Journal of Nuclear Cardiology (2025) 47, 102122

GREAT DEBATE

To screen or not to screen for transthyretin cardiac amyloidosis

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Keywords: Bone avid tracer cardiac scintigraphy, Cardiac amyloidosis, Screening, SPECT, Transthyretin., 99mTc-PYP, 99mTc-DPD, 99mTc-HMDP

Screening for cardiac amyloidosis: Is bone avid tracer cardiac scintigraphy ready for prime time?

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We have witnessed tremendous progress over the last decade in systemic amyloidosis. For transthyretin amyloidosis (ATTR), there are now two therapeutic approaches, including TTR stabilizers and TTR suppression, which are currently approved for transthyretin amyloid cardiomyopathy (ATTR-CM) and transthyretin amyloid polyneuropathy (ATTR-PN) in the setting of variant disease, respectively [1]. The recent data on acoramidis now also approved TTR knockdown with vutrisiran suggests we can anticipate approval of additional therapies for what was an unrelenting life-threatening disease in the absence of disease-modifying therapy [2,3]. For light chain amyloidosis (AL), the first and only Food and Drug Administration (FDA)-approved therapy, daratumumab, a monoclonal antibody targeting the CD38 cell surface protein on plasma cells has been shown to be safe and highly effective in reducing the abnormal toxic light chains [4]. Collectively, these drugs have led to substantial improvement in morbidity and mortality and are more effective when administered early in the course of the disease before significant cardiac dysfunction has ensued. While there are also several ongoing trials that may expand the clinical indications for these therapies and novel therapies that are targeting amyloid removal with monoclonal antibodies, the need to identify patients with early-stage disease is imperative, as current therapies do not reverse the clinical phenotype [5–7]. Indeed, what patients with systemic amyloidosis lose in terms of functional capacity, quality of life, and cardiac function they do not regain with currently available therapeutic strategies. Accordingly, there is a heightened interest in improved diagnosis strategies aimed at earlier diagnosis through screening efforts.

ACTIVE ASCERTAINMENT VS SCREENING

Screening involves identifying apparently healthy, asymptomatic individuals who are at risk of a disease to implement an early treatment or intervention to change the course of the disease [8]. Active ascertainment, on the other hand, is geared toward seeking a diagnosis in patients with signs and symptoms suggestive of a particular disease. United States Preventive Services Task Force (USPTF) recommends routine screening for various conditions that are

1071-3581/
https://doi.org/10.1016/j.nuclcard.2024.102122

relatively common in the general population, such as colorectal cancer (prevalence ~4%), breast cancer (prevalence ~13%), abdominal aortic aneurysm (prevalence ~4%–8%), and others [9]. However, amyloidosis remains a relatively rare disease, although more common than previously thought. While prevalence estimates are imprecise, data suggest that the prevalence in the United States is <.001%. As such, general screening involving healthy or asymptomatic individuals is not warranted and is unlikely to be clinically useful. Accordingly, the focus has been on active ascertainment in patients with findings suggestive of amyloidosis.

This is because the diagnostic accuracy of a test is influenced greatly by the prevalence of the disease in the target population. The currently available data to support the use of bone avid tracers for the diagnosis of ATTR-CA was derived from patients with high pre-test probability of disease. The diagnostic accuracy of the test cannot be generalized to other less selected populations with a lower prevalence of disease [10]. With lower prevalence of a disease, false positive results increase significantly. Accordingly, if we apply scintigraphy to a population with a lower pretest probability of the disease, attention to image acquisition and required expertise in interpretation will be paramount to minimize false positives, including mandatory SPECT and ideally SPECT/CT imaging, delayed imaging to minimize the confounding effect of blood pool, and systematic assessment for monoclonal proteins, which are required for accurate interpretation of results of scintigraphy.

In this issue of the Journal, two perspectives are offered for and against the use of bone avid tracer cardiac scintigraphy for routine screening of cardiac amyloidosis. The authors on both sides of the argument lay out the evidence supporting their claims. Lal and Masri highlight excellent diagnostic performance of bone-avid tracers for detecting ATTR-CA in at-risk populations, including patients with orthopedic manifestations, such as carpal tunnel syndrome, lumbar spinal stenosis, carriers of TTR gene mutations associated with ATTR-CA, heart failure with preserved ejection fraction, and aortic stenosis. Based on these data, Lal and Masri suggest that active ascertainment, rather than general screening, is appropriate for patients at risk for transthyretin cardiac amyloidosis. Ioannou and Fontana highlight the several shortcomings of nuclear scintigraphy in screening an asymptomatic population, including an inability to detect non-ATTR amyloid, such as AL and less common causes like apolipoprotein AI and apolipoprotein AIV. Ioannou and Fontana also emphasize that bone avid tracer imaging may be falsely negative in early disease and certain hereditary variants, such as Ser77Tyr, Tyr114Cys, and Phe64Leu, which may have disproportionately low cardiac radiotracer uptake and provide false reassurance [11]. Additionally, Ioannou and Fontana emphasize that the ideal screening test must have a high sensitivity across the spectrum of disease to capture patients at the earliest possible manifestations of the disease to allow for timely initiation of disease-modifying therapy, but current data is lacking for bone-avid tracers to detect early disease. Further, they emphasize that as we expand the criteria for screening, we will need to perform mechanistic studies to better elucidate what bone avid tracers are binding to.

Generally, before we can adopt a widespread use of a screening test, we should consider the following 7 questions as outlined by the World Health Organization (WHO) on principles and practice of screening for disease (Fig 1). These questions include:

1. ***Are we trying to diagnose an important health problem?***

Transthyretin cardiac amyloidosis is a rare but life-threatening disease that is ultimately fatal in 2-5 years if untreated. Therapies are effective and more so if administered at an early stage of the disease. While one could argue about the importance of the problem given its rarity, one only needs to talk with many patients affected by amyloidosis who have had prolonged, delayed, and circuitous paths to a correct diagnosis [12] to realize that this is an important health problem.

2. ***Are the methods and facilities to diagnose widely available?***

Accurate and timely diagnosis of transthyretin cardiac amyloidosis requires a high clinical index of suspicion, followed by a systematic laboratory assessment to exclude the possibility of light chain amyloidosis with immunofixation of the serum and urine, along with measurement of serum free light chain levels and, if negative, then bone avid scintigraphy to assess for the presence of myocardial uptake which is confirmed by SPECT or SPECT/CT imaging. In 10%–20% of cases, an endomyocardial biopsy is still required. While nuclear scintigraphy is widely available; the ability to perform an endomyocardial biopsy requires significant expertise, which needs to

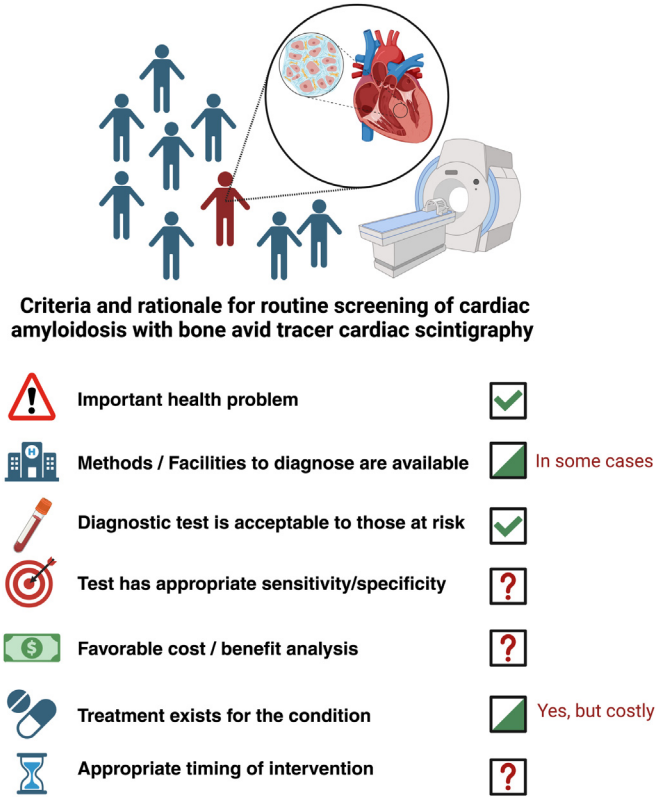

Figure 1. Criteria and rationale for routine screening of cardiac amyloidosis with bone avid tracer cardiac scintigraphy. (Figure created using BioRender.com).

be coupled with sophisticated pathologic assessments to determine the precursor protein, which are less available. Finally, accurate performance and expert interpretation is required and even more essential if pretest probability is low. Thus, we believe that this criterion is partially met.

3. *Is the diagnostic test acceptable to those at risk?*

Bone avid scintigraphy is noninvasive (except for the need for IV access), safe with minimal radiation exposure and risk, easy to perform, and carries minimal risk [13]. Most patients view the experience of testing favorably.

4. *Does the test have appropriate sensitivity/specificity?*

Bone avid tracer cardiac scintigraphy is associated with high sensitivity and specificity when combined with appropriate labs to exclude light chain amyloidosis in those with a reasonable pretest probability. However, for diagnosing other forms of cardiac amyloidosis (AL and APOAIV, Gelsolin), bone avid tracer cardiac scintigraphy is an inadequate screening modality as it is associated with unacceptably high rates of false positive and false negative results. Data on at-risk populations are beginning to emerge, providing support for active ascertainment for amyloidosis in these patients [14–16]. However, further studies are needed to assess the sensitivity and specificity of bone avid tracer cardiac scintigraphy in a wider patient population. Therefore, currently this criterion is not yet satisfied.

5. *Is there a favorable cost/benefit balance?*

When considering cost-benefit balance, we must think about the direct cost of the test and its downstream implications. Bone avid tracer cardiac scintigraphy is relatively inexpensive and is generally covered by health insurance in the United States, though ironically the main isotope employed, technetium pyrophosphate is not approved by the FDA for this indication. However, once ATTR-CM is diagnosed, the disease-modifying therapy with stabilizers is not cost-effective and is associated with substantial burden on the healthcare system [17,18]. The cost of therapy eventually will be significantly reduced when the therapy becomes generic. So, in the long term, the cost benefit of active ascertainment will be much more favorable.

6. *Is there effective treatment for the condition?*

For ATTR-CM and ATTR polyneuropathy, there are several approved therapies that are associated with better functional capacity, quality of life, and survival compared to placebo and minimal to no side effects. Early ascertainment of affected patients would lead to more patients being able to live longer, more productive lives.

7. *Is there a well-accepted appropriate timing of intervention?*

Since ATTR-CA has an age-dependent penetrance, most patients who are at risk will be older adults. However, the age to initiate testing with scintigraphy is unknown. Recent data suggest that the risk of variant disease from the Val142Ile variant emerges earlier than previously thought [19]. Additionally, how often should testing be repeated if initially negative is currently undefined.

Accordingly, we would submit that bone avid tracer scintigraphy does not meet the burden of proof for a widespread screening use (see Fig 1). Well-designed prospective studies are needed to assess the utility of more widespread screening programs and to assess the yield and cost-effectiveness of such programs. Pooling of such studies will better inform our collective desire for early and accurate diagnosis in affected patients.

Until we have enough data for a widespread screening for ATTR-CM, we can continue to perform active ascertainment of affected individuals with signs and/or symptoms consistent with systemic amyloidosis. In such patents, nuclear scintigraphy, when coupled with appropriate laboratory assessment for light chain amyloidosis will allow a nonbiopsy diagnosis of transthyretin cardiac amyloidosis in >80% of patients with genetic sequencing of TTR determining if variant disease is present, which will guide the need for family cascade testing.

PRO: Screening at risk populations for transthyretin cardiac amyloidosis: Bone avid tracer cardiac scintigraphy is always the preferred approach

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Cardiac amyloidosis (CA) presents a diagnostic challenge due to the need for histological confirmation and the difficulties in subtyping the involved amyloid fibrils. The main cardiac forms are light-chain (AL-CM) and transthyretin (ATTR-CM) amyloidosis; the latter can be due to variant (vATTR-CM) or wild-type forms (wtATTR-CM). A high index of suspicion is needed due to the nonspecific symptoms of the disease and its overlap with other common cardiac conditions such as heart failure with preserved ejection fraction (HFpEF) and aortic stenosis (AS). For patients with a known pathogenic TTR variant, identifying phenotypic development early is paramount since available therapies can only stop disease progression and not reverse it. Diagnostic delays are associated with progressive decline in cardiac function, nerve function, and worse clinical outcomes [20]. As such, identifying patients who are at risk for the development of ATTR-CM or have it with other concurrent cardiac diseases and optimal screening methods are essential for early diagnosis, initiation of treatment, and improved clinical outcomes. We present our rationale for bone-avid tracer cardiac scintigraphy being the preferred approach for screening at-risk populations for ATTR-CM.

For a screening test to be effective, it should fulfill an extensive criteria, but the most clinically relevant are ease of use, availability, high sensitivity, high specificity, and available treatments to change the natural history of the disease [21]. For practical deployment of a successful screening strategy, the disease must have enough prevalence to ensure high positive predictive value [22]. At-risk populations for ATTR-CM include genotype-positive phenotype-negative variant TTR carriers, patients with orthopedic manifestations (carpal tunnel syndrome (CTS), lumbar spinal stenosis), AS, and HFpEF.

None of the current imaging techniques that are used in routine clinical practice measure amyloid load directly. Echocardiography assesses the downstream effect of amyloid fibril deposition on cardiac structure and function and, as such, is capable mainly of screening for established amyloid phenotype, including when longitudinal strain imaging is used [23].

Cardiac magnetic resonance imaging (CMR) includes similar measures to echocardiography (with a superior three-dimensional approach and image quality), in addition to tissue characterization using late gadolinium enhancement (LGE) imaging and extracellular volume (ECV) quantification. While LGE is highly specific in advanced CA, the pattern can be nonspecific in early

disease. In a meta-analysis of 18 diagnostic studies, LGE had a 78% sensitivity (95% confidence interval 68% to 85%) [24]. The positive predictive value of LGE will likely be lower in an intention-to-screen population, as the pretest probability is lower. ECV represents another measure with robust features; however, some studies questioned its ability to directly measure amyloid load given the complex components of the extracellular space [25–28]. In addition, the lack of widespread availability of CMR combined with the required technical expertise limit the ability of using CMR as a screening tool for ATTR-CM.

Echocardiography and CMR evaluate the structural and functional phenotype resulting from amyloid fibril deposition, and while they raise the suspicion for CA and provide a high post-test probability of having CA; they still require further confirmation of having CA and its subtype. Bone-avid tracer cardiac scintigraphy has re-emerged as a highly sensitive and specific technique for the noninvasive imaging diagnosis of ATTR-CM after ruling out AL-CM. Bone-avid tracer cardiac scintigraphy in the context of ATTR-CM refers to the use of technetium-labeled (^{99m}Tc)- pyrophosphate (PYP), 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP). Wide variations in acquisition exist, but all patients should undergo single-photon emission computed tomography (SPECT) and preferably with concomitant computed tomography (SPECT/CT). The mechanism and binding site of these tracers remain unknown, and the sparse evidence of binding to microcalcifications remains unconvincing [29]. As such, uptake should not be used as a surrogate to amyloid load. After ruling out AL-CM, the sensitivity of any myocardial uptake ($\geq$ Grade I) on bone-avid tracer cardiac scintigraphy for identifying ATTR-CM was $\geq$97% [30].

The newly appreciated prevalence of ATTR-CM and the exceptional diagnostic performance of bone-avid tracer cardiac scintigraphy have resulted in an explosion in the studies evaluating its performance in multiple at-risk population, Table 1.

1. CTS

Bone-avid tracer cardiac scintigraphy allowed for deeper appreciation of the systemic involvement with amyloidosis, revealing that 10% of patients meeting certain criteria had amyloid deposits in their tenosynovium, which have significantly influenced the practice of CTS surgery worldwide [33]. While there are many studies in patients with CTS, there are limited studies comparing imaging modalities for screening in patients with CTS.

2. Lumbar spinal stenosis

Histological surveillance of patients undergoing lumbar spinal stenosis surgery has shown a high prevalence of amyloid deposits but low prevalence of clinical systemic disease [39,51]. An ongoing multicenter study evaluating patients who already underwent lumbar spinal stenosis surgery for ATTR-CM will shed some light on the screening performance of bone-avid scintigraphy in this population (NCT06034405).

3. Genotype positive phenotype negative TTR variant carrier

The traditional approach of using echocardiography to detect phenotype as defined by an interventricular septal thickness of 13 mm or more is remnant of an era where therapeutic approaches were limited [52]. Nowadays, stabilizers and silencers are available to halt the progression of disease, and the search continues for therapies that can regress amyloidosis. This fact highlights the utmost need to diagnose phenotype development as early as possible. Molecular imaging with bone-avid tracer cardiac scintigraphy should be the preferred approach, as it aims at detecting myocardial involvement with ATTR, independent of the clinician's interpretation of phenotype on echocardiography or CMR. In one study, 11 patients with ATTR gene variants and normal interventricular septum (IVS) thickness were screened with scintigraphy, and 3 patients (27%) had a positive scan reflective of ATTR-CM [41]. One caveat is the patients known to have rare variants with full length fibrils (such as Phe64Leu and early-onset Val30Met) can be negative on bone-avid tracer cardiac scintigraphy but these represent a small number of individuals [11,53,54]. A unique pathway based on phenotype should be employed in these patients.

4. HFpEF

The overlap in clinical and echocardiographic phenotypes between HFpEF and ATTR-CM requires a screening strategy to identify ATTR-CM in HFpEF. In one comparative study, systematic screening for ATTR-CM yielded a prevalence of 6.3% compared to 1.3% with clinical phenotypic-driven screening [15]. In general, it is imperative to take into account pretest probability since the yield of bone-avid tracer cardiac scintigraphy will be reliant on patient selection [10]. An ongoing study, Screening for Cardiac Amyloidosis with

Table 1. Selected studies using bone-avid tracer cardiac scintigraphy to screen at risk patients for ATTR-CM.

Study name	Inclusion criteria for scintigraphy	Number of patients who underwent scintigraphy	Type of bone tracer	Results
Carpal tunnel syndrome				
Takashio 2023 [31]	- Amyloid deposits in carpal tunnel - (IVSd) ≥14 mm or 12 mm ≤ IVSd <14 mm - Above-normal limits in high-sensitivity cardiac troponin	12	PYP	6/12 + scan
Westin 2022 [32]	- Bilateral CTS - The first surgery on the second wrist was performed between 5 and 15 years prior to study initiation - Age 60-85 years	250	PYP	11/250 + scan
Sperry 2018 [33]	- Men ≥50 years, women ≥60 years undergoing CTS - Patients with positive amyloid biopsy	10	PYP	1/10 + scan
Vianello 2021 [34]	- Males with bilateral CTS and LVH (>12 mm)	4	HMDP	2/4 + scan
Ladefoged 2023 [35]	- Patients age ≥60 years with red flags	67	DPD	10/57 + scan
Sugiura 2021 [36]	- Patients undergoing CTS found to have amyloid deposits	16	PYP	3/16 + scan
Lumbar spinal stenosis				
Godara 2021 [37]	- Patients undergoing spinal stenosis surgery with amyloid deposits in ligamentum flavum	37	PYP	4/37 + scan
Negreira-Caamano 2023 [38]	- Patients ≥65 years with spinal stenosis, yellow ligament hypertrophy, and CA red flags	57	DPD	1/57 + scan
Maurer 2022 [39]	- Patients with spinal stenosis undergoing lumbar spine decompression	10	PYP	1/10 + scan
Genotype positive phenotype negative ATTR				
Beauvais 2023 [40]	- Patients carrying ATTR mutations - Normal nerve conduction studies	95 (ATTR mutation carriers)	DPD	15/95 had Perugini score ≥1

Table 1. *continued*

Study name	Inclusion criteria for scintigraphy	Number of patients who underwent scintigraphy	Type of bone tracer	Results
Minutoli 2021 [41]	- Patients carrying ATTR mutations - No clinical signs of HF - IVSd < 12mm - NT-proBNP <125ng/L - DPD scans performed at 2 weeks, 2 years, 4 years	11 (ATTR mutation carriers)	DPD	- 6 - scans throughout study - 2 + baseline scans -1 developed + scan during follow-up
Haq 2017 [42]	- asymptomatic ATTR mutation carriers - onamyloid HFpEF - aTTR mutation carriers with symptomatic HF	12 (ATTR mutation carriers)	PYP	7/12 had + scan
Heart failure with preserved ejection fraction				
González-López 2015 [43]	- Patients ≥60 years admitted due to HFpEF with LVH ≥12 mm	120	DPD	16/120 + scan
AbouEzzeddine 2021 [15]	- Patients ≥60 years, EF ≥ 40%, LVH ≥12 mm	286	PYP	18/286 + scan
Jaramillo-Hidalgo 2023 [44]	- Patients ≥75 years, clinical history of HFpEF, atrial dilation ≥34 mL/m^2 and LVH >13 mm	50	DPD	15/50 + scan
Murat 2022 [45]	- Diagnosis of HFpEF	85	PYP	15/85 + scan
Devesa 2021 [46]	- HFpEF (EF ≥ 50%) and LV wall thickness <12 mm	58	DPD	3/58 + scan
Aortic stenosis				
Dobner 2023 [47]	- Patients with severe AS	315	DPD	30/315 + scan
Nitsche 2020 [48]	- Patients referred for TAVR	407	DPD	32/407 + scan
Rosenblum 2021 [49]	- Patients with severe AS undergoing TAVR	204	PYP	27/204 + scan
Scully 2020 [50]	- Patients age ≥75 years referred for TAVI	200	DPD	18/200 + scan

-, negative; +, positive; *AS*, aortic stenosis; *ATTR-CM*, transthyretin amyloidosis related cardiomyopathy; *CA*, cardiac amyloidosis; *CTS*, carpal tunnel surgery; *DPD*, ^{99m}Tc-labeled 3,3-diphosphono-1, 2-propanodicarboxylic acid; *ECG*, electrocardiogram; *EF*, ejection fraction; *HF*, heart failure; *HFpEF*, heart failure with preserved ejection fraction; *HMDP*, ^{99m}Tc-labeled hydroxymethylene diphosphonate; *IVSd*, interventricular septal diameter; *LVH*, left ventricular hypertrophy; *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *PYP*, ^{99m}Tc-labeled pyrophosphate; *TAVI*, transcatheter aortic valve implantation; *TAVR*, transcatheter aortic valve replacement; *TTE*, echocardiography.
Positive scan indicates a visual score of grade 2 or higher.

Nuclear Imaging in Minority Populations (SCAN-MP), is an example of employing bone-avid tracer cardiac scintigraphy for ATTR-CM screening in at-risk population with HF [55].

5. AS

The significant overlap in AS and ATTR-CM renders phenotypic-based screening is difficult, and bone-avid tracer cardiac scintigraphy is the best modality that is capable of addressing these challenges. In one study of 146 patients with calcific AS undergoing surgical valve replacement, CMR was performed along with scintigraphy and transthoracic echocardiography (TTE) in patients with histologically proven amyloidosis. Out of 6 patients with amyloid deposits, none had TTE findings suggestive of ATTR-CM, 2 had CMR findings suggestive of ATTR-CM (with LVH, LGE, ECV >50%), while bone-avid tracer cardiac scintigraphy was positive in all surviving patients. CMR findings in the remaining 4 patients could be explained by AS [56]. Such findings reiterate that bone-avid tracer cardiac scintigraphy should be the preferred screening approach that does not rely on overlapping phenotypic surrogates.

The excellent diagnostic performance of bone-avid tracer cardiac scintigraphy is complemented by its safety and near-universal eligibility to undergo the test. There are no limitations related to body habitus, acoustic windows, arrhythmias, renal function, comorbidities, claustrophobia, the presence of metal or devices, or the ability to perform breath holds. Figure 2 summarizes the advantages of bone-avid tracer cardiac scintigraphy. Radiation exposure of 3-4 millisieverts, while small and comparable to the background radiation in the United States, remains the only limitation in implementing serial bone-avid tracer cardiac scintigraphy assessment in the younger population [57]. Bone-avid tracer cardiac scintigraphy is widely available in most practice settings; imaging protocol is easy to follow by technologists, and tracers are generally widely available. Bone-avid tracer cardiac scintigraphy can also be done efficiently with 1-h protocols, but the lower pre-test probability in a screening population might require 3-h imaging [58]. There are other considerations for bone-avid tracer cardiac scintigraphy that are less commonly encountered. First, bone-avid tracer cardiac scintigraphy can be negative in some rare ATTR variants, such as Phe64Leu and early-onset Val30Met [11]. Second, cardiomyopathy secondary to hydroxychloroquine toxicity can result in uptake on bone-avid tracer cardiac scintigraphy, but a review of medication history is sufficient to recognize this rare entity [59]. Third, historical use of planar-only

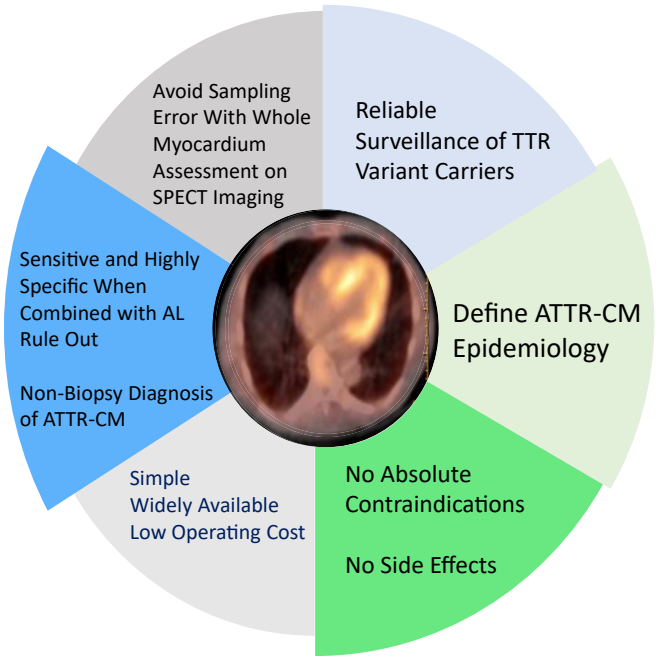

Figure 2. Advantages of bone-avid tracer cardiac scintigraphy for the screening and diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM). Aside from the test advantages, bone-avid tracer cardiac scintigraphy redefined ATTR-CM epidemiology and allowed for population-based studies. *TTR*, transthyretin; *AL*, light chain; *SPECT*, single-photon emission computed tomography.

imaging resulted in frequent false positive interpretation in patients with persistent blood pool or pericardial effusion. The use of SPECT imaging has minimized these instances, and SPECT/CT virtually eliminates such instances. Fourth, bone-avid tracer cardiac scintigraphy should not be performed in the acute settings where a myocardial infarction is suspected to avoid false positive tests in those scenarios.

Positron emission tomography (PET) imaging is another nuclear technique that holds significant promise for CA diagnosis and treatment monitoring. Amyloid PET tracers are still early in development, and further investigation is required prior to understanding their role. Overall, although it will be challenging for PET imaging to compete with the simplicity of bone-avid tracer cardiac scintigraphy, it carries tremendous advantages from higher image quality and sensitivity to being fully quantifiable and addressing extracardiac organs as well.

Due to underdiagnosis, ATTR-CM remains a highly morbid condition, largely driven by the nonspecific phenotypic features in early and intermediate stages of disease, and the phenotypic overlap with other cardiac conditions. Prior to the widespread use of bone-avid tracer cardiac scintigraphy, traditional phenotype-driven evaluation resulted in frequent underdiagnosis, mistakenly

categorizing ATTR-CM into an ultra-rare disease. Bone-avid tracer cardiac scintigraphy has introduced a revolution in the screening for and diagnosis of ATTR-CM. This revolution has influenced a recharacterization of the incidence, prevalence, natural history, and prognosis of ATTR-CM. In the current era, no other imaging modality can match the diagnostic performance, availability, ease of use, near-universal patient eligibility, and cost of bone-avid tracer cardiac scintigraphy in ATTR-CM. Future research focused on the multicenter-wide application of bone scintigraphy in screening populations will further cement bone scintigraphy as the preferred modality to screen for ATTR-CM.

CON: Screening at risk populations for cardiac amyloidosis: Bone avid tracer cardiac scintigraphy is always the preferred approach

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Cardiac amyloidosis was previously thought of as a rare disease but is being increasingly recognized as a cause of heart failure [60]. The disease process is characterized by the deposition of misfolded proteins, in the form of amyloid fibrils, within the myocardial extracellular space, leading to distortion of myocardial contractile fibers [61]. Increased awareness of this disease has occurred due to recent advances in diagnostic imaging, and has been further spurred by the knowledge that the 2 most common forms, transthyretin (ATTR) and light-chain (AL) amyloidosis have effective treatment options [61–63]. Early diagnosis and timely initiation of treatment are crucial to improving in outcomes, and hence there has been an increasing interest in screening programs for cardiac amyloidosis. Many of these proposed screening programs seek to utilize bone scintigraphy as the initial gatekeeper to further investigations. However, despite bone scintigraphy playing a key role in the nonbiopsy diagnostic criteria for patients with transthyretin cardiac amyloidosis (ATTR-CA), this imaging modality has several shortcomings that need to be appreciated before bone scintigraphy is considered a suitable screening tool.

MECHANISM OF CARDIAC UPTAKE ON BONE SCINTIGRAPHY

Bone scintigraphy was first repurposed in the 1980s, when an incidental finding of increased cardiac uptake of technetium-based bone-avid radiotracers was observed in patients with cardiac amyloidosis [64]. The mechanism responsible for the localization of these agents to amyloid fibrils within the heart remain elusive, but it is hypothesized that binding is related to microcalcifications within amyloid fibrils, with some evidence that these are more abundant in transthyretin amyloid fibrils than in other forms of amyloidosis [65]. Mechanistic studies are needed to enrich our understanding of bone tracer binding, especially when considering the expansion of bone scintigraphy into various different clinical settings, as well as different populations of patients (mutations carriers, early disease, patients with other comorbidities or patients with amyloid deposits in different organs) [66].

SENSITIVITY AND SPECIFICITY OF BONE SCINTIGRAPHY

The sensitive nature of bone scintigraphy in detecting cardiac amyloid fibrils is exclusive to patients with ATTR-CA, and the sensitivity of bone scintigraphy declines significantly when applied to other forms of cardiac amyloidosis (Fig. 3). Cardiac involvement is present in up to 70% of patients with systemic AL amyloidosis, but only 40% of patients with cardiac AL amyloidosis have cardiac uptake on bone scintigraphy [67]. Therefore, the vast majority of cardiac AL amyloidosis cases would be missed in a screening program that exclusively utilized bone scintigraphy. Furthermore, although the vast majority of cardiac amyloidosis cases are represented by ATTR-CA and cardiac AL amyloidosis, less common forms such as apolipoprotein AI and apolipoprotein AIV amyloidosis are increasingly recognized as causes of cardiac amyloidosis. Patients with biopsy-proven apolipoprotein AI and apolipoprotein AIV amyloidosis also present with either no radiotracer uptake or mild uptake in the heart, despite displaying features of cardiac amyloidosis on both echocardiography and cardiac magnetic resonance (CMR) [68,69]. Considering that many forms of cardiac amyloidosis can present with no cardiac uptake of technetium-based radiotracers, the negative predictive value of a normal bone scintigraphy scan would be far too low for utilization for screening at risk populations across the broad spectrum of infiltration. When taken in isolation, a normal bone scintigraphy scan could give false reassurance to the attending physician and result in a delayed or even missed diagnosis for many patients with cardiac amyloidosis. In patients with cardiac AL amyloidosis, the median survival is less than six months if left untreated, therefore a diagnostic delay, even of a few

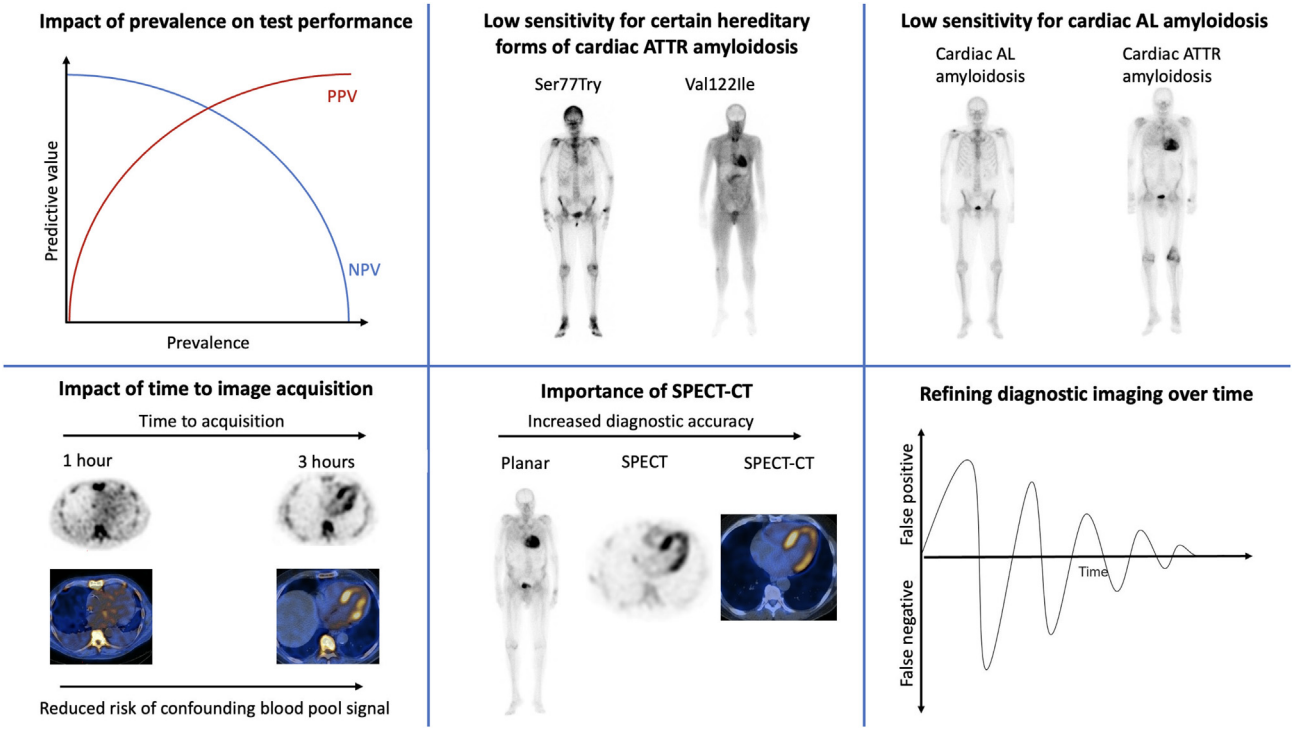

Figure 3. Illustration of the barriers that prevent bone scintigraphy from being used as an effective screening tool for cardiac amyloidosis. The top panels illustrate problems with the sensitivity and specificity of bone scintigraphy, and the bottom panels illustrate technical issues related to image acquisition and expertise.

months, could have devastating consequences [70,71].

A false negative scan may also occur in early cardiac amyloidosis, where there are minimal amyloid deposits, and hence the myocardial radiotracer uptake is below the current diagnostic thresholds. This is a specific concern for hereditary amyloidosis and therefore in the screening of mutation carriers. There are certain hereditary variants, such as Ser77Tyr, Tyr114Cys, and Phe64Leu, which present with heart failure symptoms, classical imaging features of cardiac amyloidosis on echocardiography, but a disproportionately low cardiac radiotracer uptake on bone scintigraphy (i.e. no uptake or mild uptake), and hence do not fulfill the nonbiopsy diagnostic criteria. In such cases biopsy proof of amyloid deposition is required to confirm the underlying diagnosis [69,72,73]. It is possible that these mutations may represent extremes of a phenomenon that is present across a wider range of mutations, whereby the magnitude of myocardial radiotracer uptake is disproportionate to the degree of amyloid infiltration. However, this has never been systematically investigated or indeed assessed against histology, leaving some uncertainty around the sensitivity of bone tracers across the wide spectrum of mutations responsible for ATTR amyloidosis. Early disease is less associated with the characteristic clinical features that would prompt a clinician to consider cardiac amyloidosis within the differentials, and therefore patients with early cardiac infiltration represent the exact cohort that should be detected during a screening program [69,72,73]. The ideal screening test must have a high sensitivity across the spectrum of disease severity to avoid missing patients with early disease, who would potentially derive the most benefit from the initiation of amyloid-specific disease modifying therapies [66].

The seminal study that resulted in the widespread utilization of bone scintigraphy in the non-biopsy pathway for ATTR-CA comprised 1217 patients referred with suspected cardiac amyloidosis across 9 international specialist referral centers; of which, 857 patients had histologically proven amyloid (of whom 530 had a diagnosis of ATTR-CA, with a prevalence of 43.5%), and 360 had a subsequent diagnosis of non-amyloid cardiomyopathy. The presence of any myocardial radiotracer uptake conferred a sensitivity of >99% and specificity of 68% for ATTR-CA, with most false positives occurring in patients with cardiac AL amyloidosis. The specificity for diagnosing ATTR-CA increases to 87% for grade 2-3 myocardial radiotracer uptake, but the sensitivity decreases to 91%. When grade 2-3 myocardial radiotracer uptake was combined with the absence of monoclonal proteins by

serum and urine testing (thereby excluding systemic AL amyloidosis), the specificity improved to 100%; however, this also resulted in a further reduction in sensitivity to 70% [73]. This diagnostic algorithm has since been validated in several studies, including a large multicenter study of 3354 patients with suspected or confirmed cardiac amyloidosis. This study included 2546 patients with cardiac amyloidosis (of whom 2103 had a diagnosis of ATTR-CA, with a prevalence of 62.7%) and confirmed the high specificity and positive predictive value of the nonbiopsy pathway [11]. However, the aforementioned studies have utilized bone scintigraphy in a setting with a high pretest probability of cardiac amyloidosis. The 2 largest studies have both recruited patients who were referred to specialist amyloidosis centers with a high clinical suspicion of cardiac amyloidosis [11,73], while smaller studies have recruited patients with clinical characteristics that were suggestive of cardiac amyloidosis, such as elderly patients with an increased wall thickness and heart failure preserved ejection fraction [43]. The high performance of bone scintigraphy in diagnosing ATTR-CA has been favorably skewed owing to the high pretest probability in study cohorts, many of whom had advanced cardiac phenotypes at diagnosis. It is possible that if bone scintigraphy is applied as a screening tool to populations with a lower prevalence and less severe disease, there would be a reduction in the positive predictive value [74].

Considering these limitations, it is widely accepted by multinational societies that the nonbiopsy criteria can only be applied to patients with unexplained heart failure and characteristic cardiac amyloidosis features on echocardiography or CMR [75,76]. These key clinical characteristics ensure that bone scintigraphy is only applied to patients similar to those who were enrolled into the nonbiopsy pathway validation studies. It is likely that the high performance of bone scintigraphy as a diagnostic tool for ATTR-CA has been biased by the characteristics of patients enrolled in the validation studies, and also the settings in which the results have been interpreted [77]. Real-world data on the performance of bone scintigraphy in low-prevalence populations and outside of specialist amyloidosis centers is needed before it could be considered a suitable screening tool [10].

TECHNICAL LIMITATIONS

The second limitation of this pivotal validation study is related to the expertise of the participating centers, which will have gained experience from a high volume of referrals and developed a high level of competency in the imaging protocols as well as the technical aspects of image acquisition and interpretation. In these centers, image acquisition and interpretation protocols have undergone a process of iterative optimization over time leading to higher accuracy of the technique compared to centers with low volume or which are relatively new to the technique. The last few years have seen an exponential increase in the number of centers that use bone scintigraphy for the detection of ATTR-CA. However, the widespread implementation of bone scintigraphy as a diagnostic test has been associated with implementation of inappropriate acquisition protocols, which, coupled with limited experience in image interpretation, has led to a significant increase in the number of false positive results. Contrary to expert recommendations, planar imaging without single-photon emission computed tomography is commonly performed in several centers. A SPECT-CT is a combination of a single photon emission tomography (SPECT) scan with a computed tomography (CT), which allows differentiation of anatomical compartments. Misinterpretation of blood pool as myocardial radiotracer uptake is an increasingly common cause of a false positive scan. The addition of guideline mandated SPECT-CT to planar imaging is crucial to differentiate between myocardial radiotracer uptake and blood pool [75,76]. Early image acquisition, acquired 1 hour after tracer administration (instead of 3 hours), is also associated with a higher prevalence of confounding blood pool signal [58]. Other causes of false positive scans include rib fractures overlying the heart and hence mimicking myocardial uptake, acute or subacute myocardial infarction, and hydroxychloroquine cardiotoxicity [11,78]. The expertise required to perform and interpret bone scintigraphy are largely underappreciated, and considering the lack of familiarity outside of specialist amyloidosis centers, it would be challenging to utilize this imaging modality as a screening tool in the wider healthcare settings.

IMAGE OPTIMIZATION

There are currently multiple different technetium-based radiotracers in clinical use. ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) are widely used in Europe, and ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) is the most commonly used radiotracer in the United States of America. The diagnostic performance of these agents was thought to be broadly similar; however, to date there have not been any

head-to-head trials confirming, this and concerns are increasing on the different diagnostic accuracy of the different tracers. Different image interpretation and image acquisition protocols are likely to be needed for different tracers. Optimal image acquisition time could differ for different tracers and image interpretation techniques also vary and need optimization for each tracer. Aside from the conventional qualitative Perugini score, which assigns a grade of cardiac uptake relative to bone uptake; quantitative scores are also increasingly utilized by clinicians, but these vary depending on the radiotracer being used. The heart-to-whole body ratio is used for scans acquired using ^{99m}Tc-DPD and ^{99m}Tc-HMDP; whereas the heart-to-contralateral ratio is used for scans acquired using ^{99m}Tc-PYP [75,76]. Studies focusing on accuracy, precision, reproducibility, and repeatability for each of the tracers should be performed to optimize the clinical pathway and understand the limitations of this technique.

CLINICAL CONSIDERATIONS OF IMAGING-BASED SCREENING FOR CARDIAC AMYLOIDOSIS

The use of bone scintigraphy within the confines of the nonbiopsy diagnostic algorithm in a patient population with a high pretest probability remains indispensable in the diagnosis of ATTR-CA [73]. However, its utility as a screening methodology remains unproven and is caveated with multiple important limitations. Furthermore, cardiac amyloidosis encompasses a complex group of heterogenous conditions, and therefore it is unlikely that a single investigation used in isolation will pose the sensitivity and specificity required to be utilized as a screening tool. The most accurate noninvasive diagnostic test for the detection of cardiac AL amyloidosis, the second most common type of cardiac amyloidosis, is likely to be CMR, which has also consistently demonstrated utility in diagnosing all forms of cardiac amyloidosis, across the spectrum of disease severity Administration of gadolinium-based contrast agents alongside acquisition of pre- and post-contrast T1 maps enable isolation of the extracellular signal. Elevations in extracellular volume occur early in the disease process, before changes in cardiac structure and function; and hence, extracellular volume mapping is highly sensitive in the detection of early cardiac amyloid infiltration [71,72,79]. However, despite its excellent diagnostic performance, CMR remains a highly-specialized investigation, and similarly to bone scintigraphy, represents a second-level imaging modality to be performed in patients where the suspicion of cardiac amyloidosis has already been raised.

Several amyloid-binding PET tracers have been evaluated in patients with known cardiac amyloidosis. ^{11}C-Pittsburgh compound B detects both ATTR-CA and cardiac AL amyloidosis with a high degree of accuracy [80]; whereas the ^{18}F-florbetapir myocardial retention index tends to be higher in cardiac AL amyloidosis than ATTR-CA, and in the context of systemic AL amyloidosis, ^{18}F-florbetapir has demonstrated utility in detecting early cardiac amyloid infiltration [81]. ^{124}I-evuzamitide possesses a similar diagnostic accuracy to ^{18}F-florbetapir in patients with cardiac AL amyloidosis, but in patients with ATTR-CA there was a greater uptake of ^{124}I-evuzamitide, suggesting it may confer a superior diagnostic performance [82]. Similar to CMR, PET remains a highly-specialized investigation and has only been evaluated in patients with known cardiac amyloidosis. Despite various tracers demonstrating potential diagnostic utility, these tracers remain at an early investigational stage and are not widely accessible. Large multicenter studies are required to establish the role of PET tracers in the diagnostic pathway and to assess whether PET tracers would retain diagnostic accuracy in a low prevalence population.

Effective screening would combine aspects of the clinical presentation alongside, blood biomarkers, and red flag features identified on a widely available and familiar imaging modality, such as echocardiography, to refine the likelihood of cardiac amyloidosis before advanced cardiac imaging, such as CMR and bone scintigraphy, is employed (Table 1). In cases where ATTR-CA is suspected, bone scintigraphy should be applied alongside the other key components of the nonbiopsy diagnostic pathway and sequencing of the TTR gene (to exclude rare hereditary forms with a disproportionately low myocardial radiotracer uptake). If other forms of cardiac amyloidosis are suspected, the positive and negative predictive values of bone scintigraphy in isolation would be too low to confirm or exclude a diagnosis, and CMR should be applied either alone or in combination with bone scintigraphy to refine the diagnostic differentials [69].

CONCLUSIONS

It is possible that bone scintigraphy could form a fundamental component of a screening program specific for ATTR-CA, but future research is needed to explore the sensitivity and specificity of bone scintigraphy in low-prevalence populations, as well as to define the optimal imaging protocol that could be standardized across both specialist and nonspecialist centers. Until then, bone scintigraphy remains a specialist diagnostic test that, if used in conjunction with the other

components of the nonbiopsy criteria, can diagnose ATTR-CA with a high degree of accuracy in specialist centers [11,73].

Rebuttal

Mallika Lal, MD
Ahmad Masri, MD, MS

Ioannou and Fontana present a thoughtful and detailed discussion on the role of bone-avid tracer cardiac scintigraphy in the screening for cardiac amyloidosis. They raise important points regarding the limitations of scintigraphy in patients with light-chain amyloid cardiomyopathy (AL-CM), rare transthyretin variants, rare systemic amyloid diseases, and those with early transthyretin amyloid cardiomyopathy (ATTR-CM). Bone-avid tracer cardiac scintigraphy clearly should not be used in patients suspected to have AL-CM, as it lacks sensitivity and specificity. From a screening perspective, ATTR-CM prevalence is so many folds higher than other amyloid diseases and as such, one would want a screening-approach that is focused on ATTR-CM rather than all amyloid diseases, which are better served with an intent-to-diagnose approach. Similarly, rare variants in the transthyretin gene that cause ATTR-CM are very uncommon, and in that scenario bone-avid tracer cardiac scintigraphy is not sufficient. In addition, it remains unclear if the performance of other modalities is better or worse than bone scintigraphy in early ATTR-CM. To address this, a comprehensive multimodality imaging evaluation of patients with a mild cardiac phenotype is needed. Finally, only bone-avid tracer cardiac scintigraphy allows the non-invasive diagnosis of ATTR-CM, and as such can act both as a screening and diagnostic test. Even if cardiac magnetic resonance (CMR) imaging or echocardiography are pathognomonic for cardiac amyloidosis, one still needs tissue biopsy for confirmation and to enable the use of life-saving therapies in some geographical regions (such as the US).

The authors also discuss that the majority of studies on ATTR-CM and scintigraphy are from expert centers. While this is true, bone-avid tracer cardiac scintigraphy remains a simple test to perform, widely available, easy to troubleshoot, virtually has no contraindications, and having computed tomography for attenuation and anatomic localization can overcome almost all the limitations of SPECT-only imaging. In addition, echocardiography is highly user-dependent, especially for more sophisticated techniques such as strain imaging, histological evaluation requires tremendous expertise as well, given the difficulty of Congo red staining and amyloid typing, and CMR requires highly specialized equipment, training, and experience, especially in early ATTR-CM.

We fully agree that further data are needed to understand the performance of bone-avid tracer cardiac scintigraphy in a lower prevalence population. While there are no large-scale studies to date, almost all the studies performed in populations at risk converge on the same conclusion in terms of ATTR-CM prevalence using this technique. This is a scenario where screening should be mainly focused on populations at risk, and not all-comers in a general population. There are no other techniques or approaches that deliver a similar level of practicality, cost, and diagnostic accuracy as bone-avid tracer cardiac scintigraphy to screen such at-risk populations. An all-or-none approach to capture all cases of cardiac amyloidosis would not allow us to achieve the goal of diagnosing a common condition like ATTR-CM early.

Rebuttal

Adam Ioannou, MBBS, BSc, PhD
Marianna Fontana, MD, PhD

Lal and Masri provide a thorough assessment of the current evidence surrounding the use of bone scintigraphy in screening for ATTR-CA. They cite multiple screening studies that evaluated the performance of bone scintigraphy in screening at-risk populations. These studies focused on enrolling select patients with an elevated pre-test probability due to a background of carpal tunnel syndrome, lumbar canal stenosis, HFpEF, aortic stenosis, or a TTR gene variant [15,33,39,41,56]. Due to their baseline characteristics and comorbidities, these patients already had an increased pre-test probability of ATTR-CA. However, it remains possible that if bone scintigraphy is applied as a screening tool to the wider population, with a lower prevalence, there would be a reduction in the positive predictive value [10]. Real-world data on the performance of bone scintigraphy in low-prevalence populations with absent diagnostic clues is needed before bone scintigraphy can be utilized as a screening tool.

The authors focused their assessment on whether bone scintigraphy is a suitable screening tool for ATTR-CA, but the topic of debate refers to whether bone scintigraphy can be used to screen for all forms of cardiac amyloidosis. Cardiac uptake is far less common in other forms of cardiac amyloidosis. In patients with cardiac AL amyloidosis, only 40% demonstrate cardiac

uptake, and there is also disproportionately low cardiac uptake in patients with rarer forms of cardiac amyloidosis, such as certain TTR variants, apolipoprotein AI and apolipoprotein AIV amyloidosis [67–69]. If bone scintigraphy is used in isolation, it would result in misdiagnosis in the vast majority of these cases. In cardiac AL amyloidosis, this could have devastating consequences, with delays in treatment being associated with a worse prognosis, and patients with advanced cardiac disease having a median survival of 6 months if left untreated [61].

Cardiac amyloidosis comprises a heterogeneous group of diseases with a varying clinical phenotype [69]. A single cardiac imaging modality used in isolation is unlikely to yield the sensitivity and specificity required to screen for all forms of cardiac amyloidosis. This represents a significant challenge, but it is possible this could be overcome with the use of artificial intelligence. The ability to analyze large datasets to identify patterns in the clinical presentation, biomarkers, and imaging characteristics could support the development of multifaceted screening models that highlight patients at risk of cardiac amyloidosis who require further investigation. These models are at an early investigational stage, but AI-driven analysis of echocardiograms has already demonstrated impressive diagnostic accuracy, and it is possible that incorporating key features from the clinical history and a multitude of cardiac investigations could optimize these models so they could be utilized to screen for patients with suspected cardiac amyloidosis [83].

In the meantime, there is evidence to support the use of bone scintigraphy as a screening tool for ATTR-CA in select populations with a high pretest probability, but it must be used in conjunction with TTR genotyping to ensure that variants associated with a disproportionately low cardiac uptake are not overlooked. However, bone scintigraphy cannot be used to screen for other forms of cardiac amyloidosis, and further studies are needed to evaluate the utility of bone scintigraphy in low-prevalence populations.

DISCLOSURES

Ahmad Masri reports research grants from Pfizer, Ionis, Attralus, and Cytokinetics, and personal fees from Cytokinetics, BMS, Eidos, Pfizer, Ionis, Lexicon, Alnylam, Attralus, Haya BioMarin, Prothena and Tenaya. Yevgeniy Brailovsky has received an educational grant - Pfizer. Advisory board - BridgeBio. Mathew Maurer has acted as a researcher for NIH R01HL139671 and R01AG081582-01, Alnylam Pharmaceuticals, BridgeBio Pharma (formerly Eidos Therapeutics), Ionis Pharmaceuticals, Pfizer, Attralus, and Intellia; and as a consultant or advisor for Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, NovoNordisk, and Pfizer. All other authors declare no conflicts of interested related to this work.

FUNDING

None.

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