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Cardiac amyloidosis

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Summary

Cardiac amyloidosis is a disease characterised by the accumulation of amyloid protein in the heart tissue. There are several types of amyloidosis, but the most common types affecting the heart are ATTR amyloidosis (caused by transthyretin protein) and AL amyloidosis (caused by abnormal immunoglobulin light chains). Cardiac amyloidosis causes typical signs and symptoms of heart failure. Diagnosis involves a combination of imaging tests such as echocardiography and cardiac magnetic resonance imaging, as well as nuclear imaging scans and tissue biopsies to confirm the presence of amyloid deposits in the heart. Treatment of cardiac amyloidosis depends on the type and severity of the disease and includes medications to manage symptoms as well as treatments targeting the underlying cause of amyloidosis. Importantly, cardiac amyloidosis is a serious condition requiring specialised care from a multidisciplinary team including cardiologists and haematologists as well as other specialists familiar with the management of this rare disease. This is crucial, as early diagnosis and treatment are important for improving outcomes.

Introduction

Amyloidosis is a storage disorder occurring when extracellular deposited amyloid leads to dysfunction of various organs. Amyloid is formed in the presence of a protein-folding disease. Currently, more than 30 different precursor proteins are known; however, the two most common forms are AL (light chain) and ATTR (transthyretin) amyloidosis.

Despite the heterogeneity of the precursor proteins, the ultrastructural morphology and histochemical properties of amyloid fibrils are remarkably similar. They share a common core structure of antiparallel β-strands perpendicular to the long axis of the fibril [1]. This extremely abnormal, highly ordered conformation underlies the characteristic properties of amyloid fibrils, including their relative stability and resistance to proteolysis, as well as their ability to bind molecules of Congo red dye, resulting in pathognomonic apple-green birefringence when viewed under cross-polarised light [2]. Despite the histological similarity of the amyloid itself, the mechanisms leading to the formation of the precursor proteins are completely different, and thus the pathophysiology of the disease and, of course, the options for causal therapy are completely different.

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AL amyloidosis can occur in any form of B-cell monoclonal dyscrasia, typically in plasma cell dyscrasia [3]. Instead of producing normal immunoglobulins, plasma cell or mature B-cell clones produce pathological components (light chains of monoclonal immunoglobulin), which can aggregate to form amyloid fibrils.

The liver is the main organ producing transthyretin precursor proteins in *ATTR amyloidosis*. Transthyretin is a transport protein for thyroid hormones and retinol. Transthyretin is a tetramer consisting of four monomers. Normally, the tetramers dissociate to monomers and aggregate back again [4]. With age (*wild-type ATTR* [5]), the progressive dissociation of tetramers into monomers results in the accumulation of monomers in blood and aggregation into amyloid fibrils. In rare cases, a mutation in the *TTR* gene may cause the liver to produce a pathological transthyretin form (*variant ATTR* – hereditary ATTR-amyloidosis [4].

Damage to the organs arises, on the one hand, from deposition of fibrils into the tissue and, on the other hand, through direct cytotoxic effects of circulating fibrils and precursor fibrils (proteotoxicity) [6]. Further, fibrils exhibit organotropy, tending to deposit in the heart, ligaments and nerves in case of ATTRv, while AL amyloid deposits mainly into the heart, kidney, gastrointestinal tract and nervous system.

Prognosis

Prognosis of untreated AL amyloidosis is extremely poor, particularly if the heart is affected (mean survival is 6–15 months and 10-year survival rate is below 5%) [3]. The more the heart is affected, the worse the prognosis [7]; however, the prognosis of AL amyloidosis has substantially improved with new treatment options in recent years [8, 9].

The prognosis of wtATTR amyloidosis is generally better than in AL amyloidosis. Several scores predict survival. In the most commonly used Gillmore score, prognosis mainly depends on NT-proBNP values and estimated GFR [10], with the best prognosis observed when NT-proBNP is below 3000 ng/l and estimated GFR is higher than 45 ml/min.

Prevalence

While the incidence and prevalence of AL amyloidosis remain stable (approximately 1–2 cases per 100,000 sub-

jects [11], the incidence and prevalence of ATTR amyloidosis have been increasing over the past few years [12] and may be around 4–17 cases per 100,000 [12, 13]. This is mainly due to the ageing population, greater awareness and better diagnostic tools, particularly scintigraphy. Interestingly, ATTR cardiac amyloidosis is strongly associated with aortic stenosis (15%) [5] – approximately 16% of patients in whom transfemoral aortic valve implantation (TAVI) was performed for severe aortic stenosis showed concomitant ATTR cardiac amyloidosis [14]. In patients with heart failure and preserved ejection fraction (HFpEF), ATTR cardiac amyloidosis can be found in as many as 13% of the cases [15]. Furthermore, approximately 25% of patients aged over 80 years who died were found to have transthyretin deposits in the heart [16].

Clinical presentation

In cardiac amyloidosis, signs and symptoms of heart failure are often the first manifestation, particularly due to volume overload. However, a large subset of patients present with thoracic complaints such as angina pectoris or orthostasis and syncope (for typical signs and symptoms, see table 1).

Interestingly, patients with ATTR amyloidosis may already be complaining about orthopaedic manifestations 5–15 years before cardiac amyloidosis becomes symptomatic – particularly carpal tunnel syndrome, spinal canal stenosis and biceps tendon rupture. These findings are generally attributed to amyloidosis only after cardiac amyloidosis is diagnosed [16].

Cardiac amyloidosis is associated with ECG abnormalities. A typical sign is the pseudo-infarction pattern, found in up to 83% of patients [17]. While low voltage in the limb leads has low sensitivity for ATTR amyloidosis, an abnormal voltage-to-mass ratio occurs in at least 70% of cardiac amyloidosis [18]. In addition, cardiac amyloidosis is typically associated with conduction disease [19].

Diagnostic work-up

The presence of typical signs and symptoms of cardiac amyloidosis should prompt further testing by echocardiography. Inherently, left ventricular wall thickness represents the diagnostic hallmark of cardiac amyloidosis [20]. The minimal threshold to screen for cardiac amyloidosis has recently been lowered to 12 mm by a European consensus statement [20]. Characteristic echocardiographic findings of cardiac amyloidosis include pleural or pericardial effusion; thickening of the right ventricle, valves or interatrial septum; a low stroke volume; diastolic dysfunction; and a paradoxical low-flow low-gradient aortic stenosis (figure 1) [21]. A reduced longitudinal global strain with apical sparing is another characteristic feature, which may be sensitive but has limited specificity [22]. If echocardiography has a poor acoustic window or echocardiographic findings are not suggestive of cardiac amyloidosis, cardiac magnetic resonance imaging (CMR) may distinguish structural or functional abnormalities better. Typical findings include increased left and right ventricular mass (or at least wall thickness), abnormal gadolinium kinetics, diffuse transmural or subendocardial late gadolinium enhancement, increased T1 mapping or increased extracellular volume, which has the highest specificity above 40% (figure 1) [23, 24]. Even though CMR may be highly suggestive, it is not diagnostic of cardiac amyloidosis.

Table 1:
Typical findings in amyloidosis.

Cardiac signs and symptoms	Shortness of breath (hypervolaemia)
	Oedema – Volume retention
	Thoracic pain (microvascular angina, elevated filling pressures)
	Orthostatic dysregulation, orthostatic hypotension
	Syncope
	Fatigue
	Palpitations – Arrhythmias
	Thromboembolism – Stroke
Non-cardiac signs and symptoms	Periorbital purpura (AL amyloidosis)
	Macroglossia (AL amyloidosis)
	Skin bruising – periorbital ecchymosis (AL amyloidosis)
	Bilateral carpal tunnel syndrome
	Biceps tendon rupture
	Lumbar spinal stenosis
	Sensory and motor peripheral neuropathy (vATTR)
	Weakness
	GI symptoms (nausea, diarrhoea, weight loss) – vATTR and AL
	Sexual dysfunction
	Vitreous opacification, glaucoma (vATTR)
ECG findings	Pseudo Q waves
	Atrial fibrillation
	AV conduction disease
	Widened QRS complex
	Ventricular premature beats
	Low voltage (AL)
Laboratory findings	Elevated troponin T and NT-proBNP
	Impaired kidney function (AL or cardiorenal in ATTR)
	Proteinuria (AL)

When signs and symptoms, ECG and echocardiography (or CMR) are suggestive of cardiac amyloidosis, further testing is indicated to (a) diagnose cardiac amyloidosis and (b) determine the subtype of cardiac amyloidosis. Until recently, cardiac amyloidosis was only diagnosed by a positive biopsy, but accumulating literature supports the notion that cardiac scintigraphy with bone-avid tracers (DPD, HMDP or PYP) can non-invasively diagnose the disease [20]. However, certain limitations need to be considered:

– When positive, cardiac scintigraphy (which is a planar 2D scan) always needs to be complemented by single-photon emission computed tomography (SPECT) to rule out misinterpretation of blood pool activity [25].
– Cardiac scintigraphy with bone-avid radiotracers has a sensitivity over 99% for diagnosing cardiac ATTR amyloid deposits in cardiac biopsy. The low number of false-negative findings is mainly due to rare hereditary ATTR forms (i.e. Val30Met and Phe64Leu) [26].
– The specificity of cardiac scintigraphy with bone-avid radiotracers is 68% because cardiac scintigraphy detects other non-ATTR forms of cardiac amyloidosis (e.g. cardiac AL amyloidosis). However, the sensitivity for diagnosing these non-ATTR forms is much lower than for cardiac ATTR amyloidosis. For example, 61% of patients with cardiac AL amyloidosis have grade 0 and only 10% have grade 2 or 3 in cardiac DPD scintigraphy.

Therefore, and as outlined in the diagnostic algorithm of the Swiss Amyloidosis Network [27], monoclonal gammopathy needs to be excluded prior to referral to cardiac scintigraphy. This includes quantification of serum free light chains as well as serum and urine immunofixation. In an isolated free light chain abnormality (i.e. normal immunofixation), abnormal kappa/lambda ratio may be explained by kidney dysfunction, and eGFR-adjusted ratios are used without affecting the specificity of the test [28].

If monoclonal gammopathy is *absent* (figure 2), patients should be referred to nuclear medicine.

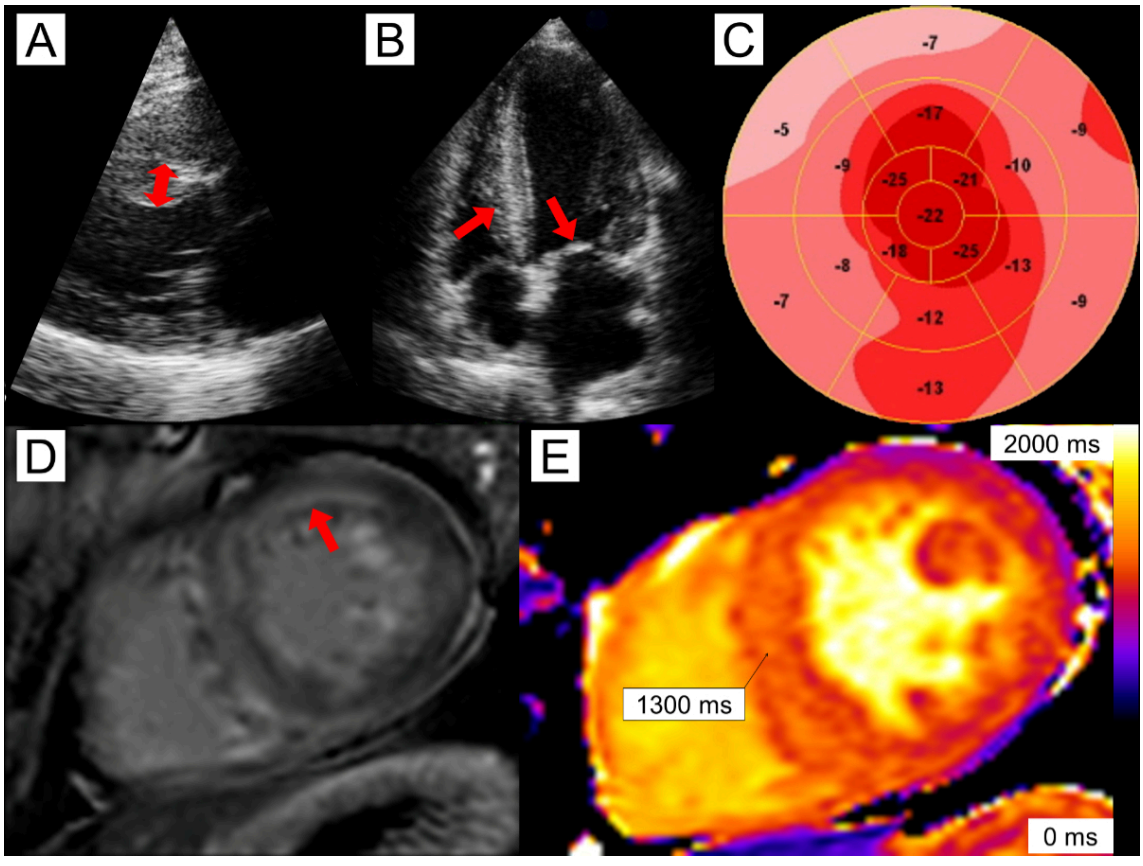
When cardiac scintigraphy/SPECT with bone-avid tracers is positive (i.e. grade 2 or 3), the patient can be diagnosed with cardiac ATTR amyloidosis without biopsy. By adhering to this diagnostic algorithm, the diagnostic performance can be summarised as following:

1. After exclusion of monoclonal gammopathy, cardiac scintigraphy/SPECT with bone-avid tracers has a specificity of 100% for diagnosing cardiac amyloidosis [26].

2. The sensitivity of the algorithm is 74% for two reasons:

– About 20% of these elderly patients suffer from concomitant monoclonal gammopathy of unknown significance (MGUS). In these patients, endomyocardial or any other organ biopsy is indicated to differentiate ATTR from AL amyloidosis.
– Some false-negative cases are due to grade 0 or grade 1 of hereditary or early wild-type forms of ATTR amyloi-

Figure 1: A 56-year-old male with cardiac AL (light chain) amyloidosis. Echocardiography reveals mild asymmetric left ventricular (LV) hypertrophy with septal wall thickness of 14 mm (panel **A**, double-headed arrow) as well as thickening of the right ventricle (RV) and mitral valve (panel **B**, arrows). There is reduced global longitudinal strain of –14.3% and relative apical sparing (panel **C**). Cardiac magnetic resonance imaging reveals diffuse, predominantly subendocardial late gadolinium enhancement (panel **D**, arrow). Native T1 times were elevated in the septum, measuring 1300 ms (panel **E**).



dosis [26]. This highlights the fact that high clinical suspicion of cardiac amyloidosis should always trigger further testing with CMR or cardiac biopsy, even if cardiac scintigraphy is negative.

If monoclonal gammopathy is present (figure 2), patients should be referred to haematology for further testing including CMR to evaluate cardiac involvement. In case of plasma cell or mature B-cell dyscrasia, a tissue biopsy must be carried out, usually of the most affected organ [29]. If cardiac amyloidosis is suspected, a diagnosis is commonly made with endomyocardial biopsy. However, a biopsy of another organ, together with typical findings on echocardiography or CMR is valid for the diagnosis of cardiac amyloidosis [29].

Patients with plasma cell dyscrasia due to MGUS pose a particular diagnostic challenge, as this condition is common in elderly patients with ATTR cardiac amyloidosis, and is significantly higher than in the general population [30, 31].

Tissue biopsies are evaluated for the presence of amyloid. Typing is generally done using immunohistochemical staining; however, this technique is challenging and prone to errors. In certain cases, the biopsy needs to be assessed by a specialised centre to ascertain the prognosis. Mass spectrometry (MS) proteomic analysis, the gold standard, can only be performed at very few centres worldwide. MS directly identifies the protein subunit in the deposit and the accompanying universal amyloid proteins. MS can detect unusual or novel types and its sensitivity and specificity are close to 100% [31].

Currently, cardiac AL amyloidosis cannot be diagnosed non-invasively, so many patients undergo endomyocardial biopsy [29]. When AL amyloidosis was detected in an extracardiac biopsy and echocardiography or CMR are suggestive of cardiac amyloidosis, AL cardiomyopathy may be diagnosed. More recently, in clinical trials, amyloid-binding positron emission tomography (PET) radiotracers like ^{18}F-florbetapir or ^{124}I-evuzamitide have evolved to diagnose cardiac AL amyloidosis non-invasively [32] and quantify cardiac amyloid burden. In the near future, this may hold clinical implications for monitoring treatment response [33].

Treatment

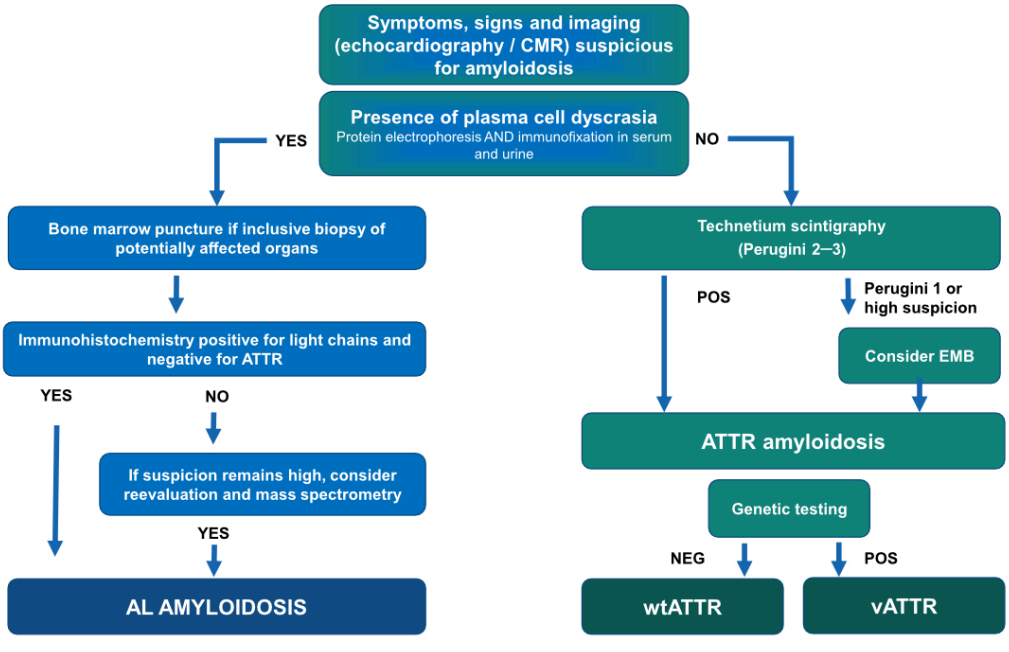
Symptomatic treatment of cardiac amyloidosis

High left ventricular filling pressure due to severe diastolic dysfunction is the main clinical problem of patients with cardiac amyloidosis. Therefore, diuretic treatment, together with patient education to reduce fluid intake, remain the mainstay of treatment. Diuretic treatment is challenging due to over-proportional blood pressure decline with an altered pressure/volume relationship.

Patients with cardiac amyloidosis mainly present with HFpEF. In these patients, traditional heart failure treatment with renin-angiotensin-aldosterone inhibition is not established. A recent large retrospective analysis in more than 2000 ATTR cardiac amyloidosis patients did not show benefit of ACE inhibitors or angiotensin-receptor blockers on outcome, but a high rate of withdrawal due to side effects [34]. Beta-blockers have been used in cardiac amyloidosis patients; however, low heart rates should be avoided because cardiac output is solely dependent on heart rate given that stroke volume is fixed in cardiac amyloidosis. In the later analysis, beta-blocker therapy showed benefit in patients with cardiac amyloidosis and an ejection fraction below 40% (HFrEF) [34]; however, the withdrawal rate due to intolerance remains high. Mineralocorticoid receptor antagonists, however, showed a better tolerability and lower mortality and morbidity in these ATTR patients [34].

SGLT-2 inhibitors are the mainstay of heart failure treatment irrespective of ejection fraction. There are no signs of harm with SGLT-2 inhibitors in cardiac amyloidosis pa-

Figure 2: Diagnostic algorithm for the diagnosis of cardiac amyloidosis.



tients, in AL and ATTR alike [35]. However, as well as with MRAs more data on outcomes are needed [36, 37].

Very few data are available for patients with AL cardiac amyloidosis. In these patients, the abovementioned drugs are usually not tolerated and may induce severe symptomatic orthostasis.

Prevention and treatment of arrhythmias

Arrhythmias are very common in cardiac amyloidosis. The most common arrhythmia in cardiac amyloidosis is, by far, atrial fibrillation. Almost all patients develop atrial fibrillation over time, due to elevated filling pressures and structural changes in the left atrium. Therefore, regular screening for atrial fibrillation is important (at 6-month intervals). Stroke risk in cardiac amyloidosis is very high, particularly in AL cardiac amyloidosis [19]. This is why oral anticoagulation is mandatory if atrial fibrillation is present. Even in sinus rhythm, the risk of stroke is increased – this may be due to elevated left atrial filling pressure and reduced atrial contraction [19]. Therefore, many groups initiate oral anticoagulation even in the absence of atrial fibrillation. There are no data on atrial appendage closure and very limited data on atrial fibrillation ablation in amyloidosis. One study showed a recurrence rate of almost 90% in the latter [38]. Therefore, we do not recommend these interventions in cardiac amyloidosis. Rhythm control should be attempted with electroconversion and amiodarone; however, the success rate is not very high. Beta-blocker therapy or sometimes amiodarone can be used for rate control; however, a lenient strategy should be adopted, due to the fixed stroke volume [38]. Digoxin should be used, if at all, only under very careful monitoring [39]. Finally, as in any case of atrial fibrillation refractory to medical therapy, atrioventricular nodal ablation and a permanent pacemaker implant can be considered [40].

Scarring, fibrosis and amyloid itself may have proarrhythmogenic properties leading to the emergence of tachyarrhythmias [41]. Although sudden cardiac death (SCD) is more common in cardiac amyloidosis (particularly AL cardiac amyloidosis) than in other cardiomyopathies and studies show a high number of appropriate (and inappropriate) shocks, no study has so far convincingly demonstrated a mortality benefit with ICD in patients with cardiac amyloidosis [42]. Nevertheless, the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias advocated for ICD implantation in patients who have haemodynamically not-tolerated ventricular tachycardias (class IIA, C recommendation) [43]. Certainly, the decision concerning ICD implantation should be made in an amyloidosis centre after in-depth discussion with the team and the patient.

Toxicity of amyloid fibrils may lead to sinus bradycardia up to sinus arrest and amyloid deposition may delay impulse propagation within the conduction system [41]. Over time, about 10% of cardiac amyloidosis patients eventually require a pacemaker. The presence of a first-degree AV block, wide QRS complex (over 120 ms) and atrial fibrillation indicate the highest risk for future pacemaker implantation [44], highlighting the need for regular ECG monitoring.

Disease-modifying treatments

The treatment of AL cardiac amyloidosis is mainly in the domain of haemato-oncology, and it varies according to the underlying disease, renal and neurological parameters, and cardiac involvement. In recent years, treatment options have increased substantially, and life expectancy increased. Treatment of AL is a huge topic in itself, but not a focus of this review. Notably, AL patients should be treated in an amyloidosis centre with an opportunity for an interdisciplinary approach [45].

For ATTR cardiac amyloidosis, the only causal treatment currently approved is the tetramer stabiliser tafamidis. It prevents dissociation of the transthyretin tetramer to the four monomers, thereby preventing the build-up of amyloid oligomers and fibrils. Tafamidis was initially developed for the treatment of familial amyloid polyneuropathy and has been used in this indication for more than 10 years (approved in the EU but not in Switzerland). The "ATTR-act study" [46] proved the efficacy of tafamidis for the treatment of cardiac amyloidosis. Mortality and heart failure hospitalisation were significantly lowered compared to placebo; however, this benefit seems to be achieved after 18 months only. The effect on quality of life and exercise capacity was seen much faster. Currently, tafamidis 61 mg/d is approved for the treatment of cardiac amyloidosis in Switzerland (for limitations, see table 2). Recently, the effect of tetramer stabilisation on outcome has been confirmed with acoramidis, a tetramer stabiliser similar to tafamidis [47].

Importantly, drug development in cardiac amyloidosis is very dynamic and several new compounds show promising results for the treatment of cardiac amyloidosis. RNA therapeutics (siRNA and antisense oligonucleotides) can sup-

Table 2:
Limitations from the "Spezialitätenliste" for the treatment of cardiac amyloidosis in Switzerland with tafamidis 61 mg/d. The drug is only reimbursed by the health insurance when all of the following are present:

Established diagnosis with typical imaging findings along with exclusion of AL amyloidosis and a positive Tc scintigraphy (Perugini 2–3) or histological proof of ATTR
NYHA class I or II
At least one prior hospitalisation for heart failure and/or an episode of a symptomatic documented heart failure
NT-proBNP > 600 ng/l
Able to walk more than 100 m in a 6-minute walk test
Glomerular filtration rate > 25 ml/min/1.73 m^2
Life expectancy of at least 2 years
No prior liver or heart transplantation, no "mechanical assist devices"
Must not be combined with other specific drugs for the treatment of TTR amyloidosis (e.g. patisiran, inotersen)
Cardiology centre, included in the list of the Swiss Federal Office of Public Health

NYHA: New York Heart Association.

press the production of TTR in the liver effectively, thus eliminating the protein responsible for TTR amyloidosis.

For hereditary ATTR amyloidosis, three substances are already on the market for the treatment of amyloid polyneuropathy. Patisiran and vutisiran are small interfering RNAs (si-RNA) binding to transthyretin messenger RNA (mRNA) to mediate its premature degradation, thereby inhibiting its translation into transthyretin protein. Similarly, the antisense oligonucleotides inotersen and eplontersen inhibit the production of transthyretin.

The Apollo-A (patisiran) [48], Helios-A (vutisiran) [49] and Neuro-TTR (inotersen) [50], NEURO-TTRansform (eplontersen) [51] studies showed that the substances slowed or even halted the progression of neuropathy in these patients. The efficacy of these substances in cardiac amyloidosis patients with wild-type and hereditaryamyloidosis is promising. In the recently published Apollo-B trial, administration of patisiran over 12 months resulted in preserved functional capacity in ATTR cardiac amyloidosis [52]. Very recently, the Helios-B study demonstrated significant reduction of death and cardiovascular events with vutrisiran in patients with ATTR-CM [53]. Of note, RNA therapeutics for hereditary amyloidosis currently can only be prescribed in one of the amyloidosis centres at the university hospitals of Lausanne (CHUV) or Zurich (USZ).

Furthermore, with CRISPR-Cas9, gene silencing has been achieved in patients with hereditary amyloidosis and first-in-man data look very promising. This could be one of the first gene therapies applied to humans [54]. Recently, Fontana et al. described anti-ATTR antibodies in patients who had recovered from ATTR amyloidosis, highlighting the possibility for reversibility [55]. Further, an exciting phase I study proved the concept that amyloid can be cleared from the tissue via an antibody-mediated phagocytotic inflammatory reaction [56]. After infusion of the antibody, cardiac tracer update on scintigraphy and extracellular volume on cardiac MRI were reduced after 12 months. An ongoing phase 3 trial is evaluating this promising new treatment option.

Conclusion

Overall, amyloidosis has gained a lot of attention in the last couple of years. This is mainly based on much better diagnostic tools and treatment options. However, the diagnosis and treatment remain challenging, and misdiagnosis may pose a danger to the patient, and potential treatment may be unintentionally withheld. Further, amyloidosis remains a multiorgan disease and a multidisciplinary approach, particularly in vATTR and AL amyloidosis, is crucial. Thus, amyloidosis networks, in which the relevant disciplines work together, are critically important and a nationwide strategy is helpful in improving quality of care [27, 57, 58].

Key points

- Cardiac amyloidosis is characterised by the deposition of abnormal proteins called amyloid in heart tissue. These deposits impair the structure and function of the heart, leading to various symptoms and complications.
- There are two main types of amyloid proteins causing cardiac amyloidosis, with the most common types being ATTR and AL amyloidosis.
- Symptoms of cardiac amyloidosis vary, but mostly include unexplained heart failure symptoms in a patient with a thickened septum on echocardiography. Other red flags include hypotension in a previously hypertensive patient, syncope, unexplained stroke, bilateral carpal tunnel syndrome, ECG abnormalities (pseudo-Q waves) and others.
- Diagnosis is made by typical imaging findings with echocardiography or CMR, together with a positive technetium scintigraphy in the absence of plasma cell dyscrasia (ATTR) or via tissue biopsy (AL or ATTR).
- The treatment goals for cardiac amyloidosis are to manage symptoms and to give medication targeting the underlying cause of amyloidosis.
- Management of cardiac amyloidosis requires a multidisciplinary approach, involving cardiologists, haematologists, nephrologists and other specialists. Close monitoring and coordination of care are essential to ensure high-quality treatment.

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Potential competing interests

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