

# Metadata of the article that will be visualized in OnlineFirst

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ArticleTitle	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	
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# 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

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52  
53 **THE NEED FOR AN ADDENDUM**

54 **AQ1** There are two primary reasons for an addendum.  
55 The first is that the document reviewer list is being  
56 updated to include Dr. Richard Cheng and Dr. Roy John,  
57 who have critically reviewed the document, but were  
58 inadvertently not listed as reviewers. In addition, since  
59 the publication of this document and introduction of  
60 approved therapies for transthyretin cardiac amyloidosis  
61 (ATTR-CA), the clinical use of bone tracer cardiac  
62 scintigraphy has been extended to populations with  
63 lower prevalence of ATTR-CA. Numerous observations  
64 have raised concerns about (1) incorrect diagnosis of  
65 ATTR-CA based on <sup>99m</sup>Tc-pyrophosphate (PYP) planar  
66 imaging and heart-to-contralateral lung (H/CL) ratio  
67 without confirmation of diffuse myocardial uptake on  
68 SPECT imaging at some sites; (2) excess blood pool  
69 activity on the 1-hour planar and SPECT images being  
70 interpreted as positive scans; and (3) missed diagnosis of  
71 **AQ2** light chain (AL) amyloidosis, as serum-free light chain  
72 studies and serum and urine immunofixation elec-  
73 trophoresis studies may not be recommended in the  
74 <sup>99m</sup>Tc-PYP/-3,3-diphosphono-1,2-propanodicarboxylic  
75 acid/hydroxymethylene diphosphonate (<sup>99m</sup>Tc-PYP/  
76 DPD/HMDP) report. Incorrect diagnosis leads to inap-  
77 propriate therapy and worse patient outcomes. SPECT  
78 and planar imaging performed at 3 hour maximize  
79 specificity.<sup>1-3</sup> Additionally, technical parameters have  
80 been updated.

81 **AQ4** Accordingly, we are issuing this addendum to  
82 clarify the protocols, interpretation, and reporting of  
83 <sup>99m</sup>Tc-PYP imaging:

- 84 1. Acquisition (Table 1):  
85 a. The time between injection of <sup>99m</sup>Tc-PYP and  
86 scan is revised: 2- or 3-hour imaging is recom-  
87 mended, and 1-hour imaging is optional (Table 1).

- If excess blood pool activity is noted, 3-hour 88  
imaging is recommended. The timing between 89  
injection and scanning is now consistent for 90  
<sup>99m</sup>Tc-PYP, -DPD, and -HMDP. We recognize 91  
some experienced centers that have become 92  
proficient at 1-hour scanning; the recommendation 93  
for 2- or 3-hour imaging is particularly important 94  
for centers starting new <sup>99m</sup>Tc-PYP programs. 95  
b. SPECT imaging is required in all studies (irre- 96  
spective of time between injection and scan) to 97  
highlight the importance of directly visualizing 98  
tracer uptake in the myocardium. 99  
c. 1-hour planar-only imaging is not recommended. 100  
d. Emerging literature suggests that cadmium zinc 101  
telluride (CZT) SPECT can also be used for 102  
<sup>99m</sup>Tc-PYP/DPD/HMDP imaging.<sup>4,5</sup> 103
2. Interpretation (Table 2): 104  
a. Planar imaging and H/CL ratio alone are insuffi- 105  
cient for diagnosis of ATTR cardiac amyloidosis. 106  
SPECT imaging is necessary to identify myocar- 107  
dial uptake of <sup>99m</sup>Tc-PYP/DPD/HMDP. 108  
b. Repeat imaging is recommended at 3 hour if 109  
excess blood pool activity is noted. 110  
c. The steps in Table 2 clarify that visual grading on 111  
planar and SPECT imaging is the primary method 112  
for diagnosis of ATTR cardiac amyloidosis. 113  
d. Recommendations are clarified for ease of 114  
interpretation. 115
3. Reporting (Table 3): 116  
a. Diffuse myocardial uptake should be visualized to 117  
report a positive scan. 118  
b. The criterion for H/CL ratio > 1.5 as strongly 119  
positive has been removed (consistent with diag- 120  
nostic criteria listed in the ASNC/AHA/ASE/ 121

**Table 1.** Recommendations for standardized acquisition of <sup>99m</sup>Tc-PYP/DPD/HMDP for cardiac amyloidosis. Adapted from Reference (209)

Imaging procedures	Parameters	Recommendation
Preparation	No specific preparation. No fasting required	Required
Scan	Rest scan	Required
Dose	<sup>99m</sup> Tc-PYP: 10-20 mCi (370-740 MBq) intravenously	Recommended
	<sup>99m</sup> Tc-DPD: 10-20 mCi (370-740 MBq) intravenously	
	<sup>99m</sup> Tc-HMDP: 10-20 mCi (370-740 MBq) intravenously	
Time between injection and acquisition: <sup>99m</sup> Tc-PYP/DPD/HMDP	2 or 3 h	Recommended
Time between injection and acquisition: <sup>99m</sup> Tc-PYP only	1 h	Optional. If excess blood pool activity noted on 1-h images, 3-h imaging is recommended. See below regarding image type.
General imaging parameters†		
Field of view	Heart	Required
	Chest	Optional for planar
	Heart	Recommended
CT attenuation correction		SPECT/CT fusion images helpful to localize tracer uptake to the myocardium
Image type: planar	Chest	Recommended
	2 or 3 h	1-hour planar-only imaging is not recommended
Image type: SPECT	Heart	Required
Position	Supine	Required
	Upright	Optional
Energy window	140 keV, 15-20%	Required
Collimators	Low energy, high resolution	Recommended
Matrix-Planar	256 × 256	Recommended
Matrix-SPECT	128 × 128	Recommended
Pixel size	(at least 64 by 64 is required) 2.3-6.5 mm	Recommended
Planar imaging specific parameters†		
Number of views*	Anterior and lateral	Required

Table 1 continued

Imaging procedures	Parameters	Recommendation
Detector configuration	90°	Recommended
Image duration (count based)	750,000 counts	Recommended
Magnification	1.46 for large field of view systems	Recommended with goal of achieving recommended pixel size
	1.0 for small field of view systems	Recommended
SPECT imaging specific parameters†		
Angular range/detector configuration	180°/90° 360°/180°	Minimum Required Optional, recommended if large FOV camera is available
ECG gating	Off; Non-gated imaging	Recommended
Number of views/detector	40/32	Recommended
Time per stop	20 s/25 s	Recommended
Magnification	1.46 (180° angular range) 1.0 (360° angular range)	Recommended

\* Anterior and lateral views are obtained at the same time; lateral planar views or SPECT imaging may help separate sternal from myocardial uptake

**Table 2.** Recommendations for interpretation of  $^{99m}\text{Tc}$ -PYP/DPD/HMDP for cardiac amyloidosis. Adapted from Reference (209)**Step 1: Visual interpretation**

Evaluate planar and SPECT images to confirm diffuse radiotracer uptake in the myocardium

Differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (e.g., from rib hot spots from fractures) on SPECT images. If excess blood pool activity is noted, recommend repeat SPECT imaging at 3 h

If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semi-quantitative visual grading. If no myocardial tracer uptake is present on SPECT, the visual grade is 0

**Step 2: Semi-quantitative visual grading to diagnose ATTR cardiac amyloidosis**

Examine planar and SPECT images for relative tracer uptake in the myocardium relative to ribs and grade using the following scale:

Grade 0	No myocardial uptake and normal bone uptake
Grade 1	Myocardial uptake less than rib uptake
Grade 2	Myocardial uptake equal to rib uptake
Grade 3	Myocardial uptake greater than rib uptake with mild/absent rib uptake

**Step 3: Heart/contralateral lung uptake ratio assessment (when applicable)**

A circular ROI should be drawn over the heart on the anterior planar images with care to avoid sternal overlap and with size adjusted to maximize coverage of the heart without inclusion of adjacent lung. This ROI (same size) should be mirrored over the contralateral chest without inclusion of the right ventricle, to adjust for background and rib uptake (see Fig. 5a\*). The heart and contralateral ROIs should be drawn above the diaphragm

A H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral lung ROI mean counts.

H/CL ratios of  $\geq 1.5$  at 1 h can accurately identify ATTR cardiac amyloidosis if myocardial PYP uptake is visually confirmed on SPECT and systemic AL amyloidosis is excluded (114). An H/CL ratio of  $> 1.3$  at 3 h can identify ATTR cardiac amyloidosis

**NOTE:** Diagnosis of ATTR cardiac amyloidosis cannot be made solely based on H/CL ratio alone with PYP. H/CL ratio is not recommended if there is absence of myocardial uptake on SPECT. Additionally, if the visual grade is 2 or 3, diagnosis is confirmed and H/CL ratio assessment is not necessary. H/CL ratio is typically concordant with visual grade. If discordant or the visual grade is equivocal, H/CL ratio may be helpful to classify equivocal visual grade 1 versus 2 as positive or negative

See Fig. 5b.\* Grade 2 or Grade 3 uptake is consistent with ATTR cardiac amyloidosis if a monoclonal plasma cell dyscrasia is excluded, as this degree of uptake can be seen in  $> 20\%$  of patients with AL cardiac amyloidosis.(3) Grade 0 and Grade 1 uptake may be observed in AL cardiac amyloidosis and warrants further evaluation to exclude AL amyloidosis.(3) The writing group would like to emphasize the importance of excluding a monoclonal process with serum/urine immunofixation and a serum-free light-chains assay in all patients with suspected amyloidosis

Of note: $^{99m}\text{Tc}$ -PYP/HMDP uptake could be seen in other causes of myocardial injury, including pericarditis, myocardial infarction (regional uptake), and chemotherapy or drug associated myocardial toxicity

\*Fig. 5a and 5b refer to figures in the original document

AL amyloid light chain, ATTR amyloid transthyretin, H/CL heart/contralateral lung, ROI region of interest

**Table 3.** Recommendations for standardized reporting of <sup>99m</sup>Tc-PYP/DPD/HMDP imaging for cardiac amyloidosis. Adapted from Reference (209)

Parameters	Elements
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 (required) Quantitative findings H/CL lung ratio (optional; recommended for positive scans)
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)
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) <b>Not suggestive:</b> A semi-quantitative visual Grade of 0 (b) <b>Equivocal:</b> If diffuse myocardial uptake of <sup>99m</sup> Tc-PYP/DPD/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) <b>Strongly suggestive:</b> If diffuse myocardial uptake of <sup>99m</sup> Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3 2. Statement that evaluation for AL amyloidosis by serum FLCs, serum, and urine immunofixation is recommended in all patients undergoing <sup>99m</sup> Tc-PYP/DPD/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/CMR is strongly suggestive of cardiac amyloidosis and <sup>99m</sup> Tc-PYP/DPD/HMDP is not suggestive or equivocal and/or (b) FLCs are abnormal or equivocal (recommended)

AL amyloid light chain, ATTR amyloid transthyretin, CMR cardiovascular magnetic resonance, echo echocardiography, FLC free light chain, H/C heart-to-contralateral lung ratio

127	EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 2 of 2—Diagnostic Criteria and Appropriate Utilization, where H/CL ratio was not listed).	142
128		143
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132	c. Conclusions have been clarified.	147
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