Radiopharmaceutical supply disruptions and the use of $^{99m}$Tc-hydroxymethylene diphosphonate as an alternative to $^{99m}$Tc-pyrophosphate for the diagnosis of transthyretin cardiac amyloidosis: An ASNC Information Statement

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INTRODUCTION

There has been a transformation over the past decade in the diagnosis and management of patients with amyloid transthyretin (ATTR) cardiac amyloidosis which has been driven by the development of noninvasive approaches leveraging nuclear scintigraphy and the emergence of effective therapies that significantly improve outcomes of affected patients. Based on an international multicenter collaboration, three 99mTc-labeled radiotracers, 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), 99mTc-pyrophosphate (PYP), and 99mTc-hydroxymethylene diphosphonate (HMDP), termed “bone avid” and traditionally used for bone scintigraphy, have been shown to have high diagnostic accuracy for the identification of patients with ATTR cardiac amyloidosis when coupled with an assessment for monoclonal proteins to exclude the substrate for AL amyloidosis. The use of these three tracers for ATTR cardiac amyloidosis imaging has been described in recent multi-societal guidelines. Such testing avoids the need for invasive endomyocardial biopsy in the vast majority of affected individuals. Accordingly, patients with ATTR cardiac amyloidosis who were previously diagnosed in the later stages of the disease with limited life expectancy are less frequently encountered. This advancement in diagnostic efficacy, which allows effective disease-modifying therapy to be initiated to reduce new amyloid formation but does not address pre-existing amyloid deposits, has been jeopardized by the recent unexpected lack of availability of 99mTc-PYP, heretofore virtually the only radiotracer used in the USA for the evaluation of suspected cardiac amyloidosis. To continue to facilitate an early diagnosis and advance the care of affected patients, the American Society of Nuclear Cardiology (ASNC) is providing this Information Statement to encourage practitioners in the USA to leverage use of 99mTc-HMDP, an FDA-approved radiotracer that can diagnose ATTR cardiac amyloidosis and be used in place of 99mTc-PYP. This document serves to review the use of 99mTc-HMDP in this context.

DESCRIPTION OF THE SHORTAGE

Prior to 2020, supply chain interruptions only intermittently impacted US healthcare facilities. However, the COVID-19 pandemic has caused unprecedented disruption in industrial supply chains across the globe, which has only been exacerbated in 2022. In particular, workforce shortages due to COVID-19 surges and associated societal lockdowns slowed raw material procurement, manufacturing lines, and shipment processing. Resulting shortages in semiconductors, metals, chemicals, and other raw materials have impaired supply and increased the price of key medical supplies, devices, and pharmaceuticals. Along with other medical specialties, nuclear medicine has been impacted as well. In November 2021, two major US suppliers of radiopharmaceutical agents, Curium Pharma and Sun Radiopharma, who are the sole US providers of the lyophilized kits used to prepare 99mTc-PYP in a hot lab at a hospital or radiopharmacy, reported supply interruptions for several nuclear imaging products, including sulfur colloid, mebrofenin, mertiatide, sestamibi, medronate, and PYP. Several chemicals and metals (e.g., tin) are used to create these products, and it is important to note that the supply chain disruptions causing the shortage of PYP are different and appear unrelated to the previous shortages of nuclear cardiology radioisotopes, such as rubidium-82 or technetium-99m. Curium has provided recent updates stating they expect the PYP shortage to continue as long as Sun Radiopharma is unable to provide a supply of PYP. Despite multiple attempts, Sun Radiopharma has not responded by June 22, 2022 to ASNC’s request for comment on when expected supply will return. In the interim, cardiac 99mTc-PYP imaging studies to diagnose ATTR cardiac amyloidosis may only be available to patients on an intermittent basis.

NOMENCLATURE

The nomenclature for 99mTc-hydroxymethylene diphosphonate (HMDP) can be a source of confusion. HMDP is also sometimes abbreviated HDP and is also referred to as 99mTc-oxidronate. All three terms refer to the same compound. The chemical structure of
Oxidronate sodium (CH₄Na₂O₇P₂) is shown in Figure 1. As per the package insert, the reconstitution of oxidronate sodium with ⁹⁹mTc-sodium pertechnetate forms a complex of ⁹⁹mTc-oxidronate (CH₆O₇P₂Tc). HMDP is FDA-approved as a radiopharmaceutical in the USA for use as a skeletal imaging agent to demonstrate areas of altered osteogenesis in adult and pediatric patients and is marketed under the trade name TechneScan® HDP. Similar to PYP, it is not FDA-approved specifically for the indication of imaging ATTR cardiac amyloidosis. It is important to note that HMDP/HDP is distinct from another common bone tracer, ⁹⁹mTc-methylene diphosphonate (⁹⁹mTc-MDP), and MDP is not recommended for the diagnosis of ATTR cardiac amyloidosis based on reported reduced sensitivity. HMDP and PYP are reported to have similar rates of blood pool clearance (blood levels 10% at 1 hour), though data directly comparing cardiac blood pool clearance rates between these tracers is lacking in populations at risk for cardiac amyloidosis.

**DIFFERENCES IN ACQUISITION BETWEEN ⁹⁹mTc-HMDP AND ⁹⁹mTc-PYP**

The acquisition protocols for ⁹⁹mTc-HMDP as compared to ⁹⁹mTc-PYP are very similar. Shifting from PYP to HMDP for ATTR cardiac amyloidosis imaging does not require nuclear laboratories to purchase new equipment or software.

Imaging procedures for ⁹⁹mTc-HMDP imaging are shown in Table 1. For ⁹⁹mTc-PYP, cardiac or chest single-photon emitted computed tomography (SPECT) and planar images is recommended two to three hours after PYP injection. Although one-hour imaging has been used in many ⁹⁹mTc-PYP studies and is used by experienced centers with similar results, two- to three-hour imaging is now recommended. Similarly, for ⁹⁹mTc-HMDP, whole-body planar and chest/cardiac SPECT images are obtained two to three hours after HMDP injection using the parameters listed in Table 1. For ⁹⁹mTc-HMDP and ⁹⁹mTc-PYP, SPECT imaging is necessary in all cases. Whole-body planar imaging may be helpful to identify uptake of HMDP in the shoulder and hip girdles (a specific sign of systemic ATTR amyloidosis) and to identify soft tissue uptake in the extremities, which is a sign of systemic ATTR amyloidosis. Whole-body imaging for HMDP is commonly employed in European practice but is less common in other regions such as Latin America.

Imaging with bone-avid agents (including ⁹⁹mTc-HMDP) for amyloid has already been performed using cadmium zinc telluride (CZT) cameras. The value of ⁹⁹mTc-HMDP imaging with dedicated cardiac CZT cameras needs further validation due to the inability to accurately display bone and lung ⁹⁹mTc-HMDP uptake with these systems.
DIFFERENCES IN INTERPRETATION BETWEEN $^{99m}$Tc-HMDP AND $^{99m}$Tc-PYP

Interpretation of $^{99m}$Tc-HMDP scans for ATTR cardiac amyloidosis is very analogous to PYP with some minor differences. As with interpretation of $^{99m}$Tc-PYP, a stepwise approach for interpretation of $^{99m}$Tc-HMDP scintigraphy is recommended (see Table 2). The first step is to visually confirm diffuse myocardial radiotracer uptake and differentiate this uptake from residual blood pool activity or overlapping bone using SPECT and planar images. Interpretation and reporting should comment on focal versus diffuse radiotracer uptake. Diffuse uptake is typically consistent with cardiac amyloidosis, whereas focal uptake may represent early cardiac amyloidosis but has also been described in acute or subacute myocardial infarction.12 Both planar and

### Table 1. Recommendations for standardized acquisition of $^{99m}$Tc-HMDP for cardiac amyloidosis

| Imaging procedures                        | Parameters                                      | Recommendation |
|------------------------------------------|------------------------------------------------|----------------|
| Preparation                              | No specific preparation. No fasting required.  | N/A            |
| Scan                                     | Rest scan                                      | Required       |
| Dose                                     | $^{99m}$Tc-HMDP: 10–20 mCi (370–740 MBq)        | Recommended    |
| Time between injection and acquisition:  | $^{99m}$Tc-HMDP: 2 or 3 hours                  | Recommended    |
| General imaging parameters               | Heart or chest                                 | Required       |
| Field of view                            | Whole-body planar                              | Optional       |
| Image type                               | Planar                                         | Recommended    |
| SPECT if planar is positive              | Required                                       |
| Position                                 | Supine                                         | Required       |
| Upright                                  | Optional                                       |
| Energy window                            | 140keV, 15–20%                                 | Required       |
| Collimators                              | Low energy, high resolution                    | Recommended    |
| Matrix-Planar                            | $256 \times 256$                               | Recommended    |
| Matrix-SPECT                             | $128 \times 128$ (at least 64 by 64 is required) | Recommended    |
| Pixel size                               | 3.5–6.5 mm                                     | Recommended    |
| Number of views                          | Chest: Anterior and lateral                    | Required       |
| Whole-body: From head to toe             | Optional                                       |
| Detector configuration                   | $90^\circ$                                     | Recommended    |
| Image duration (count based)             | $750,000$ or $20$ cm per minute                | Recommended    |
| Magnification                            | $1.46$                                         | Recommended    |
| Angular range                           | $180^\circ$                                    | Required       |
| $360^\circ$                              | Optional                                       |
| Detector configuration                   | $90^\circ$                                     | Recommended    |
| $180^\circ$                              | Optional                                       |
| Angular range                           | $360^\circ$                                    | Optional       |
| Detector configuration                   | $180^\circ$                                    | Optional       |
| ECG gating                               | Off; Non-gated imaging                         | Recommended    |
| Number of views/detector                 | $40/32$                                        | Recommended    |
| Time per stop                           | 20 seconds/25 seconds                          | Recommended    |
| Magnification                            | $1.46$ ($180^\circ$ angular range)             | Recommended    |
| $1.0$ ($360^\circ$ angular range)        |                                               |

2–3-hour imaging is recommended for HMDP, heart or chest imaging is required, and whole-body imaging is optional. Adapted from Dorbala et al.5
SPECT imaging should be reviewed and interpreted irrespective of the timing of acquisition. SPECT/CT fusion images from attenuation correction CT images are recommended if available and are helpful to localize tracer uptake to the myocardium. The CT images should also be reviewed for potentially clinically meaningful incidental findings.

If myocardial uptake is confirmed visually, the next step is to proceed to semiquantitative grading using the Perugini visual grading scale. This scale is validated for whole-body \(^{99m}\text{Tc}\)-HMDP scintigraphy comparing cardiac uptake to bone uptake in the adjacent ribs. This scale ranges from Grades 0 to 3 (see Table 2). Grade 2 or Grade 3 myocardial uptake of HMDP in the absence of a plasma cell dyscrasia, is diagnostic of ATTR cardiac amyloidosis (see Figure 2). Grade 0 and Grade 1 uptake may be observed in early ATTR cardiac amyloidosis and/or AL cardiac amyloidosis and warrants further evaluation to exclude AL amyloidosis.

As opposed to \(^{99m}\text{Tc}\)-PYP, studies have shown that the H/CL ratio in \(^{99m}\text{Tc}\)-HMDP imaging may be confounded by background noise with increased \(^{99m}\text{Tc}\)-HMDP described in soft tissue, predominantly muscles, in gluteal, shoulder, chest, abdominal wall, liver, skeletal muscle, and lung tissues. As such, use of the H/CL ratio is not recommended for HMDP. In addition, there may be differences between \(^{99m}\text{Tc}\)-HMDP and \(^{99m}\text{Tc}\)-PYP in the ability to image extracardiac amyloidosis. Compared to other bone-avid tracers, \(^{99m}\text{Tc}\)-HMDP in particular had been shown to have an ability to identify systemic amyloidosis, and therefore it is recommended to report extra-cardiac uptake as well. In a relatively large study from the French Referral Center for Cardiac Amyloidosis, all patients who underwent \(^{99m}\text{Tc}\)-HMDP for suspicion of...
cardiac amyloidosis between 2010 and 2017 were reviewed using a protocol that included a whole-body scan including the thyroid, lungs and pleura, myocardium, liver, spleen, gastrointestinal tract, and kidneys. Extra-cardiac uptake was found in 74 patients, including 72 with cardiac amyloidosis and 2 controls.
Extra-cardiac uptake was found predominantly in the lungs and pleura in ATTR and in AL, followed by the digestive tract and subcutaneous tissues in hereditary ATTR and AL cardiac amyloidosis. Another study by Monfort et al. specifically looked at lung retention in hereditary ATTR, showing that pulmonary retention of HMDP was higher in hereditary ATTR amyloidosis patients compared with age and sex matched control subjects. Another study from Cappelli et al. found 99mTc-HMDP scintigraphy showed lung uptake in almost 60% of subjects with ATTR amyloidosis, and that the incidence of lung uptake was significantly correlated to the grade of heart retention according to Perugini visual score.

Heart/whole-body (H/WB) ratio and standardized uptake value (SUV) measurements are not commonly used but are emerging concepts in HMDP SPECT imaging. H/WB and its cutoff values have also been described in the literature as a robust and effective way of diagnosing cardiac amyloidosis; however, further research is necessary to incorporate it into practice. Heart-to-skull (H/S) ratio has also been used but more recently was found by Gallini et al. in a small series, to have worse performance than other indices. With recent developments in imaging technology, quantitative SPECT using either kBq/cc or SUVs is feasible using the new solid-state (CZT) SPECT/CT cameras. The feasibility of this technique using 99mTc-HMDP was shown by Bellevre et al. They evaluated 15 patients with suspected cardiac ATTR amyloidosis (Perugini ≥2) with a DNM 670CZT camera and a control group consisted of 15 patients with negative scintigraphy (Perugini < 2). All ATTR amyloidosis patients demonstrated an increased cardiac HMDP SUVmax (12.2 ± 3.7 mg L) vs controls (3.5 ± 1.2, P < .0001). Despite these preliminary data on quantification, qualitative interpretation of 99mTc-HMDP uptake remains standard and recommended.

While rare, it is recognized that there is reduced sensitivity of cardiac scintigraphy with 99mTc-biphosphonate derived radiopharmaceuticals such as HMDP and DPD in patients with certain TTR mutations. Some reports suggest that patients with ATTR cardiac amyloidosis and mutations, such as Phe64Leu, have low or absent myocardial bone-tracer uptake, suggesting that heightened sensitivity for ATTR cardiac amyloidosis may be necessary in these patients, and diagnostic modalities beyond cardiac bone scintigraphy may be needed.

Detailed recommendations for standardized reporting are provided in Table 3.

**BILLING FOR 99mTc-HMDP IN THE USA**

Several Current Procedural Terminology (CPT)© billing codes can be used for reimbursement for 99mTc-HMDP scans. These include one of three Category I CPT codes selected for imaging, and a separate level II Healthcare common Procedure Coding System (HCPCS) code Level II used for the radiopharmaceutical. The selection of which CPT code depends on whether the study is performed with planar imaging alone (78800), with SPECT imaging with or without planar imaging (78803), and with SPECT/CT imaging (78830) with or without planar imaging. Use of planar imaging alone for cardiac amyloidosis is only recommended if these planar images are reviewed by a physician and determined to be Perugini Grade 0 before discharging the patient from the nuclear cardiology laboratory; otherwise, it is important to note that all patients should receive SPECT or SPECT/CT imaging. This recommendation is codified in a revision to the recent multi-societal cardiac amyloidosis imaging guidelines. In general, reimbursement is highest for SPECT/CT and lowest for planar imaging alone.

In more detail, the American Medical Association’s CPT description for 78800 is for “Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, single area (e.g., head, neck, chest, pelvis), single day imaging,” 78803 for “Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis), single day imaging,” and 78830 for “Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, single area (e.g., head, neck, chest, pelvis), single day imaging.” As described above, 99mTc-HMDP is equivalent to 99mTc-oxidronate, and thus the Category II code A9561 for “Technetium tc-99m [sic] oxidronate, diagnostic, per study dose, up to 30 millicuries” should be used to bill for the HMDP.

**COMPARISONS BETWEEN HMDP AND PYP**

Direct comparison data between the bisphosphonate derivatives 99mTc-DPD, -PYP, and -HMDP for ATTR cardiac amyloidosis are limited. Nonetheless, in aggregate the cardiac uptake of these radioisotopes is
sensitive and highly specific for ATTR cardiac amyloidosis when AL amyloidosis is excluded. Meta-analyses of published data suggest $^{99m}$Tc-HMDP may be slightly more accurate than $^{99m}$Tc-PYP and/or similar to $^{99m}$Tc-DPD. The largest report that includes all three radiotracers is a retrospective multicenter referral population experience that included 1498 patients. This study showed a positive predictive value of all bone scintigraphy agents for ATTR cardiac amyloidosis of 100% (95% confidence interval 98.0-100) in patients with an echocardiogram or CMR consistent with or suggestive of cardiac amyloidosis and absence of monoclonal protein. Of the 1217 subjects included in the analysis, 877 were imaged with $^{99m}$Tc-DPD, 199 $^{99m}$Tc-PYP, and 141 $^{99m}$Tc-HMDP. The findings for all 141 subjects who underwent $^{99m}$Tc-HMDP imaging are shown in Table 4. There was just one subject with any HMDP uptake that did not have ATTR cardiac amyloidosis, and this patient had Grade 1 uptake and had AL amyloidosis. Compared to endomyocardial biopsy, the specificity of $^{99m}$Tc-HMDP was 100%, as summarized in Table 5; these data are limited by the relative paucity of EMBs performed in the $^{99m}$Tc-HMDP cohort in that report. The sensitivity decreased for myocardial uptake of $^{99m}$Tc-HMDP is visually confirmed and the semi-quantitative visual grade is 1 or there is interpretive uncertainty of grade 1 versus grade 2 on visual grading.

**Table 3. Recommendations for standardized reporting of $^{99m}$Tc-HMDP imaging for cardiac amyloidosis**

| Parameter          | Items                                                                 |
|--------------------|----------------------------------------------------------------------|
| **Demographics**   | Patient name, age, sex, reason for the test, date of study, prior imaging procedures, biopsy results if available (Required) |
| **Methods**        | Imaging technique, radiotracer dose and mode of administration, interval between injection and scan, scan technique (planar and SPECT) (Required) |
| **Findings**       | Image quality
|                    | Visual scan interpretation (Required) |
|                    | Semi-quantitative interpretation in relation to rib uptake |
| **Ancillary findings** | Whole-body imaging if planar whole-body images are acquired (Optional) |
|                    | Interpret CT for attenuation correction if SPECT/CT scanners are used (Recommended) |
|                    | Include extra-cardiac/soft tissue uptake (Recommended) |
| **Conclusions**    | 1. An overall interpretation of the findings into categories of (1) not suggestive of ATTR cardiac amyloidosis; (2) strongly suggestive of ATTR cardiac amyloidosis; or (3) equivocal for ATTR cardiac amyloidosis after exclusion of a systemic plasma cell dyscrasia (Required) |
|                    | a. Not suggestive: A semi-quantitative visual grade of 0. |
|                    | b. Equivocal: If diffuse myocardial uptake of $^{99m}$Tc-HMDP is visually confirmed and the semi-quantitative visual grade is 1 or there is interpretive uncertainty of grade 1 versus grade 2 on visual grading. |
|                    | c. Strongly suggestive: If diffuse myocardial uptake of $^{99m}$Tc-HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3. |
|                    | 2. Statement that evaluation for light chain (AL) amyloidosis by serum-free light chain assay, and serum and urine immunofixation is recommended in all patients undergoing $^{99m}$Tc-HMDP scans for cardiac amyloidosis. (Required) |
|                    | 3. Statement that results should be interpreted in the context of prior evaluation and referral to a hematologist or amyloidosis expert is recommended if either: |
|                    | a. Recommended echo/cardiac magnetic resonance is strongly suggestive of cardiac amyloidosis and $^{99m}$Tc-HMDP is not suggestive or equivocal and/or |
|                    | b. Free light chains are abnormal or equivocal. (Recommended) |

Adapted from Dorbala et al. 5

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### Table 4. $^{99m}$Tc-HMDP scans in amyloidosis

| Diagnosis                                      | Grade 0 | Grade 1 | Grade 2 | Grade 3 | All  |
|------------------------------------------------|---------|---------|---------|---------|------|
|                                                | N = 90  | N = 11  | N = 28  | N = 12  | N = 141 |
| No cardiac amyloid                             | 77      | 0       | 0       | 0       | 77   |
| Amyloidosis without cardiac amyloid infiltration| 11      | 0       | 0       | 0       | 11   |
| AL, no cardiac amyloid                         | 0       | 0       | 0       | 0       | 0    |
| ATTR, no cardiac amyloid                       | 10      | 0       | 0       | 0       | 10   |
| AApoAI, no cardiac amyloid                     | 0       | 0       | 0       | 0       | 0    |
| ALys, no cardiac amyloid                       | 0       | 0       | 0       | 0       | 0    |
| AFib, no cardiac amyloid                       | 1       | 0       | 0       | 0       | 1    |
| AA, no cardiac amyloid                         | 0       | 0       | 0       | 0       | 0    |
| AGel, no cardiac amyloid                       | 0       | 0       | 0       | 0       | 0    |
| Unknown amyloidosis type, no cardiac amyloid   | 0       | 0       | 0       | 0       | 0    |
| Localized AL, no cardiac amyloid               | 0       | 0       | 0       | 0       | 0    |
| No amyloidosis                                 | 66      | 0       | 0       | 0       | 66   |
| Anderson-Fabry                                 | 0       | 0       | 0       | 0       | 0    |
| Heart failure with preserved ejection fraction (HFPEF) | 0       | 0       | 0       | 0       | 0    |
| Hypertrophic cardiomyopathy (HCM)              | 0       | 0       | 0       | 0       | 0    |
| Hypertensive cardiomyopathy                    | 0       | 0       | 0       | 0       | 0    |
| TTR mutation carriers, no amyloid              | 14      | 0       | 0       | 0       | 14   |
| Cardiac light chain deposition disease          | 0       | 0       | 0       | 0       | 0    |
| Undefined cardiomyopathy                       | 52      | 0       | 0       | 0       | 52   |
| **Cardiac amyloid**                            | 13      | 11      | **28**  | **12**  | **64** |
| Cardiac ATTR amyloid                           | 0       | 10      | 28      | 12      | 50   |
| Cardiac AL amyloid                              | 13      | 1       | 0       | 0       | 14   |
| Cardiac apoAI amyloid                           | 0       | 0       | 0       | 0       | 0    |
| Cardiac amyloidiosis of unknown type            | 0       | 0       | 0       | 0       | 0    |

Adapted from Gillmore et al.\(^2\)

### Table 5. Sensitivity and specificity of $^{99m}$Tc-HMDP scintigraphy vs. endomyocardial biopsy (EMB) histology

#### Perugini grade 2 or 3 $^{99m}$Tc-HMDP scan vs cardiac ATTR amyloid (N = 21 [141])

| Diagnosis                                      | Grade 2/3 scan | Grade 0/1 scan | Sensitivity | Specificity |
|------------------------------------------------|----------------|----------------|-------------|-------------|
| Cardiac ATTR amyloid                           | 11 (40)        | 3 (10)         | 79% (80%)   |             |
| No cardiac ATTR amyloid                        | 0 (0)          | 7 (90)         | 100% (100%) |             |

#### Perugini grade 2 or 3 $^{99m}$Tc-HMDP scan + absence of clone vs ATTR amyloid (N = 21 [141])

| Diagnosis                                      | Grade 2/3 scan | Grade 0/1 scan |
|------------------------------------------------|----------------|----------------|
| Cardiac ATTR amyloid                           | 8 (37)         | 6 (13)         | 57% (74%)   |
| No cardiac ATTR amyloid                        | 0 (0)          | 7 (90)         | 100% (100%) |

Results for 21 Patients with EMB with Results for All 141 in Parentheses
Adapted from Gillmore et al.\(^2\)
| Author        | Year | N Amyloidosis | N controls | Patient cohort/diagnostic standard | Criterion | Sensitivity | Specificity | Comments                                                                 |
|--------------|------|---------------|------------|------------------------------------|-----------|-------------|-------------|--------------------------------------------------------------------------|
| Galat        | 2015 | 69: wtATTR-CA: 21, AL-CA: 14, vATTR-CA: 26, vATTR-N: 4, asymptomatic carriers: 4 | 52: (other CMP [37 with LVH; 15 no LVH]) | Prospective/Various organ biopsy with IHC + genotyping + echo | (a) Visual score ≥ 1 (amyloidosis vs control) | (b) Visual score ≥ 2 (identification of ATTR pts with cardiac amyloidosis) | (a) 75% (b) 83% | Evaluation of diagnostic accuracy in the etiological diagnosis (in identification of ATTR pts) All ATTRv without cardiac amyloidosis and carriers had no cardiac uptake |
| Galat        | 2016 | 93: wtATTR-CA: 33, AL-CA: 19, vATTR-CA: 33, vATTR-N: 5, asymptomatic carriers: 3 | 31 pts with LVH | Prospective/Various organ biopsy with IHC + genotyping + echo | H/Mediastinum > 1.11 (early phase) = cardiac fixation. 1.11 - 1.21 ≈ Perugini 1 > 1.21 ≈ Perugini 2-3 | If H/M > 1.21 : 100% (for detecting ATTR pts vs AL) If H/M > 1.21 : 100% (for detecting ATTR pts vs AL) | 100% | All controls had no cardiac uptake |
| Cappelli     | 2017 | 65: ATTRwt: 23, ATTRm: 16, AL: 26 | 20 | Retrospective/Various organ biopsy with IHC + genotyping + echo | Visual score ≥ 2 | 100% (for detecting ATTR pts vs AL) | 93% | Evaluation of diagnostic accuracy in the etiological diagnosis (identification of ATTR pts) |
| Van Der Gucht | 2017 | 61: | - | Prospective/Various organ biopsy with IHC + genotyping + echo | Cardiac uptake in the early phase | Cardiac uptake in the early phase | 100% | Evaluation of LV distribution of early phase uptake |

AL-CA, light chain cardiac amyloidosis; ATTRm, amyloid transthyretin mutation; vATTR-CA, variant (hereditary) amyloid transthyretin cardiac amyloidosis; wtATTR-CA, ATTRwt, wild-type amyloid transthyretin cardiac amyloidosis
amyloidosis. One small study of 6 patients with hereditary ATTR amyloidosis assessed both 99mTc-HMDP and 99mTc-DPD and found no statistical difference between heart to mediastinal (H/M) ratios. Anecdotally, initial experience of using 99mTc-HMDP at US centers familiar with 99mTc-PYP suggest that a 3-hour HMDP imaging protocol is associated with image quality that is at least equivalent to 99mTc-PYP and potentially with lower blood pool activity. These findings need empiric confirmation. Figure 3 shows 99mTc-PYP images followed 2 months later by 99mTc-HMDP images from the same patient in early 2022 in the USA, demonstrating excellent correlation of imaging findings between the tracers with no interval treatment. This example is particularly illustrative as the grade of myocardial uptake (Grade 2) on planar images and contours on SPECT (including an apical hot spot) are similar between both 99mTc-PYP and 99mTc-HMDP images.

**SUMMARY AND CONCLUSION**

In summary, disruption of the supply of PYP should not lead to delay in the scintigraphic diagnosis of ATTR cardiac amyloidosis. Rather, HMDP is a reasonable alternative given its comparable image quality and diagnostic performance, and its use in the US and internationally, as detailed above, is endorsed by ASNC. At the same time, more data are needed comparing the existing bone-avid radiotracers in the context of amyloidosis diagnosis, including comparative human studies in which patients are imaged using more than one of these radiopharmaceuticals.

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References

1. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. J Am Coll Cardiol 2019;73:2872-91.
2. Gillmore JD, Maurer MS, Falk RH, Merlini G, Dany T, Dispensieri A. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12.
3. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007-16.
4. Hanna M, Ruberg FL, Maurer MS, Dispensieri A, Dorbala S, Falk RH, et al. Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: JACC review topic of the week. J Am Coll Cardiol 2020;75:2851-62.
5. Dorbala S, Ando Y, Bokhari S, Dispensieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol 2019;26:2065-123.
6. Maurer MS. Noninvasive identification of ATTRwt cardiac amyloidosis: The re-emergence of nuclear cardiology. Am J Med 2015;128:1275-80.
7. Cuscaden C, Ramsay SC, Prasad S, Goodwin B, Smith J. Estimation of prevalence of transthyretin (ATTR) cardiac amyloidosis in an Australian subpopulation using bone scans with echocardiography and clinical correlation. J Nucl Cardiol 2021;28:2845-56.
8. Dorbala S, Ando Y, Bokhari S, Dispensieri A, Falk RH, Ferrari VA, et al. Addendum to ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol 2020;27:659-673. Erratum in: J Nucl Cardiol 2021;28:1763-67.
9. Bokhari S, Castaldo A, Pozziakoff 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;6:195-201.
10. Sperry BW, Burgett E, Bybee KA, McGhie AI, O’Keefe JH, Saeed IM, et al. Technetium pyrophosphate nuclear scintigraphy for cardiac amyloidosis: Imaging at 1 vs 3 hours and planar vs SPECT/CT. J Nucl Cardiol 2020;27:1802-7.
11. Flaherty KR, Morgenstern R, Pozziakoff T, DeLuca A, Castano A, Maurer MS, et al. 99m Tc Technetium pyrophosphate scintigraphy with cadmium zinc telluride cameras is a highly sensitive and specific imaging modality to diagnose transthyretin cardiac amyloidosis. J Nucl Cardiol 2020;27:371-80.
12. Parkey RW, Bonte EF, Meyer SL, Atkins JM, Curry GL, Stokely EM, et al. A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 1974;50:540-6.
13. Perugini E, Guidalotti PL, Salvi F, Cooke RMT, 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;46:1076-84.
14. Hutt DF, Quigley A-MM, Page J, Hall ML, Burniston M, Gopal D, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging 2014;15:1289-98.
15. Bach-Gansmo T, Wien TN, Løndalen A, Halvorsen E. Myocardial uptake of bone scintigraphic agents associated with increased pulmonary uptake. Clin Physiol Funct Imaging 2016;36:237-41.
16. Malka N, Abulizi M, Kharebou Mi, Oghina S, Galat A, Le Bras F, et al. Extracardiac soft tissue uptake, evidenced on early 99mTc-HMDDP SPECT/CT, helps typing cardiac amyloidosis and demonstrates high prognostic value. Eur J Nucl Med Mol Imaging 2020;47:2396-406.
17. Ravezzi C, Gagliardi C, Milandri A. Analogies and disparities among scintigraphic bone tracers in the diagnosis of cardiac and non-cardiac ATTR amyloidosis. J Nucl Cardiol 2019;26:1638-41.
18. Monfort A, Rivas A, Banyeereen R, Inamo J, Farid K, Neviere R. Pulmonary 99mTc-HMDDP uptake correlates with restrictive ventilatory defects and abnormal lung reactivity in transthyretin cardiac amyloidosis patients. Respir Res 2022;23:72.
19. Cappelli F, Gallini C, Costanzo EN, Tutino F, Ciaccio A, Vaggelli L, et al. Lung uptake during 99mTc-hydroxyethylmethylene diphotonate scintigraphy in patient with TTR cardiac amyloidosis: An underestimated phenomenon. Int J Cardiol 2018;254:346-50.
20. Gallini C, Tutino F, Martone R, Ciaccio A, Costanzo EN, Taborchi G, et al. Semi-quantitative indices of cardiac uptake in patients with suspected cardiac amyloidosis undergoing 99mTc-HMDDP scintigraphy. J Nucl Cardiol 2021;28:90-9.
21. Cappelli F, Gallini C, Di Mario C, Costanzo EN, Vaggelli L, Tutino F, et al. Accuracy of 99mTc-Hydroxyethylmethylene diphotonate scintigraphy for diagnosis of transthyretin cardiac amyloidosis. J Nucl Cardiol 2019;26:497-504.
22. Bellevere D, Bailleix A, Deléis F, Blaire T, Agostini D, Mouquet F, et al. Quantitation of myocardial 99m Tc-HMDDP uptake with new SPECT/CT cadmium zinc telluride (CZT) camera in patients with transthyretin-related cardiac amyloidosis: Ready for clinical use? J Nucl Cardiol 2022;29:506-14.
23. Musumeci MB, Cappelli F, Russo D, Tini G, Canepa M, Milandri A, et al. Low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related transthyretin cardiac amyloidosis. JACC Cardiovasc Imaging 2020;13:1314-21.
24. Graves SA, Bagaeac A, Crowley JR, Merlino DAM. Reimbursement approaches for radiopharmaceutical dosimetry: Current status and future opportunities. J Nucl Med 2021;62:485-508.
25. Abulizi M, Cottereau AS, Gauglche A, Vandeventer S, Galat A, Van Der Gucht A, et al. Early-phase myocardial uptake intensity of 99mTc-HMDDP vs 99m Tc-DPD in patients with hereditary transthyretin-related cardiac amyloidosis. J Nucl Cardiol 2018;25:217-22.
26. Garcia-Pavia P, Ravezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail 2021;23:512-26.
27. Galat A, Rovolo J, Guelpich A, Van Der Gucht A, Rappeneau S, Bodez D, et al. Usefulness of 99mTc-HMDDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. Amyloid 2015;22:210-20.
28. Galat A, Van Der Gucht A, Guelpich A, Bodez D, Cottereau AS, Guendour S, et al. Early phase 99 Tc-HMDDP scintigraphy for the diagnosis and typing of cardiac amyloidosis. JACC Cardiovasc Imaging 2017;10:601-3.
29. Van Der Gucht A, Cottereau AS, Abulizi M, Guellich A, Blanck-Durand P, Israel JM, et al. Apical sparing pattern of left ventricular myocardial 99mTc-HMDP uptake in patients with transthyretin cardiac amyloidosis. J Nucl Cardiol 2018;25:2072-9.

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