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State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis

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Abstract

Cardiac amyloidosis, once considered untreatable, is now gaining well-deserved attention due to advances in imaging and the recent approval of targeted breakthrough therapies. In this paper, we discuss the role of radionuclide imaging in the evaluation and management of patients with the most common form of amyloidosis—cardiac transthyretin amyloidosis (ATTR). We provide a comprehensive summary of the literature interspersed with our institutional experience as appropriate, to deliver our perspective.

Keywords

Amyloid heart disease; SPECT; PET; modalities; molecular imaging

BACKGROUND

Cardiac amyloidosis, once considered untreatable, is now gaining well-deserved attention due to advances in imaging and the recent approval of targeted breakthrough therapies.[1,2] In this paper, we discuss the role of radionuclide imaging in the evaluation and management of

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patients with the most common form of amyloidosis—cardiac transthyretin amyloidosis (ATTR). We provide a comprehensive summary of the literature interspersed with our institutional experience as appropriate, to deliver our perspective.

Cardiac amyloidosis is a disorder in which proteins mis-fold and deposit as amyloid fibrils that infiltrate the myocardial extracellular space. Transthyretin protein (ATTR) derived from the liver or immunoglobulin light chain proteins (AL), derived from a plasma cell clone, most commonly affect the heart.[3] The former can be due to variant TTR from TTR gene mutations (ATTRm or hereditary amyloidosis) or wild-type TTR deposition where native TTR proteins mis-fold with aging and deposit as fibrils in the heart (ATTRwt, also previously known as senile systemic amyloidosis). With mutant TTR, although over hundred genotypic mutations have been identified in hereditary amyloidosis, variable penetrance results in varying degrees of heart involvement.[4] Whereas, at least 50% of primary AL patients[5] and almost all wild-type ATTR patients have cardiac involvement,[6] but can be challenging to identify.

NEED FOR ACCURATE DIAGNOSIS AND TYPING OF CARDIAC AMYLOID FIBRILS

Diagnosis of cardiac amyloidosis is frequently delayed[7] for a number of reasons. Clinical manifestations are varied, serum cardiac biomarker elevation is non-specific, awareness about the condition is lacking, and until recently, noninvasive techniques for specific diagnosis were not available. Appropriate therapies are delayed in a substantial proportion of the affected individuals. Now, advanced imaging, echocardiography[8] and cardiac magnetic resonance (CMR),[9] can detect cardiac structural and functional changes induced by amyloid deposition. However, they can neither distinguish amyloid from non-amyloid hypertrophic heart disease nor ATTR from AL (which is treated very differently using chemotherapy). This necessitates a histological diagnosis. A fat pad biopsy though simple, has low diagnostic yield in ATTR cardiac amyloidosis (sensitivity: 15% in wildtype ATTR, 45% in mutant ATTR).[10] This is why historically, endomyocardial biopsy has been used to confirm cardiac amyloidosis and identify the fibril type. The good news is that data now supports the value of radionuclide imaging with bone avid radiotracers to specifically image ATTR cardiac amyloidosis—obviating the need for endomyocardial biopsy.[11]

Radionuclide imaging plays a critical role in the diagnosis and identification of ATTR cardiac amyloidosis. Accurate diagnosis of heart failure from cardiac amyloidosis has major implications on patient care, as well. Correct identification of hereditary ATTR cardiac amyloidosis has critical and generationally relevant implications for genetic testing and family counseling. Misidentification of the type of cardiac amyloid can be life threatening if ATTR patients are misclassified as AL and erroneously treated with chemotherapy. Conventional heart failure medications, betablockers and angiotensin-converting enzyme inhibitors, are poorly tolerated by patients with amyloidosis and frequently avoided.[12] Appropriate use of bone avid radiotracer imaging can significantly increase the detection of patients with cardiac ATTR amyloidosis; these patients, will benefit from specific disease

modifying therapies targeting the cause of heart failure, TTR, that improve quality of life, heart failure, and prolong life.[13]

BONE AVID RADIOTRACERS

Cardiac imaging with bone avid radiotracers has been used clinically for over 40 years. Early studies showed high-diagnostic accuracies leading to great excitement in the field and a profusion of studies. Curiously, some of the later studies reported lower diagnostic accuracies; one paper from 1987 concluded that "when intense uptake of ^{99m}Tc-pyrophosphate (PYP) is present amyloidosis is highly likely, but the technique is not sufficiently sensitive."[14] Astute investigators, in the early 2000s, recognized greater binding avidity of ^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxylic acid (DPD) to ATTR (rather than AL). This new knowledge led to a rebirth of cardiac imaging with bone avid radiotracers for ATTR amyloidosis.

MECHANISM OF BINDING OF BONE AVID RADIOTRACERS

Pyrophosphate (PYP) and closely related bis-phosphonates (DPD, hydroxymethylene diphosphonate, HMDP) labeled with^{99m}Tc have been used for imaging cardiac ATTR amyloidosis (Figure 1). These tracers were used for myocardial infarct imaging in the 1970s and several binding sites have been identified in animal experiments, including microcalcifications, calcium deposits,[15] intracellular calcium PYP,[16] or intracellular macromolecules.[17] In the context of amyloidosis, the fibril deposits have three major structural components, the precursor protein, heparin sulfate proteoglycan, and a calcium dependent P-component that binds the fibrils together. Pepys et al. suggest that circulating amyloid P component, a universal component of all types of amyloid, could bind to amyloid fibrils via a calcium mediated mechanism, also explaining the uptake of ^{99m}Tc-bone avid tracers.[18] More recently, Stats et al.[19] demonstrated that endomyocardial biopsies of ATTR hearts had greater density of small microcalcifications but fewer macrophages when compared with AL hearts. Interestingly, even though patients with ATTR cardiac amyloidosis were older than AL cardiac amyloidosis, the extent of these microcalcifications did not correlate with age in either group. It should also be recognised that in a few cases of AL cardiac amyloidosis, there were microcalcification densities comparable with ATTR hearts. This suggests a pathophysiological basis for reports of borderline positive ^{99m}Tc-PYP or ^{99m}Tc-DPD scan in AL patients.[20,21] The other clinical scenario where cardiac microcalcifications might lead to positive scans are myocardial infarcts where uptake is typically regional and distinct from the diffuse uptake observed in ATTR amyloidosis.[15]

REVIEW OF LITERATURE ON IMAGING PROTOCOLS

Radiotracers

Three tracers, ^{99m}Tc-PYP, -DPD, -HMDP, have been evaluated for imaging ATTR cardiac amyloidosis, but they are not widely available. ^{99m}Tc-PYP is available in the United States, while ^{99m}Tc-DPD, -HMDP are more widely available in Europe. For this reason, the accuracy of each tracer in relation to the others directly in the same patients could not be studied. ^{99m}Tc-MDP (methylene diphosphonate), is a widely used bone imaging tracer that

has not been studied in ATTR cardiac amyloidosis; its diagnostic utility of compared to ^{99m}Tc-PYP (Figure 2) and DPD is likely suboptimal. In one study, 11 ATTR patients with positive ^{99m}Tc-DPD, all showed negative ^{99m}Tc-MDP imaging.[22] On the other hand, ^{99m}Tc-HMDP and DPD imaging showed similar diagnostic utility in 6 patients with hereditary cardiac ATTR amyloidosis, but using early phase imaging (5-10 minutes after injection), not a well validated protocol.[23] Direct comparison of myocardial ^{99m}Tc-PYP with ^{99m}Tc-DPD or -HMDP imaging in ATTR cardiac amyloidosis is limited.

Planar vs SPECT

Most experience in imaging protocols for ^{99m}Tc-PYP,-DPD, -HMDP is with planar and SPECT imaging routinely (our institutional practice)[24] or planar imaging followed by SPECT if planar is positive.[14,20,21] Planar imaging alone is limited as myocardial uptake cannot be discerned from blood pool uptake, overlying rib uptake may add counts to the region of the heart (Figure 3), and attenuation correction is not feasible. SPECT overcomes these challenges. Segmental evaluation, and attenuation correction offer the potential advantages of being more quantitative and a better metric of change. ^{99m}Tc-DPD studies predominantly used whole body imaging, [21,24] while ^{99m}Tc-PYP studies used chest imaging.[25] In our experience, whole body imaging for ^{99m}Tc-PYP did not provide additional diagnostic valve, and we are currently imaging only the chest with planar and SPECT/CT imaging.

Timing Between Injection and Scan

The timing of imaging after injection of radiotracer varies from 1 to 3 hours. Most experience with ^{99m}Tc-PYP protocols is at 1 or 3 hour[11,22,24] and for ^{99m}Tc-DPD, -HMDP at 3 hours.[11,22] Our institutional practice recently changed from 2.5 hours imaging to 1-hour imaging. Imaging at 1 hour offers the advantages of patient comfort, fast laboratory throughput, and high-count images allowing the use of lower radiotracer dose, but SPECT is essential to discern myocardial uptake on planar images as blood pool versus myocardial uptake (Figure 4). Data from 4 patients with multi-time point ^{99m}Tc-DPD planar images showed peak myocardial counts 60 minutes after injection of ^{99m}Tc-DPD with a gradual decline at 2 and 3 hours; bone counts increased gradually and peaked at 2-3 hours (Figure 5).[24] For this reason, the bone to heart ratio (Perugini scoring, see next paragraph) may be more stable at ≥ 2 hours post injection. With 1-hour imaging, visual assessment for diagnosis is more sensitive (but less specific) than at 3 hours.[25] However, the disadvantages of imaging at 1-hour include persistent radiotracer activity in the blood pool, particularly in patients with renal dysfunction, which may lower the specificity on planar images. The longer 2-3 hours uptake time allows bone tracer activity to accumulate, along with a parallel reduction in blood pool and myocardial radiotracer activity leading to an enhanced specificity at the cost of reduced sensitivity (Table 1). Following similar principles, a H/CL (heart-to-contralateral lung uptake) ratio threshold of ≥ 1.5 has been established for imaging at 1 hour and a lower cutoff of ≥ 1.3 for 3-hour imaging to distinguish ATTR from AL amyloidosis to allow for decreasing myocardial counts with time.[25] In addition, studies have documented high intrareader and interreader reproducibility for visual score and H/CL ratio determination.[11,26]

Quantitation

As ^{99m}Tc-PYP, -DPD, -HMDP are hot spot imaging agents, image interpretation typically includes a ratio of myocardial uptake to other organ uptakes (bone, whole body, lung), either visually or using semiquantitative metrics.

Visual method.—Perugini and colleagues[22] described a grading scheme for 3 hours imaging where, Grade 0 = no myocardial uptake; Grade 1 = myocardial uptake < bone uptake; Grade 2 = myocardial uptake equal to bone uptake, Grade 3 = myocardial uptake > bone uptake (with attenuation of bone uptake on whole body images) (Figure 6). This is a very simple metric and includes all the limitations of 3-hour imaging listed above. The percentages of patients with the different grades of radiotracer uptake varies by center and by radiotracer used. With ^{99m}Tc-DPD/HMDP and whole-body imaging, attenuation of long bone uptake is required criterion for a Grade 3, while with ^{99m}Tc-PYP, most sites only perform chest imaging and Grade 3 is reported when myocardial tracer uptake is greater than rib uptake. Accordingly, the proportion of patients with Grade 3 uptake from major amyloidosis centers for ^{99m}Tc-PYP (46%) is higher compared to DPD/HMP (^{99m}Tc-DPD 9%; ^{99m}Tc-HMDP 9%).[11] However, in this multicenter study, the proportion of ATTR positive cases (Grade 2 plus Grade 3 derived from this paper[19]) was 56%, 40%, and 29%, respectively with PYP, DPD, and HMDP. This may reflect differences in enrolled patient characteristics, imaging protocols, or radiotracers used.

Semiquantitative method.—Rapezzi and colleagues[21] described a heart-to-whole body retention ratio using early (5 minutes) and delayed images (3 hours). Decay-corrected counts in the late images (corrected for decay and scan speed, and subtracting the activity in the kidneys, bladder) were compared to the counts in early images to derive the heart and whole body retention.[21] This method has the advantage of quantitation of radiotracer retention, but requires long time (two whole body scans, 3 hours apart), its value is not established with SPECT/CT, and novel metrics of SUV offer the potential of superior quantitation.

Bokhari and colleagues[20] defined a heart-to-contralateral lung uptake ratio (H/CL ratio) on 1-hour planar imaging for distinguishing ATTR from AL amyloidosis (≥ 1.5) and validated it also for 3-hours imaging with slightly different cut off values (≥ 1.3).[25] This is a simple metric, but includes all the challenges of 1-hour imaging and planar imaging outlined in the previous paragraph. As this is a ratio metric, optimally, it is used to distinguish AL from ATTR, when the scan shows cardiac uptake of radiotracer visually.

The optimal metric to use is likely a combination of above depends on the tracer used, timing of scan, and use of planar vs SPECT images. We interpret our scans using the visual score and review the H/CL in select cases. The semiquantitative metrics have demonstrated prognostic value as discussed later.

DIAGNOSIS OF CARDIAC ATTR AMYLOIDOSIS

Several single-center studies have confirmed high-diagnostic accuracy (sensitivity and specificity > 90%) of ^{99m}Tc-PYP,[20] -DPD[21,22,27] and -HMDP[28] imaging for cardiac ATTR amyloidosis. Specificity was lower in the presence of circulating monoclonal protein and AL

amyloidosis. In these studies, 25-50%[11,24] of patients with AL cardiac amyloidosis demonstrated myocardial uptake of ^{99m}Tc-PYP and DPD, typically, low grade (Grade 1 or 2).

In a recent large international collaboration by Gillmore et al.,[11] 1217 patients (n: ^{99m}Tc-pyrophosphate, PYP = 199, ^{99m}Tc-HMDP (hydroxy methylene diphosphonate) = 141 and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid, DPD = 877) who were referred for evaluation of suspected cardiac amyloidosis with bone compound tracers were analyzed. The authors concluded that the collective findings of ≥ Grade 2 myocardial radiotracer uptake on bone tracer cardiac scintigraphy along with absence of monoclonal gammopathy on serum and urine analysis demonstrated a specificity and positive predictive value of 100% for ATTR cardiac amyloidosis. Interestingly, up to 1/5th of patients had a monoclonal protein spike on lab evaluation, and the specificity of ≥ Grade 2 scan was only 91% in the absence of exclusion of AL cardiac amyloidosis. This highlights the absolute necessity to exclude monoclonal protein in serum and urine using immunofixation studies concurrently with bone avid tracer imaging (Figure 7). For these same parameters (≥ Grade 2 uptake and absence of monoclonal gammopathy) with a specificity of 100%, the sensitivity was 72%, 70%, and 57% for ^{99m}Tc-PYP, DPD, and HMDP respectively. As discussed previously, differences in enrolled patient features, imaging protocols, or radiotracer characteristics may account for these differences. When the clinical findings are discordant with imaging endomyocardial biopsy can be considered, in select cases, for improved detection. These data came from internationally renowned centers with expertise in clinical amyloidosis, and the diagnostic accuracy of this test when applied more broadly to centers without clinical amyloidosis expertise is yet to be determined. Integrating bone tracer cardiac scintigraphy into diagnostic algorithms could reduce healthcare costs relative to the expenses of an invasive procedure with endomyocardial biopsy (Figure 8).[29]

Increased ^{99m}Tc-DPD uptake in the muscle has been described in ATTR cardiac amyloidosis on planar imaging,[30] and more recently in the gluteal, shoulder, chest, and abdominal walls using SPECT/CT. This pattern of increased muscle uptake of radiotracer appears to be specific to ^{99m}Tc-DPD and has not been observed with ^{99m}Tc-PYP.[31] This has been our institutional experience as well.

A recent study evaluated 55 patients with biopsy proven ATTR with ^{99m}Tc-DPD scan and typing of amyloid fibril composition. In that study, 97% of patients with type A (mix of full length TTR and truncated TTR fragments) and none of the patients with type B amyloid fibrils (full length TTR only) demonstrated uptake on ^{99m}Tc-DPD scintigraphy.[32] These findings of differential myocardial uptakes based on fibril type in hereditary ATTR cardiac amyloidosis have been confirmed with ^{11}C-acetate PET,[33] but not yet widely reported by other groups.

SCREENING FOR CARDIAC ATTR AMYLOIDOSIS

The prevalence of wild type ATTR amyloidosis increases with advancing age. On autopsy studies, close to 25% of individuals above the age of 80 years demonstrated cardiac ATTR amyloid deposits.[34,35] In addition to older individuals, there is an increasing recognition that

cardiac amyloidosis is an under-diagnosed cause of heart failure in several populations. (Table 2)^{99m}Tc-PYP and DPD imaging has been used to diagnose ATTR cardiac amyloidosis in patients with hereditary ATTR,[36] heart failure with preserved ejection fraction,[37,38] degenerative aortic stenosis,[39] carpal tunnel syndrome,[40] cardiomyopathies supposed to be idiopathic or sarcomeric (Table 2). Unexpected myocardial uptake of ^{99m}Tc-PYP, or -DPD suggesting ATTR cardiomyopathy has been reported in two large series of patients undergoing bone scintigraphy for non-cardiac reasons[41,42] (Table 2). However most of these studies are limited due to the lack of a reference standard for cardiac amyloidosis in the patients with negative scans.

PROPOSED CLINICAL INDICATIONS FOR ^{99M}TC-PYP/DPD/HMDP IMAGING

Cardiac imaging with ^{99m}Tc-PYP, -DPD, and -HMDP are indicated in the below clinical scenarios (Reproduced with permission from ASNC ^{99m}Tc-Practice Points).

- Individuals with heart failure and unexplained increase in left ventricular wall thickness.
- Elderly African-Americans over the age of 60 years with heart failure, unexplained or with increased left ventricular wall thickness (> 12 mm).
- Elderly individuals (age over 60 years) with unexplained heart failure with preserved ejection fraction.
- Individuals, especially elderly males, with unexplained neuropathy, bilateral carpal tunnel syndrome or atrial fibrillation in the absence of usual risk factors, and signs/symptoms of heart failure.
- Evaluation of cardiac involvement in individuals with known or suspected hereditary amyloidosis.
- Diagnosis of cardiac ATTR in individuals with CMR or echocardiography consistent with cardiac amyloidosis.
- Patients with suspected cardiac ATTR amyloidosis and contraindications to CMR such as renal insufficiency or an implantable cardiac device.[43]

An upcoming publication in JNC on multi-societal consensus recommendations on multimodality imaging in ATTR cardiac amyloidosis will provide an update on the indications for imaging.

ASSESSMENT OF RISK IN ATTR CARDIAC AMYLOIDOSIS

Current literature supports the ability of semiquantitative metrics of heart/whole body (H/WB) retention on ^{99m}Tc-DPD (Figure 9A),[21] and H/CL ratio on ^{99m}Tc-PYP(Figure 9B)[25] to identify higher risk of major adverse cardiac events (MACE) and survival, respectively. However, visual grading of ^{99m}Tc-PYP -DPD was not found to be an independent predictors of outcomes, (Figure 9C).[25,44]

In one study using ^{99m}Tc-DPD, Rapezzi et al.[21] assessed 63 patients with ATTR (40 with and 23 without echocardiographic evidence of amyloid cardiomyopathy) and exhibited

significant myocardial tracer uptake (visual score ≥ 2) in all patients, signifying that ^{99m}Tc-DPD scintigraphy has the ability to identify amyloid myocardial infiltration even before the appearance of echocardiographic abnormalities, and this has prognostic value. In addition, a combination of left ventricular wall thickness > 1.2 cm and heart/whole body retention (H/WB) > 7.5 was associated with the highest major adverse cardiac events (MACE) rate.[21]

In a multicenter, retrospective cohort study of 229 patients, Castano et al.[25] highlighted the prognostic importance of a higher ^{99m}Tc-PYP radiotracer activity as quantified by H/CL ratio. A H/CL ratio of ≥ 1.5 was associated with a significantly worse survival (along with echocardiographic characteristics of a more advanced disease stage) over a 5-year period, whereas a visual Grade of 2 or 3 was not. This finding also emphasizes the higher sensitivity of the H/CL ratio compared to visual grading of radiotracer uptake, as quantitative assessment corrects for background, blood pool, and soft tissue activity.

Likewise, in a study of 602 patients by Hutt et al.,[44] survival was significantly better in patients with ^{99m}Tc-DPD scan Grade 0 compared to Grades 1, 2, and 3. However, there was not a significant difference in survival by increasing grade of ^{99m}Tc-DPD. The only independent predictors of mortality included functional status (ECOG performance status, HR for 3 vs 0 of 9.5 [CI 1.9-47.4], P = .006), and renal function (eGFR, HR 0.98 [CI 0.96-0.99], P = .002), after adjustment for NT-proBNP levels, age, left ventricular ejection fraction, supine systolic blood pressure (< _100 mmHg vs > 100 mmHg) and ^{99m}Tc-DPD scan Grade 0 vs Grade 1/2/3.

ASSESSMENT OF DISEASE PROGRESSION AND RESPONSE TO THERAPY

Currently there are very minimal data available on the utility of serial imaging to either identify disease progression or assess response to therapy in ATTR cardiac amyloidosis. In a single-center study, 20 ATTR cardiac amyloidosis patients (wild type =10, mutant = 10) with a positive ^{99m}Tc-PYP imaging, an average of 1.5 years prior, were invited to undergo a repeat ^{99m}Tc-PYP scan. Cardiac radiotracer retention assessed by both semiquantitative (visual score) and quantitative (H/CL ratio) methods did not demonstrate any significant changes, despite clinical progression of disease as determined by worsening lab biomarkers, echocardiographic parameters, New York Heart Association (NYHA) class, progression to heart transplantation and/or death. With emerging therapies for ATTR,[45–47] there is an urgent need for sensitive imaging biomarkers to monitor disease progression and response to treatment in cardiac ATTR. Quantitative imaging with echocardiography and longitudinal strain, CMR ECV, or amyloid imaging with PET tracers may play an important role.

FUTURE OF RADIONUCLIDE AMYLOID IMAGING: PET TRACERS

The PET tracers, originally developed for imaging β-amyloid and Alzheimer's disease,^{18}F-florbetapir, -florbetaben, and -flutemetamol, and ^{11}C-Pittsburgh Compound-B (Figure 10A), have been successfully used to diagnose cardiac amyloidosis.[48] These tracers are structurally similar to thioflavin-T and likely bind to the beta-pleated motif of amyloid fibril explaining their ability to image amyloid deposits independent of the precursor protein (Figure 10B). Also, compared to SPECT tracers, PET tracers are quantitative, allowing the possibility of

quantifying amyloid burden and detecting a change. The ^{18}F-tracers have the added advantage of a long half-life (109.7 minutes) and unit dose delivery to sites without a cyclotron on site. Notably, amyloid binding PET tracers are the sole clinically available radiotracers to adequately image AL amyloid burden in the heart.

The initial publications of cardiac amyloidosis in humans were based on ^{11}C-PiB followed by ^{18}F-florbetapir, and ^{18}F-florbetaben PET/CT. In these studies, all patients with AL and ATTR cardiac amyloidosis showed significant myocardial uptake while none of the control subjects showed myocardial uptake of amyloid tracer. Figure 11 shows representative images of ^{18}F-florbetapir PET/CT in AL (A), ATTR (B) and in a healthy subject (C) from a research study.[49] In that study myocardial SUV [3.84 (1.87-5.65) vs 1.35 (1.17-2.28), $P < .00010$]; retention index [0.043 (0.034-0.051) vs 0.023 (0.015-0.024), $P < .001$], were significantly higher in patients with amyloidosis compared to non-amyloid control subjects; in the ATTR cohort, myocardial retention index ranged from 0.031-0.045.[49]Similar results were reported by other investigators.[50–52] In most of these studies, although the radiotracer signal intensity trended higher in AL compared to ATTR hearts, there was significant overlap in values making a distinction of AL from ATTR impossible.[50–52] An autoradiography study evaluated 30 myocardial sections from patients with autopsy-proven ATTR (n = 10), AL (n = 10) and nonamyloid controls (n = 10) and demonstrated specific binding of ^{18}F-florbetapir to AL and ATTR cardiac amyloidosis.[53] Also, percentage myocardial ^{18}F-florbetaben retention was an independent determinant of biventricular myocardial dysfunction as measured by longitudinal strain.[54] ^{18}F-flutemetamol is an ^{18}F structural analogue of ^{n}C-Pittsburgh compound B, however harbors the additional benefit of a longer half-life compared to ^{11}C-PIB ($t_{1/2}$ = 20 minutes) that requires an onsite cyclotron for production; this has not yet been studied in cardiac amyloidosis imaging. Access to sites without a cyclotron makes ^{18}F-tracers more real-world surrogates for research and clinical applications compared to ^{11}C-PIB, though they have not yet been evaluated in multicenter studies.

CONCLUSIONS

Early diagnosis of ATTR cardiac amyloidosis is now more important than ever before. Bone avid tracer cardiac imaging has revolutionized the field’s ability to specifically diagnose ATTR cardiac amyloidosis noninvasively, obviating the need for endomyocardial biopsy. This test enables screening of specific populations at high risk for ATTR cardiac amyloidosis. Patients with heart failure can, for the first time, be diagnosed with ATTR cardiac amyloidosis and risk stratified using semiquantitative radionuclide metrics. Using bone avid tracer cardiac imaging to accurately identify ATTR cardiac amyloidosis makes possible targeted therapy with novel disease-modifying agents to substantially reduce heart failure hospitalization and improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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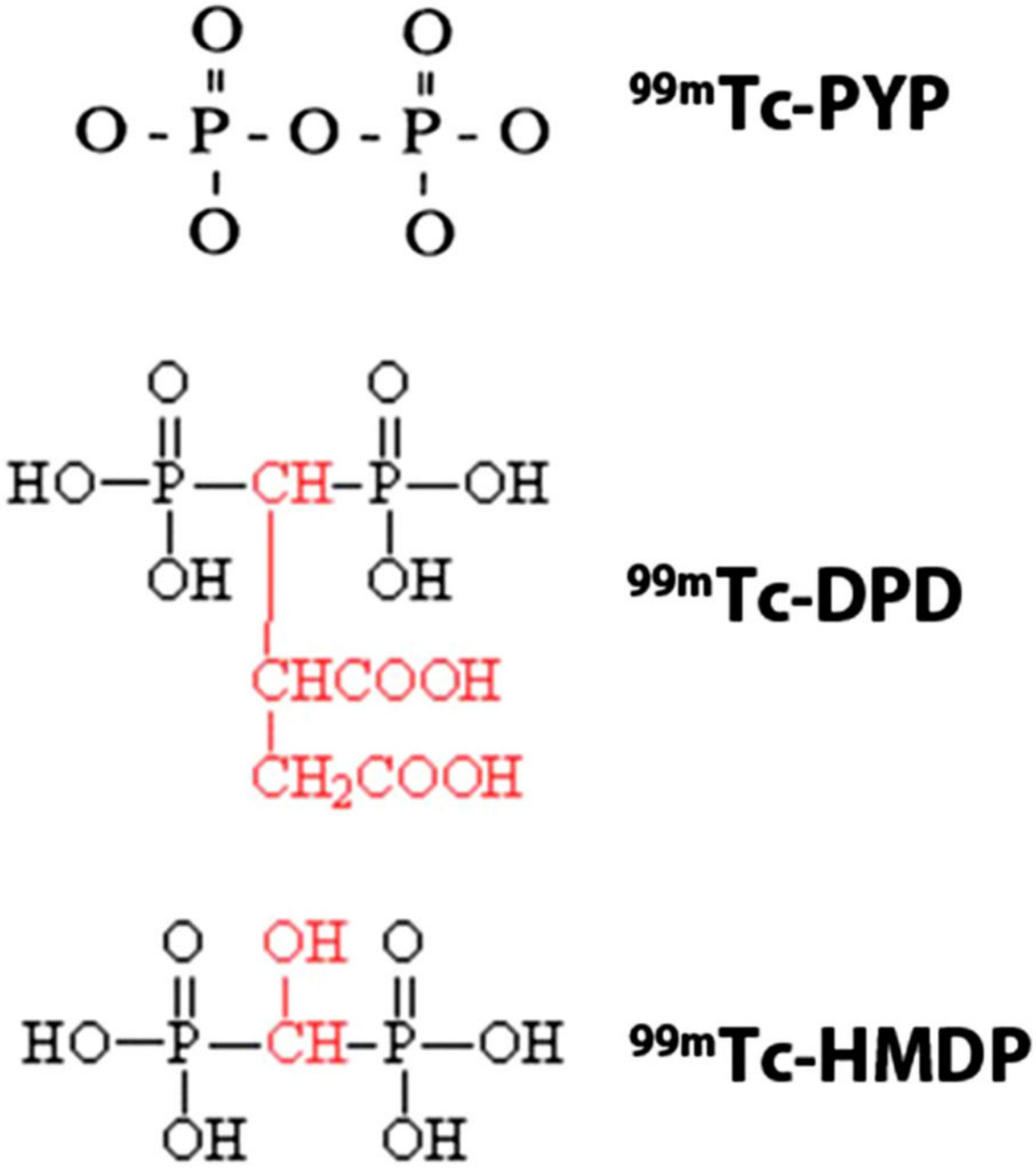


Figure 1.

Bone avid SPECT radiotracers for imaging cardiac amyloidosis. ^{99m}Tc pyrophosphate (PYP), 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP) have been used for imaging ATTR cardiac amyloidosis. These bone avid SPECT tracers show greater uptake in ATTR cardiac amyloidosis. Images adapted from package insert of ^{99m}Tc PYP, and from Human Health Campus, IAEA.

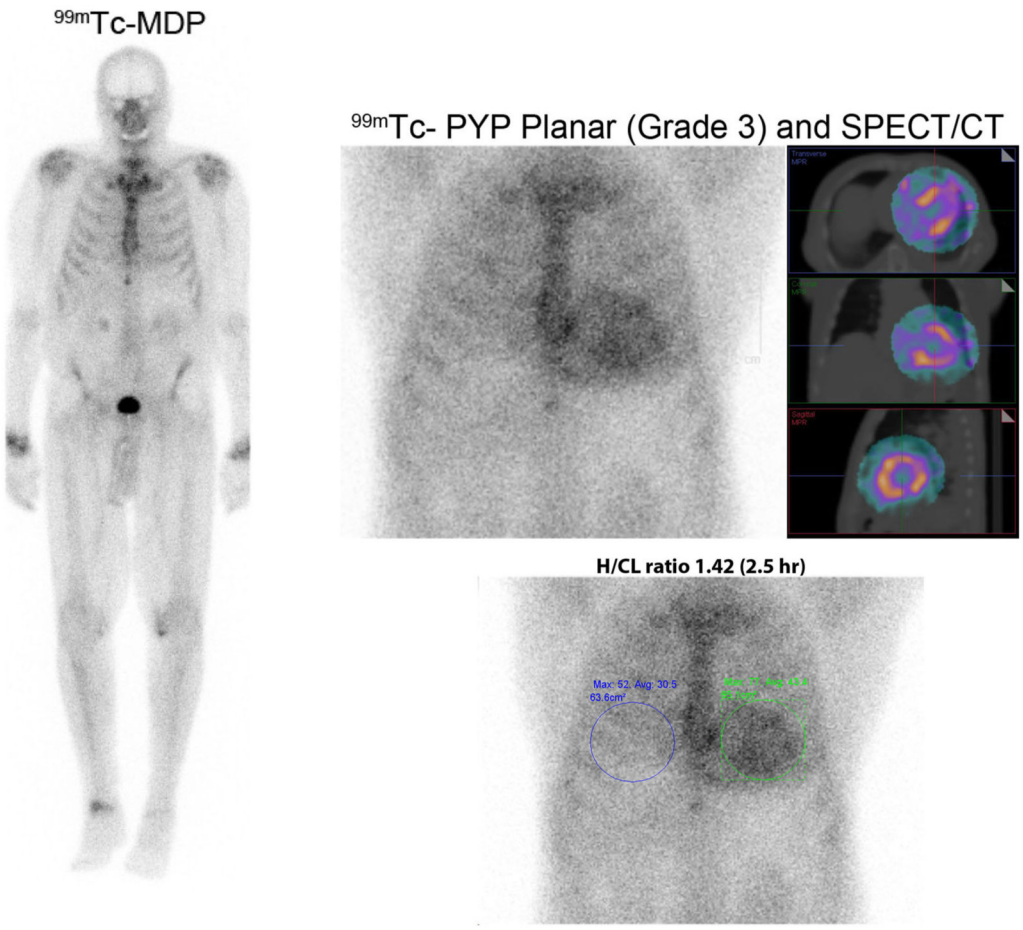


Figure 2.

^{99m}Tc-MDP and ^{99m}Tc-PYP images in cardiac ATTR amyloidosis. Images of an 86-year-old man with prostate cancer and a ^{99m}Tc-MDP scan showing no myocardial radiotracer uptake. He presented a month later with heart failure, and echocardiography revealed classic features of cardiac amyloidosis. A clonal abnormality was excluded by serum and urine immunofixation, and serum-free light chain levels. A ^{99m}Tc-PYP scan was performed using chest planar and SPECT imaging 2.5 hours after injection of radiotracer; Grade 3 myocardial uptake on ^{99m}Tc-PYP planar, and SPECT with a heart-to-contralateral ratio of 1.42 on planar images (≥ 1.3 abnormal for late images) diagnosed cardiac ATTR amyloidosis.

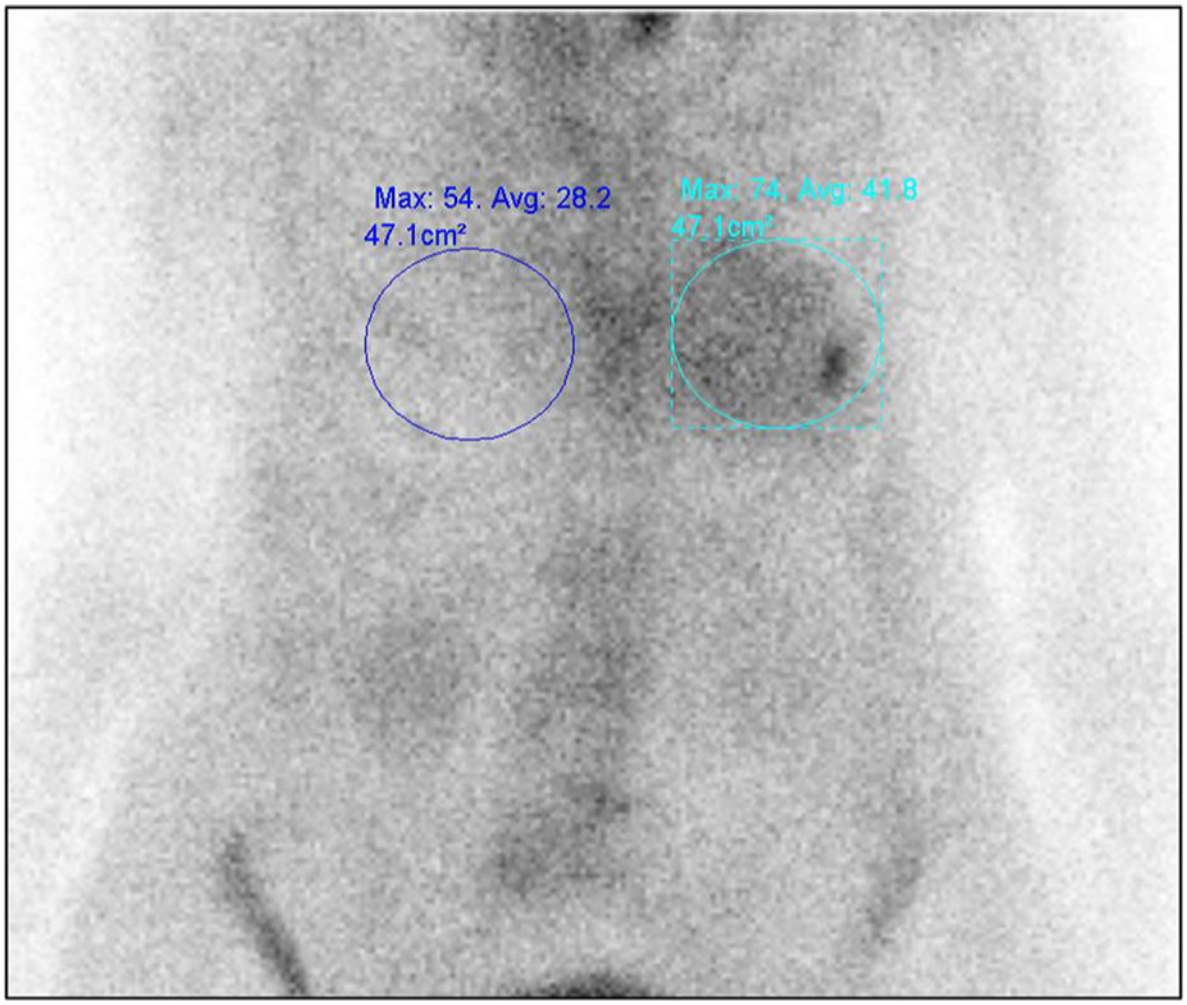


Figure 3.
Planar ^{99m}Tc-PYP imaging limited by overlying rib uptake. When evaluating the heart-to-contralateral lung uptake ratio (H/CL), care must be taken to avoid increase the bone activity overlying the myocardial region. In this chest planar ^{99m}Tc-PYP image, focally increased radiotracer uptake in the left chest is due to a recent rib fracture.

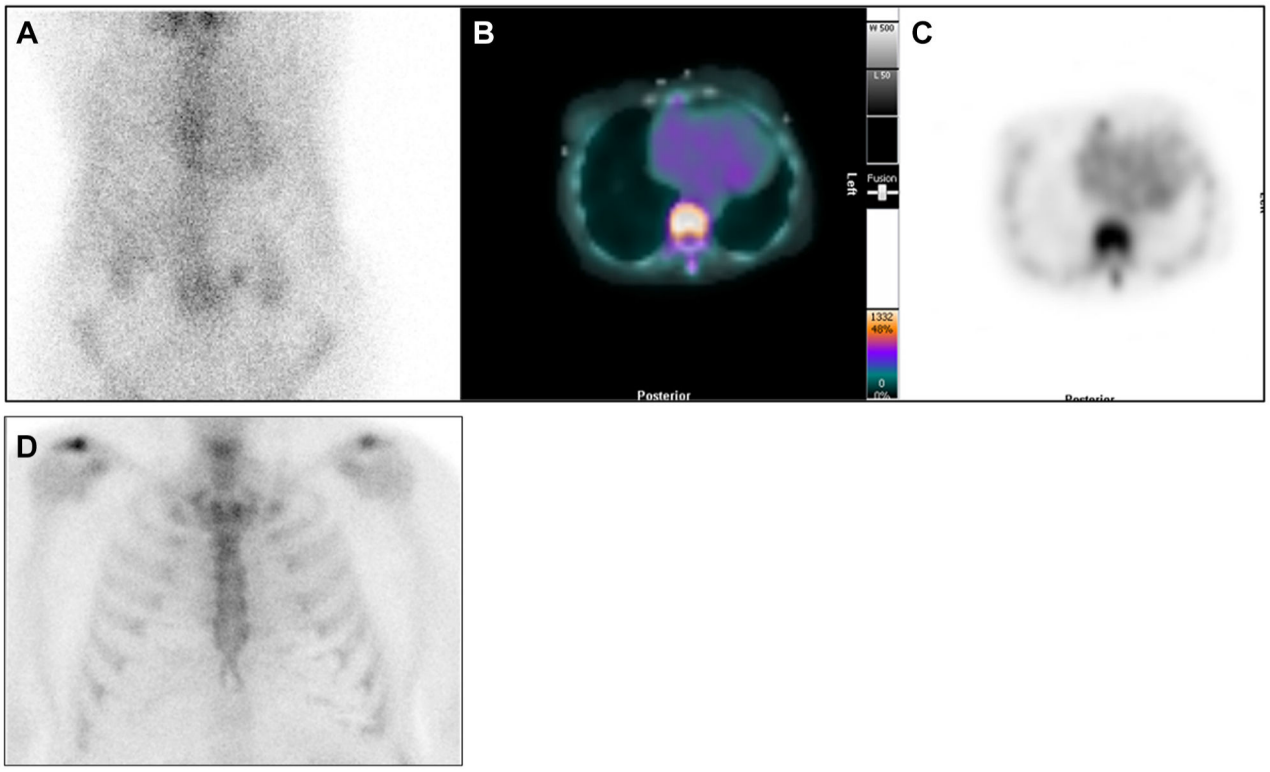


Figure 4.

^{99m}Tc-PYP on the 1-hour planar chest images and corresponding cardiac SPECT images. ^{99m}Tc-PYP with Grade 2 cardiac uptake on the planar chest images (**A**), which was confirmed as blood pool activity on SPECT/CT fusion images (**B**), and SPECT images (**C**). These are 1-hour images, and low rib uptake is noted. In contrast, Panel **D** shows 3-hour planar chest images from another patient showing Grade 0 (no) cardiac uptake and expected rib uptake.

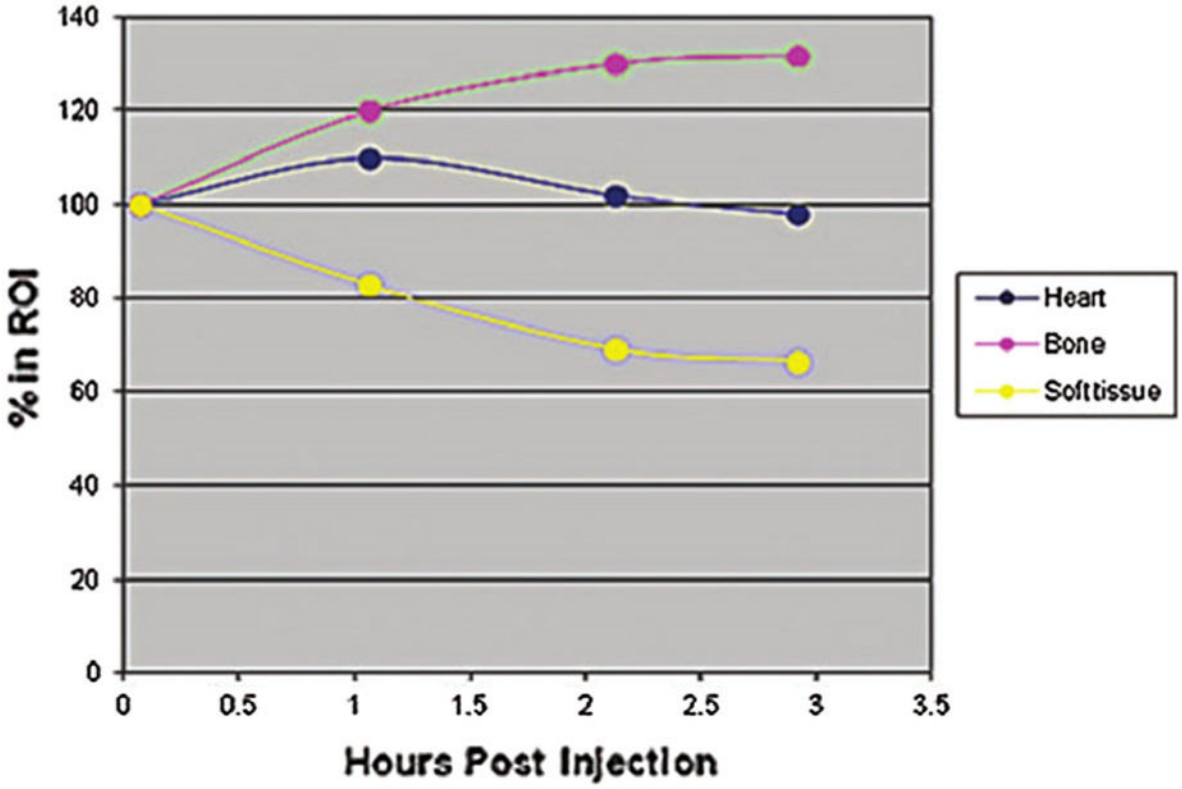


Figure 5.

Changes in heart and bone ^{99m}Tc-DPD counts over time. Hutt et al. evaluated planar images at multiple time points after injection of ^{99m}Tc-DPD in 4 patients. As seen in this figure, myocardial counts peaked at 60 minutes, while bone counts peaked between 2 and 3 hours after injection of ^{99m}Tc-DPD.

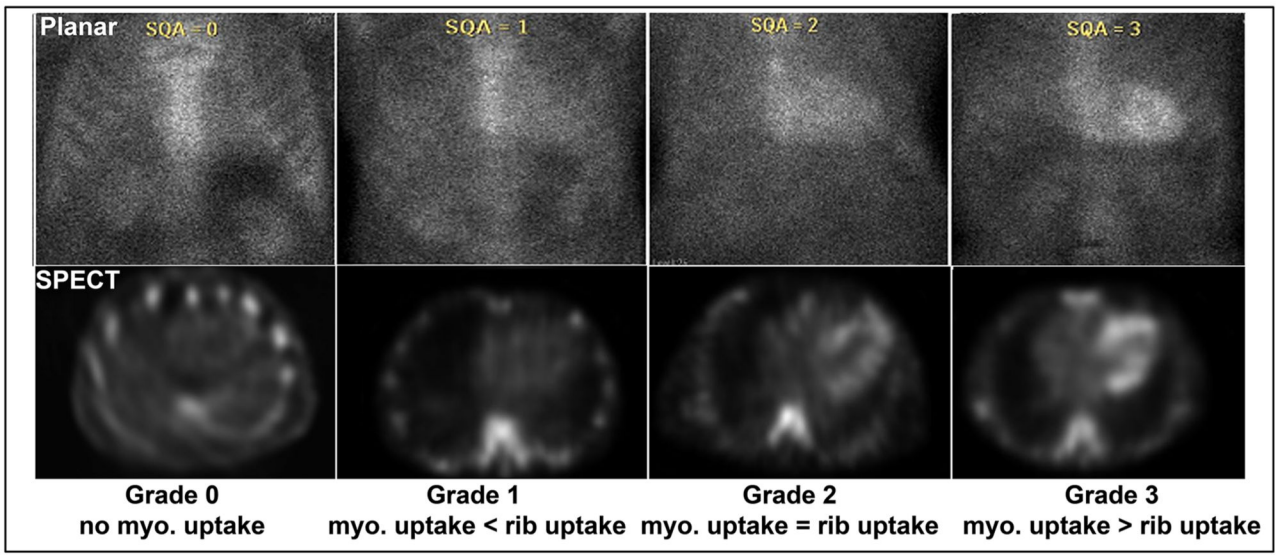


Figure 6.

Visual grading of ^{99m}Tc PYP planar and SPECT scans. ^{99m}Tc pyrophosphate (PYP) scans are graded visually into Grades 0, 1, 2, and 3, comparing myocardial radiotracer uptake-to-rib uptake. Myo = myocardial. Grades 2 and 3 are considered positive for ATTR cardiac amyloidosis. Figure reproduced with permission.[55]

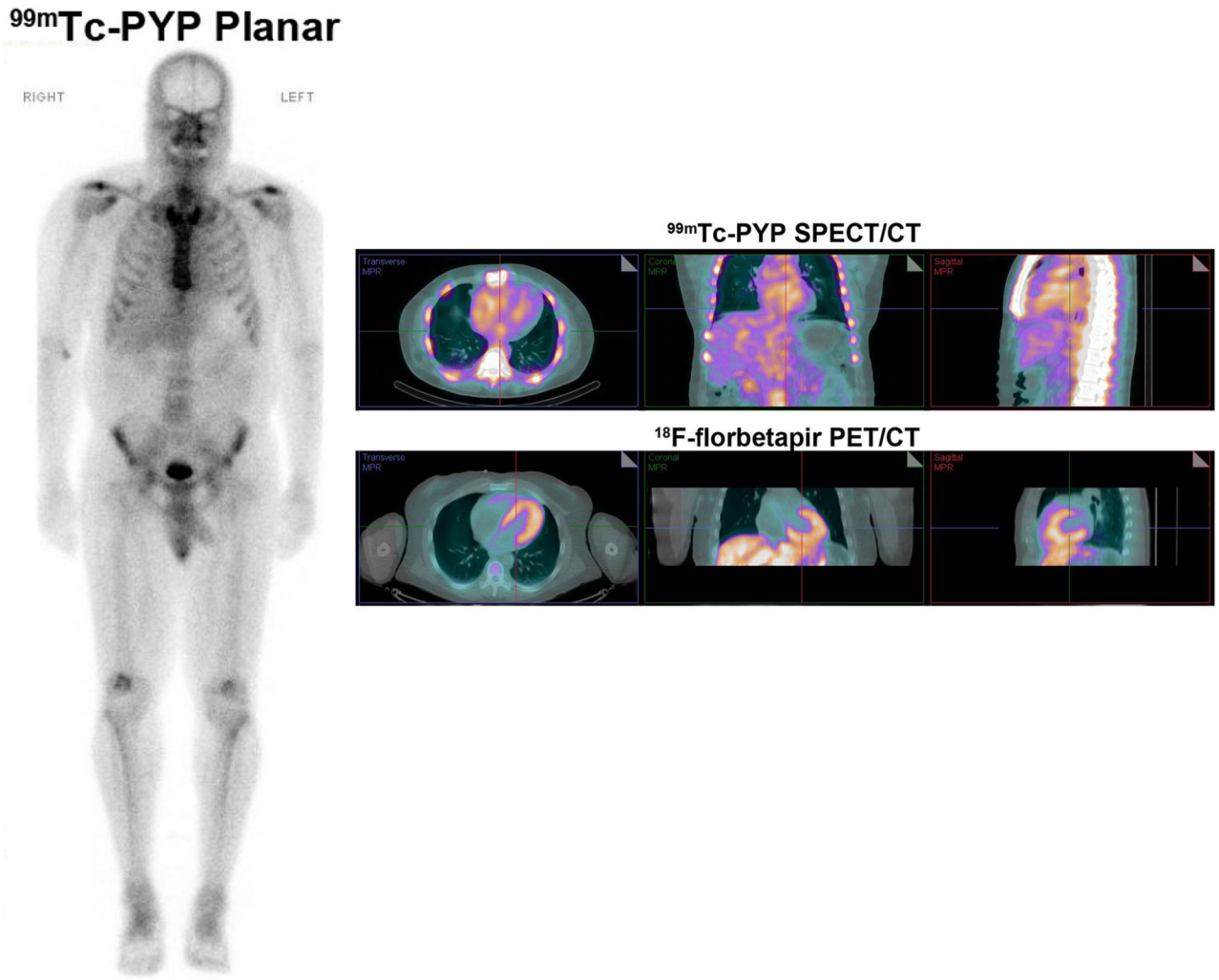
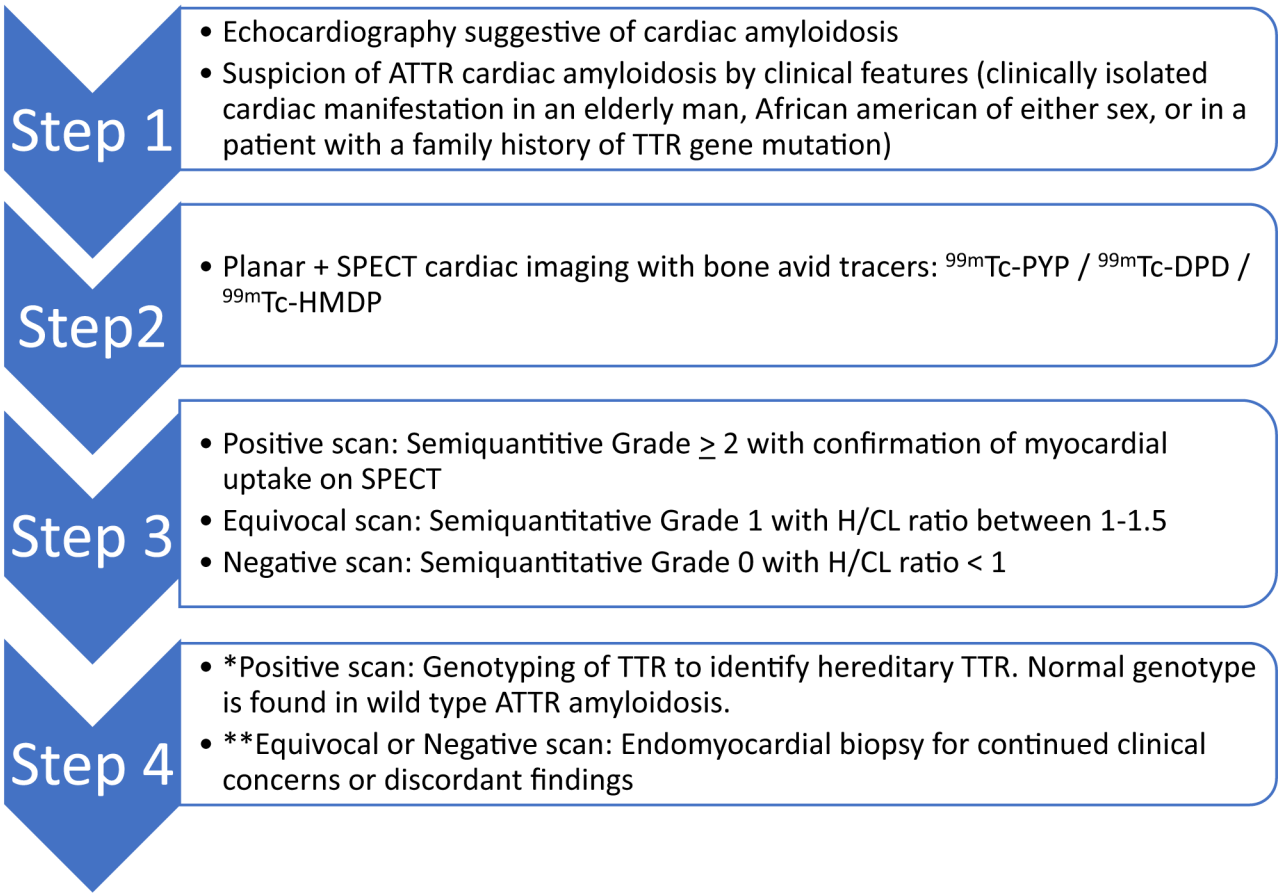


Figure 7.

A negative ^{99m}Tc-pyrophosphate scan does not exclude cardiac amyloidosis. A 59-year-old man with Val 122 I mutation and heart failure had typical echocardiographic findings. He was referred for ^{99m}Tc-PYP imaging which was negative (Grade 0 uptake on planar whole-body images on the left; SPECT/CT fusion images in the right panel, top row show blood pool activity without myocardial uptake). Further evaluation with serum and urine immunofixation, and bone marrow biopsy confirmed AL amyloidosis. A PET/CT scan obtained as part of a research protocol using 8 mCi ^{18}F-florbetapir with dynamic imaging, and static images reconstructed from 4 to 30 minutes, showed intense myocardial uptake (PET/CT fusion images on the right panel bottom row) confirming cardiac amyloidosis.



ATTR = transthyretin amyloidosis; SPECT = single-photon emission computerized tomography; **99m**Tc = **99m** Technetium; PYP = pyrophosphate; DPD = 3,3-diphosphono-1,2-propanodicarboxylic acid; HMDP = hydroxymethylene diphosphonate; ATTR = transthyretin amyloidosis; AL = light chain amyloidosis. Adapted from Gillmore et al.(11)

*If strongly positive, serum and urine immunofixation and serum free light chain assay have been recommended to rule out rare cases of AL cardiac amyloidosis. **If equivocal or negative, these tests to rule out AL should be done in selected patients if suspicion of cardiac amyloidosis remains high to seek evidence of AL amyloidosis.

Figure 8.

A proposed algorithm incorporating ^{99m}Tc-PYP, DPD, and HMDP for the evaluation of suspected ATTR cardiac amyloidosis. Evaluation of patients with suspected cardiac amyloidosis typically starts with echocardiography or CMR to evaluate cardiac structure and function, and if ATTR is suspected a bone avid scintigraphy is performed. If the bone avid tracer cardiac scintigraphy is strongly positive, and monoclonal protein is excluded, transthyretin cardiac amyloidosis is diagnosed with higher specificity. In equivocal or negative cases, further evaluation may be considered including endomyocardial biopsy.

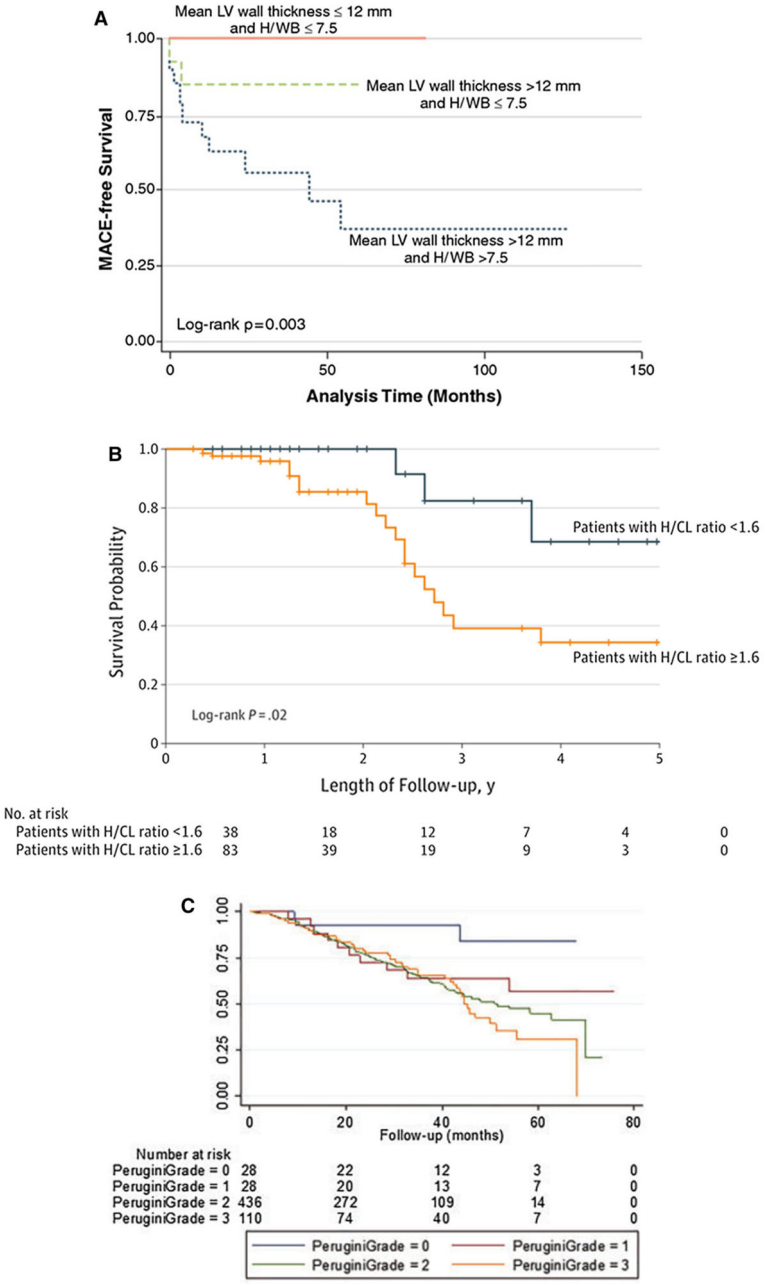


Figure 9.

Prognostic value of ^{99m}Tc-DPD/PYP imaging in cardiac amyloidosis. Patients with mean LV wall thickness < 12 mm, heart-to-whole body retention (H/WB) ratio < 7.5 on ^{99m}Tc-DPD (**A**), heart/contralateral (H/CL) ratio < 1.6 on ^{99m}Tc-PYP (**B**), and Grade 0 uptake on ^{99m}Tc-DPD (**C**) showed best outcomes. Patients with Perugini Grades 1, 2, and 3 showed similar survival, and worse compared to Grades 0 (no amyloidosis). Figures reproduced with permission from refs. 21,25,44

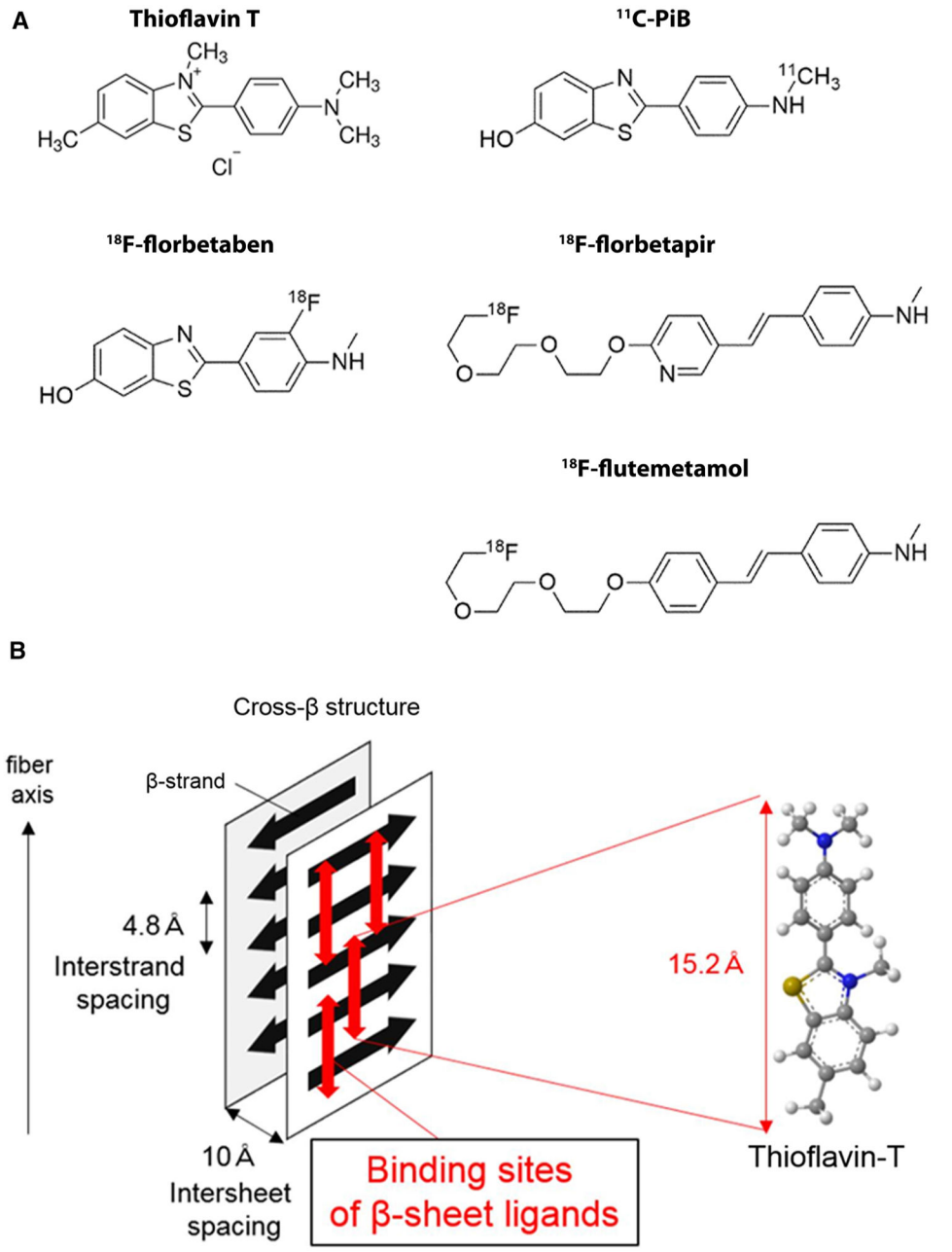


Figure 10.

Amyloid PET tracers (**A**) and proposed mechanism of binding of amyloid PET radiotracers (**B**). ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol are FDA approved for β-amyloid imaging in Alzheimer's disease. ^{11}C-PIB is not FDA approved. Studies have reported the utility of the ^{11}C-PIB, ^{18}F-florbetapir, and ^{18}F-florbetaben for imaging AL and ATTR cardiac amyloidosis, and these tracers appear to show greater uptake in AL than ATTR cardiac amyloidosis. These tracers are structurally similar to Thioflavin T and likely bind to the motif of the β pleated sheet structure. Molecular structures in Figure 10A were adapted from package inserts/product catalogue and reproduced with permission from ref. 57 Figure 10B reproduced with permission from ref. 58

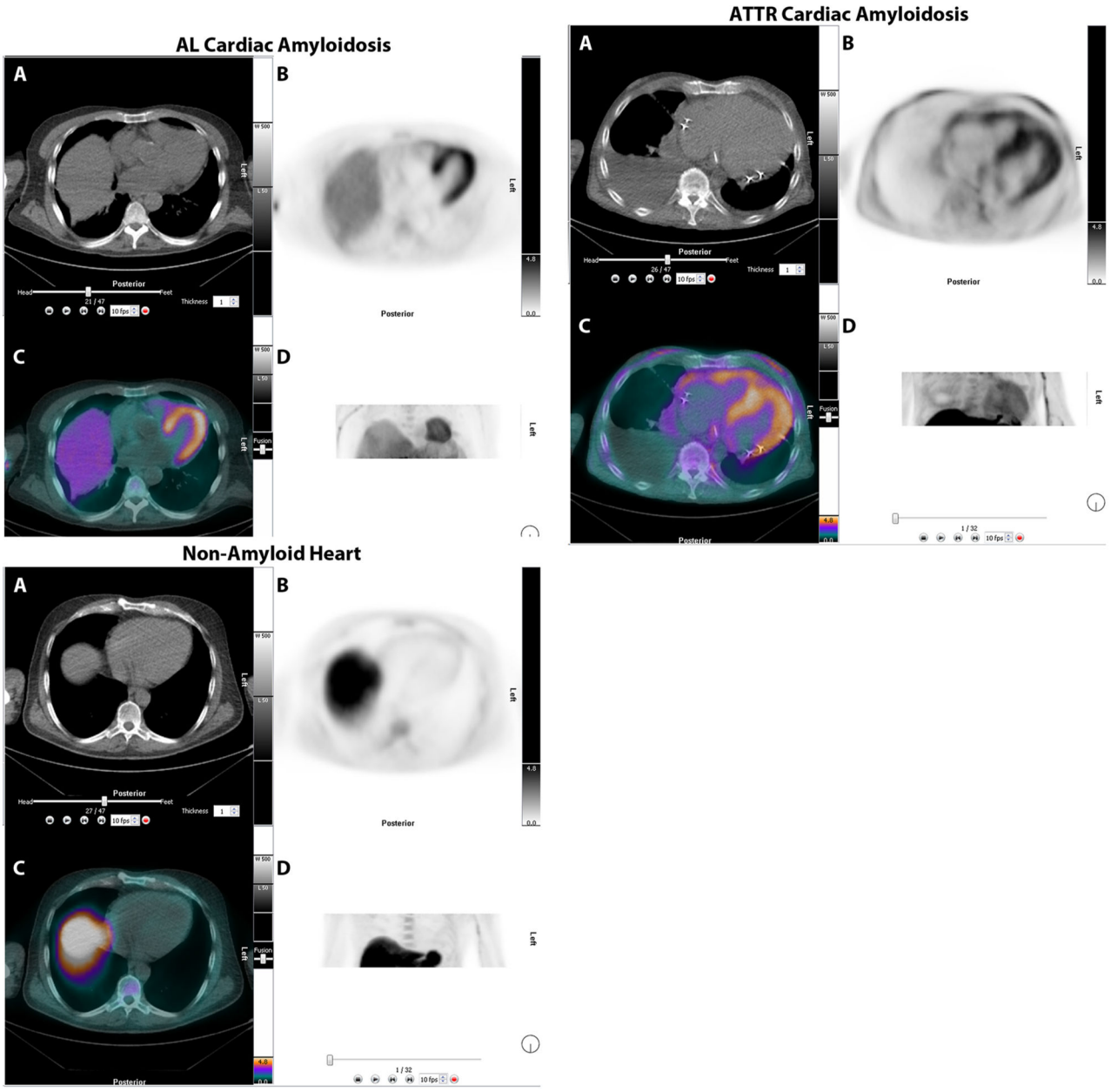


Figure 11.

^{18}F-florbetapir PET/CT imaging in patients with AL, ATTR, and no-amyloidosis. Images are displayed as axial CT transmission (**A**), axial emission (**B**), fused transmission/emission (**C**), and a maximum intensity projection image (**D**). Both AL (top left), ATTR (top right) images show intense ^{18}F-florbetapir uptake in the left ventricle. The patient without amyloidosis, volunteer, (bottom), showed no myocardial uptake of ^{18}F-florbetapir.

Table 1.

Accuracy of Tc-pyrophosphate scan for detecting ATTR Cardiac amyloidosis based on semiquantitative and quantitative assessments

	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Semiquantitative visual Score			
1-hour delay positive scan ≥ 2	95	79	0.938 (0.873-0.984)
3-hour delay positive scan ≥ 2	58	100	0.980 (0.932-1.000)
Combined analysis	88	88	0.945 (0.901-0.977)
Quantitative H/CL ratio			
1-hour delay positive scan ≥ 1.5	92	97	0.971 (0.949-0.992)
3-hour delay positive scan ≥ 1.3	88	86	0.935 (0.848-0.988)
Combined analysis	91	92	0.960 (0.930-0.981)

Tc-PYP, Tc pyrophosphate; *ATTR*, transthyretin amyloidosis; *AUC*, area under the curve; *CI*, confidence interval; *H/CL*, ratio = heart-to-contralateral lung ratio. Adapted from Castano et al.[25]

Table 2.

Screening for cardiac ATTR amyloidosis using ^{99m}Tc-PYP or DPD

First Author	Radiotracer	N	Cohort	Prevalence of ATTR
Gonzalez-Lopez[38]	^{99m}Tc-DPD	120	Heart failure with preserved EF Hospitalized patients 42% women	13.3%
Castano[39]	^{99m}Tc-PYP	151	TAVR Age > 75 years Severe aortic stenosis Low flow low gradient AS Mean LVEF 46%	16%
Haq[36]	^{99m}Tc-PYP		Hereditary ATTR No heart failure Normal echocardiogram Normal cardiac biomarkers	83%
Bennani-Smires[37]	^{99m}Tc-DPD	49	Age > 65 years Heart failure with preserved EF	18%
Longhi S[56]	^{99m}Tc-DPD	43	Aortic stenosis 5 with echo red flags underwent ^{99m}Tc-DPD and all were strongly positive	11.6%
Longhi S[41]	^{99m}Tc-DPD	12400	All bone scans performed over a 5 + year period for clinical reasons	0.36%
Mohamed-Salem[42]	^{99m}Tc-DPD	1114	Age ≥ 75 years Bone scan for clinical reasons	2.78%
Sperry[40]	^{99m}Tc-PYP	98	Carpal tunnel surgery Men ≥ 50 years Women ≥ 60 years 10 patients with biopsy proven amyloid from carpal tunnel procedure were evaluated by ^{99m}Tc-PYP	10.2%