Myocardial amyloidosis – the exemplar interstitial disease

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Abstract:
Cardiac involvement drives prognosis and treatment choices in cardiac amyloidosis. Echocardiography is the first-line examination for patients presenting with heart failure, and is the imaging modality that most often raises the suspicion of cardiac amyloidosis. Echocardiography can provide an assessment of the likelihood of cardiac amyloid infiltration versus other hypertrophic phenocopies and can assess the severity of cardiac involvement. Visualizing myocardial amyloid infiltration is challenging and, until recently, was restricted to the domain of the pathologist. Two tests are transforming this; cardiovascular magnetic resonance (CMR) and bone scintigraphy. After the administration of contrast, CMR is highly sensitive and specific for the two main types of ventricular myocardial amyloidosis, light chain (AL) and transthyretin (ATTR) amyloidosis. CMR structural and functional assessment combined with tissue characterization can redefine cardiac involvement by tracking different disease processes, ranging from amyloid infiltration, to the myocardial response associated with amyloid deposition, through the visualization and quantification of myocardial edema and myocyte response. Bone scintigraphy (paired with exclusion of free light-chains) is emerging as the technique of choice for distinguishing ATTR amyloidosis from AL cardiac amyloidosis and other cardiomyopathies and has transformed the diagnostic pathway for ATTR amyloidosis, allowing non-invasive diagnosis of ATTR amyloidosis without the need for a tissue biopsy in the majority of patients. CMR with tissue characterisation and bone scintigraphy are rewriting disease understanding, disease classification and definition and leading to a change in patient care.

List of abbreviations:
AL = light chain amyloidosis;
ATTR = transthyretin amyloidosis;
ATTRm = hereditary transthyretin amyloidosis;
ATTRwt = wild type transthyretin amyloidosis;
CMR = cardiovascular magnetic resonance;
LGE = late gadolinium enhancement;
ECV= extracellular volume;
TAVE = transcatheter aortic valve implantation;
AS = aortic stenosis;
aAVR = surgical aortic valve replacement;
PSIR = phase sensitive inversion recovery reconstruction;
DPD scintigraphy = ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy.

Highlights:
- Cardiac amyloidosis is an underdiagnosed cause of heart failure, significantly more common than previously thought, and with specific treatments now available, diagnosing cardiac amyloidosis is more important than ever.
- Non-invasive imaging methods, including echocardiography, bone scintigraphy and cardiac magnetic resonance, play a key role in the diagnostic algorithm.
- Non-invasive imaging could also be used to track disease burden, as well as response to therapy.

Overview of Cardiac Amyloidosis.

Amyloidosis is the clinical disease caused by the deposition of proteins with unstable tertiary structure that misfold, aggregate and deposit as amyloid fibrils. Cardiac amyloidosis is the condition when this primary interstitial protein deposition occurs in the extracellular space of the heart. This phenomenon is independent of cardiomyocyte disease and leads directly to organ dysfunction and adverse events. This scenario contrasts with myocardial fibrosis where "replacement" fibrosis may occur specifically as a secondary phenomenon to fill voids following primary cardiomyocyte necrosis/apoptosis. Unlike myocardial fibrosis, cardiac amyloidosis therefore represents a pure primary interstitial process, not triggered by cardiomyocyte disease, yet still associated with very poor prognosis.

More than thirty proteins can form amyloid fibrils and the difference in the precursor protein form the basis for the classification. Almost all clinical cases of myocardial cardiac amyloidosis are from either misfolded monoclonal immunoglobulin light-chains (AL or primary systemic) from an abnormal clonal proliferation of plasma cells, or transthyretin (ATTR), a liver-synthesised protein normally involved in the transportation of the hormone thyroxine and retinol-binding protein (1,2). ATTR may in turn be either hereditary (ATTRm) arising from misfolded mutated TTR, or non-hereditary, from misfolded wild-type TTR (ATTRwt) (3); this latter type was previously known as senile systemic amyloidosis.

Despite differences in prevalence, clinical phenotype, prognosis and treatment strategies for the different types of amyloidosis (Table 1), it is the cardiac involvement that drives prognosis. Until very recently, systemic AL amyloidosis was thought the most common type of amyloidosis, with an estimated prevalence of 8-12 per million person-years (4). It can infiltrate different organs, including the liver, kidneys, the autonomic and peripheral nervous systems, the lungs as well as the heart - where clinically recognised involvement occurs in 60%, and determines survival. Symptoms are mostly non-specific, including fatigue,

dyspnoea, weight loss, peripheral edema, bleeding tendency and symptoms of peripheral neuropathy or autonomic dysfunction. "Classical" signs, such as periorbital bruising and macroglossia, only occur in around a third of cases. This non-specific clinical presentation often means that the diagnosis is delayed. The mainstay of treatment is cytotoxic chemotherapy, aimed at suppressing the production of pathogenic light chains. Autologous stem cell transplantation can be considered only in a select group of low risk patients. Even with standard chemotherapy, patients with cardiac AL and elevated cardiac biomarkers, who are not candidates for autologous stem cell transplantation continue to have poor outcomes – with 40% of patients dying within 2 years of diagnosis and only 20% of responders experiencing cardiac improvement by biomarker criteria (5). The recognition of ATTRwt amyloidosis has increased exponentially over the last few years. Considered until very recently rare, current reports estimate a prevalence of 10-16% in some cohorts – particularly elderly (>80 year old) patients with either heart failure, hypertrophy or aortic stenosis (6,7). Amyloid-AS refers to the dual pathology of cardiac amyloidosis and aortic stenosis (AS), which is seen in 14-16% of elderly patients with AS being considered for transcatheter aortic valve implantation (TAVI) (7,8) and 6% of patients undergoing surgical aortic valve replacement (sAVR).(9) Whether and how often this cardiac amyloid is the primary disease, a disease modifier or simply bystander is under investigation. ATTRwt has a near exclusively cardiac phenotype with heart failure symptoms being the most common presentation and typically only carpal tunnel syndrome in addition. ATTRm amyloidosis is more varied depending on the specific mutation, geographical area, ethnicity, age and gender. Both ATTRm and ATTRwt amyloidosis are under-recognized, yet important causes of heart failure (6). There are more than 120 amyloidogenic TTR mutations. Some of these are common – for example Val122Ile is found in 3.4% of African Americans and causes cardiomyopathy (10). While the penetrance is still unclear and likely to be relatively low,

approximately 2 million people in the US are carriers of this variant and at risk. Clinical

presentations are related to mutant TTR tetramer protein thermodynamic and kinetic stability

(11) with a clinical presentation ranging from a primary polyneuropathy (V30M),

cardiomyopathy (Val122Ile, Leu111Met, Ile68Leu) or a mixed phenotype. However, patients

who present primarily with polyneuropathy can develop cardiomyopathy, and vice versa (12).

Peripheral neuropathy and autonomic dysfunction have a significant impact on quality of life,

but cardiac involvement is still key, with a median survival of 4-5 years when infiltration is

present.

The diagnosis of cardiac amyloidosis remains challenging. Advanced disease has

characteristic features but is much less treatable than early disease - so early diagnosis with

sufficient confidence to implement therapy is really important. Phenotypic heterogeneity,

clinical overlap with more common phenocopies (i.e., hypertension, chronic renal failure,

hypertrophic cardiomyopathy, aortic stenosis), sufficient rarity, the lack of non-invasive

diagnostic tests and the belief that there are limited effective treatments has hampered

diagnosis. Blood biomarkers (e.g. N-terminal pro-brain natriuretic peptide or NT-proBNP

and troponin) are widely used for risk assessment in cardiac amyloidosis – they combine to

create the Mayo classification for AL amyloid, but are not specific, as the serum levels are

confounded by renal function and overlap with other common cardiomyopathies. However

diagnostic pathways have dramatically changed in the last few years, mainly driven by the

improvement in imaging techniques and the evolution in treatment options (13-16).

Imaging myocardial infiltration

Echocardiography. Amyloid can infiltrate all cardiac chambers. The infiltrative process

results in biventricular wall thickening (most commonly symmetric in AL amyloidosis, but

asymmetric in ATTR) with non-dilated or small ventricles. In asymmetric patterns in ATTR,

the wall with the maximal hypertrophy is the septum, that shows either a sigmoid shape (70% of cases) or reverse septal curvature (30% of cases) (17). Cardiac amyloidosis is often listed as a cause of heart failure with preserved ejection fraction, but this does not fully characterize the functional phenotype that typically shows both systolic and diastolic impairment. Ejection fraction is typically normal until end-stage. Stroke volume index and myocardial contraction fraction (ratio of stroke volume to myocardial mass) are better markers than ejection fraction. In addition, reduction in peak systolic wall motion velocities, disproportionally affecting the longitudinal rather than the radial axes, are present early. This is much more marked than other causes of increased LV mass, and the reduction in longitudinal strain typically spares the apex giving the characteristic "relative apical sparing" picture on parametric longitudinal strain polar maps(18) - a useful tool to help differentiate cardiac amyloidosis from hypertrophic phenocopies and a strong prognostic marker (19). Initial infiltration in the left ventricle is characterized by impaired relaxation, which then invariably progresses to typical restrictive physiology. Similar changes are present in the diastolic function of the right ventricle (cardiac amyloidosis being an exemplar cardiomyopathy of biventricular diastolic dysfunction). The effects of systolic and diastolic ventricular dysfunction with reduced cardiac output along with direct amyloid infiltration of atrial walls can cause blood stasis and risk of thrombus formation, even in sinus rhythm, particularly in AL.(20) There is also a high prevalence of intracardiac thrombi in AF despite long-term anticoagulation, suggesting the need for specific imaging to exclude intracardiac thrombi before undergoing cardioversion.(20) Non-specific but extensively described findings include thickening of the valves and the interatrial septum, as well as a speckled appearance of the myocardium. Pericardial and pleural effusions are relatively common findings, especially in AL amyloidosis.

There are structural and functional differences between cardiac AL and ATTR amyloidosis, with ATTR being characterized by a greater degree of increase in LV and RV mass, and more systolic dysfunction, but significant overlap exists, making these echocardiographic features relatively unsuited to differentiate between the types.

Cardiovascular magnetic resonance. CMR offers accurate information regarding the heart's structure and function with precision advantages over echocardiography. However, the key advantage of CMR in cardiac amyloidosis is its unique ability to give information about the tissue composition by "myocardial tissue characterization". Healthy and pathological myocardium may have different "intrinsic contrast", without the use of gadolinium, as pathology may change myocardial magnetic properties (T1, T2 and T2*), and different "extrinsic contrast" with the addition of a gadolinium-based contrast agent Gd-DTPA (gadolinium diethylenetriamine penta-acetic acid), as in the late gadolinium enhancement technique (LGE). Gadolinium-based contrast agents are small and cross the vascular endothelium into the extracellular space but not the intact myocyte cell membrane. They accumulate passively in the gaps between cells – this interstitial compartment increases in cardiac amyloidosis (due to the extracellular nature of the amyloid deposition). Cardiac amyloidosis has a highly characteristic appearance, with initially sub-endocardial later transmural LGE coupled with abnormal gadolinium kinetics with the myocardium and blood nulling at the same time (21). However, caution should be used for protein bound contrast agents when cardiac amyloidosis is suspected, as the diagnostic performance may not be the same as for non-protein bound variants. The traditional LGE technique is a difference test for focal lowering of T1. Infiltrative diseases, especially amyloid, that affect the entire myocardium may have no remote regions of normal myocardium for comparison so operator can erroneously choose to null the abnormal myocardium missing global infiltration or creating a sub-endocardial sparing (false negative) appearance, (figure 2). Fortunately, the

phase-sensitive inversion recovery (PSIR) approach overcomes this because the PSIR reconstruction cannot erroneously null the tissue with the shortest T1 (most gadolinium). It is also easier for the operator (less precision in setting T1 needed) and is available from all CMR manufacturers. With the PSIR approach, 3 LGE patterns are recognised; none, sub-endocardial and transmural (22), which show good correlation with the degree of myocardial infiltration. However, LGE has limitations: is not quantitative, making it difficult to track changes over time, and gadolinium-based contrast agents are relatively contraindicated in patients with a severe reduction in renal function (a relatively common finding in patients with systemic amyloidosis).

T1 mapping adds value. T1 mapping offers a quantitative measure of the myocardial T1 relaxation time – either pre-contrast (native) or post-contrast. Native myocardial T1 increases in both AL and ATTR cardiac amyloidosis. This tracks markers of systolic and diastolic function, as well as cardiac amyloid infiltration – as measured by ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy (23). Native myocardial T1 elevation is associated, in single centre studies, with a high diagnostic accuracy for cardiac amyloidosis when the pre-test probability is high (24) and is an early disease marker – being elevated before the onset of left ventricular hypertrophy, presence of LGE or elevation in blood biomarkers. This may find clinical utility particularly in severe kidney failure, when gadolinium contrast is contraindicated. However, native T1 is a composite myocardial signal from both interstitium and myocytes and does not differentiate fully the underlying processes (fibrosis, edema, amyloid, myocyte response)(25) and while the elevation is high in advanced disease, it is less in early disease, making it important to know the normal range for the centre where measurement is being performed. Using gadolinium-based contrast agents permits ECV measurement. This is a measure of the free water in myocardium – the gaps between cells. The normal ECV is usually in the range of 22-28%. It can increase hugely in focal scar

(e.g. 70%) or edema, but for diffuse fibrosis, the increases are almost never more than 40%.

A global increase of more than 40% is likely to be cardiac amyloidosis (or rarely global

myocardial edema) (26-28). ECV elevations are early, before LGE and conventional clinical

testing detects cardiac involvement in high pre-test probability patients so is an early disease

marker.(26,28) It tracks a wide variety of markers of disease activity, such as cardiac

function, blood biomarkers and patient functional performance (28). T1 mapping (native and

ECV) can track changes over time and this is changing our disease understanding. For

example, with successful chemotherapy for AL where there is a complete response and

switch-off of clonal light chains: T1, ECV and even LGE can reverse and the time course for

these processes can be tracked. Both native T1 and ECV can track disease severity but ECV

is a more robust marker of pure infiltration: ECV remains an independent predictor of

prognosis in cardiac ATTR after adjusting for known predictors and is the earliest disease

marker to track amyloid regression (25,29). ECV can also be used to measure the myocyte

response – detecting differences between AL and ATTR with an apparent relative

(compensatory) hypertrophy response in ATTR not present in AL – highlighting that

amyloidosis is not just an interstitial disease (30). Other techniques are also delivering

insights. Native T2 mapping with current measurement techniques is really only sensitive to

edema, where it increases. T2 is elevated in cardiac amyloidosis and histological correlation

demonstrates that edema is part of acute cardiac amyloidosis particularly AL and is linked to

prognosis (31). When combined, CMR structure, function, PSIR LGE and mapping (native

T1, T2, ECV) permit a redefinition of cardiac involvement by cardiac processes: **(1)**

infiltration (amyloid burden, ECV); **(2)** edema (T2 being the most specific marker); **(3)**

myocyte response (derived from LV mass and ECV from the formula = LVmass*(1-ECV))

and **(4)** stages based on the combination of LGE and ECV (ECV elevation no LGE,

subendocardial LGE, transmural LGE). These categories are not yet fully defined and

destination staging of myocardial disease will likely involve CMR but also biomarkers (NT-proBNP and troponin) and, for early disease, advanced echocardiography.

Bone scintigraphy. The value of bone scintigraphy in the diagnosis of cardiac amyloidosis first became apparent in the 1980s, when it was demonstrated that the hearts of patients with this condition avidly took up ^{99m}Tc-phosphate derivatives on cardiac radionuclide imaging (32). In 2005, the diagnostic potential of this was shown in identifying ATTR cardiac amyloidosis (33) with the Perugini staging system based on simple visual scoring system of the delayed (3-hour) planar image – grade 0 being negative (no cardiac uptake) and grades 1-3 progressively more positive (increasing cardiac uptake) (33). This initial paper used the tracer DPD and was small (15 ATTR and 10 AL) suggesting very high specificity and sensitivity for cardiac ATTR (33). Subsequent studies confirmed the utility of bone scintigraphy using multiple tracers (DPD, HMDP, PYP) and the high sensitivity to detect ATTR amyloidosis was preserved. It was also shown however that that mild uptake of ^{99m}Tc-DPD (grade 1) could be noted in other subtypes of amyloidosis (Serum Amyloid A amyloidosis, and Apolipoprotein A1) (34,35) and that established AL frequently had grade 1 or even grade 2 uptake (advanced AL cardiac amyloidosis has grade 2 uptake in up to 10% of cases). This led to a new diagnostic algorithm for the non-invasive diagnosis of ATTR amyloidosis without the need for a tissue diagnosis – with a grade 2/3 positive DPD scan and the absence of a plasma cell dyscrasia (no free light chains) being sufficient to diagnose TTR cardiac amyloid (36).

Cardiac uptake on bone scintigraphy linked to the exclusion of free lightchains is extremely useful to confirm the diagnosis of ATTR amyloidosis, but also represents an early disease marker, as changes on bone scintigraphy imaging may also be seen prior to the onset of abnormalities detectable by echocardiography, (being positive for example in patients with a maximal wall thickness less than 12 mm) (37), therefore offering the possibility of an earlier

diagnosis. Cardiac uptake on bone scintigraphy may also have a prognostic role in cardiac ATTR amyloidosis, as it has been shown that increased tracer retention, a heart to contralateral ratio greater than 1.6 and presence of apical sparing (with a similar pattern to that of longitudinal strain apical sparing on echocardiography) correlate with prognosis (37-40). There are remaining problems however - PYP is commonly used in the United States, HMDP in France, DPD in countries like the UK and Italy with comparative tracer performance relatively unknown. Similarly, grading systems and imaging protocols are different in the US compared to Europe. With the advent of new therapies, the relative implications of (in particular) grade 1 vs 2 are not yet known – for example in ATTRwt in the elderly whether low levels of infiltration can be considered normal with age (a difference between cardiac *amyloid* and cardiac *amyloidosis*). Widespread availability of expensive therapy will bring such questions into sharp focus around cost-benefits.

Positron emission tomography. Several PET amyloid binding tracers have been evaluated in AL and ATTR cardiac amyloidosis but the studies are small. ^{11}C-Pittsburgh compound B (PIB), commonly used in cerebral amyloid imaging in Alzheimer's disease detects both AL and ATTR cardiac amyloidosis (41,42). Cardiac uptake of ^{11}C-PIB was present in 10 patients with cardiac amyloid (3 ATTR, 7 AL), but not in healthy controls (n=5) (31). This was later confirmed by Lee et al, who showed that 13/15 patients with biopsy proven cardiac AL showing cardiac uptake of ^{11}C-PIB (32). However, an onsite cyclotron is required for carbon-11 production (the half-life is only 20 minutes). ^{18}F-florbetapir shows biventricular uptake in all patients with cardiac amyloid (5 AL and 4 ATTR), which was absent in controls (n=5), with a trend towards a higher myocardial retention index in AL vs ATTR cohort (p=0.057) (43,44); and in a later study of 11 patients (3 controls, 4 cardiac AL, 4 cardiac ATTR) there was noticeable cardiac uptake of ^{18}F-florbetapir in both cardiac AL and ATTR within 10 minutes of tracer injection (34). The longer half-life of fluorine-18 (110 minutes) means that

its distribution to sites without a cyclotron is feasible. ^{18}F-florbetaben, another fluorine-based agent, has also been evaluated in both cardiac AL (n=5) and ATTR (n=5) amyloidosis with hypertensive heart disease as a control (n=4) (45). Percentage myocardial retention of ^{18}F-florbetaben was higher in patients with AL and ATTR cardiac amyloid, compared to controls (76% vs 71% vs 29%, p=0.018) (35). Percentage myocardial retention seemed to also inversely correlate with both LV global and RV free wall longitudinal strain (35). Overall, these agents hold promise for the absolute quantification of amyloid burden, but are still early in development and further work is needed.

Clinical utility of cardiac imaging

Cardiac imaging is interpreted alongside other clinical findings, and different imaging techniques are frequently complementary. The question is not what the best investigation is, but which is the most useful and appropriate for the specific clinical question. Broad reasons for imaging are to make the diagnosis of amyloid (high and low pre-test probability scenarios), to type the amyloid (AL vs TTR), to stage disease (identifying amyloid burden, myocardial responses) and to monitor change (with therapy or over time) (Table 2). An integrated approach using echocardiography, CMR, bone scintigraphy, genetic analysis, biomarkers and tissue biopsy forms the basis of current diagnostic algorithms to non-invasively confirm the diagnosis of suspected cardiac amyloidosis (figure 4).

Diagnosis. There are three common clinical scenarios (in order of descending prevalence) in which the diagnosis may be considered: (1) differential diagnosis in the hypertrophic phenotype (hypertensive heart disease, aortic stenosis, hypertrophic cardiomyopathy and restrictive cardiomyopathy); (2) identifying cardiac involvement in patients with systemic AL amyloidosis; (3) identifying cardiac amyloidosis in patients with ATTR associated polyneuropathy or ATTR mutation carriers. Echocardiography is the first-line test for all

patients presenting with heart failure and may raise the suspicion of cardiac amyloidosis. While nearly all echocardiographic findings are non-specific, in the appropriate clinical context these can be highly suggestive of cardiac amyloidosis and selectively change the pre-test probability (figure 1).

Differential diagnosis in the hypertrophic phenotype. Once echocardiography has raised the suspicion of cardiac amyloidosis, CMR should be considered if both AL and ATTR or another underlying cause of myocardial hypertrophy (HCM, hypertension, AFD) are in the differentials. CMR shows good sensitivity for both types of amyloidosis, while also being able to identify other common phenocopies. Following a CMR suggestive of cardiac amyloidosis, serum free light chains, serum and urine immunofixation and bone scintigraphy (99mTc PYP/DPD/HMDP) should be considered to differentiate between AL and ATTR amyloidosis. Grade 2 or 3 bone scintigraphy coupled with no evidence of a plasma cell dyscrasia in blood or urine is highly specific for ATTR cardiac amyloidosis (36).

Identifying cardiac involvement in patients with systemic AL amyloidosis. If cardiac AL amyloidosis is suspected, CMR may confirm cardiac involvement, as several studies have shown both high specificity and sensitivity (21,46-49). CMR in AL amyloidosis can also detect early disease, being positive before hypertrophy and sometimes identifying rare manifestations such as a dilated phenotype.

Identifying cardiac amyloidosis in patients with ATTR associated polyneuropathy or ATTR mutation carriers. Bone scintigraphy or CMR should also be considered in patients with ATTR associated polyneuropathy or ATTR mutation carriers, but further studies are needed to confirm the sensitivity and specificity of these tests in these clinical scenarios.

Prognosis. As cardiac involvement is so adverse, almost any measurement of cardiac involvement in AL or TTR amyloid predicts outcome. The best tests seem to be the ones that are most reproducible, with narrow (compared to amyloid) healthy reference ranges; are least

confounded by the common amyloid comorbidities; which change early continuously as disease progresses and, it appears, which track most closely infiltration. These can be measured by a variety of imaging techniques. All imaging techniques are complemented prognostically by NT-proBNP and troponin measurement, which form the basis of the Mayo classification of AL (Grade 0: both negative; grade 1: one elevated; grade 2: both elevated) (36), while NT-proBNP and eGFR can be used to stage cardiac ATTR (troponin elevation is less a feature of ATTR compared with AL) (50,51).

Focusing on imaging-derived measures of structure and function first: traditional markers of diastolic and (52-54) systolic dysfunction, as well as strain parameters (55) (56,57) have been associated with worse prognosis. Tricuspid annular plane systolic excursion (TAPSE) and indexed stroke volume (SV) are strong markers of prognosis (58). RV failure is important in primary left heart failure, but here direct RV infiltration may be key to TAPSE performance (58) and it may be that the RV is relatively protected from common amyloid confounders such as hypertension, providing a cleaner signal of cardiac infiltration. The strong prognostic role of indexed SV is expected, as low indexed SV with preserved EF (until late in the disease) is characteristic of cardiomyopathies with restriction and hypertrophy such as amyloid (58). The typical apical sparing on strain imaging is also predictive of prognosis (19).

In terms of tissue characterisation: markers of amyloid infiltration (DPD grade, transmurality of LGE and ECV by CMR) (22,59) and markers of edema (native T1 and T2) (59,60) are strong predictors of prognosis in AL, with direct myocardial infiltration measurement (ECV) performing better in ATTR (being independent after adjustment for more basic measures such as demographics, biomarkers, structure and function measures)(17). For bone scintigraphy, grade 2 and 3 are associated with a significantly worse prognosis than grade 0 (61).

Tracking change over time or with therapy. Serum biomarkers particularly NT-proBNP and echocardiographic parameters are currently the reference standard for assessing response to therapy in cardiac AL amyloid (62,63), but neither directly quantifies amyloid burden, changes in NT-proBNP are not fully understood during treatment, are confounded by renal impairment and strain is not well standardised and is affected by changes in preload and afterload (64). Cardiac organ response has historically been sought using echocardiography, but improvements are seldom evident, at least out to a year post therapy (65) There is little evidence for the use of bone scintigraphy for monitoring as it is currently only semi-quantitative and carries a significant ionising radiation dose. CMR seems most promising as it can selectively track different disease mechanisms (infiltration, edema, myocyte response) and has been shown to demonstrate progression/regression linked to clonal response to therapy in AL over a year (29). CMR however may not be widely available/adopted in all countries. Methods for monitoring treatment response in ATTR are now being explored.

Future directions

Cardiac amyloidosis is now an increasing focus for the imaging community driven by expensive new therapeutic options, increasing survival of AL patients, the need for early diagnosis of AL and wider recognition of ATTR in the elderly (a growing demographic) particularly when in combination with other cardiac diseases, such as amyloid-AS. AL treatment success with bortezomib, melphalan combined with dexamethasone, daratumumab, and other agents, mostly derived from experience in treating multiple myeloma with or without autologous stem cell transplantation (66) is making major progress. In addition, monoclonal antibody therapies designed to remove amyloid fibrils deposited in the heart and other tissues are being evaluated (16). One approach using antibody therapy directed at the serum amyloid P component found in all forms of systemic amyloidosis with (R)-1-[6-[(R)-2-

carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine2-carboxylic acid (CPHPC) to deplete circulating serum amyloid P can clear hepatic amyloid (phase 1 study), and further studies including cardiac patients are planned (67). New treatment strategies for ATTR reduce transthyretin production, stabilize it or disrupt deposited amyloid fibrils (68), moving treatment on from the former approach of liver transplantation used in some ATTRm populations mainly for neurological disease. Latest data are encouraging for cardiac amyloid. In a landmark study, in patients with cardiac transthyretin amyloidosis, tafamidis, a TTR stabilizer, reduced all-cause mortality and cardiovascular-related hospitalizations and reduced (but did not reverse) the decline in functional capacity and quality of life as compared with placebo (13). The treatment strategies are likely to continue to rapidly evolve in the next few years, as other compounds targeting TTR production via RNA, which have already proven to be effective in patients with peripheral neuropathy,(69,70) are tested in cardiac amyloidosis. Imaging to guide and support these developments will be crucial. Pressing major questions, particularly in ATTR will involve when and in whom to start expensive treatments, when to dose escalate, switch or combine therapies, and when to cease therapy through success or futility. But looking further ahead, precision therapy for optimal success will require us to measure and identify the myocardial mechanisms underpinning cardiac amyloidosis, their relative contributions in individuals, and personalize treatment approaches accordingly. With several new drug therapies currently in development, targeting a range of different mechanisms, cardiac imaging could inform on the varying responses to these treatment approaches in the different disease subclasses, with the ultimate aim of providing individualized multimodal treatment in the clinic.

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Figures

Figure 1. Typical echocardiographic findings in cardiac amyloidosis. Echocardiography in a patient with cardiac transthyretin type amyloidosis. Four chamber view (a), showing concentric left ventricular hypertrophy; pulse-wave Doppler showing restrictive flow pattern of left ventricular inflow (b); and strain pattern characteristic of an infiltrative process (c).

Figure 2. Typical cardiac magnetic resonance findings in cardiac amyloidosis. Cardiac magnetic resonance including 4-chamber cine still, corresponding native T1 map, T2 map, LGE image with phase-sensitive reconstruction and ECV map in a patient with no cardiac amyloidosis (upper row) and 2 patients with cardiac amyloidosis (middle and bottom rows). In the upper row, the patient with no cardiac amyloidosis has no LGE, with normal native T1 and ECV maps; in the middle row, the patient with cardiac amyloidosis has subendocardial LGE, elevated T1, normal T2 and ECV values; in the bottom row, the patient with cardiac amyloidosis has a very high cardiac amyloid load, with transmural LGE, very high native T1, normal T2 and ECV values.

Figure 3. Typical bone scintigraphy findings in ATTR amyloidosis. Anterior 99m Tc-DPD scintigraphy planar image (a) and single photon emission computerised tomography-CT (b) showing Perugini grade 2 uptake on a patient with cardiac transthyretin type amyloidosis.

Figure 4. Diagnostic algorithm for the diagnosis of cardiac amyloidosis. Proposed diagnostic algorithm in the three commonest clinical scenarios: (1) differential diagnosis in the hypertrophic phenotype (hypertensive heart disease, aortic stenosis, hypertrophic cardiomyopathy and restrictive cardiomyopathy); (2) identifying cardiac involvement in patients with systemic AL amyloidosis; (3) identifying cardiac amyloidosis in patients with ATTR associated polyneuropathy or ATTR mutation carriers. (CMR: cardiovascular magnetic resonance; AApoA1 indicates apolipoprotein A-I; DPD, [99mTc]-3,3-diphosphono-1,2-propanodicarboxylic acid; HDMP, hydroxymethylene diphosphonate; and PYP, pyrophosphate.

Central illustration. Imaging in cardiac amyloidosis. In this review we describe the clinical utility of imaging in cardiac amyloidosis and their integration into a multimodality diagnostic pathway.

Tables

Table 1. Clinical characteristics of the most common causes of cardiac amyloidosis.

Type	Prevalence and Demographic Features	Clinical Phenotype	Prognosis	Treatment
AL	- 8-12 cases per million person-years (4). - Male predominance. - Generally presents in 5th to 7th decade (1).	- Restrictive cardiomyopathy with additional acute toxicity from light chains. - Multi-organ disease (kidneys, peripheral and autonomic nervous system, liver and gastrointestinal tract).	- Untreated, median survival c. 6 months from onset of heart failure.(71)	- Supportive for heart failure - Chemotherapy to eliminate the abnormal plasma cell population. - Stem cell transplantation in a selected group of patients
ATTRwt	- High in some groups, e.g. elderly with severe AS/ hypertrophy/ heart failure: prevalence up to 10-16% (6,7). High male predominance in most cohorts (72)	- Restrictive cardiomyopathy - Other clinical involvement rare, apart from carpal tunnel syndrome.	- Median survival c. 6 years from onset of heart failure (73).	- Supportive for heart failure. - Pacemaker for advanced AV block. - Several agents undergoing FDA/EMA assessment or phase II/III trials (2,13)
ATTRm	- Overall 0.4 per million per year (74). - High in some populations e.g. V122I in 3.4% of African Americans (10). - 72% of clinical patients are male (72).	Variable phenotype, mutation specific: -Restrictive cardiomyopathy - Peripheral/autonomic neuropathy - Autonomic dysfunction - Renal involvement. - Eye involvement.	- Dependant on mutation, with cardiac involvement being the main driver of prognosis.	- Supportive for heart failure. - Pacemaker for advanced AV block. - Liver transplantation in selected cases (V30M variant). - Several agents undergoing FDA/EMA assessment or phase II/III trials (2,13)

Table 2. Clinical scenarios (in order of descending prevalence) and the roles of different imaging modalities in the detection of cardiac amyloidosis.

	Imaging Modality		
Clinical Question	**Echocardiography**	**Cardiac MRI**	**Bone Scintigraphy**
Identifying the cause of LVH	++	+++	+
Identifying cardiac involvement in patients with systemic AL amyloidosis	++	+++	+
Differentiation of AL vs ATTR cardiac amyloidosis	+	+	+++*
Quantifying amyloid burden	+	+++	++
Following changes over time	+	+++	+
Identifying cardiac amyloidosis in patients with ATTR-associated polyneuropathy, or mutation carriers.	+	++	++

*To differentiate AL vs ATTR cardiac amyloidosis, bone scintigraphy should be combined with serum and urine immunofixation and free light chain essay.