a strong myocardial tracer uptake and thereby confirming the diagnosis of ATTR amyloidosis.

ful. Digoxin should not be used because of potential binding with amyloid fibrils and its associated toxicity. Prevention of sudden cardiac death is another difficult task in patients with cardiac amyloidosis. Until now, no specific treatments, such as antiarrhythmics or implantable cardioverter defibrillators (ICDs) have been proven to have any benefit. Unfortunately, inadequate shocks are quite common [20]. Moreover, pulseless electrical activity – where ICD offers no benefit – is another common cause of death in advanced cardiac amyloidosis. The indication to implant an ICD should be discussed in detail within a specialised team for amyloidosis together with an informed patient.

Treatment of the underlying disease

Chemotherapy targeting clonal plasma cells and reducing production of amyloidogenic light chains is mainly used. Depending on patient characteristics a combination of alkylators (e.g., melphalan or cyclophosphamide), steroids (e.g., dexamethasone), proteasome inhibitors (bortezomib or ixazomib) and/or immunomodulators (lenalidomide or pomalidomide) are used. High-dose chemotherapy and autologous stem-cell transplantation (ASCT) can be performed in a se-

lected patient group and is associated with good response and outcome [21].

Heart transplantation can be considered in very selected patients with isolated cardiac amyloidosis, when a favourable long-term outcome with ASCT is expected but a high procedure-related mortality precludes ASCT. In this context, ASCT is performed after successful heart transplantation.

So far, there is no treatment available for patients with ATTR amyloidosis, except for patients with advanced heart failure where heart transplantation can be performed. In hereditary ATTR, with the liver as main source of TTR, patients may also undergo liver transplantation [11]. Recently, two new treatment concepts with encouraging results have emerged; tetramer stabilisation and small interfering RNA.

A recent study by Maurer and colleagues proved that in both wild type and familial ATTR amyloidosis, tafamidis, a tetramer-stabilising agent, has a favourable impact on all-cause mortality and cardiovascular-related hospitalisation compared with placebo [22]. Furthermore, symptoms and quality of life were improved significantly as well; without any notable side effects. These remarkable results led to fast-track designation by

the US Food and Drug Administration (FDA) and will hopefully result in approval in an appropriate time-frame [13]. Patisiran, a transthyretin-directed small interfering RNA, has been approved by the FDA and European Medicines Agency (EMA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults [23]. A subpopulation analysis of the APOLLO study of patients with cardiac involvement showed a decrease in mean left ventricular wall thickness, global longitudinal strain, NTproBNP and adverse cardiac outcomes compared with placebo after 18 months, suggesting that patisiran may halt or reverse progression of the cardiac manifestations of hereditary ATTR amyloidosis [24]. Further studies with enough statistical power will be needed to corroborate these remarkable findings.

In an observational study, green tea delayed the progression of cardiac amyloidosis. *In vitro*, fibril formation was inhibited by epigallocatechin-3-gallate (EGCG), the most abundant catechin in green tea. Studies demonstrated a reduction of the thickness of the intraventricular septum and a reduction of left ventricular mass [25]. In a randomised, placebo-controlled trial (TAME-AL) there was no benefit in cardiac outcome in AL amyloidosis (unpublished preliminary data presented at ISA2018 Kumamoto in March 2018 and at the Heidelberg Amyloidosis Center Meeting in October 2018).

Future treatments

Whereas patients with AL amyloidosis profit from new and successful treatments of the underlying haematological disease, trials of antibodies targeting TTR and AL are underway. Other drugs in development and in clinical trials are compounds with RNA silencing capacity (antisense oligonucleotides or small interfering RNA), TTR stabilisation (diflusinal), fibril disrupters (doxycycline) or immunotherapy [16, 26].

Conclusion

Cardiac amyloidosis is a prototype of restrictive cardiomyopathy and should be considered in any adult with unexplained heart failure and an echocardiography result suggestive of amyloidosis.

Signs and symptoms of heart failure, (orthostatic) hypotension, syncope and sudden death, thromboembolism and strokes are the most challenging cardiovascular problems in cardiac amyloidosis. Therapy consists of the treatment of heart failure symptoms and the underlying disease. Diuretic therapy is the cornerstone, but caution is needed in the presence of an altered pressure volume relationship. Many promising treatment options are under evaluation in clinical trials.

Take-home messages

- Suspect amyloidosis in patients with HFpEF and echocardiography findings typical for the disease.
- Biopsy is the gold standard, confirming the presence of amyloid with congo red dye and green birefringence in cross-polarised light; however, TTR cardiac amyloidosis can be diagnosed with bone-scintigraphy alone in the absence of a monoclonal gammopathy.
- The main clinical features of cardiac amyloidosis are signs and symptoms of heart failure, orthostatic hypotension, syncope and sudden death, as well as stroke.
- Progression and course of the disease as well as the therapy will differ greatly depending of the type of amyloid deposition.

Disclosure statement

BG, RS and AJF consulted for Pfizer and Alnylam. No other financial support and no other potential conflict of interest relevant to this article was reported.

References

The full list of references is included in the online version of the article at www.cardiovascmed.ch.

Correspondence:
Andreas J. Flammer, MD,
FESC, FHFA Head Heart
Failure and Transplantation
University Heart Centre
Zurich University Hospital
Zurich
Rämistrasse 100
CH-8091 Zürich
[andreas.flammer\[at\]usz.ch](mailto:andreas.flammer[at]usz.ch)