

## Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: State of the art review and focus on emerging nuclear techniques

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**Amyloidosis is an infiltrative disease characterized by deposition of amyloid fibrils within the extracellular tissue of one or multiple organs. Involvement of the heart, cardiac amyloidosis, is recognized as a common cause of restrictive cardiomyopathy and heart failure. The two major types of cardiac amyloidosis are cardiac amyloid light-chain (AL) and transthyretin-related cardiac amyloidosis (ATTR, mutant and wild types) (Nat Rev Cardiol 2010;7:398-408). While early recognition of cardiac amyloidosis is of major clinical importance, so is the ability to differentiate between subtypes. Indeed, both prognosis and therapeutic options vary drastically depending on the subtype. While endomyocardial biopsy with immunostaining is considered the gold standard, advances in imaging provide an attractive non-invasive alternative. Currently, electrocardiography, echocardiography, and cardiac magnetic resonance imaging are all used in the evaluation of cardiac amyloidosis with varying diagnostic and prognostic accuracy. Yet, none of these modalities can effectively differentiate the cardiac amyloid subtypes. Recent data with <sup>99m</sup>Tc-phosphate derivatives, previously used as bone seeking radioactive tracers, have shown promising results; these radiotracers selectively bind ATTR, but not AL subtype, and can differentiate subtypes with high diagnostic accuracy. This review will initially present the non-radionuclide imaging techniques and then focus on the radionuclide imaging techniques, particularly <sup>99m</sup>Tc-DPD and <sup>99m</sup>Tc-PYP, mechanism of action, performance and interpretation of the study, diagnostic accuracy, prognostic value, future clinical perspective, and outlook.**

**Key Words:** Cardiac amyloidosis • noninvasive multimodality imaging • transthyretin amyloid

### INTRODUCTION

Amyloidosis is an infiltrative disease characterized by extracellular deposition of fibrillary protein into one (localized) or multiple organs (diffuse or systemic).

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Involvement of the heart (cardiac amyloidosis) is being increasingly recognized as an important cause of restrictive cardiomyopathy and congestive heart failure. The two major types of cardiac amyloidosis are: (1) cardiac amyloid light-chain (AL), and (2) transthyretin-related cardiac amyloidosis (ATTR).<sup>1</sup> In the AL subtype, the fibril proteins are composed of immunoglobulin light chains that are produced by monoclonal plasma cells in the bone marrow. The ATTR subtype, on the other hand, is due to an autosomal-dominant mutation (more than 80-100 known mutations, also known as mutant or familial cardiac amyloidosis) or wild-type variant (also known as senile systemic amyloidosis). The mutation causes destabilization of the transthyretin protein (normally stable soluble tetramer) into misfolded monomers or dimers that form fibril sheets and get deposited into the heart and other organs.<sup>1</sup>

While both subtypes can involve the heart among other organs, the two subtypes carry different prognosis

and are targeted by different treatment options. For example, the AL subtype is associated with greater than 50% mortality within 6 months after the diagnosis, while the ATTR subtype has a more favorable prognosis of 3-5 years, 98%-100% 2-year survival, and preferentially better survival with the wild-type variant.<sup>2</sup>

Chemotherapy targeting the plasma cells is the treatment option for AL. Treatment options for ATTR include orthotopic liver transplantation (familial ATTR only) and, more recently, agents designed to stabilize the TTR tetramer (diflunisal, tafamadis),<sup>3</sup> and reduce de novo TTR synthesis in the liver using RNA interference therapy.<sup>4</sup> Therefore, differentiating the type of cardiac amyloidosis (AL vs ATTR) is crucial in guiding patient care. Furthermore, differentiating ATTR into mutant vs wild-type is also important since the former is inherited (autosomal dominant); determining the mutation and performing genetic testing on the family are recommended and standard of care.

Although endomyocardial biopsy with immunohistochemistry staining is the gold standard for the diagnosis, several imaging modalities have been used as non-invasive alternatives. While electrocardiogram, echocardiography, and cardiac magnetic resonance imaging (CMR) have been used with various diagnostic accuracy (Table 1), none of them can differentiate the type of cardiac amyloidosis. In the last decade, however, there have been increasing data on the role of nuclear tracers with single photon emission computed tomography (SPECT) and more recently with positron emission tomography (PET) on early identification of cardiac amyloidosis, and more importantly differentiating ATTR from AL subtypes. Two tracers have gained popularity and clinical use; (1) <sup>99m</sup>Tc-DPD which is used mainly in Europe and Asia but not is FDA approved for use in the United States, and (2) <sup>99m</sup>Tc-PYP which is used in the United States.

The aim of this review is to present initially the non-radionuclide imaging techniques used for the diagnosis of cardiac amyloidosis (ECG, echocardiography, CMR), and then focus on the radionuclide techniques, particularly <sup>99m</sup>Tc-DPD and <sup>99m</sup>Tc-PYP, describing the mechanism of action, performance, and interpretation of nuclear studies including diagnostic accuracy, prognostic value, and future clinical perspectives.

### **GOLD STANDARD FOR DIAGNOSIS: BIOPSY WITH IMMUNOHISTOCHEMISTRY**

The gold standard for the diagnosis of cardiac amyloidosis is tissue biopsy. Fat-pad and rectal biopsy have been used with various sensitivities (less sensitive overall in ATTR) to diagnose the presence of infiltrative amyloidosis and avoid endomyocardial biopsy.<sup>5</sup> The

latter, however, has a sensitivity close to 100% although associated with low-risk of procedural complication.<sup>6</sup> The typical appearance of amyloid is viewed with Congo red stain that produces an apple-green birefringence under polarized light microscopy, and more commonly now Thioflavin S stain. The next step is to use immunohistochemistry stain with antibodies to immunoglobulin light chain and to amyloid fibril proteins to distinguish AL vs ATTR subtypes, respectively (Figure 1). Mass spectroscopy and laser microdissection can also be used with high diagnostic accuracy although not widely available or popular.<sup>7</sup>

### **NON-NUCLEAR TECHNIQUES**

While myocardial biopsy is the gold standard, the complementary role and impact of ECG, echocardiography, and CMR in diagnosing cardiac amyloidosis have been recently highlighted.<sup>8</sup>

#### **Electrocardiogram (ECG): Diagnostic Criteria and Limitations**

The classical feature on an ECG that triggers the suspicion and workup for cardiac amyloidosis is the presence of new low voltage.<sup>9</sup> Unlike AL, where low voltage is seen in the majority of cases,<sup>10</sup> less than a quarter of patients with ATTR subtype (even less depending on the mutation) have low-voltage.<sup>11,12</sup> The main limitation of low-voltage criteria is the low sensitivity and specificity in the diagnosis of amyloidosis, not to mention differentiating subtypes. This is in part due to a large overlap with other conditions; in particular obesity, pectus carinatum, and chronic obstructive lung disease. When accounting for LV mass, a relative low voltage (voltage to mass ratio) is more sensitive in detecting cardiac amyloidosis.<sup>13</sup> Still, the presence of low voltage depends on the extent and duration of the disease.<sup>14</sup> Recent data from a single center showed improved diagnostic accuracy of 12-lead ECG using more sophisticated criteria than standard low-voltage.<sup>15</sup> In particular, a corrected QT duration >440 ms and a Sokolow-Lyon index  $\leq 1.5$  mm (S in V<sub>1</sub> + R in V<sub>5</sub> or V<sub>6</sub> or R in aVL) were found to have a sensitivity and specificity of 85% and 100%, respectively. Also, a novel index ([PQ interval minus P-wave duration in lead II multiplied by corrected QT duration]/Sokolow-Lyon index) was shown to be highly diagnostic for the differentiation of amyloidosis (area under the curve 0.92) from other disease. However, there was no distinction of the subtype of amyloidosis based on any of these criteria.<sup>15</sup> Fragmented QRS on an ECG has been recently described in cardiac amyloidosis without distinguishing subtypes.<sup>16</sup> Its presence is likely related to cardiomyopathy, scar, and fibrosis, although not

**Table 1.** Non-nuclear imaging tests in cardiac amyloidosis

Non-nuclear imaging test	Characteristics
Immunohistochemistry	Biopsy with staining is the gold standard Proper immunohistochemistry can differentiate the subtypes
Electrocardiogram	Low voltage has a very low sensitivity for ATTR, and overlap with other disease Fragmented QRS: low sensitivity and specificity New criteria Corrected QT duration >440 ms and a Sokolow-Lyon index $\leq 1.5$ mV have a sensitivity of 85% and specificity 100% [PQ interval minus P-wave duration in lead II multiplied by corrected QT duration]/Sokolow-Lyon index: AUC 0.92 Has prognostic value Most data is limited to AL subtype
Echocardiogram	Speckle tracking appearance: harmonic imaging has reduced its positive predictive value Increased LV wall thickness (ATTR > AL); overlap with other infiltrative disease such as hypertrophic CM, severe LVH, Fabry's disease Increased interatrial septal thickness, pleural and pericardial effusion, valve thickening (non-specific) Apical sparing on Bull's eye plot of Global Longitudinal strain: SN 96%, SP 88% (in patients without CAD). Does not differentiate AL vs ATTR Promising role for strain for prognostication beyond traditional markers
Cardiac MRI	Diffuse enhancement of the myocardium (ATTR > AL) Right ventricular enhancement in ATTR and less in AL Abnormal T1 kinetics (visual T1 mapping). Abnormal T2 kinetics: T2 ratio (myocardium/skeletal muscle) <1.5 Underestimation of the degree of amyloid involvement due to difficulty nulling the myocardium Does not differentiate AL vs ATTR Mixed prognostic data with LGE T1 and T2 kinetics seem to provide more robust prognostic data New promising data with equilibrium contrast to measure extracellular volume fraction and quantify amyloid burden

Adopted from Refs.<sup>4-45</sup>

very sensitive or specific given large overlap with other infiltrative disease and ischemic cardiomyopathy, especially in the elderly population.

Other common ECG features of cardiac amyloidosis include intraventricular conduction delays, blocks, and arrhythmias,<sup>17</sup> more so with ATTR as compared to AL subtypes, and decreased heart rate variability particularly with AL and in some mutations of the ATTR subtypes that are associated with various degrees of autonomic dysfunction.<sup>18</sup>

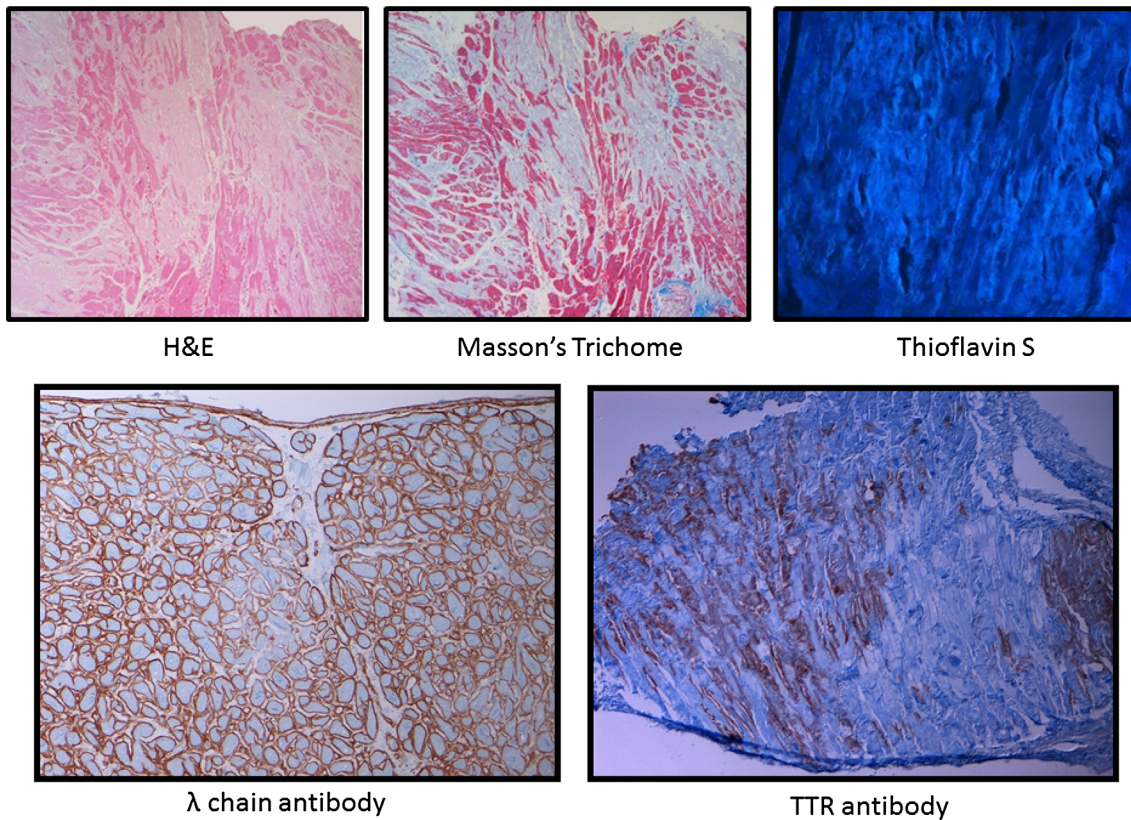
### Prognostic Value

The presence of low voltage is associated with worse outcome<sup>19</sup> with various areas-under the curves

depending on which voltage criteria are used. Fragmented QRS is also associated with worse outcome (HR 1.572 death hazard ratio [1.03-2.40],  $P = .038$ ).<sup>16</sup>

The presence of intraventricular conduction delays or blocks, particularly as they progress over time, reflect worsening of the disease and involvement of the conduction system and high likelihood of requiring a permanent pacemaker, but also higher mortality in AL subtype.<sup>20</sup> Reduced heart rate variability on a 24 hour Holter predicts high short-term mortality in AL, but limited data in ATTR subtypes on mortality is currently available.<sup>18</sup>

Despite its widespread availability and low cost, ECG has limited overall diagnostic accuracy and data on accurately differentiating amyloid subtypes. New



**Figure 1.** Endomyocardial biopsy with different staining of cardiac amyloidosis. Endomyocardial biopsy and different pathology specimen showing evidence of cardiac amyloidosis using H&E, Masson's Trichrome, and Thioflavin S stains (*upper row*). Immunohistochemistry was then performed using  $\lambda$  chain antibody (detects AL amyloidosis) and transthyretin antibody to detect ATTR in different patients (*lower row*).

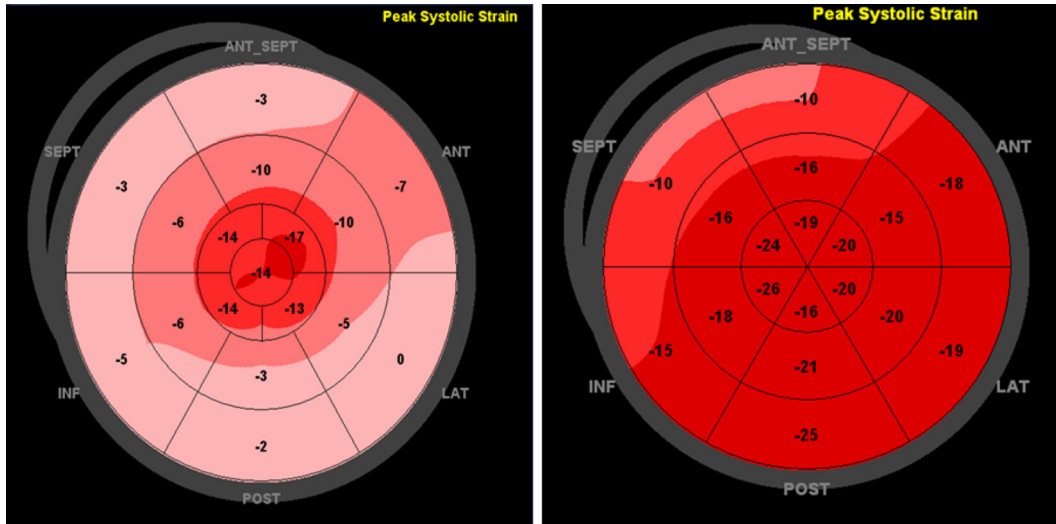
sophisticated criteria seem promising and need prospective validation in future studies.

### Echocardiography

**Criteria for diagnosis and limitations.** There are a constellation of findings seen on an echocardiogram that may trigger the suspicion of cardiac amyloidosis. In particular, there is significant increase, most often symmetrical, in left ventricular (LV) wall thickness. It is worthwhile stressing that the correct terminology for describing the increase in LV mass is increased wall thickness rather than LV hypertrophy; the latter is secondary to myocyte hypertrophy, while in amyloidosis there is increased extracellular deposition of amyloid protein without myocyte hypertrophy leading to wall thickening. The appearance of the LV wall has been classically described as “sparkling or speckled appearance.” In addition, there is thickening of the right ventricular wall, valve leaflets and interatrial septum, and often pleural and pericardial effusions. Diastolic function is often impaired with restrictive

filling pattern in the advanced stages of the disease with concomitant severe dilation of the atria, and not uncommonly atrial thrombi (27% in one case series, one quarter in the right atrium).<sup>21</sup>

However, there are several limitations to traditional echocardiography in the diagnosis of cardiac amyloidosis. First, “speckled appearance” alone is not diagnostic of cardiac amyloidosis, since harmonic imaging, glycogen storage disease, hypertrophic cardiomyopathy, and end-stage renal disease produce similar echocardiographic appearance.<sup>22</sup> Second, cardiac amyloidosis is a progressive disease without many of these findings, particularly in the early stage of the disease process.<sup>23</sup> Indeed, patients with confirmed diagnosis of cardiac amyloidosis might present with grade I (mild) diastolic dysfunction and be asymptomatic; in such early cases, significant wall thickening, and effusions might not be evident. Lastly and more importantly, echocardiography cannot distinguish the subtypes of amyloidosis. While several studies showed relatively greater LV wall thickness and more involvement of the right ventricle in ATTR as compared to AL, there are no cut-off values



**Figure 2.** Global longitudinal strain: Bull's Eye Map. Global longitudinal strains with Bull's eye map were performed on two patients with increased LV wall thickness, left ventricular ejection fraction 55%, and congestive heart failure with restrictive diastolic dysfunction. Both patients had abnormal longitudinal strain. However, one patient had apical sparing pattern (*left panel*) which is very characteristic of cardiac amyloidosis (confirmed with tissue biopsy), while the second one had decreased strain in the basal septum and anteroseptum (*right panel*) that was suggestive of hypertrophic cardiomyopathy (confirmed with cardiac MRI).

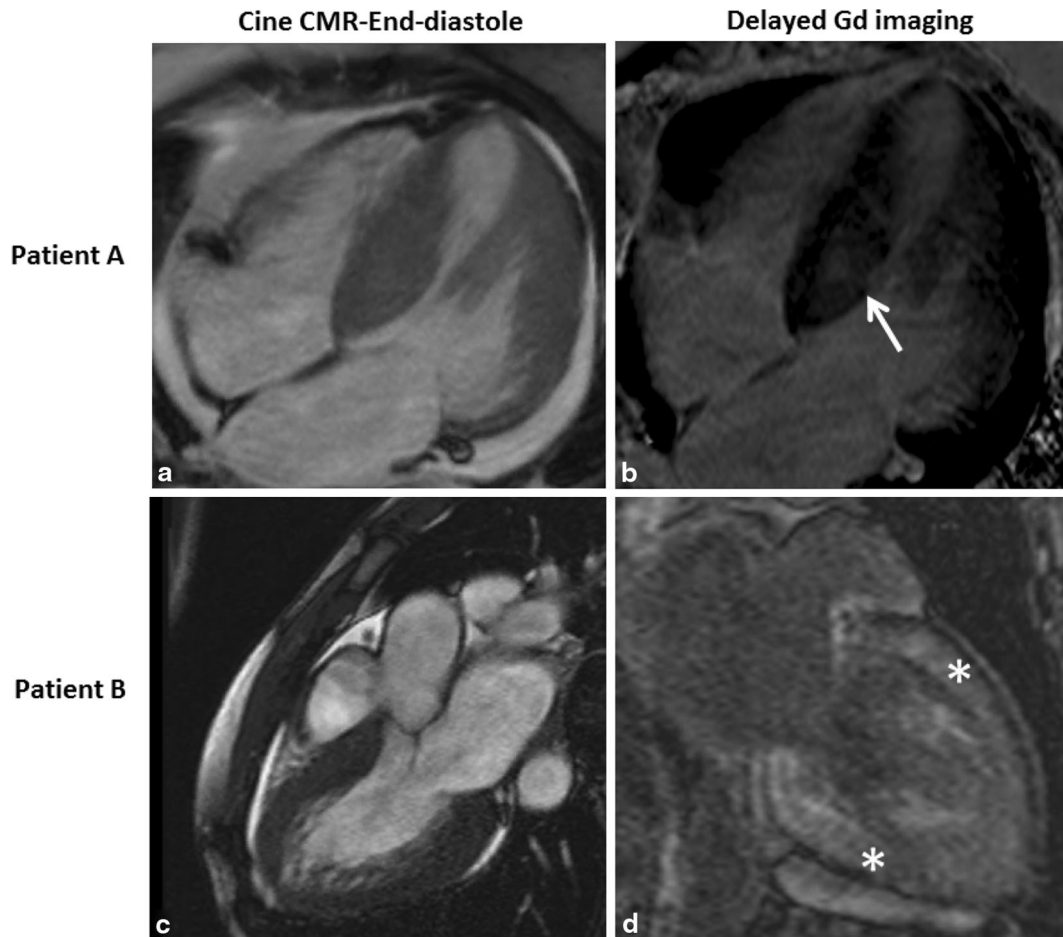
with enough diagnostic accuracy for clinical application.<sup>3</sup> Combining echocardiographic and ECG testing, however, was shown to improve diagnostic accuracy of the test, but still without differentiating subtypes.<sup>24</sup>

**Role of strain imaging.** There have been increasing data on the role of strain imaging in cardiac amyloidosis with both longitudinal and radial strains being reduced in the disease state.<sup>25,26</sup> The clinical use of such data, however, is difficult to apply clinically given the overlap of diseases that are also associated with reduced global strain. Recently, however, Phelan et al<sup>27</sup> described a characteristic regional pattern of longitudinal strain easily identified on strain polar maps or “Bull’s eye” plots; patients with cardiac amyloidosis typically display marked decrease in longitudinal strain in the basal- and mid-wall segments with relative apical sparing of longitudinal strain. This is in contradistinction to hypertrophic cardiomyopathy, where there is preferential decrease in longitudinal strain at the site of greatest hypertrophy. This pattern was integrated into a relative apical longitudinal strain formula (average apical longitudinal strain/(average basal + mid longitudinal strain); a score of >1 was associated with an impressive 93% sensitivity and 82% specificity (area under curve 0.94) for the diagnosis of cardiac amyloidosis<sup>27</sup> (Figure 2). However, it is worth mentioning that patients with known coronary artery disease were excluded from the study. In addition, both AL and ATTR were grouped together and it is less likely than strain pattern can differentiate the different subtypes.

Hence, strain imaging in patients with restrictive cardiomyopathy or other features suggestive of cardiac amyloidosis has become standard of care in our laboratories. Furthermore, new data have shown promising role of right ventricular strain in the diagnosis of AL (no data on ATTR yet),<sup>28</sup> but this technique has not been adopted in clinical practice yet.

**Prognosis.** The prognostic value of echocardiography in patients with cardiac amyloidosis was first shown couple of decades ago by Klein et al<sup>29</sup> using mitral inflow pattern; restrictive filling was associated with increased mortality. Since then, a number of echocardiographic-derived parameters such as LV wall thickness, ejection fraction, right ventricular size, and myocardial performance index have been associated with outcomes.<sup>30</sup> Increased left atrial size, a marker of diastolic dysfunction, was also associated with worse outcomes.<sup>31</sup> Given the progressive nature of the disease, Kristen et al<sup>32</sup> demonstrated rapid progression of increased LV wall thickness predicted mortality in AL. Furthermore, abnormal ejection time <240 ms (a marker of early systolic dysfunction) has a sensitivity of 73% and a specificity of 90% in predicting 1-year cardiac mortality.<sup>33</sup> However, data from Cleveland Clinic showed that only New York Heart Association class was associated with worse outcomes after adjusting for ECG, EF, and diastolic dysfunction.<sup>34</sup>

Recently, left and right ventricular strains have proven to be even more powerful prognostic markers beyond traditional risk factors. Indeed, data from Mayo



**Figure 3.** Cardiac MRI with late gadolinium enhancement. CMR was performed for two patients that had increased wall thickness on Cine images (A, C). On delayed Gd enhancement however, patient A had late Gd enhancement in the septum (B arrow), a pattern suggestive of hypertrophic cardiomyopathy; while patient B had diffuse LGE with difficulty to null the myocardium (D asterisk), a pattern consistent with cardiac amyloidosis.

clinic showed that peak longitudinal systolic strain of the basal anteroseptal segment less negative than or equal to  $-7.5\%$  was an independent predictor of death after adjusting for traditional risk factors (HR 1.05,  $P = .02$ ).<sup>33</sup> Data from Boston also showed that mean LV basal strain was the only independent predictor of both cardiac and all-cause mortality in AL patients.<sup>35</sup> Similarly, Buss et al<sup>36</sup> showed that reduced global longitudinal strain was an independent predictor of survival with incremental value in one of the largest studies. Lastly, abnormal right ventricular strain is also an independent predictor of death beyond E/A filling pattern or diastology. However, all of the cohorts consisted of patients with AL subtype, and with limited data on ATTR.

**CMR: Criteria for diagnosis and limitations.** Late gadolinium delayed enhancement (LGE) CMR has diagnostic value in cardiac amyloidosis. In

this disease, there is interstitial expansion from the amyloid deposit that avidly picks up and retains Gd leading to signal enhancement of the tissue and fast blood pool washout. Global transmural or diffuse subendocardial LGE can detect the disease early on without significant increase in LV wall thickness, and correlate with disease severity<sup>37-39</sup> (Figure 3).

In a recent study, Austin et al<sup>23</sup> showed that LGE-CMR had a sensitivity of 88%, specificity 95%, positive predictive value of 93%, and negative predictive value of 90% in patients with biopsy proven amyloidosis. However, there are several limitations to LGE-CMR: (1) patchy myocardial involvement is not uncommon and can be easily missed; (2) the diffuse nature of LGE presents a challenge for conventional CMR as normal reference myocardium—used to provide context for setting pulse sequence parameters and for visual interpretation—may be absent; as such, CMR can visually

underestimate the disease burden as compared to  $^{99m}\text{Tc}$ -diphosphonate nuclear imaging.<sup>40</sup>

Visual T1-mapping technique is an alternative technique that allows detection of abnormal Gd kinetics in the myocardial tissue; early nulling of the myocardium before the blood pool on inversion recovery reflects an abnormally low T1 of the myocardium due to significant Gd uptake in the extracellular space and is highly suggestive of the presence of infiltrative cardiac amyloidosis. This technique provides a semiobjective way of determining the presence of abnormal Gd kinetics and cardiac amyloidosis. Using receiver-operating characteristic analysis, a value of 1,020 ms on noncontrast T1 mapping has 92% accuracy for identifying either possible or definite AL amyloid cardiomyopathy.<sup>41</sup> Recent data have shown promising role for equilibrium contrast CMR for quantification of extracellular volume fraction as a more robust method that correlates with amyloid burden, and hence quantify it objectively.<sup>42,43</sup>

More recently, alteration of T2 kinetics with decreased T2 myocardium/skeletal muscle ratio, has been described in cardiac amyloidosis, in part due to pronounced local field inhomogeneity.<sup>44</sup> None of the CMR techniques, however, can differentiate subtypes of cardiac amyloidosis. One characteristic feature, however, is that ATTR subtype almost always has LGE of the right ventricle, while almost a third of patients with AL do not.<sup>45</sup>

**Prognostic value.** There have been conflicting data regarding prognostic value of LGE CMR in cardiac amyloidosis.<sup>23,39,46,47</sup> While some studies failed to establish prognostic value of LGE, other studies have shown that LGE was the only predictor of 1-year mortality ( $P = .03$ ) beyond ECG and diastology.<sup>23</sup> T1 mapping, on the other hand, seems more robust and a better predictor of outcomes with 90% accuracy, in part due to its superior discriminatory power.<sup>39</sup> Similar to T1 kinetics, T2 kinetics with a T2 (myocardium/skeletal muscle) ratio  $<1.5$  was shown to be the only independent predictor of death in 36 patients with various subtypes of cardiac amyloidosis (2 with ATTR and 31 with AL).<sup>44</sup> All the studies, however, were of small sample size with few events and inadequate power to adjust for all potential confounders.

## RADIONUCLIDE TECHNIQUES

### Nuclear Tracers

Several radiotracers have been tested and utilized with various degrees of success in the diagnosis of cardiac amyloidosis. Each of the radiotracers evaluated for the detection of cardiac amyloidosis has targeted

different components altered in the heart: sympathetic innervation, perfusion, metabolism, or amyloid-deposits.<sup>48</sup> Although more than a dozen radiotracers have been evaluated over the last couple of decades, there are very limited data on most of them (Table 2).<sup>49–59</sup> Recently,  $^{99m}\text{Tc}$ -DPD (technetium-3,3-diphosphono-1,2-propanodicarboxylic acid) and  $^{99m}\text{Tc}$ -PYP (technetium pyrophosphate) have shown promises.<sup>56,57</sup> Their main advantage is avid uptake by ATTR and minimal uptake with the AL subtype, providing one of the best non-invasive ways to differentiate the subtypes of cardiac amyloidosis. The rest of this review will focus on the  $^{99m}\text{Tc}$ -phosphate derivatives that are the most commonly used and have gained widespread acceptance in the investigation of suspected ATTR.

### Mechanism of Action

The  $^{99m}\text{Tc}$ -phosphate derivatives were originally developed for bone imaging, but were also observed to accumulate in areas of healing in the context of acute myocardial infarction. Such uptake was observed several days after the acute event and thought to be part of the healing process with deposition in mitochondria where there was calcium overloading. Later, it was discovered that these radiotracers accumulate in the myocardium of patients with cardiac amyloidosis. Although the precise mechanism is not well known, there have been several suggested theories. The first is that high calcium levels in amyloidosis bind to phosphate in the radiotracers.<sup>60</sup> The preferential binding of  $^{99m}\text{Tc}$ -phosphate derivatives to ATTR may be due to the fact that transthyretin amyloid fibrils have higher calcium content. Pepys et al<sup>61</sup> showed that normal human serum amyloid protein binds different amyloid fibrils in a highly specific calcium-dependent manner.

Another theory of the preferential binding to ATTR relates to the duration over which amyloid deposition has occurred in the affected tissue. In AL patients, fibrils tend to accumulate over a short period of time as compared to a more indolent course in ATTR.<sup>56</sup>

### How to Perform the Study: Image Acquisition and Analysis

**$^{99m}\text{Tc}$ -DPD.** The technique has been previously described in detail.<sup>40,57</sup> Briefly, after administering 740 MBq of  $^{99m}\text{Tc}$ -DPD intravenously, a whole body scan is performed 3 hours later (anterior and posterior projections) using a dual-head gamma camera equipped with low-energy high-resolution collimators. If there is active uptake in the heart, chest SPECT is performed with images acquired using a circular orbit with 360° rotation, 3° step and shoot technique, and an acquisition

**Table 2.** Nuclear tracers used in imaging cardiac amyloidosis

<b>Nuclear tracers (Ref.)</b>	<b>Mechanism of action</b>	<b>Characteristics</b>	<b>Differentiates ATTR vs AL</b>
<sup>123</sup> I-MIBG <sup>49</sup>	Sympathetic cardiac innervation	Decreased H/M ratio and increased washout rate reflect sympathetic cardiac denervation	No
<sup>123</sup> I-BMIPP <sup>50</sup>	Fatty acid Metabolism	Very limited role	No
<sup>99m</sup> Tc(V)-DMSA <sup>51</sup>	Metabolism and avid uptake	Limited role due to physiological uptake in the blood pool	No
<sup>201</sup> Tl redistribution <sup>52</sup>	Perfusion	Higher washout rate associated with amyloidosis Limited data; non-specific	No
Blood pool ventriculography <sup>51</sup>	Assesses peak filling rate and time to peak filling	Can detect features of restrictive physiology but not specific to cardiac amyloidosis	No
<sup>99m</sup> Tc-Aprotinin <sup>51</sup>	Amyloid deposit ( <i>antiproteases</i> )	5/5 biopsy proven cases had + tracer uptake More useful for extra-abdominal uptake	No
<sup>99m</sup> Tc-DPD <sup>53,54,57</sup>	Amyloid deposit ( <i>high calcium content</i> )	15/15 + uptake in ATTR vs 0/10 in AL Another study: 1/3 of patients with AL had mild uptake Has Prognostic value Not Available in the USA	Yes
<sup>99m</sup> Tc-MDP <sup>55</sup>	Amyloid deposit ( <i>high calcium content</i> )	Mixed results likely secondary to combining patients with AL and ATTR	Not well known
<sup>99m</sup> Tc-PYP <sup>56</sup>	Amyloid deposit ( <i>high calcium content</i> )	SN 97%, SP 100%, AUC 0.992	Yes
<sup>67</sup> Ga-citrate <sup>58</sup>	Unknown mechanism for deposition	Limited case reports. Less uptake than <sup>99m</sup> Tc-PYP. No role in cardiac amyloidosis	Not known
<sup>111</sup> In antimyosin <sup>50</sup>	Binds to areas of myocardial necrosis	7/7 patients had positive uptake Non-specific Only 1 case report	No
<sup>123</sup> I-Serum amyloid protein <sup>59</sup>	Labels the amyloid pool	Not FDA approved. Only used in 2 European centers Not suitable for cardiac amyloidosis due to movement, blood pool content and lack of fenestrated endothelium in the myocardium Detects visceral uptake in AL but not ATTR	No
<sup>11</sup> C-BF-227 <sup>66</sup>	Binds to aggregated amyloid fibrils	First PET tracer to be used One case report: correctly identified ATTR deposition in the heart	Not known
<sup>11</sup> C-PIB <sup>67</sup>	Binds to amyloid fibrils of any type	10/10 patients (ATTR and AL) had uptake and 0/5 volunteers had uptake	No
<sup>18</sup> F florbetapir <sup>68</sup>	Binds to amyloid fibrils of any type	5/5 patients (3 ATTR, 2 AL) had decreased myocardial washout. 0/2 healthy controls had uptake	No



time of 25 seconds per frame using a  $128 \times 128$  matrix. The data is then reconstructed using ramp filtered back projection with a Hann filter.

**$^{99m}\text{Tc-PYP}$ .** After administering 15–25 mCi of  $^{99m}\text{Tc-PYP}$  intravenously, whole body planar imaging is performed with a dual-head gamma camera with low-energy high resolution collimators, 1 hour after the injection and for a total of 8 minutes acquisition or up to 750,000 counts, with the heart in the center of the field of view ( $256 \times 256$  matrix and 1.46 zoom factor). In the presence of myocardial uptake, SPECT image acquisition follows with step and shoot technique, 360 rotation, using a  $64 \times 64$  matrix and 1.46 zoom. Reconstruction is performed using a Butterworth filter with a cut off of 0.50 and order of 5.0.

Semi-quantitative visual scoring of the cardiac uptake is performed as follows: 0 = absent cardiac uptake and intense bone uptake; 1 = mild cardiac uptake < bone uptake; 2 = moderate cardiac uptake = bone uptake; 3 = high cardiac uptake > bone uptake. Quantitative assessment using heart retention, and heart to whole body retention, is assessed using counts in the region of interest as previously described. Similarly, mean total and absolute counts are measured after correction for background counts, and the mean counts in the heart region of interest over the mean counts in the contralateral chest is defined as H/CL ratio.<sup>40,56,57</sup>

### Diagnostic Accuracy of $^{99m}\text{Tc-Derived Phosphate}$

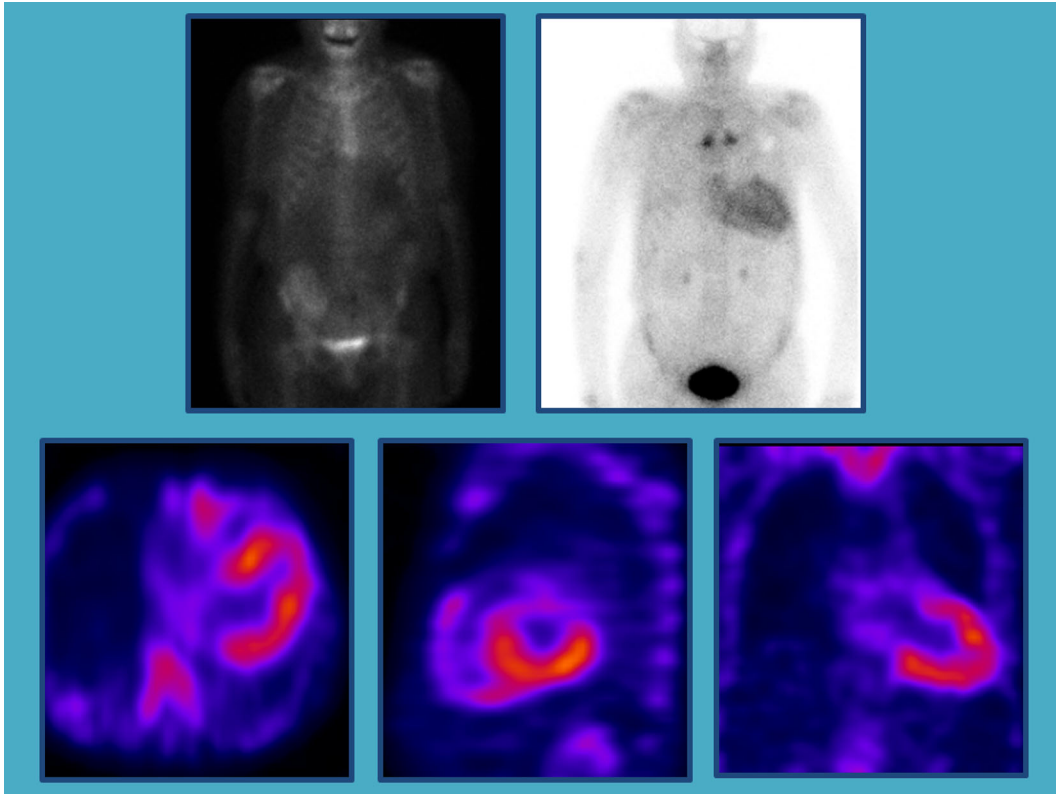
$^{99m}\text{Tc-PYP}$  imaging was first described as a potential diagnostic test for cardiac amyloidosis in the early 1980s. Although initial reports described increased cardiac uptake in patients with amyloid heart disease<sup>62,63</sup>; later studies found limited sensitivity with positive scans in less than 20% of patients casting doubt on the diagnostic accuracy of this technique.<sup>13,64</sup> These early studies, however, were done at a time when precise typing of amyloidosis was not available; hearts with AL-type amyloid do not pick up  $^{99m}\text{Tc-PYP}$  as compared to the avid uptake seen in ATTR. The few studies that attempted to differentiate between subtypes were limited to ATTR wild-type patients only, missing the most common ATTR mutant allele in the United States. In addition, there was a lack of a quantitative measure of tracer retention, and SPECT imaging was not commonly used. In view of all these limitations, the technique was not widely used.

Another tracer,  $^{99m}\text{Tc-MDP}$  (technetium-methylene diphosphonate) has been employed in several case reports and small studies for the diagnosis of cardiac amyloidosis, but has demonstrated even lower sensitivity than  $^{99m}\text{Tc-PYP}$ .<sup>55</sup>

Two decades later, the role of radionuclide techniques for cardiac amyloidosis was revived in Europe with a similar tracer,  $^{99m}\text{Tc-DPD}$ . In an initial report, cardiac uptake of  $^{99m}\text{Tc-DPD}$  was present in all 15 patients with TTR amyloidosis (ATTR) compared to none of the 10 patients with AL amyloidosis.<sup>57</sup> In a larger cohort of 79 patients (45 ATTR and 34 AL) that evaluated tracer retention (calculated by a heart-to-whole body ratio [H/WB]), the diagnostic sensitivity remained high although the specificity was lower than previously reported due to unexpected tracer uptake in about one-third of AL patients.<sup>53</sup> A recent study showed uptake in all 40 patients with echocardiographic evidence of amyloidosis and detected early evidence of disease in 4/23 patients without echocardiographic evidence that was later confirmed by biopsy.<sup>54</sup> Hence,  $^{99m}\text{Tc-DPD}$  has a very high sensitivity for the detection of ATTR even in the subclinical or early phase. The specificity, however, is more controversial; one study showed 100% specificity (0/10 uptake in patients with AL)<sup>57</sup> as compared to  $\approx 70\%$  in a larger study, where 1/3 of patients with AL had some uptake.<sup>53</sup>

Since  $^{99m}\text{Tc-DPD}$  is not FDA approved in the United States, studies are performed using  $^{99m}\text{Tc-PYP}$ . Yamamoto et al<sup>65</sup> used the “PYP score” to assess the utility of  $^{99m}\text{Tc-PYP}$  to evaluate cardiac amyloidosis in 13 subjects with heart failure due to amyloid (1 AL, 3 ATTRm, 8 ATTRwt) and 37 subjects with heart failure due to non-amyloid causes. PYP score, defined as the ratio of myocardial mean counts to ventricular cavity mean counts, had a sensitivity of 84.6% and specificity of 94.5% for distinguishing cardiac amyloidosis from non-amyloid causes of heart failure. In a recent study, Bokhari et al<sup>56</sup> evaluated the role of  $^{99m}\text{Tc-PYP}$  in 45 patients (12 AL, 16 ATTR wild-type, 17 ATTR mutant type) using semi-quantitative heart/contralateral ratio score. While patients with AL did have some uptake, the visual score was significantly less than patients with ATTR. A H/CL > 1.5 was associated with 97% sensitivity and 100% specificity in differentiating ATTR vs AL. The importance of this study is that although patients with AL can still have some tracer uptake, a quantitative score can differentiate ATTR from AL with almost 100% specificity. Therefore, radionuclide tracer imaging not only detects ATTR, but can differentiate it from AL with high degree of certainty (Figure 4).

There are no data that compare  $^{99m}\text{Tc-DPD}$  vs  $^{99m}\text{Tc-PYP}$ .  $^{99m}\text{Tc-DPD}$  is more sensitive than echocardiography in diagnosing early disease, and can differentiate subtypes, while echocardiography does not. There is one study that compared  $^{99m}\text{Tc-DPD}$  vs CMR; CMR underestimated the degree of amyloid involvement compared to  $^{99m}\text{Tc-DPD}$ , in part due to the



**Figure 4.** Radionuclide imaging with  $^{99m}\text{Tc}$ -PYP in patients with cardiac amyloidosis.  $^{99m}\text{Tc}$ -PYP planar imaging was performed in two patients with suspected cardiac amyloidosis based on clinical and echocardiographic data. The first patient had almost no uptake (*upper row, left panel*) and underwent biopsy confirming AL subtype. The second patient had significant uptake (*upper row, right panel*); SPECT imaging was then performed which showed increased tracer uptake in the heart (axial, sagittal and coronal views) (*lower row, respectively*) consistent with ATTR subtype. Biopsy was not performed.

limitation of the technique and difficulty nulling the myocardium<sup>40</sup>.

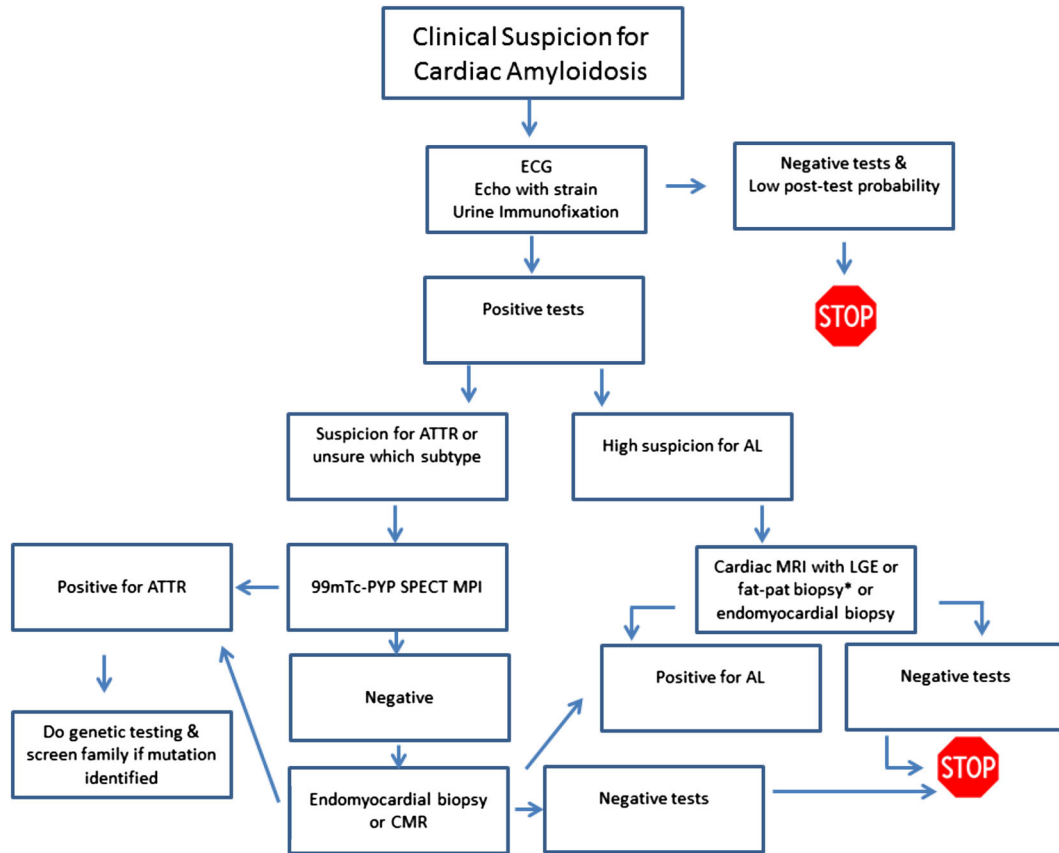
The role of PET imaging in the diagnosis of cardiac amyloidosis has been evaluated in one case report in 2012 using  $^{11}\text{C}$ -BF-227,<sup>66</sup> and recently two studies using new tracers: *N*-[methyl-( $^{11}\text{C}$ )2-(4'-methylamino-phenyl)-6-hydroxybenzothiazole (( $^{11}\text{C}$ -PIB) and  $^{18}\text{F}$  florbetapir<sup>67,68</sup> (Table 2). In both studies, there was selective uptake of the tracer in the myocardium of patients with confirmed cardiac amyloidosis (ATTR and AL) but not in healthy volunteers. The importance of these studies is that for the first time these new tracers offer the potential to quantify amyloid burden in the heart beyond a dichotomous (yes/no) or subjective grading scale 0-4. However, none of the tracers is selective for ATTR as they equally bind light chain amyloid deposits. PET has a higher spatial resolution than SPECT, can be fused with CT for better anatomic definition, and therefore is an appealing alternative with promising diagnostic role.

### Prognostic Value

The prognostic value of  $^{99m}\text{Tc}$ -DPD uptake in the myocardium has been evaluated in a study of 63 patients with ATTR. Heart/whole body retention was used to quantify the degree of myocardial uptake, and was an independent predictor of major adverse cardiovascular events. A H/WB ratio  $\geq 7.5$  was associated with the highest event rate.<sup>54</sup> However, one has to caution the discussion of prognosis as ATTR has better long-term prognosis, especially in senile cases. Also, we do not necessarily know the denominator of patients with amyloid as we have often scan predominantly suspicious cases. There are no prognostic data with  $^{99m}\text{Tc}$ -PYP.

### Suggested Diagnostic Workflow in Suspected ATTR

In patients with suspected ATTR (based on clinical presentation, ECG, and echocardiographic findings),



**Figure 5.** Suggested workflow diagram in the diagnostic workup of cardiac amyloidosis.

radionuclide imaging with either  $^{99m}\text{Tc}$ -DPD or  $^{99m}\text{Tc}$ -PYP can be used as a non-invasive screening method to differentiate between ATTR vs AL. In the presence of positive myocardial uptake, endomyocardial biopsy may not be needed; genetic testing, however, is helpful to differentiate ATTR mutant from wild type, and if a mutation is identified, family screening should be performed (Figure 5). Such a workflow scheme, however, needs to be tested prospectively for efficiency, diagnostic accuracy, and more importantly cost-effectiveness.

### Future Studies

$^{99m}\text{Tc}$ -PYP and  $^{99m}\text{Tc}$ -DPD possess unique affinity for ATTR, and hence for differentiating subtype of cardiac amyloidosis unlike other non-invasive imaging modalities. Whether this technique is sensitive enough in detecting early disease, and in particular those with positive genotype but negative phenotype, warrants further evaluation. Another potential role for nuclear imaging is monitoring disease progression and more importantly response to therapy. Radiation burden in such serial follow-up needs to be taken into

consideration, although the risk of radiation-related complications is likely to be very low given the average age at presentation and the poor prognosis for cardiac amyloidosis. The potential role for new tracers with PET imaging also warrants further investigation.

### Conflict of interest

*The authors have indicated that they have no financial conflict of interest.*

### Disclosures

*None.*

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