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COMORBIDITIES OF HEART FAILURE (C ANGERMANN, SECTION EDITOR)

Amyloidosis in Heart Failure

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Abstract

Purpose Amyloidosis represents an increasingly recognized but still frequently missed cause of heart failure. In the light of many effective therapies for light chain (AL) amyloidosis and promising new treatment options for transthyretin (ATTR) amyloidosis, awareness among caregivers needs to be raised to screen for amyloidosis as an important and potentially treatable differential diagnosis. This review outlines the diversity of cardiac amyloidosis, its relation to heart failure, the diagnostic algorithm, and therapeutic considerations that should be applied depending on the underlying type of amyloidosis.

Recent Findings Non-biopsy diagnosis is feasible in ATTR amyloidosis in the absence of a monoclonal component resulting in higher detection rates of cardiac ATTR amyloidosis. Biomarker-guided staging systems have been updated to facilitate risk stratification according to currently available biomarkers independent of regional differences, but have not yet prospectively been tested. Novel therapies for hereditary and wild-type ATTR amyloidosis are increasingly available. The complex treatment options for AL amyloidosis are improving continuously, resulting in better survival and quality of life. Mortality in advanced cardiac amyloidosis remains high, underlining the importance of early diagnosis and treatment initiation.

Summary Cardiac amyloidosis is characterized by etiologic and clinical heterogeneity resulting in a frequently delayed diagnosis and an inappropriately high mortality risk. New treatment options for this hitherto partially untreatable condition have become and will become available, but raise challenges regarding their implementation. Referral to specialized centers providing access to extensive and targeted diagnostic investigations and treatment initiation may help to face these challenges.

Keywords Cardiac amyloidosis · Amyloid cardiomyopathy · Heart failure with preserved ejection fraction (HFpEF) · ATTR amyloidosis · AL amyloidosis · Diagnostic algorithm

Introduction

Chronic heart failure (HF) is a syndromal disease with high but still growing prevalence, grave prognosis, and a major impact on caregivers and the healthcare system [1, 2]. While there is a large body of therapeutic options for patients with HF with reduced left ventricular ejection fraction (HFrEF), specific therapies to improve the outcome of patients with HF with preserved ejection fraction (HFpEF) are lacking [3]. The reasons for this disappointingly slow advancement have been discussed in detail [4]. One important factor might be that HFpEF comprises a large variety of very diverse underlying causes, ranging from hypertensive/hypertrophic heart disease to diabetic cardiomyopathy and infiltrative cardiomyopathies like Fabry disease or amyloidosis. As such, ascertaining the cause of HF has become the acknowledged focus point for the targeted development of successful treatment options.

Although previously considered a rare disease, recent smaller studies reported higher prevalence rates of cardiac amyloidosis in patients with HFpEF. Thus, in 49 non-

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ischemic HFpEF patients aged > 65 years, cardiac amyloidosis was found in 29%: 18% wild-type transthyretin (ATTRwt) amyloidosis; 10% light chain (AL) amyloidosis [5]. Another study found cardiac ATTRwt amyloidosis in 13% of 120 HFpEF patients aged > 60 years [6]. Autopsy studies revealed a prevalence of 25% of ATTRwt in 256 patients aged > 85 years [7]. These percentages indicate that cardiac amyloidosis might be underestimated, thus deserving full attention as an important differential diagnosis in HFpEF.

This review aims to provide an overview of the diversity of cardiac amyloidosis with a focus on pathophysiology, clinical presentation, recommended diagnostic investigations, and subtype- and stage-directed targeted treatment including the spectrum of innovative modalities currently under investigation.

Pathomechanisms of Cardiac Amyloidosis

Amyloidosis results from the deposition of misfolded proteins as insoluble fibrils in the interstitium of affected organs. Up to now, 36 human precursor proteins have been identified [8]. Amyloid deposits may cause organ dysfunction due to cytotoxic and pro-apoptotic effects, mechanical interference, but also direct cardiotoxicity of circulating precursors. Organ tropism depends in part on the precursor protein and is not yet completely understood. Cardiac involvement is predominantly found in AL (75%) and ATTRwt amyloidosis (96%) but may occur in other types of amyloidosis (Table 1) [10].

AL Amyloidosis AL amyloidosis is characterized by deposition of light chains produced by monoclonal plasma cells. In most cases, the plasma cell clone is small and manifests clinically with amyloid organ involvement. However, amyloidosis can occur in patients with overt multiple myeloma (10%) and rarely in B cell lymphoma. Organ tropism seems to depend at least in part on the light chain variable region and the gene family of the plasma cell clone. Therefore, IGLV2-14, IGVL6-57, and IGLV3-1 are known to be linked with amyloidogenic light chains [16–18]. Cardiac involvement was found associated with the LV1-44 germline gene, whereas LV3-01 was less commonly linked with advanced cardiac and renal involvement [19, 20]. Beyond the direct cytotoxic, pro-apoptotic, and mechanical effects of amyloid deposits on the cardiomyocytes, circulating free light chains (FLC) themselves independently exert direct cardiotoxic damage [21–23]. Infusions of light chains obtained from AL amyloidosis patients with cardiac involvement and impaired cardiac function, induced pericardial edema and increased cell death, and increased mortality in zebrafish despite the absence of amyloid deposits [24]. Consistently, diastolic dysfunction can be induced in isolated mouse hearts by infusion of amyloidogenic light chains purified from urine of patients with cardiac AL amyloidosis [25]. Investigations in *C. elegans* support these findings, showing that amyloidogenic light chains rapidly reduce the pump rate of the nematode's pharynx considered an analog of the vertebrates' heart [26].

A transgenic zebrafish model with conditional hepatic expression of amyloidogenic light chains yielded concentrations of circulating FLC comparable to levels found in newly diagnosed patients [27], which impaired cardiac contractility and increased cardiomyocytic cell death and autophagy. At an early stage, light chain toxicity also induced regeneration processes by increased proliferation of cardiomyocytes and therefore unaltered mortality [27]. This mechanism could be abrogated by a small molecule proliferation inhibitor [27]. When studied long-term, zebrafish develop cardiac dysfunction as already shown in other disease models, e.g., mouse or *C. elegans* [25–27].

Mechanistically, amyloidogenic light chains cause apoptosis, cellular dysfunction, and oxidative distress via activation of the p38 mitogen–activating protein kinases (MAPK) pathway. It is considered independent of the upstream MAPK type 3 or 6, but dependent upon autophosphorylation of TGFβ activated protein kinase-1 binding protein-1 [28]. Other factors aggravating light chain–induced cardiotoxicity are inappropriate production of reactive oxygen species [29, 30] and impaired lysosomal function, thus compromising autophagy and enhancing proteotoxicity [31]. This is in accordance with indirect evidence in humans, demonstrating that a rapid reduction of FLC was associated with a marked reduction in NT-proBNP, a marker of myocardial dysfunction, and better survival [21–23, 32].

ATTR Amyloidosis Central to the pathophysiology in ATTR amyloidosis is transthyretin (TTR; formerly known as prealbumin). It is the transport protein of thyroxine and retinol-binding protein/vitamin A complex. It is mostly found in serum and cerebrospinal fluid [33–35]. TTR is secreted as a tetramer, predominantly by the liver (95%) and only in very small amounts by the choroid plexus and retinal pigment epithelium (< 5%) [36, 37]. Proteolytic cleavage of the TTR tetramer, promoting dissociation and misfolding of full-length monomers and C-terminal fragments mostly spanning residues 49–127, is regarded as a crucial pathogenetic step [38, 39] as C-terminal fragments are needed to induce amyloid fibril formation in vitro at nearly physiological conditions [38, 39]. Recently, it has been shown that plasmin is uniquely able to trigger wild-type and variant TTR amyloid fibril formation under mechanical shear forces and pH conditions that recapitulate the physiological milieu [40]. TTR mutations associated with hereditary ATTR amyloidosis (ATTRv), increase TTR amyloidogenic propensity by reducing tetramer stability, by exposing protease-sensitive loops, and by increasing the thermodynamic instability of the released monomeric species

Table 1 Different subtypes of cardiac amyloidosis and their clinical presentation

	AL amyloidosis	ATTR amyloidosis		AA amyloidosis	ApoAI amyloidosis	ApoAII amyloidosis
		Hereditary (*ATTRv*)	Wild-type (*ATTRwt*)			
Precursor protein	Free light chains (lambda > kappa)	Transthyretin	Transthyretin	Serum amyloid A (SAA)	Apolipoprotein A-I (ApoAI)	Apolipoprotein A-II (ApoAII)
Frequency among patient with cardiac amyloidosis*	49%	10%	40%	< 1%	< 1%	< 1%
Physiological function	Monoclonal variant without physiological function	Transport of thyroxine/retinol-binding protein/vitamin A complex		Acute phase protein	Principal component of high-density lipoproteins (HDLs; ca. 70%)	Component of HDLs
Underlying disease	Plasma cell dyscrasia (mainly monoclonal gammopathy, multiple myeloma [10%]), B cell lymphoma	None	None	Inflammatory arthritis inflammatory bowel diseases hereditary and required immunodeficiencies neoplastic disorders chronic infections hereditary autoinflammatory disorders systemic vasculitides patients under risk of chronic infection obesity	None	None
Hereditary form	No	Yes (> 120 mutations are known)	No (age-related)	No	Yes	Yes
Pathomechanism	Cytotoxic, pro-apoptotic and mechanical local effects on cardiomyocytes; direct cardiotoxicity of circulating precursor via MAPK pathway	a) Destabilizing, mainly missense mutations result in dissociation of transthyretin tetramer with consecutive tissue deposition b) Proteolytic cleavage as possible trigger for dissociation c) Cytotoxicity of transthyretin monomers and dimers		Chronic elevation of serum amyloid A levels; homozygously expressed SAA1.1 or SAA1.3	Conversion of ApoAI monomers to HDL-bound ApoAI dimers by lipid binding; changes in structure and function of ApoAI proteins by amyloidogenic mutations shifts the equilibrium towards monomers with deposition as amyloid fibrils [9]	
Pattern of organ involvement	All organs except for CNS: heart (75%), kidney (65%), liver (15%), soft tissue (15%), gastrointestinal tract (5%), peripheral and autonomous nervous system (10%) [10]	Heart, peripheral and autonomous nerve system, eye, leptomeninges	Heart (96%), nerve system, ligaments, tendosynovium	All organs except for CNS: predominantly kidney, gastrointestinal tract, heart (10%)	Kidney, liver, heart, peripheral nerve system, testis, larynx (C-terminal variants), skin (C-terminal variants)	Kidney, heart
Cardiac manifestation in bisphosphonate scintigraphy	Might be positive (in about 1/3 of patients) [11••]	Positive (grading according to Perugini et al. [12])		Might be positive [13]	Might be positive [14]	Unknown
Diagnostic sensitivity of fat aspiration [15]	84% (78–88)	45% (36–54%), but dependent on mutation e.g. in Val122Ile 33%, in Thr60Ala 67%	15% (11–20%)	Not analyzed	Not analyzed	Not analyzed

*Frequency among patients with cardiac amyloidosis according to the data base of the Amyloidosis Research and Treatment Center Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (2018)

AL and ATTR amyloidosis is common cause of cardiac amyloidosis, whereas ApoAI, ApoAII and AA amyloidosis represent rare underlying subtypes (< 1% each). Pathomechanism, clinical presentation, as well as the diagnostic value of bisphosphonate scintigraphy and abdominal fat aspiration depend on the precursor protein/subtype

[41–43]. Rare mutations that increase TTR stability such as Thr119Met (p.Thr139Met) prevent proteolytic cleavage and tetramer dissociation and protect from amyloid formation [42, 44]. Up to now, more than > 120 amyloidogenic mutations have been identified. A cardiac phenotype is apparent in some of them and may occur alone or in combination with mainly neurological involvement. Typical mutations are, e.g., Val122Ile (p.Val142Ile), Thr60Ala (p.Thr80Ala), Leu111Met (p.Leu131Met), Ile68Leu (p.Ile 88Leu), and late-onset Val30Met (p.Val50Met) [45]. Although ATTRv amyloidosis follows an autosomal dominant trait, penetrance is highly variable both inside families and across regions.

Two different forms of fibrils in ATTR amyloidosis have been identified, type A and type B fragments [44, 46]. Type A fragments consist of full-length TTR and TTR fragments resulting from proteolysis, especially C-terminal fragments starting at residues 46, 49, and 52 [44, 46]. Type A fragments are typically found in ATTRwt, but also in most ATTRv patients [46, 47]. Type B fibrils result from full-length TTR only and are common among patients with early-onset Val30Met (p.Val50Met), but also found in Tyr114Cys (p.Tyr134Cys) patients [47, 48]. Associations between early-onset and type B fibrils as well as later onset with type A fibrils have been observed in Swedish and Japanese patients [47, 48].

Type B but no type A fibrils show strong positivity at Congo red staining [46]. Bisphosphonate scintigraphy might fail to detect type B amyloid [49], whereas Pittsburgh component B (PIB) seems to function independent of the fibril type [50]. Differences in fibril composition seem to associate with different clinical phenotypes. Type A fibrils are predominantly associated with cardiomyopathy and peripheral sensory/motor neuropathy [48, 51]. In contrast, type B amyloid is linked with axonal polyneuropathy starting with small fiber involvement, affection of the autonomous nerve system, gastrointestinal symptoms, and conduction abnormalities in the absence of cardiac hypertrophy [44, 48, 52–54].

AA Amyloidosis AA amyloidosis is a rare complication of long-term, systemic inflammatory conditions such as rheumatoid arthritis, auto-inflammatory syndromes, inflammatory bowel diseases, inflammatory active malignancies, or chronic infections [55]. A sustained and substantial increase of the acute phase reactant serum amyloid A (SAA), as observed in chronic inflammation conditions due to IL-1- and IL-6-mediated stimulation, is required for the occurrence of AA amyloidosis [22]. The risk to develop AA amyloidosis is modulated by genetically determined factors, i.e., homozygosity for the SAA1.1 allele in Caucasians and SAA1.3 allele in Japanese subjects [56, 57].

ApoAI Amyloidosis ApoAI amyloidosis is caused by apolipoprotein A-I (ApoAI), the main component of high-density lipoproteins (HDL) [9], which is produced by the liver and gastrointestinal tract [9]. More than 20 dominantly inherited, amyloidogenic ApoAI mutations have been associated with hereditary systemic ApoAI amyloidosis [9]. Amyloid fibrils are largely formed by N-terminal ApoAI fragments spanning the first 80–100 residues [9]. Amyloidogenic mutations have been shown to promote conformational changes and N-terminal proteolytic cleavage, exposing peptide regions prone to aggregation and deposition as amyloid fibrils [58].

ApoAII Amyloidosis Analogously, ApoAII amyloidosis results from apolipoprotein A-II, another HDL component. There, stop-codon mutations result in C-terminal peptide extension [59–61].

Clinical Presentation

Advanced cardiac involvement in amyloidosis causes global, i.e., biventricular HF. Affected patients feature signs of right-sided HF such as raised jugular venous pressure, peripheral edema, hepatomegaly, and ascites, but also symptoms of left-sided HF like pulmonary edema and dyspnea on exertion or at rest. Some patients present with exertional syncope or presyncope due to low cardiac output. Typically, these patients do not well tolerate conventional HF treatment with beta blockers and blockers of the renin-angiotensin-aldosteron system (RAAS) due to the hypotensive effects of these substance classes.

Cardiac arrhythmias, especially atrial fibrillation, and conduction abnormalities are common in all patients with cardiac amyloidosis. Intracardiac thrombi despite sinus rhythm were found in 33% of patients with cardiac amyloidosis, with preponderance in patients with AL amyloidosis (51%) [62]. Some patients also present with angina due to small vessel disease. Additional symptoms depend on the amyloidosis subtype, the deposition pattern, and the severity of other organ involvement. Thus, the amyloidosis subtype cannot reliably be diagnosed based on clinical presentation alone.

ATTR Amyloidosis This predominantly affects the heart and the peripheral and autonomic nervous systems [10]. The leading organ manifestation in patients suffering from ATTRv amyloidosis is related to the genotype, whereas patients with ATTRwt amyloidosis usually develop cardiac disease (96%). Patients with leading heart involvement present with cardiomyopathy, arrhythmia, conduction blocks, and usually mild valve regurgitation (detailed description see above) [63]. Patients with a predominant neurologic phenotype present with axonal sensory-motor polyneuropathy which is length-dependent and symmetric [63]. Autonomic neuropathy may also occur resulting in orthostatic hypotension, recurrent urinary tract infections because of urinary retention, sexual dysfunction, and sweating abnormalities [63, 64]. As both the

choroid plexus and retinal epithelium also produce transthyretin, eye manifestations, e.g., dry eyes, vitreous opacities, glaucoma, abnormal conjunctival vessels and papillary abnormalities [65], and in case of CNS manifestations progressive dementia, headache, ataxia, seizures, spastic paresis, or stroke-like episodes may also occur in patients with ATTRv amyloidosis [66–71]. Gastrointestinal involvement such as nausea, vomitus, diarrhea, constipation, or weight loss can be found as well as renal involvement, e.g., renal failure or proteinuria [54, 72]. Carpal tunnel syndrome, atraumatic biceps tendon rupture, and lumbar spinal stenosis may herald systemic manifestations in ATTR amyloidosis [73–76].

In *AL amyloidosis*, circulating FLC exerts direct cardiotoxic effects. Thus, cardiac deterioration is accelerated and death risk is higher than in ATTR amyloidosis [77]. Patients with AL amyloidosis show higher levels of cardiac biomarkers (in particular natriuretic peptides) although atrial and ventricular wall thickness is less pronounced when compared to ATTR amyloidosis because toxic FLC directly trigger natriuretic peptide synthesis via activation of the MAPK pathway [10, 28, 78, 79]. Concomitant symptoms depend on the pattern of organ involvement, which is more diverse in AL compared to ATTR amyloidosis. Renal involvement is observed in up to 65% and includes proteinuria with leading albuminuria and progressive loss of glomerular filtration [10]. Other organ manifestations and corresponding symptoms/signs are the following: liver in 15%, e.g., hepatomegaly or elevation of alkaline phosphatase; gastrointestinal tract in 5%, e.g., bleeding or motility disturbances; autonomous and peripheral nerve system in 10%, e.g., polyneuropathy or orthostatic dysregulation; soft tissue in 15%, e.g., macroglossia [10].

In *AA amyloidosis*, cardiac involvement typically occurs only in the advanced stages of the disease, i.e., about 10% of patients. Instead, presenting features and leading clinical manifestations are typically related to renal and gastrointestinal involvement [10].

In *ApoAI amyloidosis*, cardiomyopathy is not the clinically dominant manifestation, but, when occurring, invariably affects the prognosis. Patients typically show liver, kidney, testis, and skin involvement [10]. Refractory hypertension may occur in a subset of these patients.

In *ApoAII amyloidosis,* patients usually show predominant kidney involvement, and less frequently cardiac involvement [59–61].

Diagnostic Algorithm

Early signs and symptoms of cardiac amyloidosis are unspecific, e.g., dyspnea on exertion and increased left ventricular wall thickness, and frequently mimic common diseases, e.g., hypertrophic heart disease. Hence, diagnosis is usually significantly delayed. Up to 20% of patients with AL amyloidosis may receive their diagnosis more than 2 years after the onset of symptoms [80], and this time lag may be even longer in patients with ATTR amyloidosis (about 3 to 5 years) [81, 82]. Therefore, most patients present in advanced disease stages, which are associated with high mortality risk, especially in AL amyloidosis [77]. Warning signs and symptoms, which should raise suspicion of cardiac amyloidosis and trigger further diagnostic investigations (Fig. 1) might, for example, be spontaneous resolution of known hypertension, repeat unexplained syncope, biventricular/bi-atrial hypertrophy, preserved left ventricular apical deformation in the presence of impaired function of the basal, and midventricular segments ("apical sparing") on echocardiography, coincident monoclonal gammopathy with unexplained elevation of natriuretic peptides, or unexplained onset of HF symptoms. Biomarker-based screening (troponin, NT-proBNP, proteinuria/albuminuria) should be performed among patients with known monoclonal gammopathy.

The initial diagnostic steps in patients with suspected cardiac amyloidosis are screening for monoclonal components including measurement of circulating FLC and immunofixation in serum and 24-h urine sample (Fig. 1). In case of a negative result, AL amyloidosis is unlikely and bisphosphonate scintigraphy using ^{99m}Tc-DPD, ^{99m}Tc-PYP or ^{99m}Tc-HMDP as tracer should be performed [11••]. Positive scintigraphy, i.e., grade 2 or 3 uptake, may establish a diagnosis of cardiac non-AL amyloidosis [11••, 12]. In patients with monoclonal gammopathy or grade 0 or 1 uptake at scintigraphy, further tissue biopsy for histological confirmation and typing is required [11••]. Importantly, evidence of monoclonal gammopathy should not be equated with AL amyloidosis, as monoclonal gammopathy is found in about 20% of ATTR amyloidosis patients [11••]. On the other hand, intense cardiac bone tracer uptake may also be seen in AL amyloidosis. Abdominal fat aspirate represents the first choice for non-invasive tissue harvesting. Its diagnostic sensitivity varies among the subtypes in patients with cardiac amyloidosis: 84% (78–88%) in systemic AL amyloidosis, but only 15% (11–20%) in ATTRwt amyloidosis [15]. In case of a negative abdominal fat aspirate, salivary gland biopsy should be explored as an alternative [10, 83].

Amyloid tissue should be classified by mass spectrometry, immune-electron microscopy with commercial antibodies, or light microscopy immunohistochemistry with custom-made antibodies [84, 85]. Light microscopy immunohistochemistry with commercial antibodies cannot reliably differentiate between AL and ATTR amyloidosis [86]. Moreover, pattern and extent of organ involvement need to be assessed applying an array of diagnostic assays including cardiac biomarkers (NT-proBNP, troponin), glomerular filtration rate, quantification of total protein loss, Holter-EKG, echocardiography, cardiac magnetic resonance imaging, abdominal ultrasound with

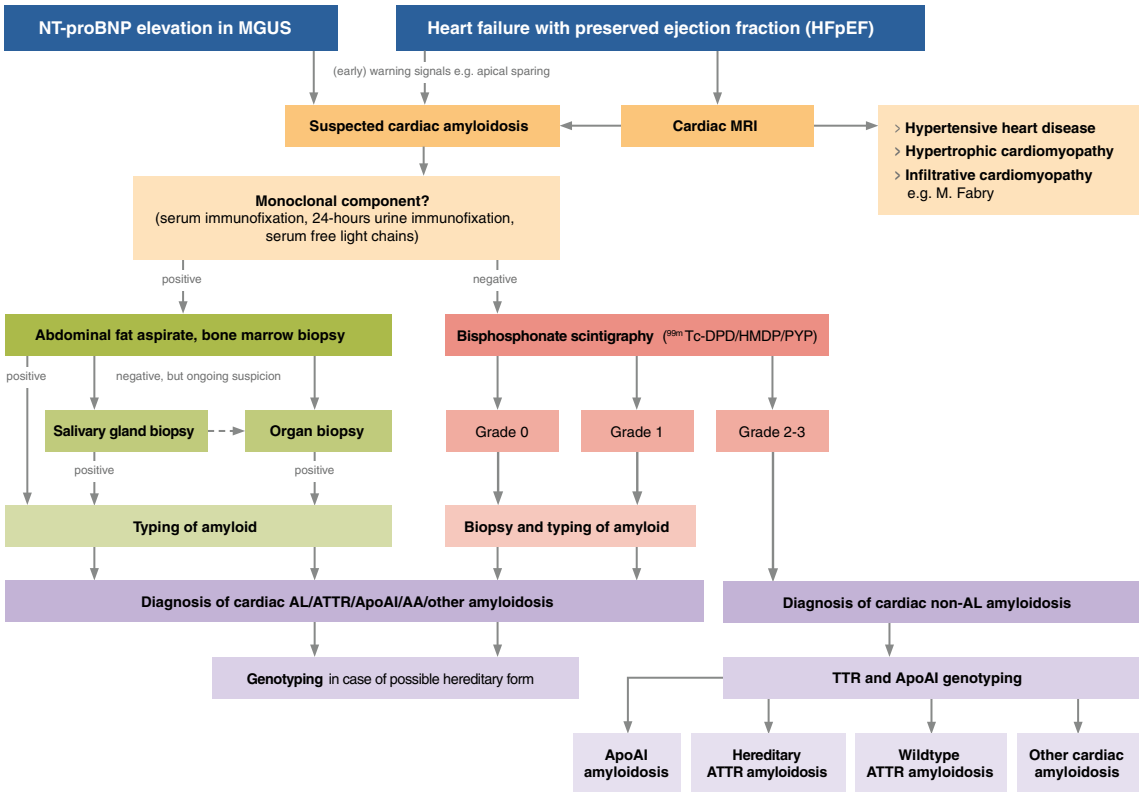

Fig. 1 Diagnostic algorithm in heart failure with preserved ejection fraction and suspected cardiac amyloidosis

evaluation of liver size, and neurologic assessment including electrophysiological examinations and small-fiber diagnostics if indicated.

If a hereditary variant is suspected, e.g., in proven ATTR or ApoAI amyloidosis, genetic testing should be performed. In case of a hereditary form, genetic counseling and presymptomatic testing can be offered to relatives at risk facilitating a risk-adapted follow-up. It is advantageous to perform such complex interdisciplinary diagnostic investigations in a dedicated amyloidosis center.

Imaging in Cardiac Amyloidosis—a Brief Overview

Depending on the clinical situation (suspected versus established amyloidosis, suspected versus established cardiac involvement, diagnostic versus prognostic versus monitoring intention), various and in parts complementary imaging modalities need to be hierarchically employed. In brief:

Echocardiography, in the hands of an experienced sonographer, may raise the suspicion of cardiac involvement. Typical features are these restrictive cardiomyopathy with impaired diastolic function in combination with biventricular hypertrophy, granular sparkling of the ventricular myocardium, bi-atrial dilation, thickening of interatrial septum, diastolic dysfunction, pericardial effusion, and moderate pulmonary hypertension [87]. However, these findings are evident in advanced cardiac amyloidosis, whereas reliable early indicators are missing. Strain imaging modalities hold promise to provide superior utility in diagnosing and monitoring cardiac involvement, but further investigations are needed [88, 89].

Cardiac MRI allows characterizing morphology and function with superior resolution and facilitates tissue characterization by late gadolinium enhancement (LGE) and T1 mapping [90–92]. LGE utilizes the regional distribution of a contrast agent in the extracellular space, which is enlarged in patients with cardiac amyloidosis due to the deposited amyloid. Typical patterns of LGE showed high sensitivity and specificity (each about 90%) [93]. T1 mapping typically shows an increase of T1 time in cardiac amyloidosis.

Bone scintigraphy utilizes technetium-labeled radionuclides such as ^{99m}Tc-DPD, ^{99m}Tc-HMDP, and ^{99m}Tc-PYP to image amyloid [11••]. Non-biopsy diagnosis of cardiac ATTR amyloidosis has thus become possible regardless of the mutational status (only in cases with excluded monoclonal component and normal free light chain concentrations) [11••]. However, about one-third of patients with AL amyloidosis is also positive in scintigraphy, and there are also rare cases with AA and ApoAI amyloidosis [13, 14].

Positron emission tomography (PET) utilizing tracers such as ^{18}F-florbetapir and ^{18}F-florbetaben seems to specifically identify cardiac amyloid. Differentiation between cardiac amyloidosis and hypertensive heart disease was possible in first

smaller case series [94]. Moreover, the retention index seems to depend on the underlying amyloid subtype [13].

Respective methods are discussed in more detail in [87, 90, 95].

Staging of Cardiac Involvement

Biomarkers as natriuretic peptides and troponins facilitate staging of the severity of cardiac involvement (Table 2):

In AL amyloidosis, the Standard Mayo Clinic staging system has been widely used [96]. A European collaborative study sub-stratified patients with advanced cardiac amyloidosis (Standard Mayo Clinic stage III) demonstrating the existence of a subgroup with particular dismal prognosis (median survival 3 months) if systolic blood pressure was low (< 100 mmHg) and NT-proBNP very high (> 8500 ng/mL) [97]. A well-accepted and widely used modification of Standard Mayo Clinic staging system includes only NT-proBNP > 8500 ng/mL among stage III patients (IIIA: NT-proBNP ≤ 8500 ng/mL; IIIB: NT-proBNP > 8500 ng/mL) as additional risk factor [105]. The Revised Mayo Clinic staging system also includes the difference of involved and uninvolved free light chain (dFLC; according to Freelite® assay) as risk factor [101].

More recent investigations incorporated high-sensitive (hs) troponin and BNP to overcome poor regional availability of some markers and to adjust systems to state of the art [98–100]. All staging systems are vulnerable to renal impairment, drugs, and atrial fibrillation as cardiac biomarkers are elevated under these conditions [105–107]. Performance analysis in patients with atrial fibrillation combined with impaired renal function (eGFR < 50 mL/min/1.73 m^2) confirmed best performance of modified Standard Mayo Clinic staging system [105]. BNP should be preferred in patients with end-stage renal failure [107]. As levels of cardiac biomarkers are increased by immunomodulatory drugs, their interpretation requires clinical context and caution [106].

In ATTR amyloidosis, three staging systems have been proposed [103, 104, 108]. Their clinical utility has not been tested prospectively. Staging systems for other forms of cardiac amyloidosis, especially AA and ApoAI/II amyloidosis, are not available, yet.

Assessment of Extra-Cardiac Organ Involvement

Beyond cardiac involvement, staging systems have only been defined for renal involvement in AL amyloidosis that typically is characterized by proteinuria (with leading albuminuria) and impaired renal function. A reduced eGFR (< 50 ml/min/1.73 m^2) and proteinuria (> 5 g/d) were shown to predict the 2-year risk for the onset of dialysis in AL amyloidosis for stages I, II, and III with 0–3% (both criteria are not fulfilled), 11–25% (one criterion fulfilled), and 60–75% (both criteria fulfilled) [109]. Further, the ratio of 24-h proteinuria to eGFR (measured in mg per ml/min/1.73 m^2) represents a sensitive marker of renal risk. A ratio < 30 versus 31–99 versus ≥ 100 was associated with a 2-year progression to dialysis of 0% versus 9% versus 35%, respectively [110]. Reduction of this ratio by at least 25% (or below a threshold of 100 if initially above 100) at 3 months translated into a 2-year progression to dialysis of 0% versus 24% for patients without such reduction.

Other organ manifestations have to be assessed qualitatively after diagnosis has been established, e.g., by abdominal fat aspirate. Usually, no additional tissue biopsy of affected organs is required; e.g., hepatic involvement can be assumed non-invasively from alkaline phosphatase (AP) elevation and/or evidence of hepatomegaly.

Treatment Options

General treatment principles are based on suppressing the precursor protein production or stabilizing the precursor protein. Recently explored alternatives include inhibiting the misfolding processes and fibrillogenesis as well as promoting fibril disruption and degradation of deposited amyloid. The treatment strategy depends on the precursor protein, i.e., varies among the subtypes, and must therefore be tailored to the individual patient.

AL Amyloidosis

The main treatment strategy aims to eradicate the causal plasma cell clone and rapidly remove circulating toxic FLC. Therefore, treatment consists of chemotherapy adapted from regimens used in multiple myeloma (Table 3) taking into account the frailty of patients with amyloidosis, but also chromosomal aberrations of the monoclonal plasma cell clone in the bone marrow, e.g., translocation t(11;14) or gain 1q21 [10].

Risk stratification: Patients with AL amyloidosis undergo risk stratification into three risk groups: low-, intermediate-, and high-risk patients [10].

Low risk ("fit") patients represent the minority (10–25%) [10]. They show limited organ involvement, especially with no severe cardiac involvement. They can be identified by the following criteria, which are also used as eligibility criteria for high-dose chemotherapy with autologous stem cell support (all criteria have to be fulfilled) [111]: biological age ≤ 65–70 years, NT-proBNP < 5000 ng/mL, systolic blood pressure ≥ 90 mmHg, creatinine clearance > 50 mL/min (unless on chronic stable dialysis), Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, New York Heart Association (NYHA) functional status class I or II, no large pleural effusions, lung CO diffusion capacity > 50%, and < 3 significantly involved the organs (liver, heart, kidney, autonomic nerve system). However, the majority of

Table 2: Cardiac staging systems in amyloidosis

Subtype	Publication	Year	Population studied	Staging system	Thresholds applied	Stages	Median survival (months) per stage
AL	Dispenzieri [96]	2004	98 patients with AL undergoing PBSCT; 1979–2000	Standard Mayo Clinic staging system	NT-proBNP > 332 ng/L cTnT > 0.035 ng/mL (or cTnI > 0.01 ng/mL)	I. No marker above cutoff II. One markers above cutoff III. Two markers above cutoff	26 11 4
	Wechalekar [97]	2013	346 patients with cardiac stage III AL amyloidosis; 2001–2010*	European staging system of advanced cardiac involvement	Standard Mayo Clinic stage III + systolic blood pressure < 100 mmHg NT-proBNP > 8500 ng/L	I. One risk factor II. Two risk factors III. Three risk factors	26 6 3
	Dispenzieri [98]	2014	224 newly diagnosed AL patients; 1989–2006	"Modified" Standard Mayo Clinic staging system including high-sensitive troponin	NT-proBNP > 332 ng/L hs-TnT > 54 ng/L	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff	69 29 6
	Dispenzieri [98]	2014	224 newly diagnosed AL patients; 1989–2006	High-sensitive troponin-based staging system	hs-TnT 14 ng/L hs-TnT 54 ng/L	I. No marker above cutoff II. One markers above cutoff III. Two markers above cutoff	71 43 6
	Lilleness [99], Tomlinson [100]	2019	Derivation cohort: 249 AL patients, 04-09/2016; complementary cohort: 592 AL patients, 2004–2014; 44 AL patients	BNP-based staging system associated with Standard Mayo Clinic staging system	BNP 81 pg/mL cTnI > 0.1 ng/mL	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff	n.a. 72 48
	Kumar [101]	2012	810 newly diagnosed AL patients; 303 patients undergoing PBSCT; 103 patients onto different clinical trials	Revised Mayo Clinic staging system	NT-proBNP > 1800 ng/L cTnT > 0.025 ng/mL dFLC > 180 mg/L	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff IV. Three markers above cutoff	94 40 14 6
	Kumar [102]	2019	224 newly diagnosed AL patients; 1989–2006	"Modified" Revised Mayo Clinic staging system including high-sensitive troponin	NT-proBNP > 1800 ng/L hs-TnT > 0.025 ng/mL dFLC > 180 mg/L	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff IV. Three markers above cutoff	79 29 15 5
ATTRwt	Grogan [103]	2016	360 ATTRwt patients; 1965-2013		cTnT >0.05 ng/mL NT-proBNP > 3000 pg/mL	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff	66 40 20
ATTRv/ATTRwt	Gillmore [104]	2017	553 ATTRwt and 316 ATTRv amyloidosis patients		NT-proBNP > 3000 ng/L eGFR < 45 mL/min	I. No marker above cutoff II. One marker above cutoff III. Two markers above cutoff	62 47 24

cTnT, cardiac troponin T; *cTnI*, cardiac troponin I; *hs-TnT*, high-sensitive troponin T; *NT-proBNP,* N-Terminal pro-brain natriuretic peptide

*stage III according to Dispenzieri et al. 2004: UK/London 71 patients, Italy/Pavia 164 patients, Germany/Heidelberg 92 patients, Greece/Athens 19 patients

Cardiac staging systems are mainly based on cardiac biomarkers and allow risk stratification in AL and ATTR amyloidosis. In AL amyloidosis, cardiac stages have distinct impact on treatment decisions.

Table 3 Causal concepts for treatment of cardiac amyloidosis

Cardiac amyloidosis	General treatment principle	Specific treatment
AL amyloidosis	Rapid reduction of free light chains by targeting the monoclonal plasma cell clone	Chemotherapy/plasma cell derived treatments: High-dose chemotherapy in fit patients* Standard chemotherapy/plasma cell depleting treatments − Bortezomib-based protocols (CyBorD, BMDex, VelDex, bortezomib monotherapy) − Ixazomib − Lenalidomide − Pomalidomide − Bendamustine − Daratumumab (ongoing phase III study, EudraCT 2016-001737-27) − Venetoclax No approved drugs except for steroids
ATTRv amyloidosis	Interrupt disposition process a) suppression of hepatic production of transthyretin b) suppression of tetramer dissociation and resolution of existing fibrils	Liver transplantation (in well-selected patients combined transplantations, e.g., liver and heart transplantation) Gene silencer − Patisiran (approved for polyneuropathy stage 1 and 2) − Inotersen (approved for polyneuropathy stage 1 and 2) TTR stabilizer − Tafamidis (approved for polyneuropathy stage 1) − Diflunisal − Epigallocatechin-3-gallate (EGCG) − AG10 (ongoing cardiac phase III trial, NCT03860935) − Tolcapone Fibril disruption/degradation: − Doxycycline/TUDCA (ongoing phase III study; NCT03481972) − PRX004
ATTRwt amyloidosis		Tafamidis (not approved yet in Europe, approved by FDA) Doxycycline/TUDCA (ongoing phase III study; NCT03481972) Patisiran not approved yet Inotersen not approved yet
AA amyloidosis	Control of inflammation	a) Treatment of underlying disease b) Interruption of inflammatory cascade by anti-IL-1/IL-6 agents
ApoAI amyloidosis	No specific treatment available	No specific treatment available
ApoAII amyloidosis	No specific treatment available	No specific treatment available

*Eligibility criteria for high-dose chemotherapy [111]: biological age ≤ 65–70 years, NT-proBNP < 5000 ng/mL, systolic blood pressure ≥ 90 mmHg, creatinine clearance > 50 mL/min (unless on chronic stable dialysis), Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, New York Heart Association (NYHA) functional status class I or II, no large pleural effusions, lung CO diffusion capacity > 50%, and < 3 significantly involved organs (liver, heart, kidney, autonomic nerve system)

General treatment principles aim to stop or suppress the production of the precursor protein. Alternative strategies include inhibition of the misfolding processes and fibrillogenesis, fibril disruption, and degradation of amyloid deposits. The treatment options in detail depend on several factors such as precursor protein, severity and pattern of organ involvement, and ECOG performance status. Therefore, they vary among subtypes and have to be adjusted individually.

patients (75–90%) does not meet these criteria [10]. According to the severity of cardiac involvement assessed by modified Standard Mayo cardiac staging system and NYHA class, these patients are categorized into "intermediate risk" (Standard Mayo cardiac stage I–IIIA) and "high risk" (Standard Mayo cardiac stage IIIB; NYHA class ≥ III).

Risk-adapted treatment: Treatment intensity strictly depends on the risk group.

Low-risk patients should undergo high-dose chemotherapy with autologous stem cell support after stem cell collection out of steady state [10, 84]. Especially, patients with evidence of *t*(11;14) among monoclonal plasma cells in the bone marrow benefit from high-dose melphalan [112]. Patients can receive induction therapy first according to CyBorD protocol (bortezomib, cyclophosphamide, dexamethasone) that was reported to improve the outcome

in case of more than 10% plasma cell infiltration in the bone marrow. In case of very good partial remission (VGPR) or worse remission post-transplant, bortezomib-based consolidation should be offered [10].

Patients with *intermediate risk* should receive standard-dose chemotherapy with bortezomib-based regimens such as CyBorD or BMDex (bortezomib, melphalan, dexamethasone) [10]. Bortezomib rapidly diminishes levels of circulating toxic free light chains [77]. Combination with dexamethasone, but also alkylating agents, increases efficacy [77]. CyBorD should be considered especially in patients with renal failure or with gain 1q21 [113]. Additionally, cyclophosphamide should be preferred in younger patients because of its less intrusive stem cell toxicity compared to melphalan allowing crossover to a high-dose concept in case of reached eligibility after the first cycles of chemotherapy. Patients with *t*(11;14) show favorable response rates and longer hematologic event-free survival under treatment with melphalan-containing regimens, but do not benefit from bortezomib [112, 114] so that MDex represents a reliable treatment strategy. Moreover, patients with neuropathy are candidates for MDex. In patients with a high dFLC (> 180 mg/l), BMDex should be preferred [10, 115].

In *high-risk patients*, dose intensity needs to be adjusted individually. Usually, these patients only tolerate low-dose combination regimens [10]. Monotherapy with bortezomib can be an option as well, especially in frail patients who do not tolerate steroids because of fluid retention.

In well-selected, younger patients with isolated advanced cardiac involvement, organ transplantation may antedate chemotherapy [116]. New treatment strategies, e.g., upfront treatment with daratumumab in combination with CyBorD (NCT03201965), are under investigation [117•].

Response evaluation: Evaluation of the treatment response is crucial. It should be performed every two to three cycles, and should include both the hematologic response and organ involvement (Table 4) [118, 119].

Hematologic response means reduction of FLC. Dimensions of hematologic response include complete remission (CR; normalized FLC ratio, negative immunofixation of serum and 24-h urine), very good partial remission (VGPR; dFLC < 40 mg/L in patients with measurable disease which is defined by dFLC before treatment > 50 mg/l; < 10 mg/L in low-burden amyloidosis patients with dFLC before treatment < 50 mg/L, but > 20 mg/L), partial remission (PR; FLC decrease > 50% compared with baseline), and no response (NR; FLC decrease < 50% compared with baseline) [10]. The treatment goal is a profound hematologic response, i.e., complete remission or at least VGPR [120]. In case of hematologic non-response or even progression, immediate switch to second-line treatment is necessary.

Organ response means improvement of organ function. In case of cardiac involvement, cardiac response is defined as a reduction of NT-proBNP by at least 30% and at least 300 ng/L from baseline (if NT-proBNP was ≥ 650 ng/L at baseline) or improvement of NYHA class ≥ 2 classes with baseline NYHA class III–IV [10]. Renal response means at least a 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of renal progression defined as a > 25% decrease in eGFR [10]. Hepatic organ response requires 50% decrease in abnormal alkaline phosphatase value or at least 2-cm decrease in liver size radiographically. Well-defined response criteria for other organ involvement are still missing.

Muchtar et al. suggested grading the depth of cardiac, renal and hepatic organ response in analogy to hematologic response considering NT-proBNP, proteinuria, and alkaline phosphatase (AP) as markers for cardiac, renal, and hepatic involvement, respectively [119]. Complete response is thus defined by nadir NT-proBNP ≤ 400 pg/mL, nadir proteinuria ≤ 200 mg per 24 h, and nadir AP ≤ two times lower limit of normal. Very good partial organ response means > 60% reduction of markers from baseline level without fulfilling criteria of complete response; partial response is defined by 31–60% reduction of markers from baseline level and no response by ≤ 30% reduction of markers from baseline.

Hematologic and organ response, especially cardiac response, can be often observed simultaneously [21], but sometimes the hematologic response antedates organ response by months [119]. Importantly, hematologic response is a strong predictor of organ response [121] and may be used for decision-making. Both, hematologic and organ response predict survival [122].

Progression/Relapse: Progression (increase of disease activity under treatment or during follow-up) and relapse (recurrence of disease activity during follow-up after achieving remission) may occur both dimensions: Hematologic progression is defined from CR as any detectable monoclonal protein or abnormal FLC ratio (light chain must double) and from PR, 50% increase in serum M protein to > 0.5 g/dl, or 50% increase in urine M protein to > 200 mg/day (a visible peak must be present); beyond, a FLC increase of 50% to > 100 mg/L. [10] However, hematologic progression criteria have not been validated. Progression of cardiac affection in AL amyloidosis can be established by NT-proBNP increase (> 30% and absolute > 300 ng/l), or troponin T increase (≥ 33%), or ejection fraction decrease (≥ 10%) [10, 119]. Renal progression is defined by 50% increase (at least 1 g/day) of 24-h urinary protein to > 1 g/day or 25% worsening of serum creatinine or creatinine clearance, whereas 50% increase of AP from nadir value represents hepatic progression [119]. Cardiac and renal progressions predict poorer patient and kidney survival, respectively.

Disease progression under ongoing treatment requires immediate switch to next treatment line. Although there are no clear consensus criteria, treatment of recurrent disease should be initiated as soon as possible, even in case of hematological

Table 4 Response criteria in AL amyloidosis

Quality of response	Hematologic response [10, 118]	Organ response [118, 119]		
		Cardiac	Renal	Hepatic
Complete response	Negative serum and urine immunofixation and normal FLC ratio	Nadir NT-proBNP ≤ 400 pg/mL	Nadir proteinuria ≤ 200 mg/24 h	Nadir AP ≤ X2 lower limit of normal
Very good partial response	dFLC < 40 mg/L (low-burden disease*: < 10 mg/L)	> 60% reduction in NT-proBNP from baseline level to a nadir > 400 pg/mL	> 60% reduction in proteinuria from baseline level to a nadir level > 200 mg/24 h	> 60% reduction from baseline AP level to a nadir above X2 lower limit of normal
Partial response	FLC decrease > 50% compared with baseline	31–60% reduction in NT-proBNP from baseline level	31–60% reduction in proteinuria from baseline level	31–60% reduction from baseline AP
No response	All patients not meeting criteria for other response qualities	≤ 30% reduction in NT-proBNP from baseline level	≤ 30% reduction in proteinuria from baseline level	≤ 30% reduction from baseline AP
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double).From PR, 50% increase in serum M protein to > 0.5 g/dl or 50% increase in urine M protein to > 200 mg/day (a visible peak must be present).Free light chain increase of 50% to > 100 mg/l	Increase in NT-proBNP (>30% and > 300 ng/l) or increase in cardiac troponin (≥ 33% increase) or decrease in ejection fraction (≥ 10%)	50% increase (at least 1 g/day) of 24-h urine protein to > 1 g/d or 25% worsening of serum creatinine or creatinine clearance	50% increase of alkaline phosphatase above the lowest value

*Low-burden disease is defined by dFLC < 50 mg/L and dFLC > 20 mg/L before treatment initiation

Response criteria are validated for assessment of hematologic response 3 months after treatment initiation. Cardiac response assessment has to consider potential alterations of natriuretic peptides by impairment of renal function as well as immunomodulatory drugs.

progression in absence of signs of organ progression in affected organs [23, 123]. Treatment strategies in this situation include iteration of first-line treatment in case of previously good response. Alternative options include immunomodulatory drugs as lenalidomide [124] or pomalidomide [125], or new generation proteasome inhibitors as ixazomib [126]. Daratumumab may be considered because of quick and high percentage of deep remissions such as CR and VGPR [84]. Further innovative treatment approaches in relapsed patients are currently under development. However, as early mortality in cases with advanced cardiac involvement remains high despite new and effective treatment options, early diagnosis is crucial.

ATTR Amyloidosis

Liver Transplantation Liver transplantation alone or combined with heart transplantation has been the only available treatment option in ATTRv amyloidosis for many years. The 20-year long-term survival is about 55% among ATTRv amyloidosis patients [127]. Benefits are more significant for patients with higher body mass index, age < 50 years, short disease duration, and presence of Val30Met (p.Val50Met) mutation [127, 128]. The metabolic liver function of patients with ATTRv amyloidosis is not altered. Therefore, explanted livers of ATTRv amyloidosis patients are used for patients requiring liver transplantation because of other reasons. This so-called domino liver transplantation concept has resulted in cases of iatrogenic ATTR amyloidosis as liver transplant recipients have developed symptomatic amyloidosis manifestations with a latency of years [129–131]. Beyond the invasiveness of this treatment, liver transplanted ATTRv patients are also at risk to develop progression of pre-existing disease manifestations due to deposition of wild-type TTR [128, 130, 132]. There is now general agreement that liver transplantation should be offered to well-selected patients with very limited organ involvement. Liver transplantation is no option for patients with ATTRwt amyloidosis as the liver of ATTRwt amyloidosis patients produces the unaltered natural transthyretin protein. In these patients, isolated cardiac transplant remains a valuable therapeutic strategy, although largely limited by the advanced age of these patients. Transplantation strategies will continue losing importance thanks to upcoming new, more effective and non-invasive treatment options.

TTR Stabilizer Tafamidis is approved for ATTRv patients with stage 1 neurological involvement in Europe as well as in Israel, several South American countries, and Japan. Additionally, there is an approval for tafamidis for patients with cardiac ATTR amyloidosis in USA and Japan. The phase III ATTR-ACT trial demonstrated improved survival and quality of life, and reduced hospitalization frequency in patients with cardiac manifestation of ATTRv and ATTRwt

amyloidosis treated with this agent [133••]. In contrast to NYHA class I and II patients, benefit regarding hospitalization frequency was not evident in NYHA class III patients [133••]. TTR stabilizing properties are also proven for diflunisal [134], AG10 [135, 136], and tolcapone [137]. Diflunisal has shown efficacy in reducing neurological progression in a phase III trial [138]. AG10 is under clinical development in a phase III trial among patients with transthyretin cardiomyopathy (NCT03860935).

Gene Silencers Patisiran is a small interfering RNA (siRNA) molecule [139], whereas inotersen is an antisense oligonucleotide [140]. Both drugs suppress the hepatic production of ATTRwt and ATTRv, and are approved for ATTRv amyloidosis with stage 1 and 2 neuronal involvement by EMA and FDA [141]. A post-hoc analysis of the phase III APOLLO study in a prespecified population of 126 patients with cardiac involvement randomized to patisiran or placebo showed benefits of patisiran regarding a composite endpoint of cardiac hospitalizations and all-cause mortality [142•]. Moreover, left ventricular (LV) wall thickness, global longitudinal strain, NT-proBNP, and adverse cardiac outcomes at month 18 implied stabilization or improvement of cardiac impairment in ATTRv amyloidosis on patisiran treatment [143]. Inotersen showed stabilization of cardiac involvement in a phase II study by reduction of LV wall thickness, LV mass, 6-min walking distance, and global systolic strain [140], but did not show significant findings in the subgroup with cardiac involvement of the multicentre phase III study [144].

Fibril Disruption and Degradation Doxycycline with tauroursodeoxycholic acid (TUDCA) induces fibril disruption in ATTR amyloidosis [145]. Small non-randomized studies suggested stabilization or decelerated progression in cardiac ATTR amyloidosis [146, 147]. A phase III trial in patients with ATTRwt and ATTRv amyloidosis evaluating the efficacy of this strategy on hard endpoints is ongoing in Italy, with results expected in 2020 (NCT03481972).

Currently, availability of these drugs varies among countries with resulting impact on treatment decisions. Further investigations are needed to conclusively evaluate efficacy, especially of gene silencers in cardiac ATTR amyloidosis, and to clarify the relative importance of each drug in the context of subtype, pattern of organ involvement and disease stage.

AA Amyloidosis

Complete and sustained suppression of inflammation is the main therapeutic goal in AA amyloidosis [55]. SAA levels lower than 10 mg/l should be achieved. Even short episodes of recurrent inflammation can cause worsening of organ function [55]. Treatment strategies focus on control of the underlying disease. In case of futility, anti-IL-1 and anti-IL-6 agents may be used [148, 149]. Organ transplantation can be evaluated in well-selected patients with satisfactory long-term control of inflammation [55].

ApoAI and ApoAII Amyloidosis

Up to now, there are no specific treatment options available, except cardiac transplantation.

Symptomatic and Supportive Treatment Options in Cardiac Amyloidosis

Diuretics constitute the backbone of HF treatment in cardiac amyloidosis. Repeat dose adjustments are required to reliably control dyspnea and congestion, especially in patients with advanced cardiac involvement and/or severe diastolic dysfunction. Evidence for a prognostic benefit of beta blockers and RAAS blockers is lacking. These substance classes are frequently poorly tolerated requiring dose reduction or discontinuation [150]. Calcium channel blockers should be avoided because of negative inotropic effects [151]. Digoxin may be used for frequency control in patients with atrial fibrillation [152], although earlier data suggested an interaction between this drug and amyloid fibrils with increased sensitivity [153–155].

It is likely albeit unproven that optimized care strategies will impact on prognosis in amyloidogenic cardiomyopathy. As such, structured implementation of specialized staff, e.g., HF nurses, might constitute a valuable adjunct. Remote monitoring strategies also hold promise. For example, HF management based on non-invasive monitoring of the pulmonary artery pressure using the CardioMEMS-HF™ system improved mortality and HF-related rehospitalization in patients with HFpEF [156, 157].

Anticoagulation for atrial fibrillation or because of intracardiac thrombi can be performed using warfarin or novel anticoagulants. As patients with cardiac amyloidosis, especially AL amyloidosis, are at risk to develop intracardiac thrombi regardless of rhythm, indication for anticoagulation should be individualized [158]. Despite the high incidence of sudden death, implantable cardioverter-defibrillators have not shown to improve survival rate in non-randomized studies [159, 160]. Symptomatic hypotension may require support stockings. In case of concomitant involvement of autonomous nervous system, midodrine or fludrocortisone may be used to stabilize blood pressure.

Conclusion

Cardiac amyloidosis is a very heterogeneous disease, but represents a relevant cause of HFpEF. If cardiac amyloidosis is suspected, care givers should be aware of this differential diagnosis and trigger goal-directed diagnostic investigations via an interdisciplinary approach. Diagnosis and treatment requires dedicated technology and expertise. Patients should thus be referred to specialized centers whenever possible. Upcoming treatment options render cardiac amyloidosis a rapidly evolving and rewarding area for integrated research and patient care.

Patients presenting with typical imaging findings or (early) warning signals of cardiac amyloidosis such as spontaneous resolution of known hypertension, repeated unexplained syncopes, biventricular/biatrial hypertrophy, apical sparing on echocardiography, unexplained elevation of cardiac biomarkers troponin or/and NT-proBNP, coincidence of monoclonal gammopathy with unexplained symptoms of HF or elevation of cardiac biomarkers should undergo further investigations. First step includes detection of a possible monoclonal component. Exclusion of monoclonal gammopathy makes diagnosis of AL amyloidosis unlikely. Therefore, these patients should undergo bisphosphonate scintigraphy, e.g., ^{99m}Tc-DPD, ^{99m}Tc-PYP, or ^{99m}Tc-HMDP; tracer uptake of grade 2 or 3 proves the diagnosis of non-AL amyloidosis. TTR and ApoAI genotyping should be performed.

In patients with evidence of a monoclonal component or uptake grade 0 or grade 1 in bisphosphonate scintigraphy, tissue biopsy is stringently required for detection of amyloid and subsequent typing by mass spectrometry, immunohistochemistry, or immune-electron microscopy. Less invasive options are abdominal fat aspirate or salivary gland biopsies (if abdominal fat aspirate was negative). Organ biopsies should be avoided if possible, but they rate high in patients remaining suspect of amyloidosis despite negative abdominal fat and salivary gland biopsy. If hereditary variants are suspected, genotyping should be performed.

Compliance with Ethical Standards

Conflict of Interest Dr. Ihne reports personal fees from Takeda, personal fees from Akcea, other from Janssen, personal fees from ONLUS, grants from IZKF Würzburg, grants from Comprehensive Heart Failure Center (CHFC), personal fees from Pfizer, and personal fees from Alnylam, outside the submitted work

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- • Of importance
- •• Of major importance

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