Advances in Diagnosis and Treatment of Cardiac and Renal Amyloidosis

Steven Law, MBBS, Marianna Fontana, PhD, Julian D. Gillmore, PhD*

KEYWORDS

• Amyloidosis • Amyloid • Cardiorenal syndrome • Heart failure • Transthyretin • Cardiomyopathy

KEY POINTS

- Amyloidosis diagnoses, in particular ATTR cardiomyopathy, are increasing annually.
- Cardiac MRI and bone scintigraphy assist in differentiating cardiac amyloidosis from other cardiac pathologies.
- ATTR cardiomyopathy can often be diagnosed without histology by validated nonbiopsy criteria.
- Ongoing phase III clinical trials of novel agents in ATTR cardiomyopathy, alongside the discovery of increasingly effective chemotherapies in AL amyloidosis, show great promise for the future treatment of systemic amyloidosis.
- In the absence of effective therapies targeting amyloid removal, early diagnosis before the development of advanced organ disease remains key in improving outcomes.

INTRODUCTION

The amyloidoses represent a spectrum of rare conditions ranging from slow-growing localized disease in a single organ to rapidly progressive life limiting multiorgan disease. Amyloid is an abnormal misfolded, insoluble protein deposit that aggregates in the extracellular space, disrupts cellular structure, and impairs organ function. Proteins may form amyloid *in vivo* when they are structurally abnormal (eg, mutated transthyretin in hereditary transthyretin [ATTR] amyloidosis), when they are structurally normal but present in high concentration (eg, serum amyloid A [SAA] protein in reactive systemic [AA] amyloidosis), or for unknown reasons in association with aging (wild-type ATTR amyloidosis).[1] There are more than 30 known amyloidogenic proteins in humans that form the basis for the classification of the different types of amyloidosis and determine the clinical phenotype, prognosis, and treatment. Diagnosis is usually by demonstration of amyloid deposits and identification of the causative amyloid fibril precursor protein histologically. However, recent diagnostic advances in cardiac MRI (CMR) and bone scintigraphy have enabled one particular type of amyloid cardiomyopathy, ATTR cardiomyopathy (ATTR-CM), to be diagnosed without recourse to histology in most affected patients.[2–4] Despite this, diagnostic delay remains common.[5,6] Patient survival in systemic amyloidosis is improving with increasingly effective chemotherapies in systemic light chain (AL) amyloidosis and novel therapies in ATTR amyloidosis.[7,8] Multiple phase III therapeutic trials are ongoing and show great promise for treatment of systemic amyloidosis in the future.

EPIDEMIOLOGY

The prevalence of systemic amyloidosis is increasing annually.[9,10] On review of 11,006 patients referred to the UK National Amyloidosis Center (NAC) between 1987 and 2019, referrals have increased sixfold, with systemic AL amyloidosis being the commonest diagnosis accounting

Division of Medicine (Royal Free Campus), National Amyloidosis Centre, Centre for Amyloidosis and Acute Phase Proteins, University College London, Rowland Hill Street, London NW3 2PF, UK
* Corresponding author.
E-mail address: j.gillmore@ucl.ac.uk

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for ~55% of the total.[11] The proportion of patients diagnosed with systemic AA amyloidosis declined from 13% to 3% of the total during the same period, whereas diagnoses of wild-type ATTR-CM (wtATTR-CM) increased dramatically.[11] The true prevalence of ATTR-CM remains unknown. It is noteworthy that autopsy studies have demonstrated ATTR amyloid deposits in the hearts of up to 25% of men older than 80 years, although the majority were not diagnosed in life with cardiomyopathy or symptoms of heart failure (HF).[12] It remains unclear to what extent ATTR-CM may have been missed or whether ATTR amyloid was of no clinical consequence in a substantial proportion of such individuals; what is clear, however, is that ATTR-CM is far more common than previously suspected, accounting for more than 10% of HF with preserved ejection fraction.[12,13]

AMYLOIDOSIS TYPES

The amyloid type is defined by the amyloid fibril precursor protein and determines the clinical phenotype, management, and prognosis (**Table 1**).

Systemic AL amyloidosis occurs as a result of production of abnormal amyloidogenic monoclonal light chains from an underlying clonal dyscrasia. The median age of diagnosis is 63 years, with 1.3% diagnosed at the age of less than 34 years.[14] Multiorgan involvement is common, with renal involvement present in 58% at diagnosis, cardiac involvement present in 71% at diagnosis, and cardiorenal involvement present in 38% at diagnosis.[14,15] Gastrointestinal, liver, soft-tissue, and both peripheral and autonomic nervous systems may also be affected. Clinical presentation is dependent on organ involvement, with proteinuria, renal impairment, and rapidly progressive HF commonest alongside nonspecific symptoms of weight loss, weakness, and fatigue. Patients can present via almost any medical specialty, and a high index of suspicion is key to early diagnosis before significant organ damage has occurred.

ATTR amyloidosis is due to amyloidogenic transthyretin (TTR) protein and is subdivided based on the *TTR* genotype into acquired wtATTR amyloidosis and hereditary variant ATTR (vATTR) amyloidosis, the latter being associated with pathogenic mutations in the *TTR* gene, the mutations of which are now more than 130. wtATTR amyloidosis commonly presents as a restrictive cardiomyopathy (ie, ATTR-CM), with a history of soft-tissue disease such as carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, or osteoarthritis, often predating diagnosis by many years. The median age at diagnosis of wtATTR-CM is ~79 years, and there is a strong male preponderance (94% in the UK cohort).[16] vATTR amyloidosis presents more heterogeneously, although it is most commonly dominated by cardiac failure, neuropathy, or both in combination. There is an association between clinical phenotype and the specific causative *TTR* mutation (**Table 2**).

Systemic AA amyloidosis usually presents with renal dysfunction and occurs as a complication of prolonged elevation of SAA protein concentration. The concentration of SAA, an acute phase reactant, is elevated in chronic inflammatory conditions such as chronic inflammatory arthritis (60%), chronic sepsis (15%), periodic fever syndromes (9%), and inflammatory bowel disease (5%).[17] Renal and splenic infiltration by amyloid are common at diagnosis, and cardiac amyloidosis is rare (<1%).[9] The increasing use of biologic therapies, allowing better control of several inflammatory conditions, has been associated with a reduction in incidence of systemic AA amyloidosis.

Rarer causes of renal amyloidosis include leukocyte chemotactic factor 2 (ALECT2) amyloidosis, hereditary fibrinogen Aα-chain (AFib) amyloidosis, hereditary lysozyme amyloidosis, hereditary apolipoprotein A-I (AApoAI) and apolipoprotein A-II (AApoAII) amyloidosis, and hereditary apolipoprotein C-II (AApoCII) and apolipoprotein C-III (AApoCIII) amyloidosis, which, with the exception of AApoAI and AApoCIII amyloidosis, rarely involve the heart.

CLINICAL PRESENTATION

Owing to the insidious, nonspecific, and diverse nature of symptoms, alongside its rarity, the diagnosis of amyloidosis is frequently delayed until advanced amyloidotic organ dysfunction has occurred.[5,6,18] It is crucial for specialties such as cardiology, nephrology, neurology, and gastroenterology to remain vigilant for amyloidosis red flags, which include the presence of plasma cell dyscrasia, carpal tunnel syndrome, neuropathy, multisystem disease, macroglossia, and periorbital bruising.

Cardiac amyloidosis commonly presents with HF or arrthymias, and a restrictive cardiomyopathy on echocardiography. In cardiac AL amyloidosis, HF symptoms progress rapidly over months, whereas in ATTR-CM, symptoms develop gradually over years, typically with less severe HF and lower N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentration for the degree of cardiac amyloid infiltration. Atrial fibrillation occurs in up to 70% of patients with ATTR-CM and

Table 1
Common causes of cardiac and renal amyloidosis

			Organ Involvement					
	Fibril Precursor Protein	**Underlying Pathology**	**Cardiac**	**Kidneys**	**Liver**	**Nerves**	**Additional Clinical Findings**	**Treatment**
AL	Monoclonal light chain	Plasma cell dyscrasia	70%	50%	16%	23%	Macroglossia, periorbital bruising, nail dystrophy	Chemotherapy and/or ASCT
wtATTR hATTR	Wild-type transthyretin Variant transthyretin	None Abnormal TTR gene	100% ~[a]	0% Rare	0%	0% ~[a]	Carpal tunnel syndrome, spinal stenosis, aortic stenosis	TTR stabilizer or gene silencing therapy
AA[17]	Serum amyloid A	Chronic inflammation or infection	1%	97%	23%	0%	Features of underlying inflammatory disorder	Control of inflammation
ALECT2[76]	LECT2	Unknown	0%	92%	46%	0%	None	Supportive
AFib[77]	Variant fibrinogen	Abnormal fibrinogen gene	0%	100%	3%	1%	Cardiovascular disease	Supportive
AApoA1	Variant ApoA1	Abnormal ApoA1 gene	-[a]	-[a]	-[a]	-[a]	Renal, liver, cardiac involvement common	Supportive

[a] Organ involvement depending on the specific gene mutation.

Table 2
Clinical manifestations by common TTR mutations

TTR Mutation	Epidemiology	Age of Onset (y)	Features at Presentation
Val122Ile	Almost isolated to patients of African origin (4% of African Americans)	77[52]	Heart failure and cardiomyopathy with neuropathy in 10%
T60A	Commonly patients of Irish heritage (1% of County Donegal)	Mid-60's	80% peripheral neuropathy, 95% autonomic neuropathy 53% heart failure symptoms, 100% cardiac uptake on DPD scintigraphy[78]
Val30Met	Foci in Portugal, Japan, and Sweden, among others[a]	30–60's[a]	Commonly peripheral and autonomic neuropathy, with variable cardiac conduction disease and cardiomyopathy[a,23]

Abbreviation: DPD, 3,3-diphosphono-1,2-propanedicarboxylic acid.
[a] The Val30Met TTR mutation is present in several geographic foci, the best studied being in Portugal, Japan, and Sweden. Age of onset and clinical phenotype vary significantly between foci.

26% of those with cardiac AL amyloidosis and is poorly tolerated. Intracardiac thrombus and thromboembolic stroke are common regardless of the CHA_2DS_2-VASc score.[19] Conduction disease requiring pacemaker insertion is particularly common in ATTR-CM.[19] Hypotension develops as the disease progresses, often occurring disproportionately following the introduction or escalation of angiotensin convertase enzyme inhibition or beta-blockade.

Renal amyloidosis presents with a combination of reduction in glomerular filtration rate (GFR) and proteinuria, depending on the location of amyloid deposits within the kidney. Systemic AL and AA amyloidosis commonly present with nephrotic range proteinuria associated with extensive glomerular amyloid deposition. ALECT2 amyloidosis presents with minimal or no proteinuria, reflecting interstitial and vascular amyloid deposition. Significant proteinuria is rare in ATTR-CM despite frequent loss of GFR, the latter thought to be largely due to poor renal perfusion from poor cardiac output, hypotension, and diuretic therapy, and its presence in the context of cardiac amyloidosis usually indicates systemic AL amyloidosis.

Peripheral and autonomic neuropathy commonly occur in AL, hereditary ATTR, and hereditary AApoAI amyloidosis. Peripheral neuropathy presents as painful paresthesia with small fiber involvement and may progress to numbness and weakness as large fibers become affected.[20] It is important to distinguish amyloid neuropathy owing to direct nerve infiltration from compression neuropathy (ie, carpal tunnel syndrome), for which decompression surgery may be indicated. Autonomic dysfunction may present with erectile dysfunction, postural hypotension, diarrhea, constipation, nausea, early satiety, and weight loss. The identification of neuropathy is important because its presence affects treatment options. In hereditary ATTR amyloidosis, gene silencing therapy is only licensed in the presence of neuropathy, whereas in systemic AL amyloidosis, certain potentially neurotoxic chemotherapeutic agents may be avoided.

Soft-tissue involvement is common in AL amyloidosis, with macroglossia and periorbital bruising being pathognomonic features of the disease. Macroglossia presents as painful dry tongue, increased tongue biting, and dental indentation. Carpal tunnel syndrome is strongly associated with both systemic AL and ATTR amyloidosis. A history of carpal tunnel syndrome is present in ~50% patients with wtATTR-CM, preceding diagnosis of cardiomyopathy by a median of ~8 years.[21]

DIAGNOSIS

The diagnostic process begins with clinical suspicion, is supported by noninvasive investigation of the affected organ, and is usually confirmed by histology. ATTR-CM is the exception, as histology is not always required for diagnosis.

Cardiac Investigations

Electrocardiographic changes in cardiac amyloidosis may include low voltages in the limb leads, a pseudoinfarction pattern, atrioventricular blocks, and atrial arrhythmias, among others, although these are of low diagnostic sensitivity.[22]

Echocardiographic findings in cardiac amyloidosis include biventricular wall thickening, reduced ventricular chamber volumes, biatrial enlargement, pericardial effusion, thickened valves, granular speckled myocardial appearance, and diastolic dysfunction.[23,24] Left ventricular ejection fraction is usually preserved although longitudinal myocardial function is impaired early in the disease and may help to raise clinical suspicion and differentiate cardiac amyloidosis from other hypertrophic cardiac phenotypes.[25,26] An interventricular wall thickness of more than 12 mm in the absence of an alternative cause is commonly used to define cardiac amyloidosis in the medical literature, although CMR, which is significantly more sensitive and specific than echocardiography, has shown that there may be significant cardiac amyloidosis, particularly the AL type, despite lesser degrees of wall thickening.[27] Given the fact that echocardiographic changes in patients with end-stage renal disease (ESRD) may resemble those in patients with cardiac amyloidosis, the specificity of echocardiography for cardiac amyloidosis is likely reduced further in the presence of ESRD.

CMR is the gold standard imaging modality for cardiac amyloidosis, providing assessment of structure, function, and myocardial tissue characterization.[28] Amyloid deposition expands the myocardial extracellular space, resulting in diffuse late gadolinium enhancement (LGE) contrasting other causes of left ventricular hypertrophy.[29] LGE alone has a sensitivity and specificity of 85% and 92%, respectively, for cardiac amyloidosis; this improves with the addition of T1 mapping and extracellular volume (ECV) measurements.[30,31] Transition from subendocardial to transmural LGE, increasing ECV, and increasing T1 values all predict mortality in cardiac amyloidosis.[32,33] Serial CMR offers the potential to determine cardiac amyloid burden and monitor treatment response and has recently demonstrated regression of both cardiac AL and cardiac ATTR amyloid following treatment.[34,35] One potential concern of CMR is related to the risk of nephrogenic systemic fibrosis (NSF) in patients with advanced chronic kidney disease (CKD); however, a review of 4931 patients with chronic kidney disease stage IV or V, who received group II gadolinium-based contrast agents, demonstrated a pooled NSF incidence of 0% (95% confidence interval: 0–0.07).[36] Alternatively, nongadolinium-enhanced CMR with T1 mapping offers a sensitive and accurate assessment of cardiac amyloidosis.[31]

Technetium-labeled bisphosphates (3,3-diphosphono-1,2-propanedicarboxylic acid, pyrophosphate, and hydroxymethylene diphosphonate) localize to ATTR amyloid deposits in the myocardium, producing cardiac uptake on bone scintigraphy.[3,37] Bone scintigraphy has a sensitivity of more than 99% and a specificity of 68% in ATTR-CM, and uptake can occur before the development of clinical symptoms or serum biomarker, echocardiographic, or CMR abnormalities.[4] The poor specificity of cardiac uptake for ATTR-CM reflects cardiac uptake in other forms of cardiac amyloidosis, particularly AL amyloidosis, in which up to 25% of patients have Perugini grade $\geq$2 (**Fig. 1**) cardiac uptake,[38] but also in cardiac AApoAI amyloidosis, which is associated with low-grade (Perugini grade 1) uptake. The diagnosis of ATTR-CM cannot therefore be confirmed by bone scintigraphy alone.[4]

Electrocardiography, echocardiography, CMR, and bone scintigraphy findings differ between cardiac AL, wtATTR, and vATTR amyloidosis.[39–41] However, none of these tests offer sufficient sensitivity or specificity to confirm amyloid type alone, and other investigations are imperative to establish the correct amyloid type so that appropriate therapy can be administered.

Renal Investigations

Renal amyloidosis presents with variable proteinuria and renal impairment. Investigations should include analysis of serum creatinine levels and quantification of proteinuria by 24-hour urinary collection, urinary protein/creatinine ratio, or urinary albumin/creatinine ratio. Renal dysfunction and proteinuria in the presence of a monoclonal protein has a wide differential diagnosis, and renal biopsy is crucial to confirm amyloid and/or exclude the ever-increasing list of alternative pathologic lesions.

Hematological Workup

All patients with a suspicion of amyloidosis require urgent hematological investigations to identify patients likely to have systemic AL amyloidosis who may require urgent treatment, especially patients with cardiac amyloidosis. Owing to the often subtle nature of the clonal dyscrasia underlying AL amyloidosis, a combination of serum and urine immunofixation electrophoresis and the serum free light-chain assay is essential in order to achieve a sensitivity of more than 98% in detecting clonal dyscrasia.[42,43] In health, serum free kappa light chains are produced at twice the rate of lambda light chains, and both are removed by the kidneys. In renal impairment, serum free light-chain concentrations are raised, with kappa light chains increasing more than lambda light

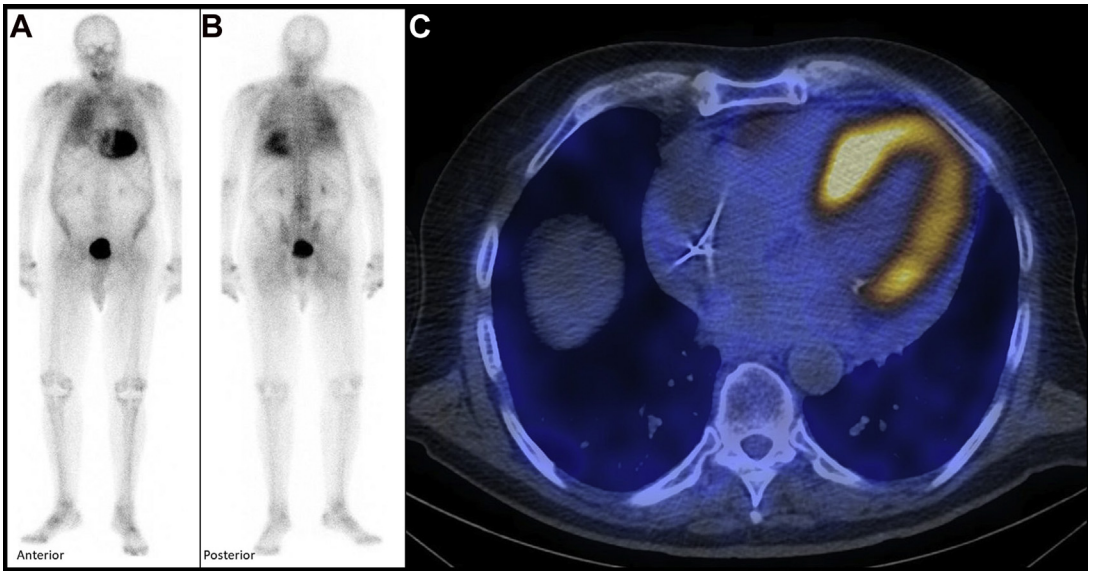

Fig. 1. 99mTc-DPD scintigraphy: 83-year-old man with wtATTR-CM showing Perugini grade 2 cardiac uptake on whole-body anterior (*A*) and posterior (*B*) scintigraphy and left ventricular myocardial uptake (*C*) on single-photon emission computed tomography. DPD, 3,3-diphosphono-1,2-propanedicarboxylic acid.

chains, thus increasing the expected serum kappa/lambda ratio.[44]

Histology

Histologic confirmation of amyloid deposits, with subsequent amyloid fibril typing, remains the gold standard investigation for the diagnosis of amyloidosis. Amyloid deposition is confirmed by the finding of apple green birefringence under cross-polarized light following Congo red staining (**Fig. 2**). Electron microscopy displays randomly orientated nonbranching fibrils of 8- to 10-nm diameter, which, in early disease, may occasionally be detected in the absence of positive Congo red histology.[45] Amyloid fibril typing by either immunohistochemistry (IHC) or laser dissection mass spectrometry (LDMS) is key. IHC is accessible, but sensitivity varies with the amyloid type, being particularly poor in AL amyloidosis.[46] LDMS is now the gold standard method for amyloid fibril typing, identifying the amyloid fibril protein in more than 85% of cases.[47] Histology can be obtained through biopsy of an affected organ, or through screening biopsies (eg, fat, salivary gland, or gastrointestinal biopsy), when obtaining an affected organ biopsy is deemed high risk or the clinical picture is highly suggestive of systemic amyloidosis. The sensitivity of screening biopsies is limited, with fat aspiration having a sensitivity of 73% in AL amyloidosis, but only 27% in ATTR amyloidosis.[48]

Nonbiopsy Diagnosis of Cardiac ATTR Amyloidosis

ATTR-CM can be diagnosed without histology as per validated nonbiopsy diagnostic criteria.[4] A diagnosis is confirmed when all of the following criteria are met:[4]

1. Symptoms and echocardiography or CMR findings suggestive of cardiac amyloidosis
2. Perugini grade $\geq$2 cardiac uptake on bone scintigraphy
3. No serum or urine monoclonal protein by immunofixation electrophoresis
4. Normal serum free light-chain ratio (adjusted for GFR)

TTR genotyping is then required to distinguish between wtATTR and vATTR amyloidosis. If any of the aforementioned criteria are not met, histology is required to confirm the presence and type of amyloid.

Genetic Testing

The commonest hereditary causes of cardiac amyloidosis are due to mutations in the *TTR* gene. *TTR* mutations are inherited in an autosomal dominant manner with incomplete penetrance, and the specific mutation tends to dictate the clinical phenotype (see **Table 2**). Rare hereditary amyloidoses such as hereditary AApoAI and AFib amyloidosis should be considered in the presence of a family history, in the presence of an atypical

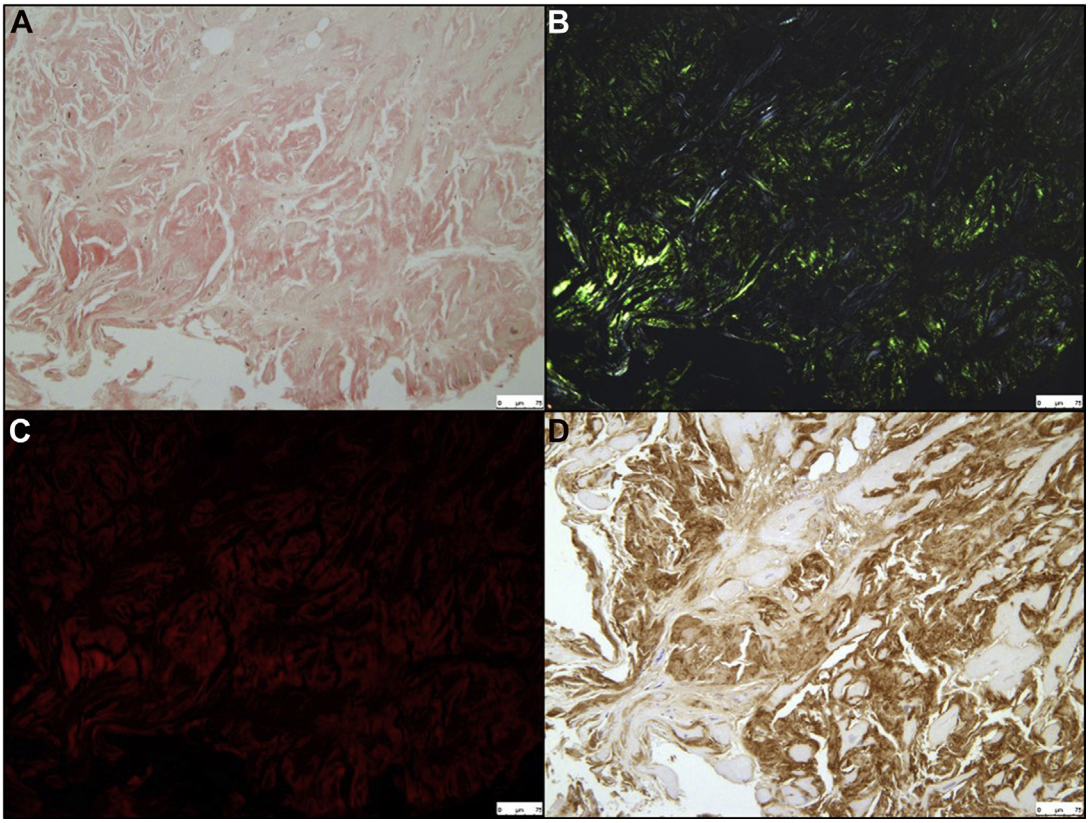

Fig. 2. Endomyocardial histology demonstrating congophilia within the myocytes following Congo red staining (*A*), apple green birefringence when viewed under polarized light (*B*), congophilia under fluorescent light (*C*), and positive immunohistochemistry with transthyretin antibody (*D*).

clinical presentation, in the absence of plasma cell dyscrasia or inflammatory condition, and in the case of certain histologic morphologies (eg, isolated and extensive glomerular amyloid in AFib amyloidosis). A suspicion of hereditary amyloidosis should be further investigated by IHC or, preferably, by LDMS and sequencing of the known hereditary amyloidosis genes.

ASSESSING ORGAN INVOLVEMENT

Given the frequent multisystem nature of systemic amyloidosis, when amyloid is identified in one tissue, it is important to assess for other organ involvement. In addition to a thorough clinical history and examination, screening investigations include:

- Lying and standing blood pressures
- Urine dipstick for proteinuria
- Serum creatinine with estimated GFR (eGFR)
- Liver function tests including alkaline phosphatase and gamma-glutamyl transferase.
- Serum NT-proBNP and troponin levels
- Electrocardiography
- Echocardiography and consideration of CMR

Where available, radiolabeled serum amyloid P component scintigraphy identifies amyloid deposits in the liver, spleen, kidneys, adrenal glands, and bones and can monitor response to treatment; the technique is unable to show amyloid deposits in the heart, nerves, or gastrointestinal tract (Fig. 3).[49]

STAGING AND PROGNOSIS

Biomarker-based staging systems allow stratification of patients into prognostic groups in both cardiac AL and ATTR amyloidosis. The revised Mayo classification stratifies patients with AL amyloidosis into four stages based on cardiac troponin T concentration, NT-proBNP concentration, and the difference between the involved and uninvolved serum free light-chain concentration, producing four stages with median survivals of 94, 40, 14, and 6 months, respectively.[50] In addition, a diagnostic NT-proBNP concentration of more than 8500 ng/L and systolic blood pressure less than 100 mm Hg identify an especially poor

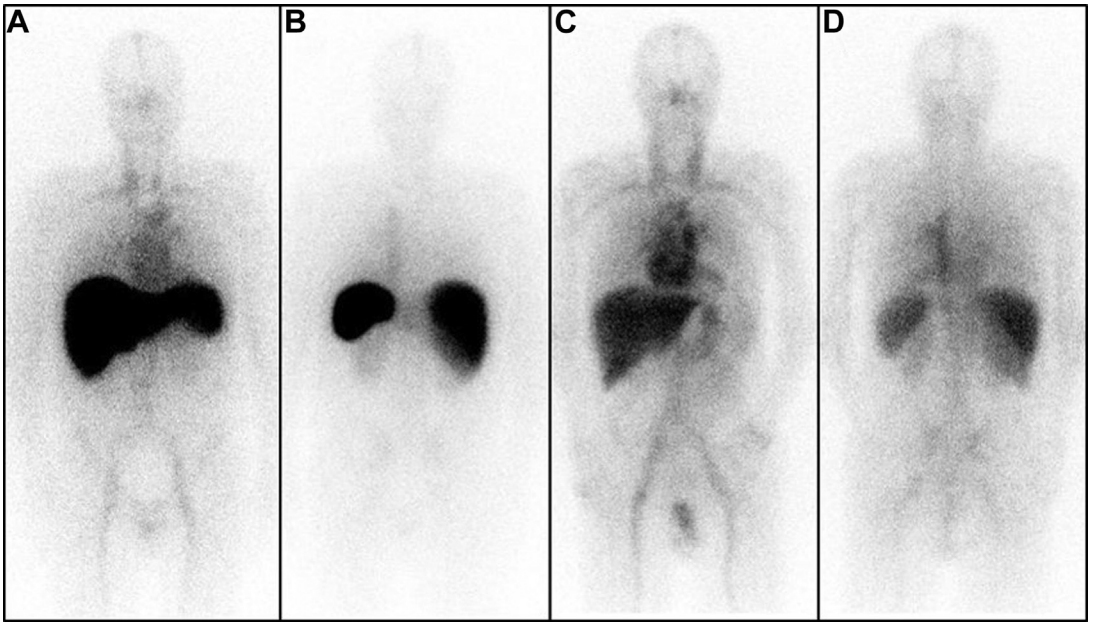

Fig. 3. Whole-body anterior (*A*, *C*) and posterior (*B*, *D*) scintigraphy following injection of ^{123}I-labeled serum amyloid P component (SAP). (*A*, *B*) 72-year-old man with multiple myeloma and cardiac failure showing a moderate amyloid load in the liver, spleen, and kidneys. (*C*, *D*) 68-year-old man with chronic inflammation showing no visceral amyloid deposits; uptakes in the visceral organs match the myocardial blood pool.

prognostic group.[51] Cardiorenal involvement in systemic AL amyloidosis is associated with a median survival of 18.5 months.[15] At diagnosis, NT-proBNP levels higher than 8500 ng/L and eGFR lower than 30 mL/min/m^2 predict mortality and dialysis requirement, whereas reductions in NT-proBNP levels and improvements in eGFR following treatment predict ongoing survival.[15] In cardiac ATTR amyloidosis, patients can be stratified into three prognostic (NAC ATTR) disease stages at diagnosis: stage I, NT-proBNP $\leq$3000 ng/L and eGFR $\geq$45 mL/min/1.73 m^2; stage III, NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2; and the remainder being stage II. The median survival is 69, 47, and 24 months for stage I, II, and III, respectively; the NAC ATTR staging system also provides prognostic information during follow-up.[52,53] Of note, the effects of disease-modifying therapy on change in the disease stage during follow-up have not been studied in ATTR-CM.

TREATMENT

Disease-modifying treatment is dependent on the amyloid type. The universal aim is to reduce the concentration of the fibril precursor protein as rapidly, completely, and durably as possible. This prevents ongoing amyloid deposition and organ damage, but does not lead to rapid reversal of amyloid deposition or rapid improvement of amyloidotic organ dysfunction. If fibril precursor protein suppression is maintained, gradual amyloid regression and improvement in organ function can occur over the course of months to years.[54] Unfortunately, early mortality remains high in patients with advanced cardiac amyloidosis at diagnosis.[11,51] Novel treatments targeting amyloid disruption and removal are under investigation, but are unlikely to be imminently available for use in clinical practice.

Systemic AL Amyloidosis

Treatment of systemic AL amyloidosis is targeted at the underlying plasma cell dyscrasia, reducing the concentration of amyloidogenic monoclonal immunoglobulin light chains as rapidly and durably as possible. Treatment includes consideration of high-dose melphalan with autologous stem cell transplantation (HDM-ASCT) in eligible patients, and or combination chemotherapy.[55] HDM-ASCT may be considered later in patients' disease course if they improve following initial chemotherapy.[56] Combination chemotherapy is directed at the underlying hematological disorder with frequent use of first-line bortezomib regimens in plasma cell disorders and lymphoma regimens in lymphproliferative disorders. Throughout and following treatment, hematologic

response is assessed and monitored by measuring the change in amyloidogenic serum free light-chain concentration. Amyloidotic organ response is assessed by change in surrogate markers of organ function such as NT-proBNP in cardiac amyloidosis and proteinuria and eGFR in renal amyloidosis. These biomarkers are predictive of outcomes and should be serially monitored throughout the disease course along with serum free light chains; hematologic relapse accompanied by worsening amyloidotic organ function typically requires further treatment.[15,27,57,58] Patient outcomes have improved dramatically since the introduction of proteasome inhibitors such as bortezomib, with multiple other highly effective new therapies such as daratumumab, ixazomib, and venetoclax, offering an ever-greater array of treatment options in systemic AL amyloidosis.[14,59] Retrospective studies suggest that doxycycline may reduce early mortality in patients with cardiac AL amyloidosis, and this is the subject of a prospective ongoing study.[60,61] Advanced cardiac AL amyloidosis is associated with a high risk of sudden cardiac death, with both electromechanical dissociation and ventricular arrhythmias demonstrated.[62] Prophylactic antiarrhythmic therapy with amiodarone and cardiac monitoring during initial bortezomib dosing for Mayo stage $\geq$III patients is used by some clinicians, although evidence of clinical benefit is lacking. Prophylactic implantation of cardiac defibrillators has not been found to improve survival.[62] Supportive treatment of cardiorenal amyloidosis includes loop diuretics and aldosterone antagonists to maintain euvolemia as serum potassium and blood pressure allow. In the presence of significant cardiac amyloidosis, hypertension is rare and angiotensin blockade may be poorly tolerated owing to symptomatic hypotension. Renal transplantation in selected patients with systemic AL amyloidosis is associated with low rates of allograft failure, and survival rates are comparable with patients with diabetic kidney disease. Hematologic response and interventricular wall thickness on echocardiography predict post-transplantation patient survival, although the vast majority of patients with cardiorenal amyloidosis are considered to be of too high risk for transplantation.[63]

Cardiac ATTR Amyloidosis

In ATTR amyloidosis, there are two key approaches to disease-modifying therapy: stabilizing the TTR tetramer and reduction of TTR production with gene silencing therapies. TTR becomes amyloidogenic when the normal tetramer dissociates or is selectively cleaved into monomers and oligomers.[64] Tafamidis, a TTR stabilizer, binds to the TTR tetramer, inhibiting dissociation *in vitro*, and in a phase III placebo-controlled trial of patients with ATTR-CM, namely, Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy (ATTR-ACT), tafamidis was associated with a reduction in all-cause mortality and cardiovascular-related hospitalizations and a slowing of decline in 6-minute walk test distance and quality of life compared with placebo; it also slows progression of neuropathy in vATTR amyloidosis.[65] Subgroup analysis in ATTR-ACT highlighted patients with New York Heart Association class $\leq$II HF as benefiting most from tafamidis, emphasizing the importance of early diagnosis. The nonsteroidal anti-inflammatory drug (NSAID), diflunisal, also stabilizes TTR *in vitro* and slows the progression of neuropathy in vATTR amyloidosis, although evidence of benefit in ATTR-CM is limited, and the inherent fluid retentive and nephrotoxic properties associated with NSAIDs are unattractive in this cohort.[66–68] A phase III randomized placebo-controlled trial of acoramidis, another small-molecule TTR stabilizer, is ongoing after phase II trials demonstrated safety and near-complete *in vitro* stabilization of the TTR tetramer in both wtATTR and vATTR amyloidosis (**Table 3**).[69]

Patisiran, a ribonucleic acid interference agent, and inotersen, an antisense oligonucleotide inhibitor, reduce hepatic production of TTR, achieving a median TTR reduction of 81% and 79%, respectively.[70] Both agents were shown in phase III trials to stabilize or improve neuropathic, functional, and quality of life scores in vATTR amyloidosis with neuropathy.[70,71] Subgroup analysis of patients with vATTR-CM in the patisiran phase III trial (APOLLO) showed improvements in NT-proBNP levels, and post hoc analysis of this cohort showed a reduction in mortality and cardiovascular-related hospitalizations among those receiving patisiran compared with placebo.[72] A recent small series of patients with vATTR-CM treated with patisiran and diflunisal showed CMR evidence of cardiac amyloid regression.[35,72,73] Several such therapies are currently being specifically evaluated in ATTR-CM within phase III clinical trials, which is summarized in **Table 3**.

Historically, liver transplantation was the only disease-modifying treatment for vATTR amyloidosis, replacing production of variant amyloidogenic TTR with structurally normal TTR. Liver transplantation improves survival in patients with transthyretin V30M amyloid polyneuropathy (V30M-associated vATTR-PN), particularly when performed early in the disease course, but caution is advised in advanced disease or when significant pre-existing vATTR-CM is present.[74,75] The role of

Table 3
Ongoing clinical trials in ATTR-CM

	Trial	Phase	Mechanism	Administration	Primary Outcome Measures
Acoramidis	ATTRibute-CM, NCT03860935	III	TTR stabilizer	Oral, twice daily	Change in 6MWT, mortality
Patisiran	APOLLO-B, NCT03997383	III	RNA interference	Intravenous infusion 3-weekly	Change in 6MWT
Inotersen	NCT03702829, open-label extension	II	Antisense oligonucleotide inhibitor	Subcutaneous injection weekly	Change in longitudinal left ventricular strain
Vutrisiran	HELIOS-B, NCT04153149	III	RNA interference	Subcutaneous injection 3-monthly	Composite of mortality and cardiovascular events
AKCEA-TTR LRx	CARDIO-TTRansform, NCT04136171	III	Ligand-conjugated antisense agent	Subcutaneous injection 4-weekly	Composite of cardiovascular mortality and events, change in 6MWT
Doxycycline and tauroursodeoxycholic acid[a]	NCT01171859	III	Amyloid fibril disruption	Oral, twice and thrice daily	Combination of change in modified BMI, NIS-LL, and NT-proBNP

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; NIS-LL, neuropathic impairment score of the lower limbs.
[a] Only recruiting patients with wATTR-CM or vATTM-CM due to LLe68Leu or Val122Ile TTR mutations.

liver transplantation in the era of gene silencers has diminished and remains to be determined.

Other Types of Amyloidosis

In systemic AA amyloidosis, identification and treatment of the underlying inflammatory condition is essential, and response to treatment can be assessed by serial measurements of SAA protein concentration accompanied by renal biomarkers; specific treatments are beyond the scope of this review.[17]

There are no proven disease-modifying treatments for ALECT2, AFib, AApoAI, AApoAII, AApoCII, or AApoCIII amyloidosis, and treatment is supportive.

SUMMARY

Diagnoses of amyloidosis are increasing on an annual basis, and advances in bone scintigraphy and CMR accompanied by development of nonbiopsy diagnostic criteria and greater disease awareness have specifically led to a huge increase in ATTR-CM diagnoses worldwide. Before the development of tafamidis, no disease-modifying therapies were available for ATTR-CM. However, tafamidis use is increasing, and there are several phase III clinical trials of potentially even more effective novel agents in progress that promise to transform the treatment landscape for patients with ATTR-CM. In systemic AL amyloidosis, development of new, more effective chemotherapeutic agents continues to improve patient outcomes. Accelerating the removal of existing amyloid deposits to accompany existing therapies to slow their ongoing accumulation is the holy grail. In the meantime, however, early diagnosis is undoubtedly the key in improving patient outcomes.

CLINICS CARE POINTS

- Diagnoses of amyloidosis, particularly ATTR-CM, are increasing annually.
- Systemic AL and ATTR amyloidosis are the commonest forms of cardiac amyloidosis; determination of the amyloid type is key to identify patients with AL amyloidosis who require urgent chemotherapy.
- Systemic AL amyloidosis is a cause of cardiorenal syndrome.
- Renal amyloidosis presents with varying degrees of proteinuria and renal impairment.
- Cardiac MRI is sensitive and specific for cardiac amyloidosis, assisting differentiation from other cardiac pathologies.
- The risk of nephrogenic systemic fibrosis is low with the modern group II gadolinium-based contrast agents in ESRD.
- Supportive management of systemic amyloidosis with cardiorenal involvement is diuretic based; angiotensin receptor blockers may be poorly tolerated owing to hypotension.
- Cardiac uptake on bone scintigraphy is highly sensitive for ATTR amyloid, but specificity is poor as cardiac uptake is also seen in other amyloid types.
- The gold standard investigation in amyloidosis is histologic confirmation of amyloid deposits and laser dissection mass spectrometry to identify the amyloid fibril type.
- ATTR-CM can be diagnosed without histology based 'on validated' nonbiopsy criteria.
- Biomarker based staging systems allow prognostication at diagnosis in both cardiac AL and ATTR amyloidosis.
- Treatment of systemic AL amyloidosis involves autologous stem cell transplantation in eligible patients and or combined chemotherapy.
- Tafamidis has been shown to improve survival and reduce cardiovascular-related hospitalizations in ATTR-CM.
- Patisiran and inotersen were shown to stabilize or improve neuropathic, quality of life, and functional scores in vATTR amyloidosis with neuropathy.
- Several phase III therapeutic clinical trials are ongoing investigating novel RNA-targeted therapies for ATTR-CM.
- Early diagnosis before the development of advanced organ disease remains key in improving outcomes in amyloidosis.

DISCLOSURE

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