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Transthyretin Cardiac Amyloidosis in Older Adults: Optimizing Cardiac Imaging to the Corresponding Diagnostic and Management Goal

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Abstract

Purpose of review—Transthyretin cardiac amyloidosis is increasingly recognized as an important cause of heart failure in older adults. Many cardiac imaging modalities have evolved to evaluate transthyretin cardiac amyloidosis and include 2D echocardiography with tissue Doppler and speckle-strain imaging, nuclear scintigraphy, cardiac magnetic resonance imaging, and positron emission tomography. The purpose of this review is to highlight the optimal selection of advanced cardiac imaging techniques with corresponding diagnostic goals including raising suspicion, making an early diagnosis, and subtyping transthyretin cardiac amyloid, as well as management goals including assessment of ventricular impairment, prognosticating, and monitoring disease progression. Potential benefits of optimizing cardiac imaging in the elderly patient with transthyretin cardiac amyloidosis may include enhanced and earlier diagnosis and refined long-term management.

Recent findings—Advances in cardiac imaging techniques are changing diagnostic and management algorithms for transthyretin cardiac amyloidosis.

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Manson declares no conflicts of interests

Dr. Bokhari declares no conflicts of interests

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Summary—With a new era of novel therapeutics, enhanced recognition, and earlier diagnosis approaching, selecting the appropriate non-invasive cardiac imaging modality will be essential for optimal care in the elderly patient with transthyretin cardiac amyloidosis.

Keywords

Transthyretin Cardiac Amyloidosis (ATTR-CA); Technetium Pyrophosphate (^{99m}Tc -PYP); Cardiac Magnetic Resonance (CMR); Echocardiographic Strain

Introduction

Refinements in cardiac imaging modalities are influencing the understanding and management of cardiac amyloidosis (CA). In transthyretin cardiac amyloidosis (ATTR-CA), a disease predominantly affecting elderly adults [1], transthyretin protein (TTR), a liver-synthesized tetramer, destabilizes into its component monomers, which misfold and aggregate into amyloid fibrils. Extracellular cardiac deposition of fibrils from either wild-type (ATTRwt) or mutated TTR (ATTRm) disrupts tissue architecture causing diastolic dysfunction, heart failure, eventual systolic dysfunction, and death [2].

Several advanced cardiac imaging modalities for ATTR-CA have evolved including advanced echocardiographic tissue Doppler (TDI) and speckle-tracking imaging (STI), cardiac magnetic resonance imaging (CMR), bone isotope imaging with technetium ($\text{Tc}^{99\text{m}}$) based isotopes, and positron emission tomography (PET). While regional and center-related practices may influence the choice of cardiac imaging modality that is used, clinicians could further refine standard of care by first establishing a clear ATTR-CA diagnostic and management goal and then pairing the best available modality optimized to achieve that specific goal.

Diagnostic goals for ATTR-CA include raising suspicion of the diagnosis, making a definitive diagnosis, preferably early in the disease course before overt heart failure ensues, and identifying amyloid subtype. Management goals include assessment of ventricular impairment, prognostication, and monitoring disease progression [3]. With numerous disease-modifying therapies currently in development, selecting the optimal cardiac imaging modality to achieve each goal will become increasingly important [4]. Furthermore, given the demographics of ATTR-CA, it is important to understand the challenges and considerations unique to the elderly population when selecting imaging modalities. The present article reviews the utility and application of advanced cardiac imaging modalities for each diagnostic and management goal in the older patient with ATTR-CA (Figure 1).

Epidemiology

In the United States, ~26% of the population is ≥ 65 years of age, a proportion which has more than doubled since 2010 [5], and which accounts for more than half of all cardiovascular hospitalizations and ~80% of cardiovascular deaths [6]. As the population ages, the prevalence of ATTR-CA will climb, given its age-dependent penetrance. Advances in non-invasive cardiac imaging have facilitated diagnosis of cardiac amyloidosis and have demonstrated that ATTRwt is not as rare as previously thought [7]. Among elderly adults

hospitalized with heart failure with a preserved ejection fraction (HFpEF) of 50% and a left ventricular (LV) wall thickness >12 mm, the incidence of ATTR-CA was 13.3%, a proportion that likely underestimates its true burden given that the study pre-selected a specific wall thickness threshold that may not capture patients with borderline LV hypertrophy[8]. Amyloid deposition may not be heralded initially by increased wall thickness and hence, a focus on increased wall thickness as a screening criterion may underestimate true prevalence. Data from the Transthyretin Amyloid Outcomes Survey (THAOS), a global observational database of patients with ATTR, revealed that approximately 48% of patients with ATTR-CA in the United States have ATTRwt. This was followed by 23% with ATTRm due to a valine to isoleucine substitution at position 122 (Val122Ile), a mutation present almost exclusively in African Americans with an allele frequency of ~4% [1, 9]. The most commonly encountered CA subtypes in elderly adults is ATTRwt, followed by ATTRm, and light-chain (AL) [2].

ATTR-CA Diagnostic and Management Goals in Elderly Adults: Raising clinical suspicion

Conventionally, standard transthoracic echocardiography (TTE) is often the first imaging modality to raise suspicion for CA. TTE is safe and easy to perform in the elderly population. Typical echocardiographic features of CA include left ventricular (LV) and right ventricular (RV) wall thickening without an explanatory stimulus (i.e. hypertension or valvular disease, specifically aortic stenosis) [10], bi-atrial enlargement, thickening of the interatrial septum, and the presence of a pericardial effusion [11–14]. Diastolic dysfunction is common [13, 15] and often advanced, typically with a restrictive filling pattern with high early (E) and relatively low atrial (A) wave with an E/A ratio >2, and a short deceleration time [10, 13, 15]. The myocardium may have a “granular sparkling” or “speckled” appearance [13]. In a recent study using the THAOS registry [16], 59% of patients with ATTR (252/425) were found to have an IVS ≥13mm, thereby meeting the International Consensus Criteria for cardiac amyloidosis [17]. Of these patients with ATTR-CA, 49% had a LV ejection fraction (EF) <50%, 77% had RV thickening >7mm, 79% had left atrial dilation >40mm, 66% had myocardial sparkling, 37% had aortic valvular thickening, 44% had mitral valvular thickening, and 18% had a restrictive filling pattern (E/A>2) [16]. Poor RV function, as measured by decreased RV fractional shortening, low tissue Doppler S’ of the RV free wall, and decreased tricuspid annular plane systolic excursion (TAPSE), may also be present in advanced disease [18]. Further studies using comparisons with controls and patients with LVH of other etiologies are required to determine the sensitivity and specificity of the above features.

In the elderly patient, it is the constellation of the above echocardiographic features and not any single parameter that typically elevates suspicion for ATTR-CA. Other causes of left ventricular hypertrophy (LVH), such as hypertension, hypertrophy due to increased central artery stiffness, aortic stenosis (AS), and hypertrophic cardiomyopathy (HCM), can present with similar TTE findings. Furthermore, TTE typically signals the possibility of ATTR-CA only after lifelong myocardial infiltration of amyloid fibrils [19] as it lacks sensitivity for

detection of early myocardial infiltration. Therefore, TTE is a tool best applied in older adults for raising suspicion of late-stage, but usually not early disease [12, 13, 15].

Advanced echocardiographic speckle-strain imaging (SSI) can raise suspicion for ATTR-CA earlier and with greater accuracy than conventional 2D TTE by detecting changes in regional myocardial deformation specific to amyloid. Impairments in strain may occur earlier in the pathophysiology of CA [13] than overt structural 2-dimensional TTE changes [15, 20, 21] and clinical heart failure [22, 23]. Compared to patients with other forms of LVH, patients with amyloid cardiomyopathy have significantly reduced longitudinal and radial strain [24, 25] and demonstrate a characteristic pattern of diminished global longitudinal strain (LS) in the basal and mid left ventricular segments with preserved strain in the apex [26–28]. In contrast, HCM may present with focally impaired global longitudinal strain in the specific myocardial segment known to be hypertrophied while strain in remaining segments remains normal [27]. In amyloid, apical sparing can occur irrespective of LVEF, degree of wall thickening (i.e. early in the course of CA), or amyloid subtype [20, 28]. Apical sparing can be quantified as the relative regional strain ratio (RRSR), calculated as the average apical LS / (average basal + mid LS) [27, 29]. In a cohort of 55 patients with confirmed CA, a RRSR >1 was 93% sensitive and 82% specific for CA compared to HCM or AS [27]. Likewise, a ratio of septal apical to basal segmental longitudinal peak systolic strain > 2.1, in combination with shortened diastolic deceleration time of early filling <200ms, differentiated CA from other causes of LVH (including hypertension, Fabry disease, and Friedreich ataxia) with a sensitivity of 88% and specificity of 85% [30].

CMR can assess morphological and functional characteristics of myocardial tissue using specialized post-contrast techniques, including inversion recovery imaging for late gadolinium enhancement (LGE) and T1 mapping for fractionation of extracellular volume (ECV) [10, 31]. A shortened post-contrast T1 signal is seen in CA due to interstitial expansion by amyloid infiltration and subsequent gadolinium deposition. Patients with CA demonstrate characteristic patterns of LGE including global subendocardial [32–36] and transmural enhancement [37, 38]. A recent meta-analysis of five studies (257 patients) assessing the diagnostic accuracy of LGE assessment by CMR demonstrated a sensitivity of 85% and specificity of 92% for CA [39].

CMR T1 mapping can analyze changes in myocardial longitudinal relaxation. Pre-contrast T1 signal was increased in 85 elderly patients with ATTR-CA (mean age 73) compared to 46 patients with HCM and 52 healthy controls [40]. In a cohort of 85 elderly patients with ATTR, 79 with AL, 46 with HCM, and 52 healthy controls, T1 elevations were found to have an area under the receiver operator characteristic curve (AUC) of 0.85 for distinguishing ATTR-CA or AL from HCM and healthy controls [40]. Pre-contrast and post-contrast T1 data can be used together to calculate the ECV, a measurement of interstitial expansion [34, 38] which is significantly elevated in patients with CA, due to interstitial amyloid deposition [31, 41]. In a study comparing 36 elderly patients with CA to 30 healthy controls, a cutoff of ECV >0.316 was 79% sensitive and 97% specific (AUC of 0.884) for CA [41]. Therefore, while CMR may be a reasonable tool for diagnosis of cardiac amyloid, it is usually performed to evaluate cardiomyopathy and the above findings are incidentally found, which ultimately raise suspicion but do not define the diagnosis.

CMR is safe, painless, and requires no radiation. However, its use may be limited in the elderly population, as select patients may have implanted ferromagnetic hardware or may not tolerate lying immobile for the duration of the examination due to comorbidities such as spinal stenosis or heart failure. Furthermore, for elderly patients with concomitant renal impairment, CMR protocols requiring the use of contrast may be contraindicated.

Diagnosis

Until recently, the gold standard for a definitive diagnosis of CA required endomyocardial biopsy and tissue typing with histological staining, immunohistochemistry, and mass spectrometry [10]. However, procedural risk in a frail elderly population and the need for pathologic expertise at experienced centers limits this approach and may delay the diagnosis. Recent advances in nuclear cardiac imaging have challenged this traditional paradigm and offer an alternative non-invasive diagnostic approach in selected patients.

Nuclear scintigraphy using bone isotope imaging has shown promise as a non-invasive method to diagnose ATTR-CA. Common isotopes used include technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (Tc99m-DPD), routinely used in Europe but not available in the United States, technetium pyrophosphate (Tc99m-PYP), Food and Drug Association (FDA) approved for use in the United States for bone imaging, also used in Canada and Japan, and technetium hydroxymethylene diphosphonate (Tc99m-HMDP). Scintigraphy was first noted to visualize amyloid deposits in case studies in the 1970s and 1980s [42–44], however, the modality went quiescent due to a perceived lack of sensitivity for ATTR-CA, likely given heterogeneous study cohorts that included patients with both ATTR and AL cardiac amyloidosis [33].

A revival in nuclear scintigraphy for CA was sparked in 2005 when Perugini et al. demonstrated that 15/15 patients with ATTR-CA had strong myocardial uptake of Tc99m-DPD whereas no uptake was observed in 10 patients with AL, suggesting 100% sensitivity and specificity for diagnosing ATTR-CA [33]. Subsequent studies confirmed high sensitivity and specificity for Tc99m-DPD in differentiating ATTR-CA from other causes of LVH using a semiquantitative visual score ranging from 0–3 (score 0 = absent cardiac uptake and normal bone uptake; 1 = mild cardiac uptake, inferior to bone uptake; 2 = moderate cardiac uptake with attenuated bone uptake; 3 = strong cardiac uptake with mild/absent bone uptake) [33, 45, 46] and a quantitative heart-to-whole body (H:WB) ratio, comparing uptake in the heart to the remainder of the body [47, 48].

Like Tc99m-DPD, the North American isotope Tc99m-PYP, was shown to bind ATTR cardiac deposits with high affinity. In a cohort of 45 elderly patients with biopsy proven CA (16 ATTRwt, 17 ATTRm, and 12 AL), a visual score 2 or greater and a heart-to-contralateral chest (H/CL) ratio (comparing myocardial tracer uptake in the heart to an equivalent region in the contralateral chest) > 1.5 was 97% sensitive and 100% specific for diagnosing ATTR-CA [49]. High diagnostic accuracy was replicated in a subsequent multicenter study of 121 patients with biopsy proven ATTR-CA that demonstrated >90% sensitivity and specificity [50]. The patient population included in these two studies, mean age 70±2 and median age 73 (65–79), reflects the near exclusivity of this diagnosis to the elderly population.

Tc99m-HMDP has also shown high diagnostic accuracy for detection of ATTR-CA [47, 51]. Increased uptake, assessed by an elevated heart-to-skull ratio, was found in 21/21 patients with ATTRwt, 24/26 patients with ATTRm, and 1/14 patients with AL; a visual score >2 was 100% specific for ATTR-CA [51]. A study of 6 patients with ATTR-CA (age 66–81) found comparable uptake intensity of Tc99m-HMDP and –DPD, supporting the utility of Tc99m-HMDP in diagnosing ATTR-CA [52].

In an international multicenter collaboration among 857 patients with CA who had undergone Tc99m-DPD, –PYP, or –HMDP radioisotope scintigraphy, grade 2 or 3 myocardial uptake was found to be 100% specific for the diagnosis of ATTR-CA in patients with no evidence of an abnormal monoclonal protein [53]. This led to the international consensus that in select patients without evidence of an abnormal monoclonal protein, a positive radioisotope nuclear scan can diagnose ATTR-CA without the need for biopsy.

Nuclear imaging is therefore an accurate and feasible imaging modality that may spare select elderly patients the need for invasive biopsy. Scans are faster than CMR, though they do require a supine position and minimal radiation exposure. Recently, a standardized protocol for Tc99m-PYP was published (45 patients, mean age 70±2) with a faster incubation period (1 hour vs. 2–4 hours), less radiation exposure compared to other protocols (3 mSv vs. 8–10 mSv), and only 10 minutes under the camera [54].

PET radiotracers have also demonstrated an affinity for amyloid fibrils and may aid in the diagnosis of CA. Several radiotracers have been studied, including 11C-Pittsburgh compound B (PIB), (18)F-florbetapir, and (18)F-florbetaben. 11C-PIB myocardial uptake was found to be elevated in 10/10 patients with CA (7 AL, 3 ATTR, mean age 66) with no uptake in five controls [55]. Subsequent studies found equally promising results with significant myocardial 11C-PIB uptake in 10/10 patients with ATTRm (V30M) [56] and even in patients who had ATTR with peripheral neurologic disease without known cardiac involvement [56].

(18)F-florbetapir, (18)F-florbetaben, and (18)F-sodium fluoride (NaF) have also shown potential in diagnosing CA. (18)F-florbetapir myocardial uptake was elevated in 9/9 patients with CA (4 ATTR-CA, 5 AL) but not in amyloid-negative controls [57]. An autopsy study showed that all myocardial sections of patients with CA (10 ATTR-CA, 10 AL) had elevated uptake of (18)F-florbetapir compared to controls [58]. (18)F-florbetaben also localized to myocardial amyloid fibrils in 10 patients with CA (5 ATTR-CA, 5 AL) with no uptake seen in 4 controls with LVH secondary to longstanding hypertension [59]. (18)F-NaF may be of benefit in diagnosing ATTR-CA as well. In a cohort of 7 subjects (2 ATTRwt, 2 ATTRm, 3 AL), (18)F-NaF uptake was elevated in all patients with ATTR but in no patients with AL or 7 non-amyloid controls [60], indicating specificity for ATTR.

PET imaging is a reasonable and safe option in the elderly population. In fact, research into the utility of PET for CA was sparked by evidence that 11C-PIB, (18)F-florbetapir, and (18)F-florbetaben can be useful in the diagnosis of dementia, a disease that predominantly affects elderly adults [61]. While patients must assume a supine position, a potential limiting factor in select older patients with orthopedic spine problems, the duration of the supine part

of the examination lasts approximately 20 minutes, which is less than for most MRI protocols.

Early Diagnosis

Early detection of ATTR-CA, before the disruption of tissue architecture and organ failure, remains an important clinical goal, especially given that emerging disease-modifying therapies can prevent disease progression but do not reverse existing damage [62]. Therefore, employment of cardiac imaging to detect ATTR-CA early will be essential to identify patients who would benefit from early intervention before late-phase cardiac impairment occurs. Clinical clues in asymptomatic patients may include increased a family history of cardiac amyloidosis, increased wall thickness, peripheral neuropathy, a history of carpal tunnel syndrome and/or orthopedic surgery for bilateral carpal tunnel surgery or degenerative lumbar spinal stenosis.

Abnormal patterns of LGE on CMR were found to occur before increases in LV wall thickness and other late echocardiographic signs of amyloid infiltration [34, 63], with one study demonstrating abnormal LGE in 17/36 of patients with suspected amyloidosis without LV wall thickening [34]. Patchy intramural focal LGE on CMR has also been associated with less severe CA than global subendocardial or transmural enhancement [34].

Nuclear scintigraphy may also be useful for the early diagnosis of CA. In elderly cohorts, both Tc99m-DPD and Tc99m-PYP detected ATTR-CA before any evidence of cardiac involvement on TTE [45, 47, 48, 64]. 99mTc-DPD cardiac uptake was found in 12 patients with ATTR (4 ATTRwt, 8 ATTRm) who had no echocardiographic evidence of cardiac involvement by wall thickness [45]. In another study, among 12 patients with ATTRm and no evidence of infiltrative cardiomyopathy by normal TTE and biomarkers (N-terminal pro b-type natriuretic peptide [NT-proBNP], troponin-I), 10/12 had some abnormal Tc99m-PYP uptake and 7/12 had diagnostic levels of tracer uptake (grade 2 or 3) [64]. Although myocardial radiotracer uptake in these asymptomatic patients was lower than that seen in patients with ATTRm-related heart failure, it was significantly higher than in patients with non-ATTRm-related HFpEF, suggesting a role for Tc99m-PYP nuclear scintigraphy for early detection of ATTR-CA.

Preliminary data suggest that PET cardiac imaging may also play a role in early diagnosis. Of 10 patients with ATTRm (V30M), mean age 68.7 years, with primary neurological manifestations of ATTR, 11C-PIB myocardial PET detected abnormal cardiac uptake in all patients, indicating cardiac involvement before overt heart failure symptoms [56].

Subtyping

Differentiating between AL and ATTR-CA is crucial, as the prognosis for AL is worse than ATTR-CA [2] and the therapeutic options for AL (including chemotherapy and stem cell transplantation) have no role and may be harmful if given to a patient with ATTR-CA.

Among the non-invasive cardiac imaging modalities studied to-date, nuclear scintigraphy has demonstrated strong evidence for accurate subtyping given the preferential affinity of

these agents for TTR amyloid fibrils [33, 45, 46, 49, 51, 52, 65]. In 45 elderly patients with biopsy proven CA (16 ATTRwt, 17 ATTRm, 12 AL, mean ages 77, 70, 63, respectively), a Tc99m-PYP H/CL ratio >1.5 was found to be 97% sensitive and 100% specific for distinguishing ATTR-CA from AL [49]. In a multicenter study of 171 elderly patients, median age 73 (65–79), (121 ATTR-CA, 34 AL, 16 non-amyloid HFpEF), a Tc99m-PYP H/CL ratio of 1.5 in subjects scanned after 1 hour radioisotope incubation (and 1.3 for 3 hour incubation) was 91% sensitive and 92% specific for detecting ATTR-CA and differentiating it from AL [50]. False positives were typically patients with AL who had trace but not insignificant myocardial radiotracer uptake or in patients with AL and focal uptake suggesting a history of myocardial infarction. The multicenter international collaboration in patients with CA who had undergone Tc99m-DPD, -PYP, or -HMDP, demonstrated that a positive nuclear scan with myocardial uptake of grade 2 or higher and the absence of an abnormal monoclonal protein (ruling out AL) was 100% specific for ATTR-CA [53].

Recent reports using PET imaging have demonstrated promise in subtyping CA [66–68]. In a case study using (18)F-NaF, also a bone seeking tracer, diffuse myocardial enhancement was observed in a patient with ATTRm (Val122Ile) with no uptake in a patient with AL [66]. In a study of 7 elderly patients with CA (3 ATTRwt, 2 ATTRm-V122I, 2 AL, mean age 71.1), qualitative and quantitative (18)F-NaF uptake was significantly increased in ATTR-CA and absent in controls and patients with AL, further suggesting a role for (18)F-NaF in subtyping [67]. However, another case report of two patients with ATTR-CA (1 ATTRwt and 1 ATTRm-Ile68Leu) demonstrated no cardiac uptake of (18)F-NaF in either patient. The authors concluded that the presence and type of ATTR mutation may influence (18)F-NaF tracer uptake [68]. A recent study of (18)F-florbetapir uptake in myocardial autopsy specimens (10 AL, 10 ATTR, 10 controls) found increased uptake in all CA patients and no controls, with uptake greater in AL than ATTR [58], while another study demonstrated increased liver uptake of (18)F-florbetapir in AL and normal liver uptake in ATTR-CA [69], suggesting that (18)F-florbetapir may preferentially bind AL fibrils.

TTE has demonstrated limited utility in subtyping amyloid since ATTRwt, ATTRm, and AL all share similar echocardiographic features, though data from one study suggested that CMR may have a role. Among 97 patients with CA (51 ATTR-CA, 46 AL, mean age 68), a scoring system using a logistic regression model including LGE, age, and wall thickness was 87% sensitive and 96% specific for differentiating ATTR-CA from AL [37].

Despite lack of data supporting the utility of 2D TTE, strain, and CMR to accurately subtype CA, these modalities have revealed subtle differences between subtypes. By TTE comparisons of 15 ATTRwt, 61 ATTRm, and 157 AL patients, one study demonstrated that mean LV and IVS wall thickness was greatest in patients with ATTRwt, followed by ATTRm, and AL (mean LV wall thickness - 18.8mm vs. 16.0mm vs. 15.2mm, $p<0.0001$; IVS 19.7mm vs. 16.6mm vs. 15.8mm, $p<0.0001$) [2]; subsequent studies have replicated these findings [20, 49, 70, 71]. While apical strain sparing on SSI is found among all CA subtypes [20, 28], a study of 172 patients (56 ATTRwt, 36 ATTRm, 80 AL), showed that patients with ATTRwt and AL had worse LS than patients with ATTRm [20] and another demonstrated that elderly patients with ATTRwt had worse radial and circumferential strain

than elderly patients with ATTRm [72]. CMR studies have demonstrated that patients with ATTR-CA, and ATTRwt in particular, had greater LV mass [37, 70] and were more likely to have RV LGE than patients with AL [37]. Additional studies are required to determine whether LGE patterns (subendocardial vs. transmural) relate to CA subtype [31, 37]. Together, these differences suggest that ATTRwt is usually diagnosed later with greater myocardial deposition of amyloid compared to ATTRm and AL, perhaps related to the lower myocardial toxicity of TTR deposits than those of AL.

Once echocardiography or CMR have elevated clinical suspicion for CA, the above metrics can help delineate subtle anatomic differences but should not be used for the purpose of subtyping disease.

Assessment of ventricular impairment

Evaluating the degree of ventricular functional impairment in elderly patients with CA is an important management goal not only to gain insight into functional status, but also to risk stratify and determine the appropriateness of specific forthcoming therapies. Accurately quantifying amyloid burden may also aid in determining disease severity. As endomyocardial biopsy is prone to sampling error and therefore may not accurately quantify myocardial amyloid burden, non-invasive approaches may capture a more clinically relevant picture.

Conventional echocardiographic techniques play an important role in functional assessment, measuring wall thickness and LVEF, as well as identifying patterns of diastolic dysfunction and restrictive physiology. These indices are important markers of disease severity, but conventional echocardiography is limited in its ability to detect and stratify early functional impairment. Strain echocardiography can detect impairments in myocardial function before overt systolic or diastolic dysfunction are detected on standard TTE [15]. Impairments in LS also correlate with impaired LVEF [23, 28], increased wall thickness [20], and LGE on CMR [26, 28] in later stages of disease.

On CMR, patterns of LGE reflect different stages of disease severity and may offer clues as to the degree of myocardial involvement. Patchy intramural focal enhancement is typically seen in less severe disease, while global subendocardial LGE is associated with increasing disease severity (i.e. worse heart failure symptoms, ECG changes, and elevated troponin-T and BNP) [34], and transmural LGE represents advanced disease. Transmural LGE is associated with a host of markers of functional impairment including low systolic blood pressure, conduction disease, elevated NT-proBNP, increased wall thickness, severe diastolic dysfunction, and decreased functional capacity on 6-minute walk test [38]. Additionally, the degree of native T1 elevation [38, 40] and ECV expansion [31, 38] both correlate with disease severity. Increasing ECV has been associated with depressions in systolic function, increased wall thickness, worsening diastolic dysfunction, and elevations in NT-proBNP and troponin-I [41]. Increasing ECV was also associated with increasing LGE on CMR (a progression of none to subendocardial to transmural enhancement) and increasing Tc99m-DPD visual grade (all comparisons $p < .0001$) [38].

Nuclear scintigraphy may also aid in the functional assessment of the elderly patient diagnosed with ATTR-CA as the degree of radiotracer uptake has correlated with markers of disease severity. In elderly patients with ATTR-CA, an increased Tc99m-DPD H:WB ratio correlated with increased cardiac biomarkers, renal failure, increased wall thickness and LV mass index, worse LVEF, diastolic dysfunction, and low mitral annular plane systolic excursion, an echocardiographic measure of longitudinal systolic dysfunction [47, 48, 73, 74]. An increased Tc99m-HMDP heart:skull ratio correlated with increased cardiac biomarkers and worse LVEF [51]. And among elderly patients with ATTR-CA, a Tc99m-PYP H/CL ratio of > 1.6 vs. < 1.6 was associated with lower LVEF, increased IVS thickness, lower stroke volume, and a lower myocardial contraction fraction, a ratio of stroke volume to myocardial volume [50] that has been associated with worse survival in patients with AL amyloid [75].

PET imaging has shown preliminary promise in quantifying disease burden. A recent study demonstrated that the percent of (18)F-florbetaben uptake was an independent determinant of LV and RV LS [59]. More data is required, as PET tracers are in early phases of evaluation for ATTR-CA.

Prognostication

Recently, a three-tier staging system was developed to predict overall survival of patients with ATTRwt using the biomarker cutoffs troponin-T > 0.5 ng/mL and NT-proBNP > 3000 pg/mL. Median survival was 66 months for patients with both biomarker values below threshold (Stage I), 40 months for patients with one value above threshold (Stage II), and 20 months for patients with both biomarkers above threshold (Stage III) [76]. In addition to biomarkers, cardiac imaging techniques have also been shown to inform prognosis in elderly patients with ATTR-CA.

2D TTE features, including systolic and diastolic dysfunction, as well as restrictive filling patterns have been associated with worse outcomes [77, 78]. Among all CA subtypes, a TAPSE < 14 mm predicted major adverse cardiac events (MACE), including acute decompensated heart failure, orthotopic heart transplantation, and death [18]. Strain assessment of 172 patients with CA (56 ATTRwt, 36 ATTRm, 80 AL, mean age 66) demonstrated that impaired LV basal LS was independently associated with all-cause mortality [20]. Of 97 patients with CA (38 ATTR 59 AL, mean age 64) a higher RRSR (indicating more basal and mid ventricular strain impairment relative to the apex) predicted MACE [29].

Global subendocardial LGE on CMR correlated with worse New York Heart Association (NYHA) functional class, elevated troponin-T and BNP [34], and death [36, 79] and a transmural LGE pattern independently predicted death [38]. In elderly patients with ATTRwt, increased LV mass and maximal apical wall thickness on CMR also independently predicted worse outcomes [70] and among all CA subtypes, a hypo-intense T2 signal predicted worse survival [80].

Nuclear scintigraphy may also be helpful in prognosticating survival in elderly patients diagnosed with ATTR-CA. While a recent study demonstrated that stratification by the semiquantitative visual score of Tc99m-DPD uptake, derived by Perugini et al., did not assist in prognosticating [81], quantitative assessments have been more successful. Among 63 patients with hereditary ATTR-CA, increased myocardial uptake of Tc99m-DPD using the heart-to-whole body ratio in conjunction with mean LV wall thickness >12mm was associated with worse MACE free survival [48]. In a study of 55 patients with ATTR-CA and 14 with AL, increased myocardial retention of Tc99m-HMDP using the heart-skull ratio > 1.94 was associated with increased acute heart failure and/or death [51]. And finally, among 121 patients with biopsy proven ATTR pooled from 3 centers in the United States, despite a referral population with high pre-test probability of disease and the employment of two scan protocols, a ratio of 1.6 or greater of Tc99m-PYP uptake was associated with worse survival [50].

Monitoring disease progression and assessing response to therapy

Among elderly adults with ATTR-CA, general treatment principles include maintaining euvolemia, avoiding symptomatic hypotension, and assessment for pacemaker therapy in those with clinically significant conduction disease [4]. Select patients with advanced disease may undergo heart transplant, however many elderly patients with ATTR-CA are beyond institutional age cut-offs at the time of diagnosis or may have other comorbidities that preclude them from transplantation. Disease-modifying therapies for ATTR-CA are under active clinical investigation and include TTR stabilizers, silencers, and amyloid degrading therapies [4]. In a phase 2 trial of 31 patients with ATTRwt (mean age 76.7), 30/31 patients treated with Tafamidis achieved TTR stabilization after 6 weeks, and of the 28 patients that completed therapy for 1 year, NT-proBNP levels and echocardiographic findings remained unchanged, and 20/28 patients maintained the same NYHA functional class [82]. Though no agents are currently FDA approved for ATTR-CA, a new era in the treatment of this disease is rapidly approaching [4, 83] and with it, the need for cardiac imaging to effectively monitor therapeutic response. Cardiac imaging in the elderly will be needed to quantify the degree of pre- and post-treatment myocardial amyloid and associated functional impairment and therefore is likely to play a significant role in monitoring response to emerging therapies for ATTR-CA

Conclusions

A host of advanced, non-invasive cardiac imaging modalities are now available to not only provide an accurate diagnosis of ATTR-CA in elderly adults with suspected disease, but also to aid in early diagnosis, amyloid subtyping, assessment of cardiac functional impairment, prognosticating disease severity, and soon, tracking response to therapy. Selecting the appropriate non-invasive imaging modality will be essential for optimal patient care in the elderly patient with ATTR-CA as we enter an era of enhanced recognition, earlier diagnosis, and potential therapeutics.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016; 68(2):161–72. [PubMed: 27386769]
2. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidosis: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009; 120(13):1203–12. [PubMed: 19752327]
3. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, et al. Cardiac amyloidosis: the great pretender. *Heart Fail Rev*. 2015; 20(2):117–24. [PubMed: 25758359]
4. Castano A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev*. 2015; 20(2):163–78. [PubMed: 25408161]
5. Wan He, DG., Paul Kowal. *An Aging World: 2015: United States Census Bureau* 2016. Mar. 2016
6. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016; 133(4):e38–360. [PubMed: 26673558]
7. Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin Cardiac Amyloidosis in Older Americans. *J Card Fail*. 2016; 22(12):996–1003. [PubMed: 27769906]
8. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral F, Cobo-Marcos M, Robles C, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015
9. Givens RC, Russo C, Green P, Maurer MS. Comparison of cardiac amyloidosis due to wild-type and V122I transthyretin in older adults referred to an academic medical center. *Aging health*. 2013; 9(2): 229–35. [PubMed: 24073013]
10. Narotsky DL, Castano A, Weinsaft JW, Bokhari S, Maurer MS. Wild-Type Transthyretin Cardiac Amyloidosis: Novel Insights From Advanced Imaging. *Can J Cardiol*. 2016; 32(9) 1166 e1- e10.
11. Cappelli F, Baldasseroni S, Bergesio F, Perlini S, Salinaro F, Padeletti L, et al. Echocardiographic and biohumoral characteristics in patients with AL and TTR amyloidosis at diagnosis. *Clin Cardiol*. 2015; 38(2):69–75. [PubMed: 25645201]
12. Aljaroudi WA, Desai MY, Tang WH, Phelan D, Cerqueira MD, Jaber WA. Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: state of the art review and focus on emerging nuclear techniques. *J Nucl Cardiol*. 2014; 21(2):271–83. [PubMed: 24347127]
13. Di Bella G, Pizzino F, Minutoli F, Zito C, Donato R, Dattilo G, et al. The mosaic of the cardiac amyloidosis diagnosis: role of imaging in subtypes and stages of the disease. *Eur Heart J Cardiovasc Imaging*. 2014; 15(12):1307–15. [PubMed: 25190073]
14. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J*. 2012; 164(2):222–8. e1. [PubMed: 22877808]

15. Liu D, Niemann M, Hu K, Herrmann S, Stork S, Knop S, et al. Echocardiographic evaluation of systolic and diastolic function in patients with cardiac amyloidosis. *Am J Cardiol.* 2011; 108(4): 591–8. [PubMed: 21807135]
16. Damy T, Maurer MS, Rapezzi C, Plante-Bordeneuve V, Karayal ON, Mundayat R, et al. Clinical, ECG and echocardiographic clues to the diagnosis of TTR-related cardiomyopathy. *Open Heart.* 2016; 3(1):e000289. [PubMed: 26870387]
17. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. *Am J Hematol.* 2005; 79(4):319–28. [PubMed: 16044444]
18. Bodez D, Ternacle J, Guellich A, Galat A, Lim P, Radu C, et al. Prognostic value of right ventricular systolic function in cardiac amyloidosis. *Amyloid.* 2016; 23(3):158–67. [PubMed: 27348696]
19. Zhao L, Fang Q. Recent advances in the noninvasive strategies of cardiac amyloidosis. *Heart Fail Rev.* 2016; 21(6):703–21. [PubMed: 27554493]
20. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation.* 2014; 129(18):1840–9. CIRCULATIONAHA.113.006242 [pii]. [PubMed: 24563469]
21. Rocha AM, Ferreira SG, Nacif MS, Ribeiro ML, Freitas MR, Mesquita CT. Speckle Tracking and Transthyretin Amyloid Cardiomyopathy. *Arq Bras Cardiol.* 2017; 108(1):21–30. [PubMed: 27992035]
22. Lindqvist P, Olofsson BO, Backman C, Suhr O, Waldenstrom A. Pulsed tissue Doppler and strain imaging discloses early signs of infiltrative cardiac disease: a study on patients with familial amyloidotic polyneuropathy. *Eur J Echocardiogr.* 2006; 7(1):22–30. [PubMed: 15869906]
23. Porciani MC, Lilli A, Perfetto F, Cappelli F, Massimiliano Rao C, Del Pace S, et al. Tissue Doppler and strain imaging: a new tool for early detection of cardiac amyloidosis. *Amyloid.* 2009; 16(2): 63–70. [PubMed: 20536397]
24. Di Bella G, Minutoli F, Pingitore A, Zito C, Mazzeo A, Aquaro GD, et al. Endocardial and epicardial deformations in cardiac amyloidosis and hypertrophic cardiomyopathy. *Circ J.* 2011; 75(5):1200–8. [PubMed: 21427499]
25. Engvall C, Henein M, Holmgren A, Suhr OB, Morner S, Lindqvist P. Can myocardial strain differentiate hypertrophic from infiltrative etiology of a thickened septum? *Echocardiography.* 2011; 28(4):408–15. [PubMed: 21323993]
26. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, et al. Differentiating cardiac amyloidosis and hypertrophic cardiomyopathy by use of three-dimensional speckle tracking echocardiography. *Echocardiography.* 2012; 29(6):668–77. [PubMed: 22486396]
27. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart.* 2012; 98(19):1442–8. [PubMed: 22865865]
28. Ternacle J, Bodez D, Guellich A, Audureau E, Rappeneau S, Lim P, et al. Causes and Consequences of Longitudinal LV Dysfunction Assessed by 2D Strain Echocardiography in Cardiac Amyloidosis. *JACC Cardiovasc Imaging.* 2016; 9(2):126–38. [PubMed: 26777222]
29. Senapati A, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, et al. Prognostic implication of relative regional strain ratio in cardiac amyloidosis. *Heart.* 2016; 102(10):748–54. [PubMed: 26830665]
30. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. *Circ Cardiovasc Imaging.* 2013; 6(6):1066–72. [PubMed: 24100046]
31. Fontana M, Banyersad SM, Treibel TA, Abdel-Gadir A, Maestrini V, Lane T, et al. Differential Myocyte Responses in Patients with Cardiac Transthyretin Amyloidosis and Light-Chain Amyloidosis: A Cardiac MR Imaging Study. *Radiology.* 2015; 277(2):388–97. [PubMed: 25997029]

32. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation*. 2005; 111(2):186–93. [PubMed: 15630027]
33. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol*. 2005; 46(6):1076–84. [PubMed: 16168294]
34. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2010; 3(2):155–64. [PubMed: 20159642]
35. Vogelsberg H, Mahrholdt H, Deluigi CC, Yilmaz A, Kispert EM, Greulich S, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. *J Am Coll Cardiol*. 2008; 51(10):1022–30. [PubMed: 18325442]
36. White JA, Kim HW, Shah D, Fine N, Kim KY, Wendell DC, et al. CMR imaging with rapid visual T1 assessment predicts mortality in patients suspected of cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2014; 7(2):143–56. [PubMed: 24412191]
37. Dungu JN, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2014; 7(2):133–42. [PubMed: 24412186]
38. Fontana M, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banyersad SM, et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation*. 2015; 132(16):1570–9. [PubMed: 26362631]
39. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2016; 16:129. [PubMed: 27267362]
40. Fontana M, Banyersad SM, Treibel TA, Maestrini V, Sado DM, White SK, et al. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging*. 2014; 7(2):157–65. [PubMed: 24412190]
41. Barison A, Aquaro GD, Pugliese NR, Cappelli F, Chiappino S, Vergaro G, et al. Measurement of myocardial amyloid deposition in systemic amyloidosis: insights from cardiovascular magnetic resonance imaging. *J Intern Med*. 2015; 277(5):605–14. [PubMed: 25346163]
42. Hongo M, Hirayama J, Fujii T, Yamada H, Okubo S, Kusama S, et al. Early identification of amyloid heart disease by technetium-99m-pyrophosphate scintigraphy: a study with familial amyloid polyneuropathy. *Am Heart J*. 1987; 113(3):654–62. [PubMed: 3030086]
43. Kula RW, Engel WK, Line BR. Scanning for soft-tissue amyloid. *Lancet*. 1977; 1(8002):92–3. [PubMed: 63730]
44. Wizenberg TA, Muz J, Sohn YH, Samlowski W, Weissler AM. Value of positive myocardial technetium-99m-pyrophosphate scintigraphy in the noninvasive diagnosis of cardiac amyloidosis. *Am Heart J*. 1982; 103(4 Pt 1):468–73. [PubMed: 6278906]
45. Hutt DF, Quigley AM, Page J, Hall ML, Burniston M, Gopaul D, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. *Eur Heart J Cardiovasc Imaging*. 2014; 15(11):1289–98. [PubMed: 24939945]
46. Rapezzi C, Guidalotti P, Salvi F, Riva L, Perugini E. Usefulness of 99mTc-DPD scintigraphy in cardiac amyloidosis. *J Am Coll Cardiol*. 2008; 51(15):1509–10. author reply 10. [PubMed: 18402909]
47. Glaudemans AW, van Rheeën RW, van den Berg MP, Noordzij W, Koole M, Blokzijl H, et al. Bone scintigraphy with (99m)technetium-hydroxymethylene diphosphonate allows early diagnosis of cardiac involvement in patients with transthyretin-derived systemic amyloidosis. *Amyloid*. 2014; 21(1):35–44. [PubMed: 24455993]
48. Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging*. 2011; 4(6):659–70. [PubMed: 21679902]
49. Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ Cardiovasc Imaging*. 2013; 6(2):195–201. CIRCIMAGING.112.000132 [pii]. In this study of 45 patients with ATTR wild-type, ATTR

mutant, and AL cardiac amyloidosis, a heart: contralateral ratio greater than 1.5 using Tc99m-PYP nuclear scintigraphy was found to differentiate ATTR cardiac amyloidosis from AL with a sensitivity of 97% and specificity of 100%, with an area under the curve 0.992 ($p < 0.0001$). [PubMed: 23400849]

- 50•. Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol.* 2016 This multicenter retrospective cohort study of 171 participants demonstrated that a Tc99m-PYP heart:contralateral ratio >1.5 was 91% sensitive and 92% specific (area under the curve 0.960) for diagnosing ATTR cardiac amyloidosis compared to AL amyloidosis and non-amyloid heart failure with preserved ejection fraction. Furthermore, among patients with ATTR cardiac amyloidosis, a heart:contralateral ratio of 1.6 or greater was associated with worse survival. Therefore, in this multicenter study, Tc99m-PYP cardiac imaging was diagnostic and prognostic for ATTR cardiac amyloidosis.
51. Galat A, Rosso J, Guellich A, Van Der Gucht A, Rappeneau S, Bodez D, et al. Usefulness of (99m)Tc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. *Amyloid.* 2015; 22(4):210–20. [PubMed: 26465835]
52. Abulizi M, Cottreau AS, Guellich A, Vandeventer S, Galat A, Van Der Gucht A, et al. Early-phase myocardial uptake intensity of 99mTc-HMDP vs 99mTc-DPD in patients with hereditary transthyretin-related cardiac amyloidosis. *J Nucl Cardiol.* 2016
- 53•. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation.* 2016; 133(24):2404–12. This international, multicenter study showed that in patients with histologically proven cardiac amyloidosis, abnormally elevated myocardial radiotracer uptake of Tc99m-DPD, -PYP, or -HMDP was $>99\%$ sensitive and 86% specific for ATTR cardiac amyloidosis. A myocardial uptake visual score of 2 or 3 without evidence of an abnormal monoclonal protein was found to be 100% specific for ATTR cardiac amyloidosis without the need for biopsy. These findings led to the international consensus that in the absence of an abnormal monoclonal protein, a positive nuclear scan confirms diagnosis without the need for biopsy. [PubMed: 27143678]
54. Bokhari S, Morgenstern R, Weinberg R, Kinkhabwala M, Panagiotou D, Castano A, et al. Standardization of 99mTechnetium pyrophosphate imaging methodology to diagnose TTR cardiac amyloidosis. *J Nucl Cardiol.* 2016
55. Antoni G, Lubberink M, Estrada S, Axelsson J, Carlson K, Lindsjo L, et al. In vivo visualization of amyloid deposits in the heart with 11C-PIB and PET. *J Nucl Med.* 2013; 54(2):213–20. [PubMed: 23238792]
56. Pilebro B, Arvidsson S, Lindqvist P, Sundstrom T, Westermarck P, Antoni G, et al. Positron emission tomography (PET) utilizing Pittsburgh compound B (PIB) for detection of amyloid heart deposits in hereditary transthyretin amyloidosis (ATTR). *J Nucl Cardiol.* 2016
57. Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, et al. Imaging cardiac amyloidosis: a pilot study using (1)(8)F-florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging.* 2014; 41(9):1652–62. [PubMed: 24841414]
58. Park MA, Padera RF, Belanger A, Dubey S, Hwang DH, Veeranna V, et al. 18F-Florbetapir Binds Specifically to Myocardial Light Chain and Transthyretin Amyloid Deposits: Autoradiography Study. *Circ Cardiovasc Imaging.* 2015; 8(8)
59. Law WP, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac Amyloid Imaging with 18F-Florbetaben PET: A Pilot Study. *J Nucl Med.* 2016; 57(11):1733–9. [PubMed: 27307344]
60. Trivieri MG, Dweck MR, Abgral R, Robson PM, Karakatsanis NA, Lala A, et al. 18F-Sodium Fluoride PET/MR for the Assessment of Cardiac Amyloidosis. *J Am Coll Cardiol.* 2016; 68(24):2712–4. [PubMed: 27978955]
61. Mallik A, Drzezga A, Minoshima S. Clinical Amyloid Imaging. *Semin Nucl Med.* 2017; 47(1):31–43. [PubMed: 27987555]
62. Coelho T, Merlini G, Bulawa CE, Fleming JA, Judge DP, Kelly JW, et al. Mechanism of Action and Clinical Application of Tafamidis in Hereditary Transthyretin Amyloidosis. *Neurol Ther.* 2016; 5(1):1–25. [PubMed: 26894299]
63. Deux JF, Damy T, Rahmouni A, Mayer J, Plante-Bordeneuve V. Noninvasive detection of cardiac involvement in patients with hereditary transthyretin associated amyloidosis using cardiac

- magnetic resonance imaging: a prospective study. *Amyloid*. 2014; 21(4):246–55. [PubMed: 25211144]
64. Haq M, Pawar S, Berk JL, Miller EJ, Ruberg FL. Can 99m-Tc-Pyrophosphate Aid in Early Detection of Cardiac Involvement in Asymptomatic Variant TTR Amyloidosis? *JACC Cardiovasc Imaging*. 2016
 65. Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol*. 2016; 1(8):880–9. [PubMed: 27557400]
 66. Van Der Gucht A, Galat A, Rosso J, Guellich A, Garot J, Bodez D, et al. [18F]-NaF PET/CT imaging in cardiac amyloidosis. *J Nucl Cardiol*. 2016; 23(4):846–9. [PubMed: 26403145]
 67. Morgenstern R, Yeh R, Castano A, Maurer MS, Bokhari S. 18Fluorine sodium fluoride positron emission tomography, a potential biomarker of transthyretin cardiac amyloidosis. *J Nucl Cardiol*. 2017
 68. Gagliardi C, Tabacchi E, Bonfiglioli R, Diodato S, Nanni C, Guidalotti P, et al. Does the etiology of cardiac amyloidosis determine the myocardial uptake of [18F]-NaF PET/CT? *J Nucl Cardiol*. 2016
 69. Osborne DR, Acuff SN, Stuckey A, Wall JS. A Routine PET/CT Protocol with Streamlined Calculations for Assessing Cardiac Amyloidosis Using (18)F-Florbetapir. *Front Cardiovasc Med*. 2015; 2:23. [PubMed: 26664895]
 70. Kristen AV, aus dem Siepen F, Scherer K, Kammerer R, Andre F, Buss SJ, et al. Comparison of different types of cardiac amyloidosis by cardiac magnetic resonance imaging. *Amyloid*. 2015; 22(2):132–41. [PubMed: 26053103]
 71. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banyersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc*. 2013; 2(2):e000098. [PubMed: 23608605]
 72. Minamisawa M, Koyama J, Sekijima Y, Ikeda S, Kozuka A, Ebisawa S, et al. Comparison of the standard and speckle tracking echocardiographic features of wild-type and mutated transthyretin cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging*. 2016; 17(4):402–10. [PubMed: 26873458]
 73. Kristen AV, Haufe S, Schonland SO, Hegenbart U, Schnabel PA, Rocken C, et al. Skeletal scintigraphy indicates disease severity of cardiac involvement in patients with senile systemic amyloidosis. *Int J Cardiol*. 2013; 164(2):179–84. [PubMed: 21764155]
 74. Kristen AV, Scherer K, Buss S, aus dem Siepen F, Haufe S, Bauer R, et al. Noninvasive risk stratification of patients with transthyretin amyloidosis. *JACC Cardiovasc Imaging*. 2014; 7(5): 502–10. [PubMed: 24726252]
 75. Tendler A, Helmke S, Teruya S, Alvarez J, Maurer MS. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. *Amyloid*. 2015; 22(1):61–6. [PubMed: 25510353]
 76. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol*. 2016; 68(10):1014–20. [PubMed: 27585505]
 77. Klein AL, Hatle LK, Taliencio CP, Oh JK, Kyle RA, Gertz MA, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiography study. *Circulation*. 1991; 83(3):808–16. [PubMed: 1999031]
 78. Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. *J Am Coll Cardiol*. 1996; 28(3):658–64. [PubMed: 8772753]
 79. Raina S, Lensing SY, Nairooz RS, Pothineni NV, Hakeem A, Bhatti S, et al. Prognostic Value of Late Gadolinium Enhancement CMR in Systemic Amyloidosis. *JACC Cardiovasc Imaging*. 2016; 9(11):1267–77. [PubMed: 27568115]
 80. Wassmuth R, Abdel-Aty H, Bohl S, Schulz-Menger J. Prognostic impact of T2-weighted CMR imaging for cardiac amyloidosis. *Eur Radiol*. 2011; 21(8):1643–50. [PubMed: 21720941]
 81. Hutt DF, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, et al. Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging*. 2017

82. Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, et al. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. *Circ Heart Fail.* 2015; 8(3):519–26. [PubMed: 25872787]
83. Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. *Ann Med.* 2015; 47(8):625–38. [PubMed: 26611723]

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Imaging Modality		Diagnostic and Management Goals						
		Raise suspicion	Early Diagnosis	Diagnosis	Subtyping	Ventricular assessment	Prognosis	Response to Therapy
2D TTE		Established Utility	Low Utility	Low Utility	Low Utility	Established Utility	Established Utility	Potential Utility
Speckle tracking strain		Established Utility	Potential Utility	Low Utility	Low Utility	Established Utility	Established Utility	Potential Utility
Cardiac MRI		Established Utility	Potential Utility	Potential Utility	Potential Utility	Established Utility	Established Utility	Potential Utility
Bone Isotope Nuclear Scintigraphy		Potential Utility	Potential Utility	Established Utility	Established Utility	Low Utility	Potential Utility	Potential Utility
PET		Potential Utility	Potential Utility	Potential Utility	Potential Utility	Potential Utility	Potential Utility	Potential Utility

Key

Established Utility

- ✓ Multicenter experiences and/or
- ✓ Multiple publications and/or
- ✓ International expert consensus

Potential Utility

- ✓ Single-center experiences

Low Utility

- ✓ Case reports and
- ✓ Case series

Figure 1. Utility of advanced cardiac imaging modalities for various ATTR-CA diagnostic and management goals. Visual depiction of the potential utility of each advanced cardiac imaging modality for each corresponding diagnostic and management goal.