Cardiac Amyloidosis Imaging, Part 3: Interpretation, Diagnosis, and Treatment

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Cardiac amyloidosis was thought to be rare, undiagnosable, and incurable. However, recently it has been discovered to be common, diagnosable, and treatable. This knowledge has led to a resurgence in nuclear imaging with ^{99m}Tc-pyrophosphate—a scan once believed to be extinct—to identify cardiac amyloidosis, particularly in patients with heart failure but preserved ejection fraction. The renewed interest in ^{99m}Tc-pyrophosphate imaging has compelled technologists and physicians to reacquaint themselves with the procedure. Although ^{99m}Tc-pyrophosphate imaging is relatively simple, interpretation and diagnostic accuracy require an in-depth knowledge of amyloidosis etiology, clinical manifestations, disease progression, and treatment. Diagnosing cardiac amyloidosis is complicated because typical signs and symptoms are nonspecific and usually attributed to other cardiac disorders. In addition, physicians must be able to differentiate between monoclonal immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). Several clinical and noninvasive diagnostic imaging (echocardiography and cardiac MRI) red flags have been identified that suggest a patient may have cardiac amyloidosis. The intent of these red flags is to raise physician suspicion of cardiac amyloidosis and guide a series of steps (a diagnostic algorithm) for narrowing down and diagnosing the specific amyloid type. One element in the diagnostic algorithm is to identify monoclonal proteins indicative of AL. Monoclonal proteins are detected by serum or urine immunofixation electrophoresis and serum free light-chain assay. Another element is identifying and grading cardiac amyloid deposition using ^{99m}Tc-pyrophosphate imaging. When monoclonal proteins are present and the ^{99m}Tc-pyrophosphate scan is positive, the patient should be further evaluated for cardiac AL. The absence of monoclonal proteins and a positive ^{99m}Tc-pyrophosphate scan is diagnostic for cardiac ATTR. Patients with cardiac ATTR need to undergo genetic testing to differentiate between wild-type ATTR and variant ATTR. This article is the third in a 3-part series in this issue of the *Journal of Nuclear Medicine Technology*. Part 1 reviewed amyloidosis etiology and outlined ^{99m}Tc-pyrophosphate study acquisition. Part 2 described ^{99m}Tc-pyrophosphate image quantification and protocol technical considerations. This article discusses scan interpretation along with cardiac amyloidosis diagnosis and treatment.

Key Words: cardiac amyloidosis; quantification; interpretation; treatment; ^{99m}Tc-pyrophosphate imaging

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Five to 10 y ago, few cardiologists were talking about cardiac amyloidosis. Now, it is being discussed at every national and local meeting. No one mentioned or even thought about cardiac amyloidosis previously because it was believed to be rare, affecting fewer than 200,000 people in the United States (*1,2*). Because it was thought to be rare, it was "okay" if physicians were not well versed in recognizing and treating the disease. Besides, differentiating cardiac amyloidosis clinical signs and symptoms from other conditions was tricky since they often overlap with other more common diseases, particularly diseases that cause myocardial thickening, such as hypertension, aortic stenosis, or hypertrophic cardiomyopathy (*3*). There is adage in medicine: "If you hear hoofbeats, think horses and not zebras." Accordingly, physicians likely attributed cardiac amyloidosis clinical manifestations to other diseases in the past.

Cardiac amyloidosis was ignored because of the false perception that it could be diagnosed only by risky endocardial biopsy or at a specialized center (*4*). Furthermore, cardiac amyloidosis was considered incurable because of the rapid progression of the disease and the lack of treatment options.

Thankfully, a lot has happened over past 5–10 y to challenge these misconceptions. The first was advancements in noninvasive diagnostic techniques such as echocardiography, cardiac MRI (CMR), and nuclear imaging (*1*). As result, diagnosing cardiac amyloidosis became easier. With improvement in noninvasive techniques came the realization that cardiac amyloidosis was not rare after all. It is now recognized as a significant cause of heart failure.

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About 5 million patients in the United States have heart failure, and approximately 80,000 patients die yearly (*5*). By 2030, the treatment of heart failure is expected to cost $69.8 billion annually and represent a substantial public health burden. Approximately 50% of heart failure patients have reduced ejection fraction, whereas the other 50% have heart failure with preserved ejection fraction (HFpEF). A study by Gonzales et al. found that 13% of patients with HFpEF had cardiac amyloidosis (*6*).

Patients with HFpEF exhibit the usual signs and symptoms of heart failure, such as shortness of breath, decreased exercise tolerance, fatigue, or swelling of the lower extremities. Yet, these same patients have normal or near-normal ejection fractions (≥50%). Although there is a plethora of guideline-directed treatment options for patients with heart failure with reduced ejection fraction, there were few options for treating patients with HFpEF because the etiology was unknown (*5*). However, new treatment options for HFpEF, particularly HFpEF related to cardiac amyloidosis, have been developed over the past few years. Several disease-modifying therapies are now approved by the Food and Drug Administration (FDA) (*3*).

In the past, when cardiac amyloidosis was considered rare, undiagnosable, and incurable, there was little impetus to look for the disease. However, now knowing it is far more prevalent, diagnosable, and treatable, there is renewed interest in identifying cardiac amyloidosis. This renewed interest has led to a resurrection of nuclear medicine cardiac amyloidosis imaging with bone-seeking radiotracers. Thus, technologists and physicians must bolster their knowledge of cardiac amyloidosis disease pathology, scan acquisition, image quantification, and interpretation.

This article is the third in a 3-part series on nuclear cardiac amyloidosis imaging in this issue of the *Journal of Nuclear Medicine Technology*. Part 1 reviews the etiology of cardiac amyloidosis and the detailed acquisition protocol (*7*). Part 2 explains image quantification and protocol technical considerations (*8*). This final part reviews cardiac amyloidosis clinical characteristics, scan interpretation, diagnosis, and treatment.

AMYLOIDOSIS AND CARDIAC AMYLOIDOSIS OVERVIEW

Amyloidosis

Amyloidosis can be challenging to grasp because multiple terms such as *light chain, transthyretin, wild type, senile, genetic,* and *mutant* are used interchangeably to describe the same or different disease subtypes. Therefore, it is essential to begin with a definition of basic terms and the disease process before discussing how to diagnose it.

Amyloidosis is a disorder of misfolded proteins (fibrils) that deposit in the extracellular spaces of various organs and tissues, including the heart (*9*). Amyloid diseases are usually chronic, as fibrils unremittingly accumulate and eventually impair the function of affected organs (*1*). Although there are several types of amyloids, two are most relevant to this discussion, and they account for 95% of cardiac amyloidosis: monoclonal immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) (Fig. 1). ATTR is further subdivided into wild type (ATTRwt), previously called senile, and variant (ATTRv), also called mutant or genetic type.

AL arises from the unregulated proliferation (dyscrasia) of plasma cells in the bone marrow, resulting in an overproduction of immunoglobulin light chains. There are 2 types of light chains, κ and λ, that misfold and aggregate into fibrils that collect in tissues. An increase in free light chains, which can be detected by serum free light-chain assay (sFLC) and serum immunofixation electrophoresis (IFE) or urine IFE, suggests amyloidosis.

AL fibrils can deposit in any organ, but common extracardiac sites include the kidneys, liver, gastrointestinal tract,

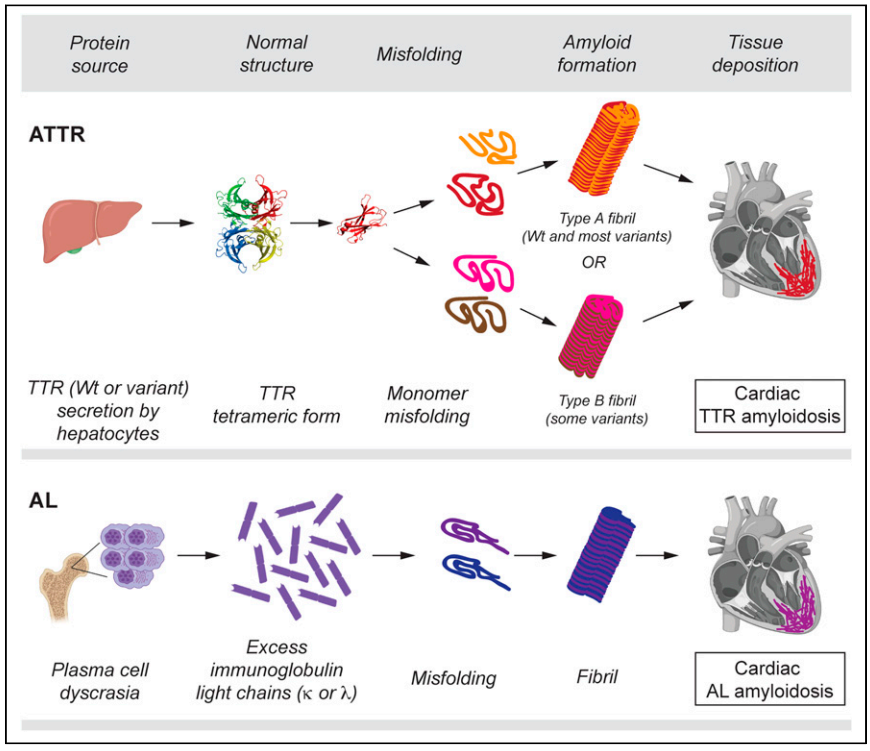

FIGURE 1. Amyloid molecular mechanisms and imaging characteristics. Source protein, misfolding, fibril formation, and deposition are depicted for cardiac ATTR and cardiac AL. In both ATTRwt and ATTRv, transthyretin proteins are secreted by liver, fold abnormally, and form fibrils that are deposited in myocardium. In AL, immunoglobulin light-chain proteins misfold and form fibrils also deposited in myocardium (*1*). TTR = transthyretin; Wt = wild-type. (Adapted from (*1*).)

tongue, and nerves (*10*). AL is frequently associated with hematologic diseases, such as myeloma (malignant tumors of the bone marrow) or monoclonal gammopathies (abnormal proteins in the blood). Additionally, AL is markedly aggressive, with a median survival of fewer than 6 mo if left untreated in patients with heart failure (*11*).

ATTR results from misfolding of transthyretin protein, protein produced primarily in the liver, which is involved in the transportation of thyroxine and retinol-binding protein (*trans* [transport] *thyr* [thyroxine] *retin* [retinol]) (*12*). Transthyretin is a tetramer (4 identical molecules [monomers] bonded together) that breaks down into individual monomers that misfold and aggregate into amyloid fibrils. There are 2 types of amyloid fibrils: type A and type B. Type A fibrils are found in both ATTRwt and ATTRv, whereas type B fibrils are the main component of ATTRv. Both types can accumulate in the myocardium, atria, and valves in addition to extracardiac organs such as the autonomic and peripheral nervous systems (*4*). Cardiac involvement in ATTR is the primary determinant of survival.

ATTRwt is the most common type of ATTR, and it is associated with aging because transthyretin proteins gradually deposit over decades (*10*). Although ATTRwt can deposit in soft tissue, such as the wrist (causing carpal tunnel syndrome) or the vasculature, the heart is the primary pathologic site of deposition. The disease generally occurs in individuals over 70 y old and more frequently in men than women (*13*). If left untreated, the median survival after diagnosis of ATTRwt is 3.6 y (*4*).

ATTRv is an autosomal dominant disease (caused by an abnormal gene passed down from one parent) resulting from a pathologic mutation in the transthyretin gene triggering accelerated amyloid deposition (*10*). Over 120 gene mutations have been identified so far. The most common genetic mutation seen in the United States is valine 122 isoleucine (V122I). It most commonly affects individuals of African descent, with mutation genetically present in 3%–4% of African Americans. ATTRv usually deposits in the heart but can also deposit in nerves.

ATTRv is less common than ATTRwt. It occurs more frequently in men than women and is usually diagnosed in individuals between 55 and 75 y old. If left untreated, the median survival of ATTRv caused by the V122I mutation is 2.5 y from diagnosis (*4*).

Amyloidosis Red Flags

Early diagnosis of amyloidosis is key to an optimal patient outcome because uninterrupted amyloid deposition leads to progressive organ dysfunction (*10*). In medicine, red flags refer to early warning signs or clinical manifestations of a serious undiagnosed or underlying disease that requires swift recognition and treatment (*14*). For example, more than a 5% unexplained weight loss over 6 mo is a red flag for hyperthyroidism. With the recent appreciation of the pervasiveness of cardiac amyloidosis, the debilitating nature of the disease, and the availability of therapies, prompt recognition of amyloidosis red flags is crucial for early treatment. The following sections will first describe the red flags of systemic amyloidosis, followed by those specific to cardiac amyloidosis (Fig. 2).

Systemic Amyloidosis Red Flags. The red flags of systemic amyloidosis can be broken down into categories based on the location of amyloid deposition. Amyloid plaques often deposit in nerves, causing damage or neuropathy; however, they can also deposit directly in any bodily tissue, causing organ dysfunction (*15*).

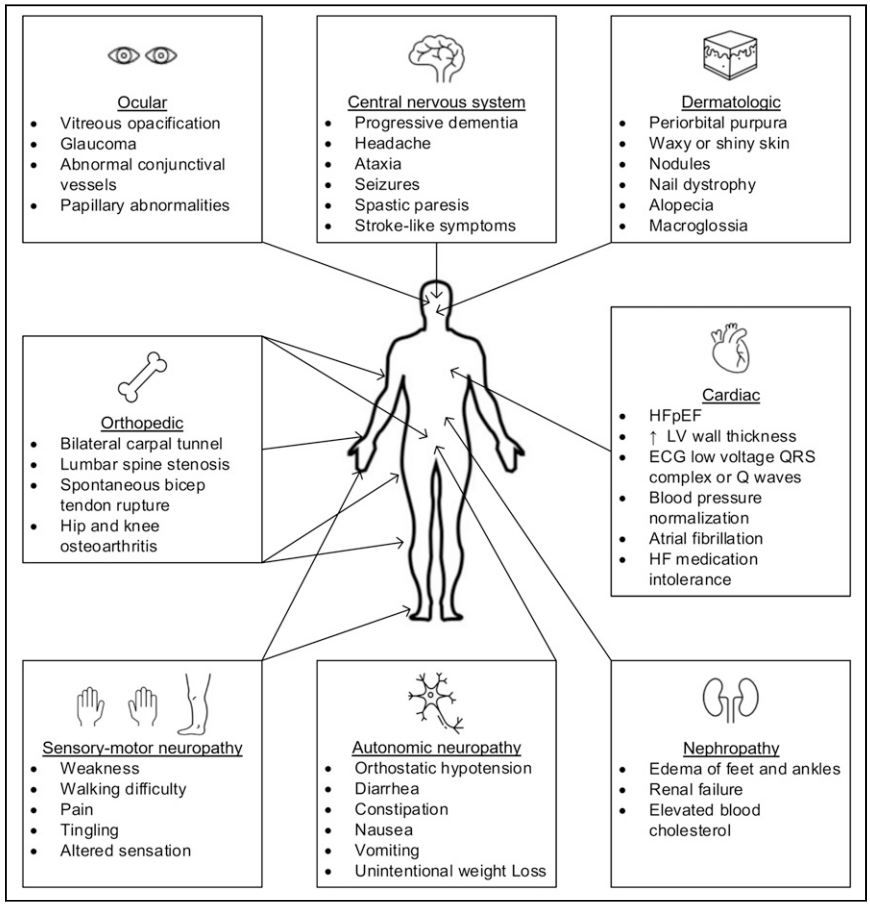

FIGURE 2. Systemic amyloidosis red flags. Pervasiveness and debilitating nature of amyloidosis compels early recognition of clinical manifestation red flags to ensure prompt initiation of disease-modifying therapies. Systemic amyloidosis can affect many organs and systems concurrently, triggering visual, central nervous, dermatologic, cardiac, renal, autonomic nervous, sensory-motor, and orthopedic signs and symptoms. ECG = electrocardiogram; HF = heart failure; LV = left ventricle.

Sensory-Motor Neuropathy. The first category is sensory-motor neuropathy. Sensory-motor neuropathy refers to conditions that cause decreased sensation or ability to move. It is also called polyneuropathy. Patients with amyloidosis sensory-motor neuropathy experience weakness, difficulty walking, pain, tingling, and altered sensation. These patients are often diagnosed with bilateral carpal tunnel syndrome. It is estimated that 1 in 4 people with amyloidosis has carpal tunnel syndrome. Many of these signs and symptoms overlap with peripheral neuropathy from other causes, such as diabetes mellitus.

Autonomic Neuropathy. The second category of systemic amyloidosis red flags is autonomic neuropathy. Autonomic neuropathy occurs when there is damage to nerves controlling everyday bodily functions such as blood pressure or digestion. Autonomic neuropathy symptoms include orthostatic hypotension, diarrhea, constipation, nausea, vomiting, and unintentional weight loss. But, again, there can be many alternative reasons for these symptoms. For example, orthostatic hypotension can also be caused by dehydration, cardiac conditions, or endocrine problems.

Central Nervous System. In addition to sensory-motor and autonomic nerve involvement, amyloidosis can also affect the central nervous system (*16*). Alzheimer disease is caused by localized (as opposed to systemic) deposition of amyloid fibrils in the brain. Systemic amyloidosis is mainly extracerebral because it does not cross the blood–brain barrier. Central nervous system amyloidosis manifestations include progressive dementia, headache, ataxia, seizures, spastic paresis, and strokelike symptoms.

Orthopedic. Orthopedic issues frequently occur in systemic amyloidosis because amyloid fibrils, particularly ATTRwt, deposit in cartilage and ligaments. Bilateral carpal tunnel syndrome is especially prominent and is estimated to occur in 15%–60% of patients with ATTR (*17*). In carpal tunnel syndrome, amyloid fibrils deposit in the wrist tendon, sheath, and transverse carpal ligaments, compressing the nerve (*18*). Several studies suggest that amyloid deposition in the carpal tunnel and ligaments may be apparent 5–15 y before cardiac amyloidosis becomes obvious, making it one of the earliest indicators of ATTR cardiomyopathy (*10,19*). Other orthopedic clinical manifestations include lumbar stenosis, spontaneous biceps tendon rupture, and hip and knee osteoarthritis (*20*).

Nephropathy. In the nephropathy category, deposits of amyloid plaque in the glomerulus damage the filtering ability of the kidney, allowing protein to leech into the urine (proteinuria) (*21*). Decreased blood protein can cause edema of the feet and ankles. In addition, a progressive build-up of amyloid plaques in the kidney eventually results in renal failure. Further, patients with kidney amyloid deposition can also have elevated blood cholesterol; however, the reason for this finding is unknown.

Dermatologic. Amyloidosis also affects the skin (*22*). One of the hallmark features of AL is periorbital purpura, also called panda or raccoon eyes. Other dermatologic clinical manifestations of systemic amyloidosis include waxy or shiny skin, nodules, nail dystrophy, alopecia, scleroderma, and macroglossia (an enlarged tongue with rippled edges).

Ocular. Finally, although less common, amyloid plaques can build up in the outer structures of the eye, conjunctiva, cornea, iris, lens, retina, and vitreous (*23*). The ocular manifestations of amyloidosis include vitreous opacification, glaucoma, abnormal conjunctival vessels, and papillary abnormalities.

The systemic amyloidosis clinical manifestations demonstrate the challenges of diagnosing systemic amyloidosis. Over 30 amyloid-producing proteins have been identified, and each can produce diverse types of amyloidosis with varying symptoms (*24*). In addition, amyloid plaques can deposit in more than one organ, producing assorted symptoms that further confound diagnosis. Added to that, many amyloidosis symptoms are nonspecific. Thus, the overlap of symptoms makes it extremely difficult to differentiate symptoms unrelated to amyloidosis from those associated with amyloidosis.

Cardiac Amyloidosis Red Flags. In addition to the plethora of other systemic clinical manifestations, there are several heart-specific manifestations. The cardiac manifestations are crucial to recognize as they are a major determinant of patient prognosis and outcome. The primary cardiac red flag is HFpEF.

Increased Left Ventricular Wall Thickness. Another red flag is an unexplained increased left ventricular wall thickness greater than 12 mm on echocardiography (*11*). Again, this is a nonspecific finding, as diseases other than cardiac amyloidosis can cause an increased left ventricular wall thickness, and it is a common finding on echocardiography. Hypertension is the usual culprit. Patients with thickened left ventricles are also frequently diagnosed with hypertrophic cardiac myopathy. However, left ventricular hypertrophy in patients with heart failure, particularly HFpEF or unexplained heart failure (in the absence of ischemic or valvular heart disease), should trigger evaluation for cardiac amyloidosis.

Electrocardiogram Low-Voltage QRS Complex. Another classic finding of cardiac amyloidosis is low voltage on electrocardiography combined with unexplained increased left ventricular wall thickness. Usually, left ventricular hypertrophy leads to increased voltage on electrocardiography. However, cardiac amyloid infiltration produces lower voltage: a QRS amplitude of less than 5 mm in limb leads or less than 10 mm in precordial leads (Fig. 3). This finding usually occurs in 50% of AL cases and 30% of ATTR cases. Therefore, absence of low voltage on electrocardiography with increased wall thickness does not exclude a diagnosis of cardiac amyloidosis. Patients with cardiac amyloidosis can also concomitantly have hypertension.

Electrocardiogram Q Waves. An additional electrocardiogram finding in patients with cardiac amyloidosis is Q waves in early precordial leads mimicking an old anteroseptal myocardial infarction (pseudoinfarct). Pseudoinfarction is seen in approximately 50% of cardiac amyloidosis patients (*25*).

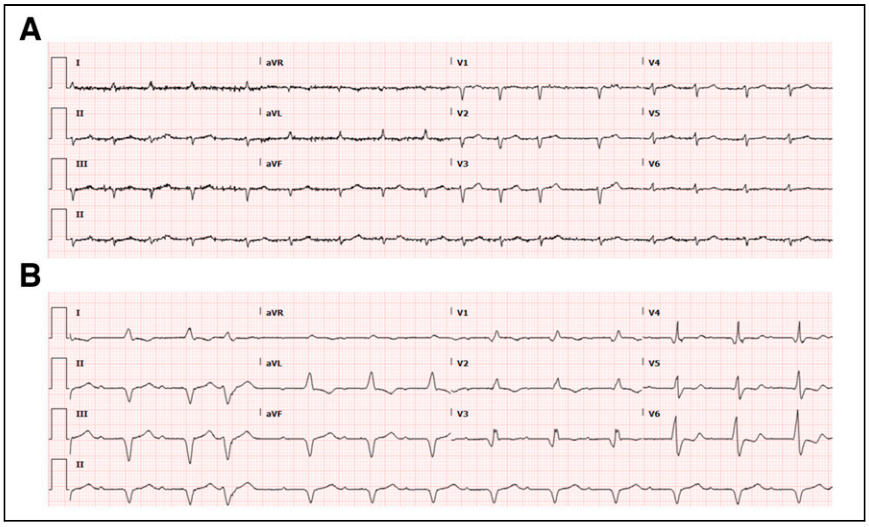

FIGURE 3. Cardiac amyloidosis electrocardiographic findings. (A) Electrocardiogram demonstrating low QRS voltage of less than 5-mm QRS amplitude in limb leads and less than 10-mm in precordial leads in patient with cardiac ATTR. (B) Electrocardiogram demonstrating pseudoinfarct pattern with Q waves in limb leads (II, III, and AVF) and early precordial leads (V1–V4) in patient with cardiac ATTR and no prior myocardial infarction. (Courtesy of Dr. Saurabh Malhotra.)

Furthermore, wide QRS complexes are seen more commonly in ATTR, whereas lower-limb lead voltages on electrocardiography are more frequent in AL.

Aortic Stenosis. Another red flag is diagnosis of aortic stenosis. Amyloid plaques can deposit in any cardiovascular structure, not just the myocardium. A study of patients undergoing transcatheter aortic valve replacement for severe aortic stenosis found cardiac amyloidosis in 16% overall and 22% among men (*26*). ATTR is the most common type of cardiac amyloidosis in aortic stenosis.

Blood Pressure Normalization. The normalization of blood pressure in patients with previous hypertension can suggest cardiac amyloidosis (*27*). When amyloid plaques deposit in the myocardium, the myocardium thickens and becomes stiff. The stiffening causes increased end-diastolic pressure and decreased left ventricular volume. The result is a decline in stroke volume, cardiac output, and blood pressure.

Atrial Fibrillation. Although atrial fibrillation is the most common cardiac arrhythmia in all patients, it is prevalent in ATTR. A study by Bukhari et al. found that 88% of patients with ATTRwt exhibited atrial fibrillation (*28*). Even though amyloid plaques can deposit in the atrial walls, the primary cause of atrial fibrillation is the thickened myocardium and restrictive filling (*29*). The elevated filling pressure causes atrial dilation, resulting in atrial arrhythmias and the loss of atrial function.

Intolerance of Heart Failure Medications. The last red flag is patient intolerance to heart failure medications (*30*). Typical therapy for heart failure includes β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor neprilysin inhibitors. Again, because of the increased end-diastolic pressure and decreased left ventricular volume that cause a decline in stroke volume, cardiac output, and blood pressure, patients with cardiac amyloidosis do not tolerate β-blockers well. These patients rely on heart rate to maintain cardiac output, and β-blockers inhibit this adaptation by decreasing heart rate. The development of profound hypotension and fatigue after β-blocker initiation strongly suggests cardiac amyloidosis. Angiotensin-converting enzyme inhibitors and angiotensin receptor neprilysin inhibitors compound orthostatic hypertension associated with autonomic dysfunction.

CARDIAC AMYLOIDOSIS DIAGNOSTIC TESTS

The standard diagnostic tests for cardiac amyloidosis include electrocardiography, echocardiography, CMR, and nuclear imaging with bone-seeking radiotracers. The typical electrocardiogram findings in cardiac amyloidosis have been described earlier in this article. This section will summarize the use of echocardiography, CMR, and nuclear imaging. In addition, the relative advantages and disadvantages of each will be discussed. The following section will provide detailed information on obtaining and interpreting ^{99m}Tc-pyrophosphate scans to detect cardiac amyloidosis.

Echocardiography

Echocardiography is widely available, quick to perform, and cost-effective (*3*). Its chief value is in identifying diastolic dysfunction. The characteristic findings of cardiac amyloidosis on echocardiography are increased left and right ventricular wall thickening and associated elevated ventricular systolic pressures (Fig. 4). Patients with cardiac amyloidosis also demonstrate a small left ventricular cavity, biatrial enlargement, increased atrial septal thickness, and thickened valves such as low-flow, low-gradient aortic stenosis.

In addition, patients with cardiac amyloidosis can have reduced global longitudinal strain and a reduction in longitudinal strain with apical sparing (*11*). Longitudinal strain is a measure of myocardial cell distortion. Left ventricular segments are displayed as a polar map, with a more negative value (coded in red) indicating better function. Apical sparing refers to a normal or near-normal strain pattern in the apical section so that the resulting polar map resembles a bull's-eye. Apical sparing can differentiate cardiac amyloidosis from other forms of left ventricular hypertrophy caused by hypertension, hypertrophic cardiomyopathy, aortic stenosis, or Fabry disease (a rare genetic disorder characterized by the lack of an enzyme to metabolize fatty substances).

The characteristic echocardiography findings of cardiac amyloidosis may not always be present. Although the typical characteristics help raise suspicion of cardiac amyloidosis,

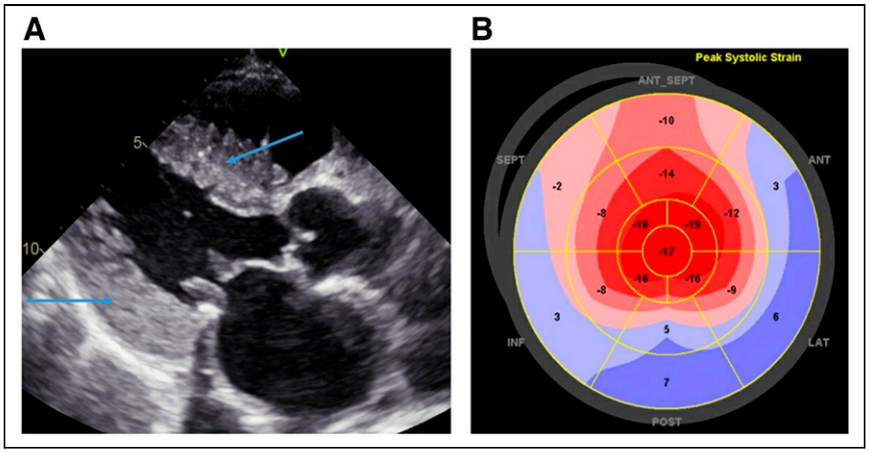

FIGURE 4. Echocardiogram cardiac amyloidosis findings. (A) Parasternal long axis view demonstrating severely increased left ventricular wall thickness in patient with cardiac ATTR (arrows). (B) Apical sparing (bull's-eye) pattern identified on longitudinal strain echocardiography from same patient. ANT = anterior; ANT_SEPT = anteroseptal; INF = inferior; LAT = lateral; POST = posterior; SEPT = septal. (Courtesy of Dr. Saurabh Malhotra.)

echocardiography cannot distinguish between ATTR and AL because it is neither sensitive nor specific (*31*). The diagnostic accuracy of echocardiography for cardiac amyloidosis is approximately 60% (*1*).

CMR

CMR is also helpful in diagnosing cardiac amyloidosis. It is used to identify structural and functional changes created by amyloid deposition (*32*). Furthermore, CMR can provide tissue characterization information to differentiate myloid from nonamyloid wall thickening disorders (*3*). However, it is expensive compared with echocardiography and nuclear imaging and is contraindicated in many patients with implanted devices.

CMR findings in amyloidosis include left ventricular and right ventricular wall thickening and atrial enlargement (*5,18*). Gadolinium contrast administration demonstrates a characteristic pattern of late gadolinium enhancement that is diffuse (not following any specific coronary distribution) and subendocardial (Fig. 5) (*11*). In ATTRwt, transmural and patchy late gadolinium enhancement can be seen in the right ventricle and the walls of the atrium. Other cardiac amyloidosis gadolinium tracer kinetics include an inability to null the myocardium on the inversion time mapping sequence and early gadolinium clearance from the blood pool (*1*). The main limitation of gadolinium is that it cannot be administered to patients with reduced renal function, a systemic amyloidosis clinical manifestation.

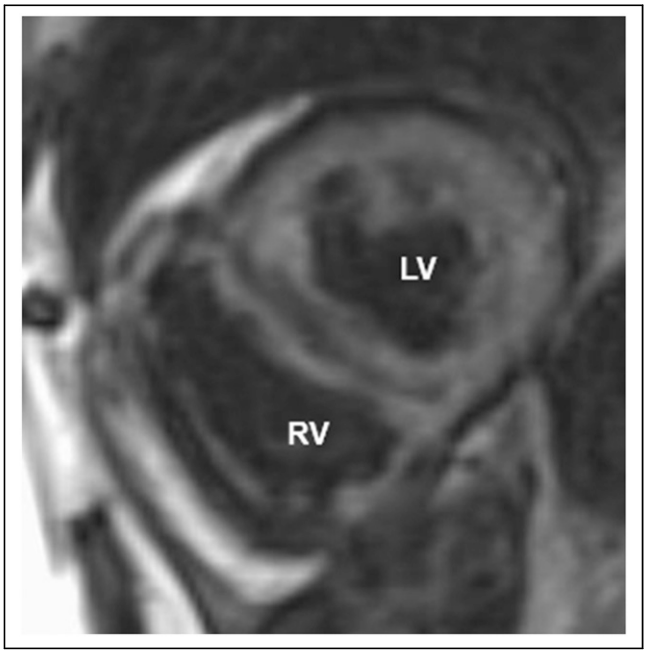

FIGURE 5. CMR amyloidosis late gadolinium enhancement. Images obtained after administration of gadolinium contrast material show accumulation in tissue with increased extracellular space. Short-axis orientation demonstrates diffuse transmural gadolinium enhancement of left ventricular myocardium. LV = left ventricle; RV = right ventricle.

Another CMR finding suggestive of cardiac amyloidosis is increased extracellular volume fraction, resulting from the deposition of amyloid fibrils, which is not seen in other conditions causing increased left ventricular thickness. High extracellular volume has an unfavorable prognosis.

A final CMR finding is significantly increased native T1 time (a quantitative assessment of myocardium composition measured by longitudinal relaxation time) (*1*). T1 mapping is a relatively new technique with the potential to monitor cardiac amyloidosis disease progression. Of benefit, native T1 myocardial mapping techniques do not require gadolinium administration.

Of CMR findings, a late gadolinium enhancement pattern is highly sensitive (93%) and specific (70%) for cardiac amyloidosis. Furthermore, transmural late gadolinium enhancement in patients with cardiac amyloidosis is associated with a 5-fold increase in mortality (*11*). Finally, similar to echocardiography, CMR cannot reliably differentiate between ATTR and AL. A negative CMR study was found to be inaccurate in 12% of patients with biopsy-proven amyloidosis (*1*).

Nuclear Imaging

Nuclear myocardial scintigraphy uses bone-avid radiotracers to detect cardiac amyloidosis. Nuclear imaging, like echocardiography, is widely available, simple to perform, and relatively inexpensive. Nuclear imaging can overcome some limitations and contraindications of echocardiography and CMR, with the ability to image patients with atrial fibrillation, implanted devices, contrast allergy, renal dysfunction,

and extreme obesity. Although echocardiography is notable for its ability to raise suspicion of cardiac amyloidosis, and certain CMR findings are specific for amyloidosis, neither can distinguish ATTR from AL, which nuclear imaging can do (*18*).

One drawback of nuclear imaging in detecting cardiac amyloidosis is the exposure to ionizing radiation, albeit the risk from a typical dose of 555 MBq (15 mCi) is low, at 3 mSv (*33*). Another disadvantage of nuclear imaging is that it cannot discern nonamyloid causes of left ventricular thickening, such as echocardiography and CMR.

Nuclear imaging with bone-avid radiotracers is highly accurate for ATTR when plasma cell dyscrasia (AL disease) is excluded by serum studies (*1*). A metaanalysis of 5 studies found a sensitivity of 92% and specificity of 95% when plasma cell dyscrasia was eliminated.

The diagnosis of cardiac amyloidosis usually occurs in the later stages of the disease. Early diagnosis of ATTR, before the condition progressively worsens, is fundamental for a better patient prognosis. A study by Castano et al. detected cardiac ATTR across all New York Heart Association heart failure classes (*34*). Almost half the cases were in patients with class I or II symptoms, suggesting that ^{99m}Tc-pyrophosphate imaging may be useful in detecting patients with mild symptoms. The high diagnostic accuracy and applicability of nuclear imaging make it a potentially valuable tool in screening for cardiac amyloidosis, as early detection of cardiac amyloidosis is an unmet clinical need.

^{99m}Tc-PYROPHOSPHATE CARDIAC AMYLOIDOSIS IMAGING

Three radiotracers have been used in cardiac amyloidosis imaging. ^{99m}Tc-pyrophosphate is approved by the FDA and is widely used in the United States. ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid is not approved in the United States and is used mainly in Europe. Finally, ^{99m}Tc-hydroxymethylene diphosphonate is available in the United States and Europe but is used less frequently because of limited availability. Although no research compares the 3 radiotracers directly, the published literature suggests that they can be used interchangeably (*35*). This article focuses on ^{99m}Tc-pyrophosphate, although the principles are similar for the other tracers.

The exact mechanism of ^{99m}Tc-pyrophosphate binding to amyloid deposits is unknown, but it is believed to be related to calcium content. Amyloid fibrils have 3 main components: a precursor protein, heparin sulfate proteoglycan (protein bonded to complex polysaccharides containing amino groups), and a calcium-dependent P-component (*32*). The calcium-dependent P-component, universally found in all amyloid fibrils, is thought to stabilize amyloid fibril aggregates (binding), preventing breakdown and inhibiting fibril removal (*36*). The calcium-dependent P-component likely explains the uptake and binding of bone-seeking radiopharmaceuticals to amyloid deposits, allowing visualization (*32*).

Brief Review of ^{99m}Tc-Pyrophosphate Cardiac Amyloidosis Imaging Acquisition and Quantification

The acquisition and quantification of ^{99m}Tc-pyrophosphate cardiac amyloid imaging have been discussed in parts 1 and 2 of this series (*7,8*). The described protocol is based on the 2019 "ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging" (*35*) (referred to as the "consensus recommendations" in this article) and a 2021 addendum to that document published by the American Society of Nuclear Cardiology, Society of Nuclear Medicine and Molecular Imaging, and several other professional societies (*39*).

The consensus recommendations prescribe 370–740 MBq (10–20 mCi) of ^{99m}Tc-pyrophosphate, ^{99m}Tc-hydroxymethylene diphosphonate, or ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid. The recommended time between injection and imaging is 3 h. At 3 h, anterior and lateral planar images of the chest are acquired for 750,000 counts (8–10 min). SPECT imaging, either a 180° or 360° acquisition, is then obtained. The overall parameters outlined in the addendum to the consensus recommendations work well for most camera systems.

The planar and SPECT images are used to visually and semiquantitatively grade the degree of myocardial uptake compared with the ribs. The SPECT images, which are critically important, are used to verify that radiotracer uptake is truly within the myocardium and not within the blood pool (Fig. 6). Finally, the planar images, which confirm but do not diagnose cardiac amyloidosis, are used to a calculate the heart–to–contralateral-lung ratio (H/CL) by regions of interest drawn over the myocardium and the opposite side of the chest.

More detailed instructions on the ^{99m}Tc-pyrophosphate study acquisition and quantitation are provided in parts 1 and 2 of this series (*7,8*). Image interpretation and semiquantitative analysis results will be explained in more detail in the next section.

Interpretation

The resurgence of interest in ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging led to an increase in the number of laboratories performing the scan. For example, a 2015 survey by Harb et al. of 100 nuclear cardiology laboratories found that 81% were performing ^{99m}Tc-pyrophosphate cardiac amyloidosis imaging, and most laboratories (92%) performed fewer than 2–4 ^{99m}Tc-pyrophosphate scans per month (*37*).

^{99m}Tc-pyrophosphate has been reported to have a high sensitivity and specificity in patients with biopsy-proven cardiac amyloidosis. However, these results were established by expert, high-volume laboratories at specialty referral centers following precise protocols (*38*). But as Harb et al. demonstrated, many labs perform only a few ^{99m}Tc-pyrophosphate scans a month.

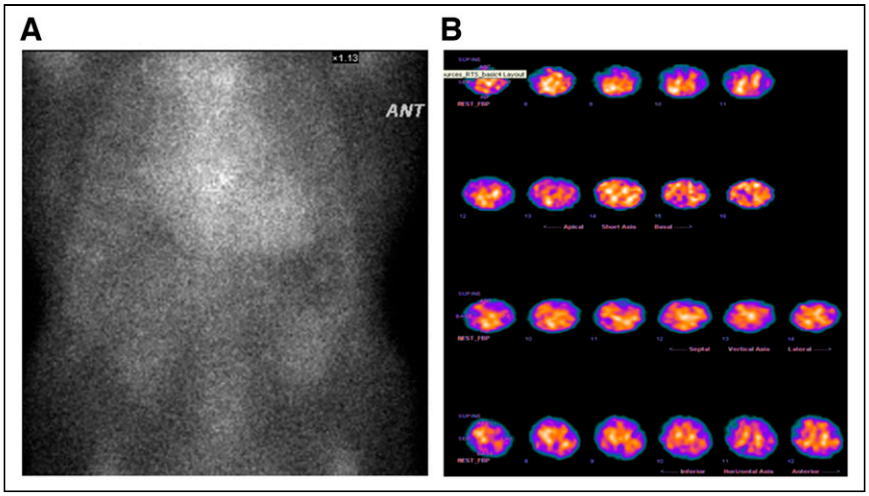

FIGURE 6. Blood pool on ^{99m}Tc-pyrophosphate scintigraphy. (A) Anterior planar image with Perugini score of 2. (B) SPECT images demonstrating no evidence of myocardial uptake. ANT = anterior.

The survey by Harb et al. also discovered that approximately one third of laboratories imaged 1 h after injection. Most laboratories (70%) performed only planar imaging (*37*). Regarding interpretation, only 57% of laboratories performed any type of analysis. Only 52% semiquantitatively scored uptake, and 43% calculated the H/CL ratio. Unfortunately, variability such as this increases the likelihood of misdiagnosis.

Inopportunely, there are no formal, published guidelines directing the performance of ^{99m}Tc-pyrophosphate imaging, as the evidence base is still being developed. However, to address the lack of guidelines, the professional societies mentioned above published expert consensus recommendations in 2019 with an addendum in 2021 clarifying best practices for injection-to-imaging time, the indispensable requirement of SPECT imaging, and instructions for study interpretation (*35,39*).

^{99m}Tc-pyrophosphate imaging is a form of hot-spot imaging in which interpretation is based on a ratio of target organ uptake compared with other organs, either visually or using a semiquantitative metric (Fig. 7) (*32*).

Step 1. The first step in interpreting ^{99m}Tc-pyrophosphate scans is qualitative inspection of the planar and SPECT images. Both the planar and the SPECT images (acquired 3 h after injection) are evaluated to confirm diffuse radiotracer uptake in the myocardium, indicative of cardiac amyloidosis (*39*). Review of the SPECT images is vitally important in ensuring that there is no residual blood-pool activity, no evidence of focal or regional uptake (indicative of myocardial infarction within 6 wk), no area of decreased uptake caused by a previous myocardial infarction (over 6 wk), and no overlapping bone activity from the ribs such as from a prior fracture or metastasis.

Step 2. Step 2 is semiquantitative grading of diffuse myocardial uptake (activity not in the blood pool) observed on the SPECT images using the method described by Perugini et al. (*40*). A scale from 0 to 3 compares tracer in the myocardium with tracer in the ribs (Fig. 8). In grade 0, there is no uptake in the heart, and there is normal bone uptake. Grade 0 is negative for cardiac amyloidosis. For grade 1, there is diffuse myocardial tracer uptake but less than in the ribs. Grade 1 is considered equivocal and requires more information to diagnose cardiac amyloidosis. Grade 2 represents a myocardial uptake intensity equal to radiotracer uptake seen in the ribs. Grade 2 on SPECT images strongly suggests cardiac amyloidosis. Finally, in grade 3, myocardial uptake is greater than uptake in the ribs. The heart can be clearly identified in

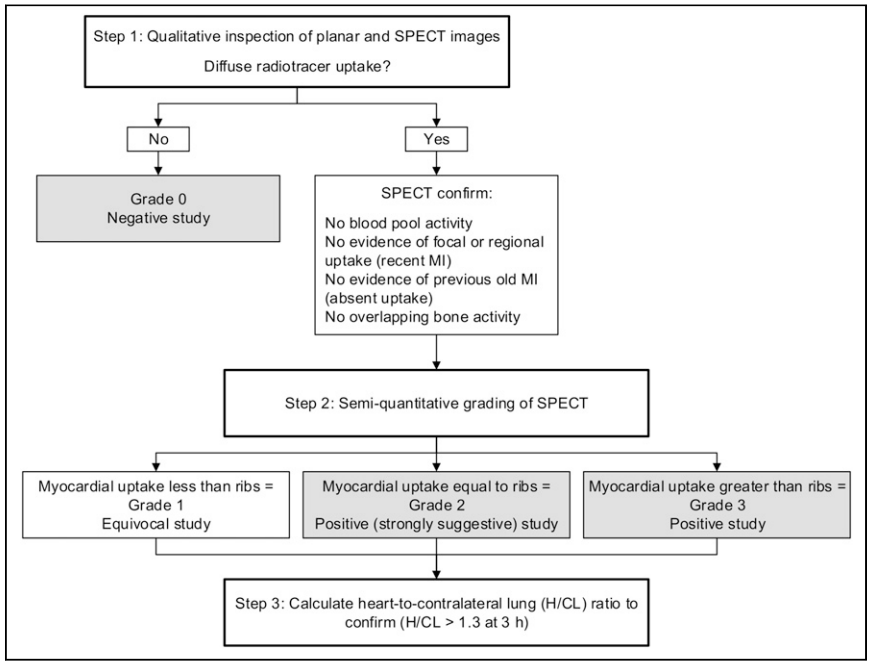

FIGURE 7. ^{99m}Tc-pyrophosphate scan interpretation steps. ^{99m}Tc-pyrophosphate images should be interpreted in logical order. Step 1 is visual inspection of both planar and SPECT images to determine presence or absence of radiotracer uptake in heart area. SPECT images are scrutinized to ensure no blood-pool activity, focal or regional uptake, areas of absent tracer, or overlapping bone activity. Step 2 is semiquantitative grading of planar and SPECT images comparing myocardial uptake with rib uptake. Step 3 evaluates H/CL ratio when grading is equivocal.

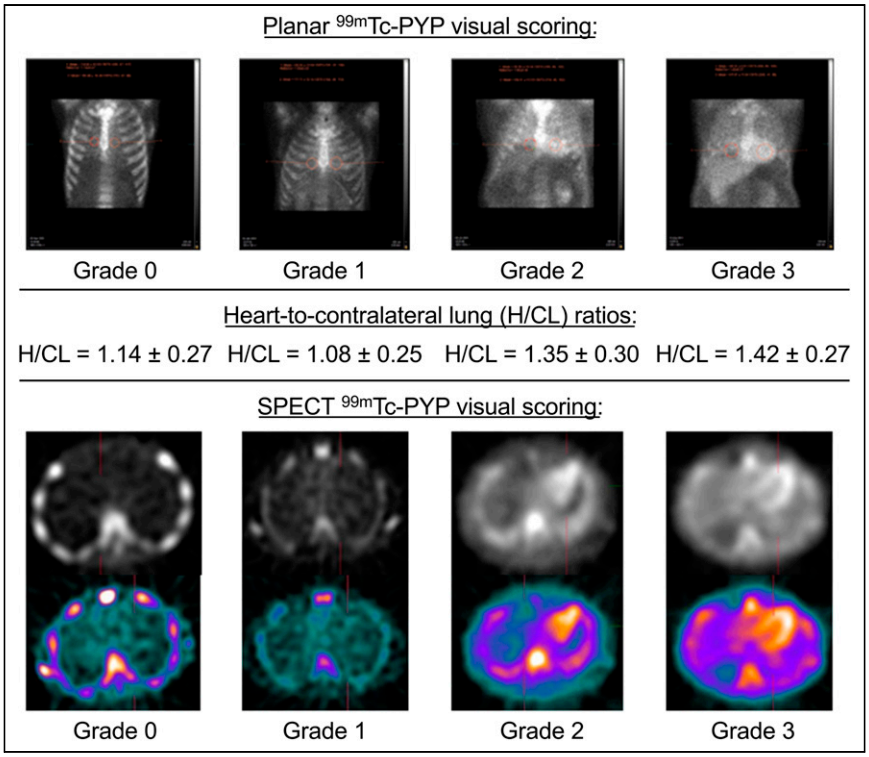

FIGURE 8. Cardiac amyloidosis ^{99m}Tc-pyrophosphate semiquantitative and quantitative interpretation. (Top) Planar 3-h images demonstrating diffuse myocardial uptake and grade based on comparison of ^{99m}Tc-pyrophosphate myocardial uptake with rib. (Middle) H/CL ratio. (Bottom) Gray-scale and color SPECT images confirming myocardial uptake. PYP = pyrophosphate.

the images. Grade 3 on SPECT images is positive for cardiac amyloidosis, with the caveat that AL must be excluded. Both grade 2 and grade 3 are considered abnormal.

Although the Perugini grading scale helps identify cardiac amyloidosis, increasing the grade from 1, 2, or 3 does not predict the prognosis because tracer uptake does not necessarily reflect more advanced cardiac involvement. A study by Hutt et al. found no difference in prognosis in patients based on grade (*41*). However, patients with no myocardial uptake (grade 0), indicating absence of cardiac amyloidosis, do far better.

Step 3. The third step in ^{99m}Tc-pyrophosphate image interpretation involves calculating the H/CL ratio to confirm the cardiac amyloidosis diagnosis determined from the SPECT images. The H/CL ratio is assessed using a method developed by Bokhari et al. (*42*). To calculate the H/CL ratio, a circular region of interest is drawn over the heart on the planar image. This region reflects the degree of ^{99m}Tc-pyrophosphate retention in the heart related to left ventricular wall thickness and mass. A same-sized region is mirrored on the contralateral chest to account for background and rib uptake (*33*). The mean counts from the heart are then divided by the mean counts of the contralateral lung region to determine the ratio. When myocardial activity is visually present on the SPECT images, a ratio of greater than 1.3 at 3 h after injection (1.5 at 1 h) from the planar images is abnormal, again assuming activity is in the myocardium and not in the blood pool. Ratios of between 1.0 and 1.3 at 3 h are equivocal (1.0 − 1.5 for 1-h imaging). A diagnosis of cardiac amyloidosis cannot be made solely from the H/CL ratio.

Perils of Skipping a Step. ^{99m}Tc-pyrophosphate cardiac amyloidosis scan interpretation must incorporate all 3 steps. In addition, interpretation must consider the clinical context and the necessity of excluding cardiac AL. Failure to follow the consensus recommendations when acquiring and interpreting the scan increases the likelihood of misdiagnosis.

For example, when planar imaging alone is used to interpret a ^{99m}Tc-pyrophosphate study, myocardial uptake cannot be differentiated from residual blood-pool activity. Research by Asif et al. retrospectively examined the diagnostic accuracy of planar-only imaging compared with the accuracy of planar imaging combined with SPECT. They found a decrease in specificity when only the planar grade was used because of the misclassification of patients as positive (*43*). Planar-only imaging increases the likelihood of a false-positive study by approximately 2%–7% (*44*).

Only using the H/CL ratio is insensitive, has a lower positive predictive value, and can fabricate disease misclassification (*44*). The same study by Asif et al. found that 35 patients had an H/CL ratio of less than 1.5 (equivocal) (*43*). However, only 15 of 35 (43%) were positive on SPECT. SPECT imaging is the gold standard for determining myocardial uptake of ^{99m}Tc-pyrophosphate.

The H/CL ratio can also confirm the diagnosis in grades 2 and 3 and serve as the tie-breaker between visual grades 1 and 2. Usually, H/CL ratios are concordant with the semiquantitative grade. If the findings are discordant or the visual grade is 1 (equivocal), the H/CL ratio can help distinguish between equivocal grades 1 and 2 and the resultant positive or negative determination.

Additionally, a ^{99m}Tc-pyrophosphate scan is considered positive for cardiac amyloidosis when the semiquantitative grade is 2 or 3, and the SPECT images confirm diffuse uptake, excluding blood pool or other focal uptake. Therefore, the H/CL ratio does not necessarily need to be reported when the grade is 2 or 3. Also, when the visual grade is 0 (absence of myocardial uptake), the H/CL need not be reported. An H/CL ratio of greater than 1.3 at 3 h after injection (1.5 at 1 h) confirms a positive study.

False-Positive and False-Negative Results

False-positive and false-negative results can occur due to various technical and physiologic factors (Table 1).

False-Positive Results. The main cause of false-positive results is residual cardiac blood pool within the left ventricular cavity, particularly when seen on planar images (*1*). Blood pool can result in a spuriously elevated planar grade, thus again showing the importance of SPECT imaging. Prominent blood-pool activity at 1 h after injection is the primary reason that imaging at 3 h after injection is recommended. Usually, ^{99m}Tc-pyrophosphate clears rapidly from the blood pool and accumulates in the bone. Approximately 15%–20% of ^{99m}Tc-pyrophosphate is typically found in the blood pool at 1 h (*45*). However, the percentage of residual blood pool may be higher in elderly patients (the patients most likely to have cardiac amyloidosis) and patients with abnormal renal function. Thus, false positives are more likely in these clinical scenarios.

Other causes of false-positive scans include things that increase counts in the heart region, such as a prior rib fracture or metastasis to the ribs (*4*). Mitral annular calcification and aortic valve calcification can also lead to increased counts in the heart area (*46*). Other causes of myocardial injury and ^{99m}Tc-pyrophosphate uptake include pericarditis, chemotherapy, or drugs associated with myocardial toxicity, such as hydroxychloroquine (*39*). Hydroxychloroquine—which became infamous early during the coronavirus disease 2019 pandemic as a possible treatment (a claim since scientifically proven to be false)—is used to prevent and treat malaria and to relieve the symptoms of autoimmune diseases (*47*).

A final cause of false-positive ^{99m}Tc-pyrophosphate studies is myocardial infarction (*1*). ^{99m}Tc-pyrophosphate imaging was first used in the 1970s to identify a recent myocardial infarction (<6 wk). Calcium deposits within newly infarcted tissue take up ^{99m}Tc-pyrophosphate, similar to amyloid microcalcifications. However, in recent myocardial infarction, the uptake pattern is regional rather than diffuse, and uptake correlates with the coronary artery distribution territory. SPECT imaging can confirm diffuse versus regional uptake of ^{99m}Tc-pyrophosphate and differentiate between cardiac amyloidosis and a recent myocardial infarction.

TABLE 1
Reasons for False-Positive and False-Negative Studies

Study category	Reason
False-positive	Residual cardiac blood pool
	Rib activity (e.g., prior fracture or metastasis)
	Mitral valve and annular calcification
	Pericarditis
	Chemotherapy
	Myocardial toxic drugs (e.g., hydroxychloroquine)
	Recent myocardial infarction (<6 wk)
False-negative	Minimal myocardial uptake in early disease stages
	Amyloidosis variants that do not accumulate ^{99m}Tc-pyrophosphate (e.g., Phe64Leu or Val30Met)
	Large old myocardial infarction

False-Negative Results. There are fewer causes of false-negative ^{99m}Tc-pyrophosphate results. One reason for a false-negative study is minimal myocardial amyloid deposition in earlier disease stages (*38*). There are several types of cardiac amyloidosis. ATTRwt was previously called senile cardiac amyloidosis because amyloid fibrils deposit in the myocardium over many years. Early in the disease process, there may not be enough amyloid plaque within the myocardium to be detected.

Another cause of false-negative findings relates to the type of cardiac ATTR. Although ATTRwt comprises most cases, there is also ATTRv—the mutant type—for which over 120 genetic mutations have been discovered. Two variants, Phe64Leu and Val30Met, have been found to have cardiac involvement by echocardiography but negative findings on ^{99m}Tc-pyrophosphate imaging (*48*).

The last cause of false-negative results is also related to a previous myocardial infarction but for a reason different from false-positive studies. A remote (old) myocardial infarction contains scar tissue (*38*). Scar tissue does not perfuse, nor will it accumulate in amyloid fibrils. ^{99m}Tc-pyrophosphate can be taken up only by noninfarcted tissue. Therefore, in patients with a previous infarction, uptake in the myocardium compared with the rib can be challenging to discern. The H/CL ratio may be below the diagnostic threshold for a positive study (especially if the myocardial infarction was large). The solution to overcome this problem is, again, SPECT imaging, which should demonstrate uptake throughout the myocardium but no uptake in the infarcted zone.

CARDIAC AMYLOIDOSIS DIAGNOSIS

The differential diagnosis of cardiac amyloidosis can be challenging because patients often present with dyspnea, fatigue, and edema, which are nonspecific findings often attributed to nonamyloid diseases. Given the nonspecific nature of symptoms, the trick to diagnosis is a high degree of suspicion combined with the results of several diagnostic tests, including electrocardiography, echocardiography, CMR, nuclear imaging, and laboratory testing for monoclonal proteins.

Recognition of Red Flags

The first step when diagnosing cardiac amyloidosis is recognizing the signs and symptoms of HFpEF (Table 2). Patients with HFpEF and at least one clinical red flag (i.e., biceps tendon rupture, carpal tunnel syndrome, being elderly, intolerance to HF medications, low-flow low-gradient aortic stenosis, lumbar stenosis, neuropathy, or transthyretin gene positivity) should be suspected of having amyloidosis (*49*).

Patients with HFpEF, at least one clinical manifestation, and findings suggestive of cardiac amyloidosis on echocardiography or CMR should undergo further noninvasive

TABLE 2
Clinical, Echocardiogram, and CMR Red Flags

Parameter	Red flag
Clinical	Biceps tendon rupture
	Carpal tunnel syndrome
	Elderly
	Intolerance to heart failure medications
	Low-flow, low-gradient aortic stenosis
	Lumbar stenosis
	Neuropathy
	Transthyretin gene positive
Echocardiogram	Left/right ventricular wall thickening
	Diastolic dysfunction
	Reduced global longitudinal strain
	Relative apical sparing
	Atrial enlargement
	Low-flow, low-gradient aortic stenosis
CMR	Left/right ventricular wall thickening
	Atrial enlargement
	Diffuse late gadolinium enhancement
	Expanded extracellular volume
	Blood-pool signal nulling before myocardial nulling

evaluation (Fig. 9). The typical echocardiogram cardiac amyloidosis findings include left or right ventricular wall thickening, diastolic dysfunction, reduced global longitudinal strain, relative apical sparing, atrial enlargement, and low-flow, low-gradient aortic stenosis. The typical CMR findings include left or right ventricular wall thickening, atrial enlargement, diffuse late gadolinium enhancement, expanded extracardiac volume, and blood-pool signal nulling before myocardial nulling.

Testing for Monoclonal Proteins

The diagnostic algorithm for cardiac amyloidosis is based on the assumption that most cardiac amyloidosis in the United States is either AL or ATTR (*11*). Laboratory testing for monoclonal proteins is performed in conjunction with ^{99m}Tc-pyrophosphate imaging to distinguish AL from cardiac ATTR. Thus, the next step in diagnosing cardiac amyloidosis is to rule out AL disease. AL is a rapidly progressive and fatal disease treated with chemotherapy, which accentuates the need to distinguish between AL and ATTR to ensure the correct diagnosis and treatment.

Three clinical laboratory tests are used to detect monoclonal proteins: sFLC, serum IFE, and urine IFE (*11*). In most patients with AL, the results of one or more of these tests will be abnormal. When the test results are normal, the negative predictive value (the probability of not having the disease) ruling out AL is high, at 99% (*50*).

The sFLC assay measures circulating κ and λ free light chains (*38*). These values are used to calculate the ratio (κ/λ). The reference values for these tests depend on the manufacturer and the patient's renal function. However, in general, the ratio should be near 1 in the absence of monoclonal protein production. For example, reference values for one manufacturer, Roche Cobas Integra (Freelite), range from 0.26 to 1.65. In patients with renal dysfunction, the reference range is 0.37–3.1. The sFLC ratio will be abnormal in approximately 91% of patients with AL (*50*).

IFE is a sensitive technique to nonquantitatively detect monoclonal proteins by immunoprecipitation (moving a dissolved protein antigen out of solution using an antibody that binds to a specific protein) (*38*). It is essential to make the distinction that IFE differs from electrophoresis (movement of charged particle in solution) alone. Immunofixation is key term. Serum protein electrophoresis or urine electrophoresis without immunofixation can be negative in more than one-third of patients with AL.

Any monoclonal protein on serum IFE or urine IFE is considered abnormal and positive for AL. The serum IFE is abnormal in 69% of patients with AL, whereas the urine IFE is abnormal in 83% of patients with AL. The combination of sFLC assay with serum IFE is abnormal in 99% of patients with AL.

^{99m}Tc-Pyrophosphate Imaging

The next step in diagnosing cardiac amyloidosis (nuclear imaging with ^{99m}Tc-pyrophosphate) is dependent on sFLC, serum IFE, and urine IFE results. There are 2 distinct pathways (positive vs. negative laboratory findings for AL). Cardiac amyloidosis diagnosis is further honed on the basis of the ^{99m}Tc-pyrophosphate Perugini grade and H/CL ratio.

Monoclonal Proteins Present (Positive for AL)

When ^{99m}Tc-pyrophosphate imaging is normal, or grade 0 (no ^{99m}Tc-pyrophosphate myocardial uptake), and laboratory testing demonstrates monoclonal proteins, the likelihood of cardiac ATTR is low. CMR may be appropriate in this scenario. The patient should also be referred to a hematologist for additional assessment and histologic confirmation of AL and amyloid typing (e.g., bone marrow biopsy to identify and quantify the plasma cell clone) (*49*).

The patient should be further assessed when there is equivocal myocardial uptake compared with the ribs (grade 1) or definite myocardial uptake (grade 2 or 3). The same holds true when the H/CL ratio exceeds 1.3 at 3 h (1.5 at 1 h). Usually, myocardial uptake points to cardiac ATTR. However, Gillmore et al. found that cardiac tracer localization on ^{99m}Tc-pyrophosphate imaging can occur in 30% of patients with AL. This finding further confounds the ability to distinguish between AL and cardiac ATTR (*10,51*). Thus, patients should again be referred to hematology for evaluation (e.g., tissue typing by endocardial biopsy), diagnosis, and treatment (e.g., chemotherapy).

Monoclonal Proteins Absent (Negative for AL)

When ^{99m}Tc-pyrophosphate imaging is normal (grade 0) and laboratory testing demonstrates the absence of monoclonal proteins, the likelihood of ATTR or cardiac AL is low, and CMR may be appropriate (*11*). When ^{99m}Tc-pyrophosphate imaging is equivocal (grade 1) and monoclonal

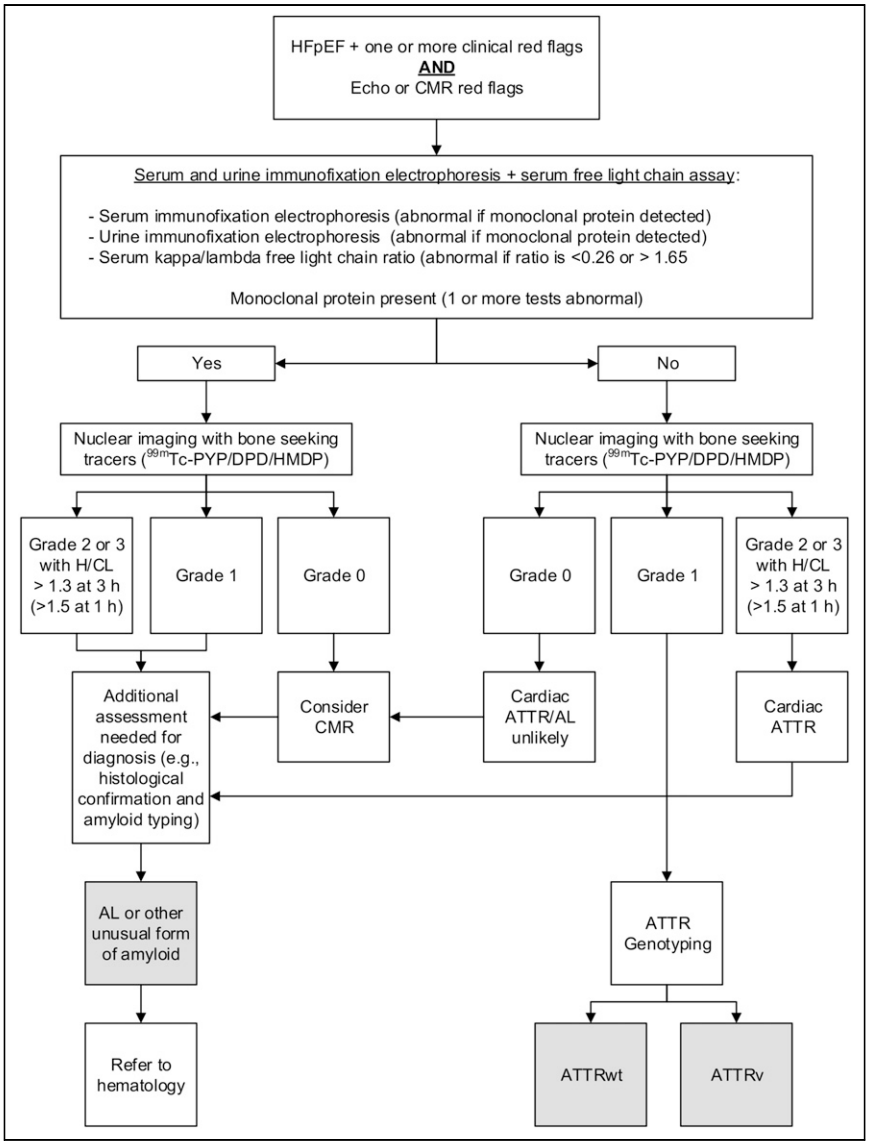

FIGURE 9. Cardiac amyloidosis differential diagnosis algorithm. First step in diagnosing cardiac amyloidosis is recognition of one or more clinical red flags in patients with HFpEF, along with one or more echocardiography or CMR red flags. Although diagram suggests that steps are sequential, serum light-chain evaluation and nuclear imaging usually occur simultaneously. If monoclonal proteins are present and nuclear imaging with bone-seeking tracer such as ^{99m}Tc-pyrophosphate is positive (grade 2 or 3), cardiac AL is likely. Patient should undergo hematologic evaluation. If monoclonal proteins are present and ^{99m}Tc results are equivocal (grade 1), additional histologic assessment is necessary for diagnosis. If monoclonal proteins are present and ^{99m}Tc-pyrophosphate scan is negative (no myocardial tracer uptake), findings are negative for cardiac amyloidosis. However, patient should be further assessed to confirm systemic AL. When monoclonal proteins are absent, and there is no ^{99m}Tc-pyrophosphate scan myocardial uptake, cardiac AL and cardiac ATTR are unlikely. However, if monoclonal proteins are absent and ^{99m}Tc-pyrophosphate scan demonstrates myocardial uptake, findings indicate cardiac ATTR, and patient should be referred for genetic testing to determine type of cardiac amyloidosis: ATTRwt or ATTRv. DPD = ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; ECHO = echocardiography; HMDP = hydroxymethylene diphosphonate; LV = left ventricle; PYP = pyrophosphate.

proteins are absent, the patient should undergo further assessment and possible endocardial biopsy to establish cardiac ATTR.

Finally, ^{99m}Tc-pyrophosphate grade 2 or 3 in the absence of monoclonal proteins is consistent with cardiac ATTR. The specificity and positive predictive value (probability that the patient has disease) in this scenario is nearly 100%. When the diagnosis of cardiac ATTR is based on a positive ^{99m}Tc-pyrophosphate study and negative monoclonal protein results, the patient should undergo genetic testing to differentiate between ATTRv and ATTRwt. Gene sequencing is necessary, even without a positive family history of amyloidosis or polyneuropathy, because the pharmacologic treatment is different (*3*). In addition, if ATTRv is identified, genetic counseling for the patient's relatives is indicated.

In some situations, endocardial biopsy may be required to determine the amyloidosis subtype (e.g., AL or ATTR) (*3,11*). Endomyocardial biopsy is an invasive test not without risks. However, the risk of significant complications such as cardiac tamponade, thromboembolism, severe arrhythmias, atrioventricular block, or valvular trauma is low, at 1% (*52*). With nearly 100% sensitivity and specificity, endocardial biopsy is the gold standard when noninvasive testing is equivocal or negative and there is a high suspicion of cardiac amyloidosis (*11*).

CARDIAC AMYLOIDOSIS TREATMENT

The treatment of cardiac amyloidosis follows 2 parallel tracks: managing cardiac symptoms, such as heart failure and arrhythmias, and treating the underlying type of amyloidosis (Fig. 10) (*4*).

Cardiac Symptom Management

Managing Heart Failure. Cardiac amyloidosis is a restrictive cardiomyopathy. Amyloid fibril deposition increases left ventricular thickness and stiffness, causing decreased stroke volume and cardiac output. The usual drugs to treat heart failure with reduced ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin receptor neprilysin inhibitors, β-blockers, and diuretics, are poorly tolerated in cardiac amyloidosis patients because they exacerbate hypotension

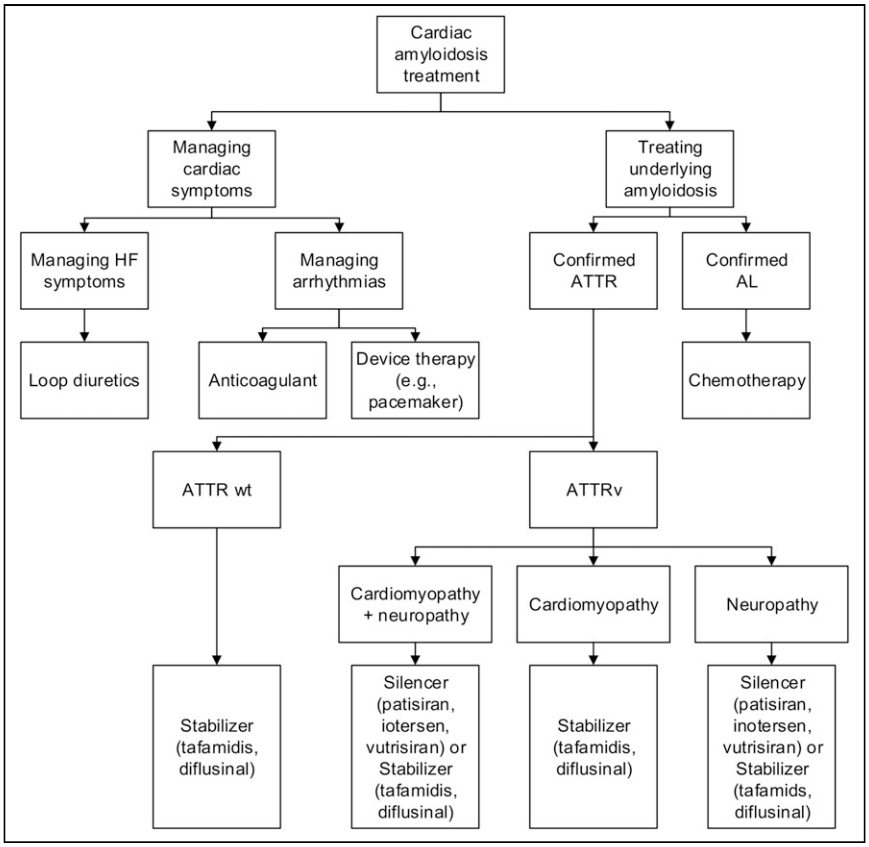

FIGURE 10. Cardiac amyloidosis treatment. Treatment of cardiac amyloidosis follows 2 parallel pathways: managing cardiac symptoms (e.g., heart failure and arrhythmias) and treatment of underlying disease process. First, AL vs. cardiac ATTR must be confirmed before plan to treat underlying disease process can be formulated. Cardiac AL is treated with chemotherapy. Treatment of cardiac ATTR depends on whether it is ATTRwt or ATTRv. Appropriate ATTRv treatment depends on whether patient has clinical manifestations of cardiomyopathy, neuropathy, or cardiomyopathy with neuropathy. ATTRwt and ATTRv are treated with transthyretin silencers (patisiran, inotersen, or vutrisiran) or stabilizers (diflunisal or tafamidis).

caused by autonomic dysfunction and decreased heart rate. Cardiac amyloidosis patients depend on heart rate response to maintain cardiac output caused by reduced stroke volume. In addition, calcium channel blockers can bind with amyloid fibrils, especially in cardiac AL, causing hypotension and syncope. Likewise, digoxin also binds to amyloid fibrils, causing digoxin toxicity, and, thus, should not be prescribed (*53*).

The appropriate treatment of HFpEF in patients with cardiac amyloidosis is administration of loop diuretics (potent diuretics that inhibit resorption of water and sodium in the renal loop of Henle). However, loop diuretics in patients with advanced cardiac amyloidosis can decrease preload (the force generated by the volume of blood returning to the heart caused by muscle stretching before contraction) and lower cardiac output. Reduced salt intake can be effective in reducing edema in these patients.

Managing Arrhythmias. Cardiac amyloidosis patients frequently develop atrial fibrillation and other atrial dysfunction. Therefore, anticoagulation is indicated to prevent thromboembolic events. The prescription of anticoagulants is also beneficial for patients with a normal sinus rhythm because these patients are at high risk for thrombus formation. Pacemakers are sometimes necessary to treat atrial arrhythmias, symptomatic bradycardia, heart block, or ventricular arrhythmias. The use of implantable cardioverter-defibrillators in cardiac amyloidosis patients is still under investigation.

Underlying Amyloidosis Treatment

Cardiac AL Treatment. After treating the effects of amyloid deposition in the heart, the next step is to treat the underlying amyloid disease. AL is caused by bone marrow plasma cell dyscrasia—the unregulated proliferation of plasma cells—that results in an overproduction of immunoglobulin light chains (*1*). Cardiac AL is markedly aggressive, with a median survival of less than 6 mo from detection in patients with heart failure. Treatment of AL involves destroying clonal plasma cells with chemotherapy, which then decreases the circulating pathologic free light chains (*53*).

Improvements in chemotherapy over the last decade have allowed most patients to attain significant reductions or near normalization of circulating light chains. A combination of antineoplastics, steroids, proteasome inhibitors (large proteins that help to destroy other cellular proteins), and immunomodulators (drugs that stimulate or suppress the immune system) is particularly effective. Autologous stem cell transplantation after high-dose chemotherapy is another option. However, a randomized trial comparing chemotherapy versus autologous stem cell transplantation found that standard chemotherapy had better outcomes (*54*).

Cardiac ATTR Treatment. Cardiac ATTR is not malignant. Therefore, chemotherapy is not warranted. Instead, the approach for ATTR relies on disease-modifying therapies, including transthyretin silencing, stabilization, and disruption (*4*).

Silencing therapies target production of transthyretin protein by the liver. The effect is a decrease in plasma transthyretin and, thus, less transthyretin to dissociate, misfold, and deposit in the heart and nerves (*11,38*). Silencers work by degrading transthyretin messenger RNA (mRNA) (*4*). The function of mRNA is to carry DNA information from the cell nucleus to the cytoplasm, where ribosomes read the mRNA sequence and synthesize protein, in this case, transthyretin (*55*). Transthyretin silencers are used to treat ATTRv with polyneuropathy.

There are 3 FDA-approved drugs available. Patisiran (Onpattro; Alnylam Pharmaceuticals, Inc), the first FDA-approved drug to treat ATTRv, is intravenously administered every 3 wk to degrade transthyretin mRNA (*4*). Inotersen (Tegsedi, Akcea Therapeutics, Inc) is a drug administered subcutaneously weekly that binds to mRNA, leading to degradation. Both patisiran and inotersen have been shown to decrease circulating transthyretin protein by over 85%. Finally, a new drug, vutrisiran (Amvuttra; Alnylam Pharmaceuticals Inc), which the FDA approved in June 2022, also degrades transthyretin mRNA, causing lower circulating transthyretin and, thus, less availability for deposition in tissues (*56*). Vutrisiran is indicated for both ATTRv and ATTRwt and is subcutaneously administered every 3 mo.

The second category of disease-modifying therapies is transthyretin stabilizers (*4*). As the name implies, stabilizers prevent the destabilization and dissociation of transthyretin monomers that misfold and aggregate into amyloid fibrils.

Two treatments are available. Diflunisal (Dolobid; Merck & Co, Inc) is a drug that relieves pain in patients with osteoarthritis. It is a nonsteroidal antiinflammatory that, in addition to its antiinflammatory properties, stabilizes transthyretin protein in vitro in patients with ATTRv with polyneuropathy. Diflunisal is prescribed off-label and administered orally with a proton pump inhibitor (stomach acid reducer) twice day. The second drug, tafamidis (Vyndaqel and Vyndamax; Pfizer Labs), was approved by the FDA in 2019 to treat ATTRv and ATTRwt. Like diflunisal, tafamidis interacts with transthyretin binding and increases tetrameric stability. Tafamidis is administered orally once a day.

The third category of disease-modifying therapy is transthyretin disruption. Silencers and stabilizers, although effective at preventing further deposition of amyloid fibrils, do little to remove the fibrils within an organ that disrupt function. Disruptors focus on clearance of amyloid fibrils from within tissues. This type of therapy is still in the research stage. Doxycycline plus tauroursodeoxycholic acid, a tetracycline antibiotic and bile acid, have been shown in preclinical studies to remove amyloid deposits. Monoclonal antibodies are another disruptor avenue of treatment under investigation.

The use of 3 disease-modifying therapy pathways depends on the presence of cardiomyopathy, the presence of cardiomyopathy with polyneuropathy, and whether a patient has ATTRv or ATTRwt. Patients with primarily cardiac manifestations of ATTRv or ATTRwt are treated with stabilizers (tafamidis). The earlier the treatment, the better to slow disease progression. Tafamidis has not been shown to benefit patients with severe (class IV) heart failure symptoms.

Patients with ATTRv and polyneuropathy are treated with either of the silencers (patisiran or inotersen). However, neither silencer is indicated for patients with ATTRwt or ATTRv without polyneuropathy.

These disease-modifying pathways for cardiac amyloidosis offer hope for treating a debilitating disease once thought incurable. However, that hope comes at a price. The drugs are costly. For example, for the 2 silencing drugs, the average wholesale price of patisiran is $414,162 per year, and inotersen is $359,840 per year. The average wholesale price of tafamidis is $225,000 annually (*4*). The cost of tafamidis for patients with Medicare part D prescription drug coverage is still prohibitive, at $18,000 per year. Diflusinal, although not as effective, at $60 per month, is often substituted in patients with asymptomatic ATTRv, patients with ATTRv not eligible for silencers, and patients with ATTRwt intolerant of or who cannot afford tafamidis.

CONCLUSION

Cardiac amyloidosis was previously believed to be rare, undiagnosable, and incurable. However, recently it has been discovered to be common, diagnosable, and treatable. This knowledge has led to a resurgence in nuclear imaging with ^{99m}Tc-pyrophosphate—a test once believed to be extinct—to identify cardiac amyloidosis, particularly in patients with HFpEF. The renewed interest in ^{99m}Tc-pyrophosphate imaging has compelled technologists and physicians to reacquaint themselves with the procedure. Although ^{99m}Tc-pyrophosphate imaging is relatively simple, procedure interpretation and diagnostic accuracy require an in-depth knowledge of cardiac amyloidosis etiology, clinical manifestations, disease progression, and treatment.

There is an adage in medicine: "If you hear hoofbeats, think horses and not zebras." Now with recent advances in noninvasive testing and treatments for cardiac amyloidosis, when patients present with signs and symptoms of HFpEF and one or more red flags, cardiac amyloidosis should be suspected because it is no longer rare to discover a cardiac amyloidosis zebra.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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