

## Society Position Statement

# Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis

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## ABSTRACT

Cardiac amyloidosis is an under-recognized and potentially fatal cause of heart failure and other cardiovascular manifestations. It is caused by deposition of misfolded precursor proteins as fibrillary amyloid deposits in cardiac tissues. The two primary subtypes of systemic amyloidosis causing cardiac involvement are immunoglobulin light chain (AL), a plasma cell dyscrasia, and transthyretin (ATTR), itself subdivided into a hereditary subtype caused by a gene mutation of the ATTR protein, and an age-related wild type, which occurs in the absence of a gene mutation. Clinical recognition requires a high index of suspicion, inclusive of the extracardiac manifestations of both subtypes. Diagnostic workup includes screening for serum and/or

## RÉSUMÉ

L'amylose cardiaque est une cause sous-reconnue et potentiellement mortelle d'insuffisance cardiaque et d'autres manifestations cardiovasculaires. Elle est causée par le dépôt, dans les tissus cardiaques, de protéines précurseurs mal repliées prenant la forme de fibrilles amyloïdes. On distingue deux grands sous-types d'amylose systémique entraînant une atteinte cardiaque : l'amylose à chaînes légères d'immunoglobulines (AL), une forme de dyscrasie plasmocytaire; et l'amylose à transthyrétine (ATTR), dont il existe un sous-type héréditaire, causé par une mutation du gène codant pour la TTR, et un sous-type à TTR sauvage, lié au vieillissement et se produisant en l'absence de mutation génique. La reconnaissance clinique nécessite

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary

experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

urine monoclonal protein suggestive of immunoglobulin light chains, along with serum cardiac biomarker measurement and performance of cardiac imaging for findings consistent with amyloid infiltration. Modern cardiac imaging techniques, including the use of nuclear scintigraphy with bone-seeking radiotracer to noninvasively diagnose ATTR cardiac amyloidosis, have reduced reliance on the gold standard endomyocardial biopsy. Disease-modifying therapeutic approaches have evolved significantly, particularly for ATTR, and pharmacologic therapies that slow or halt disease progression are becoming available. This Canadian Cardiovascular Society/Canadian Heart Failure Society joint position statement provides evidence-based recommendations that support the early recognition and optimal diagnostic approach and management strategies for patients with cardiac amyloidosis. This includes recommendations for the symptomatic management of heart failure and other cardiovascular complications such as arrhythmia, risk stratification, follow-up surveillance, use of ATTR disease-modifying therapies, and optimal clinical care settings for patients with this complex multisystem disease.

un fort degré de suspicion, fondé notamment sur la prise en compte des manifestations extracardiaques des deux sous-types. Le bilan diagnostique comprend le dosage des protéines monoclonales sériques et/ou urinaires évocatrices de chaînes légères d'immunoglobulines ainsi que la mesure de biomarqueurs cardiaques sériques et un examen d'imagerie cardiaque visant à mettre en évidence les signes d'infiltration amyloïde. Les techniques modernes d'imagerie cardiaque, y compris la scintigraphie à radiotracer ostéotrope mise en œuvre pour le diagnostic non effractif de l'amylose cardiaque ATTR, limitent le recours à la biopsie endomyocardique à titre de procédé de référence. Les traitements modificateurs de la maladie ont évolué de façon notable, tout particulièrement ceux ciblant l'amylose ATTR, et il est maintenant possible de recourir à des pharmacothérapies qui ralentissent ou stoppent l'évolution de la maladie. Cet énoncé de position commune de la Société canadienne de cardiologie et de la Société canadienne d'insuffisance cardiaque présente des recommandations fondées sur des données probantes appuyant une reconnaissance précoce de l'amylose cardiaque ainsi qu'une démarche diagnostique et une prise en charge optimales axées sur cette maladie. Au nombre des recommandations figurent notamment la prise en charge des symptômes d'insuffisance cardiaque et d'autres complications cardiovasculaires (telles que l'arythmie), la stratification du risque, le suivi des cas, le recours aux traitements modificateurs de la maladie et l'aménagement d'un cadre de soins cliniques optimal pour les patients atteints de cette maladie multisystémique complexe.

Cardiac amyloidosis refers to a group of heterogeneous disorders in which misfolded proteins assemble into fibrillar deposits in the myocardium and other cardiac structures, resulting in an infiltrative cardiomyopathy with associated heart failure (HF) symptoms. The 2 main precursor proteins leading to cardiac involvement are immunoglobulin light chains (light chain amyloidosis [AL]) and the liver-derived transport protein transthyretin (TTR, or transthyretin amyloidosis [ATTR] when causing amyloidosis), and are the focus of this position statement. Both have a similar phenotype, notable for increased left ventricular (LV) wall thickness and an ability to disguise itself clinically as common cardiovascular disease states, including HF, atrial arrhythmias, and aortic stenosis (AS). As a result, the disease is believed to be underdiagnosed, particularly ATTR, for which the true incidence and prevalence are uncertain. In autopsy studies, myocardial ATTR deposits have been identified in up to 25% of individuals older than the age of 80 years.<sup>1</sup> Noninvasive methods have identified ATTR in 13% of patients with HF with preserved ejection fraction,<sup>2</sup> 16% of patients who undergo transcatheter aortic valve replacement for severe AS,<sup>3</sup> and 5% of patients with presumed hypertrophic cardiomyopathy.<sup>4,5</sup>

A number of recent advances have raised awareness of cardiac amyloidosis and highlighted its importance in the pathophysiology of these common cardiovascular conditions. Among them, the repurposing of bone-seeking radiotracers has led to the ability, in many cases, to diagnose ATTR noninvasively; the development of effective TTR-targeted therapy is anticipated to improve the historically poor prognosis associated with this condition. At the same time, targeted therapies for AL continue to evolve, leading to improved outcomes for this disease.

It is therefore increasingly important for clinicians who provide care for patients with cardiovascular disease to recognize the signs and symptoms of cardiac amyloidosis, understand effective strategies for diagnosis, and be aware of important management advances. The objective of this position statement is to raise awareness of cardiac amyloidosis among members of the Canadian cardiovascular community and provide guidance on best practices for the diagnosis and management of this disease, while highlighting knowledge gaps and identifying areas of evolving understanding.

### Pathophysiology and Affected Populations

Although more than 30 different precursor proteins can deposit as amyloid, a limited number affect the heart.<sup>6</sup> AL, due to misfolded clonal immunoglobulin light chains, occurs in the context of plasma cell dyscrasias and other B-cell disorders. TTR (also called prealbumin) is a tetrameric protein predominantly produced by the liver and named for its role in the transport of thyroxine and retinol binding protein. The formation of amyloid from TTR can be directly attributed to mutations of the *TTR* gene (hereditary ATTR amyloidosis; hATTR), with certain variants altering protein stability, but is also observed in predominantly older patients without mutations (wild type ATTR; wtATTR). ATTR and AL amyloidosis are responsible for most of cardiac amyloidosis. Demographic profiles of these subtypes are provided in Table 1. Other amyloid precursor proteins have been identified in cardiac tissue but are exceedingly rare and/or seldom result in clinical manifestations.

Cardiac involvement is present in > 50% of patients with AL amyloidosis and confers a worse prognosis.<sup>7</sup> Direct light chain toxicity (causing lysosomal dysfunction and reactive oxygen species formation) also plays an important role in the pathophysiology of AL amyloidosis. This feature explains the

**Table 1. Demographic profiles of common subtypes of cardiac amyloidosis**

Characteristic	AL	hATTR	wtATTR
Age of onset (years)	Median age > 60	Variable, depends on genotype	Median age > 70
Sex	Slight male predominance	No clear predominance	Male predominance
Ethnic/geographic background	None	Most common gene mutations in North American: Val122Ile (West African descent), Thr60Ala (Northern Ireland descent), Val30Met (Swedish, Portuguese, Japanese descent)	None
Prevalence/incidence	Annual incidence 10 per million, increases with age	Variable, depends on genotype	Unknown, increases with age

AL, light chain amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild type transthyretin amyloidosis.

often dramatic improvement in cardiac function with effective light chain suppression.

Cardiomyopathy in ATTR is more heterogeneous and depends on the mutation, if any. The Val122Ile (pV142I) mutation is the most common cause of hATTR cardiomyopathy in North America, almost exclusively affecting individuals of African Caribbean descent, and usually presenting as isolated cardiomyopathy with mild or no neurologic involvement. This mutation is present in up to 3%-4% of African Americans, although the penetrance remains uncertain.<sup>8,9</sup> The Val30Met (pV50M) mutation is the most common cause of familial amyloid polyneuropathy in Europe and Japan, and might have a mixed phenotype with cardiac involvement. Other less common mutations with predominantly cardiac presentations include Thr60Ala (pT80A, Appalachian and Irish regions), Leu111Met (Denmark), and Ile68Leu (Italy).<sup>8</sup> Although predominantly found in older men, wtATTR is now increasingly recognized in women. Compared with AL cardiomyopathy, ATTR patients are older, often experience less severe symptoms despite having greater ventricular wall thickness, and might have lower LV ejection fraction (LVEF).

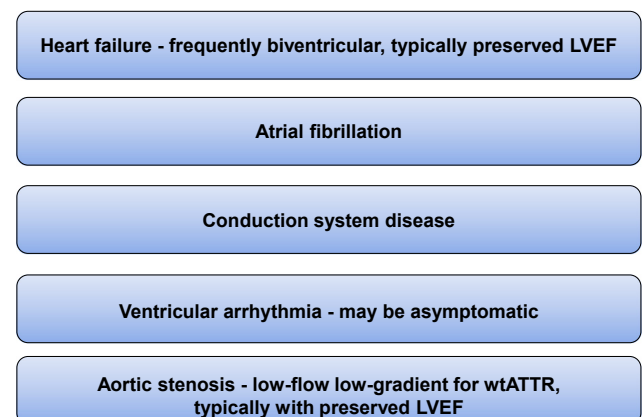
### Clinical Presentation and Manifestations

In patients with suspected cardiac amyloidosis, a thorough history and physical examination should be performed to screen for signs and symptoms of cardiovascular and extracardiovascular manifestations of the disease. HF is the most common cardiovascular presentation for AL and ATTR with cardiac involvement. This might present with predominantly left heart symptoms (dyspnea, orthopnea, paroxysmal nocturnal dyspnea), right heart symptoms (edema and/or ascites, hepatomegaly, exercise intolerance, abdominal bloating and early satiety, severe fatigue), or both. Syncope and orthostatic lightheadedness are common; the need to reduce or discontinue antihypertensive therapy in patients with a previous diagnosis of hypertension, particularly agents such as  $\beta$ -blockers or angiotensin converting enzyme (ACE) inhibitors, should prompt consideration of cardiac amyloidosis.<sup>10</sup> Conduction system disease and tachyarrhythmias are also common, particularly atrial fibrillation/atrial flutter (AF). Ventricular arrhythmias might also occur. An increased prevalence of AS, particularly low-flow low-gradient severe AS, has been reported in older patients with ATTR.<sup>3,11</sup> Amyloid deposits around coronary microvasculature can lead to angina or rarely myocardial infarction in the absence of epicardial coronary artery disease. Figure 1 shows a summary

of important cardiovascular manifestations of cardiac amyloidosis.

Extracardiac manifestations (Table 2) might be an important indicator of the presence of cardiac amyloidosis and its subtype. Symptoms of dysautonomia, including postural hypotension; gastrointestinal manifestations such as gastroparesis, diarrhea and/or constipation; sweating abnormalities; and erectile dysfunction, are common to both subtypes. Peripheral neuropathy can also manifest with both subtypes, and is the primary presentation of many hATTR genotypes. The typical presentation is that of a bilateral sensorimotor polyneuropathy that begins in the lower limbs and follows an ascending pattern.<sup>10</sup> Carpal tunnel syndrome is very common and frequently bilateral. In many ATTR patients, carpal tunnel syndrome manifests several years in advance of cardiac manifestations.<sup>5,6</sup> Lumbar spinal stenosis, a history of multiple orthopaedic procedures, and spontaneous biceps tendon rupture are also common in wtATTR.<sup>5</sup> Other noteworthy extracardiac manifestations of AL include spontaneous bleeding or bruising (commonly in the periorbital regions), soft tissue manifestations such as macroglossia, renal insufficiency, and nephrotic syndrome. Renal involvement is typically less significant in ATTR, and chronic kidney disease is more often a consequence of HF.

**Practical tip.** ATTR cardiac amyloidosis is in general a slowly progressive disorder that is most common in older men. In comparison, AL cardiac amyloidosis generally has a more rapidly progressive course, a relatively younger age of onset, and less of a male predominance.



**Figure 1.** Cardiovascular manifestations of cardiac amyloidosis. LVEF, left ventricular ejection fraction; wtATTR, wild type transthyretin amyloidosis.

**Table 2. Extracardiac manifestations of common subtypes of cardiac amyloidosis**

Manifestation	AL	hATTR	wtATTR
Renal	<ul style="list-style-type: none"><li>• Renal insufficiency</li><li>• Nephrotic syndrome</li></ul>	<ul style="list-style-type: none"><li>• Milder renal insufficiency (mainly due to heart failure)</li></ul>	
Autonomic		<ul style="list-style-type: none"><li>• Orthostatic hypotension</li><li>• Gastroparesis</li><li>• Sexual dysfunction</li><li>• Sweating abnormalities</li></ul>	
Neurologic	<ul style="list-style-type: none"><li>• Peripheral sensorimotor neuropathy (might be predominant feature of hATTR, and relatively mild or absent for wtATTR)</li></ul> <hr/> <ul style="list-style-type: none"><li>• Carpal tunnel syndrome (bilateral)</li></ul> <hr/> <ul style="list-style-type: none"><li>• Spinal stenosis (predominantly lumbar)</li></ul>		
Musculoskeletal		<ul style="list-style-type: none"><li>• Muscle weakness</li><li>• Arthropathy</li><li>• Fatigue</li><li>• Cachexia/weight loss</li></ul> <hr/> <ul style="list-style-type: none"><li>• Pseudohypertrophy (ie, macroglossia)</li></ul> <hr/> <ul style="list-style-type: none"><li>• Biceps tendon rupture</li></ul>	
Gastrointestinal	<ul style="list-style-type: none"><li>• Elevated liver enzymes</li><li>• Nausea, constipation, early satiety, abdominal bloating (gastroparesis might be secondary to dysautonomia and/or gastrointestinal involvement)</li></ul>		
Hematologic	<ul style="list-style-type: none"><li>• Bleeding and easy bruising (ie, periorbital)</li></ul>		
Ocular manifestations	<ul style="list-style-type: none"><li>• Vitreous opacities</li></ul>		

AL, light chain amyloidosis; hATTR, hereditary transthyretin amyloidosis; wtATTR, wild type transthyretin amyloidosis.

This writing panel has identified 5 features considered to be of particular importance for raising suspicion for cardiac amyloidosis in the presence of signs and symptoms of HF (Fig. 2). It is important to note that one or more of these features might be present, but also that their absence does not exclude the presence of cardiac amyloidosis. A high index of suspicion in patients with progressive HF symptoms without an identified cause is imperative to avoid delays in diagnosis.

**RECOMMENDATION**

1. We recommend diagnostic workup for cardiac amyloidosis for patients who present with signs and symptoms of HF who have one or more of the following features: (1) unexplained increased LV wall thickness; (2) older than 60 years of age with low-flow low-gradient AS and LVEF > 40%; (3) unexplained peripheral sensorimotor neuropathy and/or dysautonomia; (4) history of bilateral carpal tunnel syndrome; and (5) established AL or ATTR amyloidosis (Strong Recommendation, Moderate-Quality Evidence).

**Evaluation of Suspected Cardiac Amyloidosis**

Because the cardiovascular signs and symptoms are nonspecific, suspicion for cardiac amyloidosis is often raised after performance of standard investigations for HF. These include routine laboratory testing, 12-lead electrocardiogram (ECG), troponin and B-type natriuretic peptide (BNP)/N-terminal proBNP (NTproBNP), and cardiac imaging, typically transthoracic echocardiography. Patients with findings suggestive of cardiac amyloidosis on initial investigations should undergo confirmatory testing (Fig. 3). Classic ECG

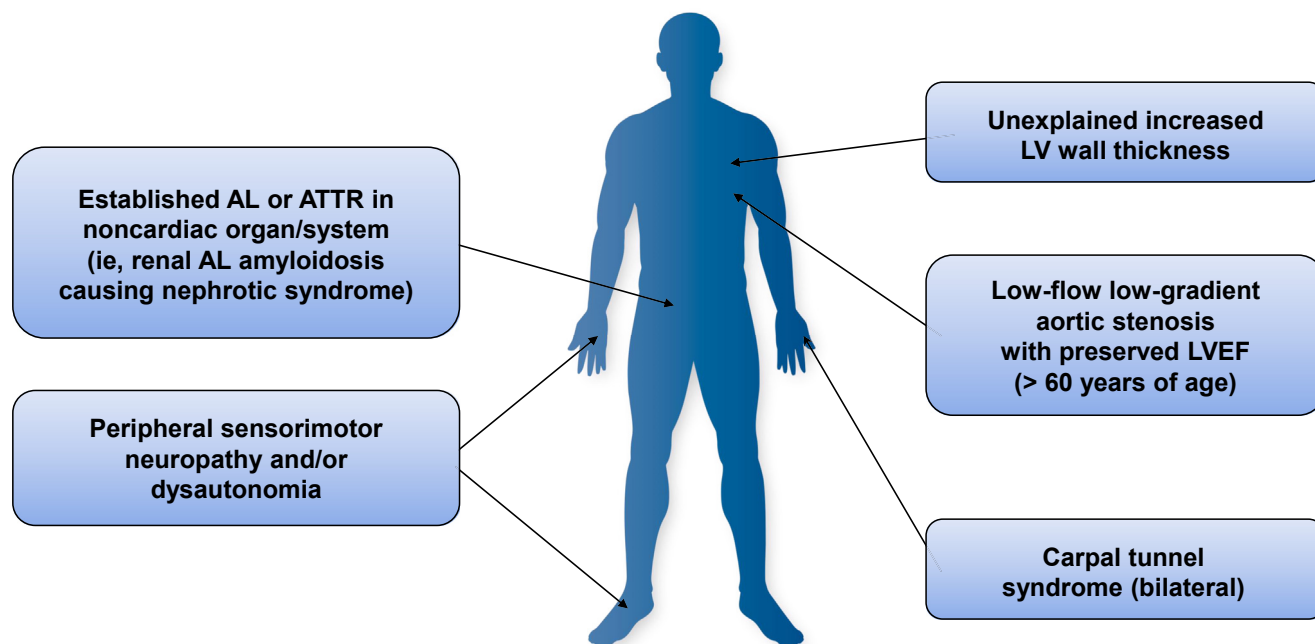
findings are well described, and include low QRS voltage, especially in the limb leads, and a pseudoinfarct pattern.<sup>12</sup> The sensitivity of these findings are low however, and the combination of disproportionately low QRS voltage on ECG and increased LV wall thickness on cardiac imaging occurs more often.<sup>13</sup> The presence of ECG criteria for LV hypertrophy does not rule out cardiac amyloidosis.<sup>5</sup> Other nonspecific findings include AF, conduction system abnormalities, and ventricular ectopy. Serum cardiac biomarkers troponin and BNP/NTproBNP are often persistently elevated in patients with cardiac amyloidosis, and frequently elevated disproportionately to the degree of clinical HF.

**RECOMMENDATION**

2. We recommend performance of routine investigations for the evaluation of HF in patients who present with suspected cardiac amyloidosis, including 12-lead ECG, troponin, and BNP/NTproBNP (Strong Recommendation, Moderate-Quality Evidence).

When suspicion of cardiac amyloidosis is raised, performance of screening tests for AL amyloidosis is critical. This includes serum and urine protein electrophoresis with immunofixation and serum free light chain (sFLC) assay. Serum protein electrophoresis and urine protein electrophoresis alone cannot exclude AL because small amounts of monoclonal protein might not be detectable, and therefore immunofixation and sFLC assay are both necessary.<sup>6</sup> The presence of monoclonal protein, and in particular an abnormal sFLC kappa/lambda ratio, should raise suspicion for AL and warrants further investigation. Patients with

## SUSPECT CARDIAC AMYLOIDOSIS WHEN NEW ONSET HEART FAILURE WITH $\geq 1$ OF THE FOLLOWING



**Figure 2.** Key clinical features to heighten index of suspicion and trigger a diagnostic workup for cardiac amyloidosis. AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; LVEF, left ventricular ejection fraction.

chronic renal insufficiency often have mildly elevated serum free kappa and lambda light chain levels (with a preserved ratio) in the absence of plasma cell dyscrasia. Concomitant monoclonal gammopathy of undetermined significance is also common in older patients with wtATTR, but when suspected a malignant plasma cell dyscrasia must be excluded through subtyping of amyloid deposits on biopsied tissue. Patients with a confirmed diagnosis of AL amyloidosis require urgent hematology referral.

### RECOMMENDATION

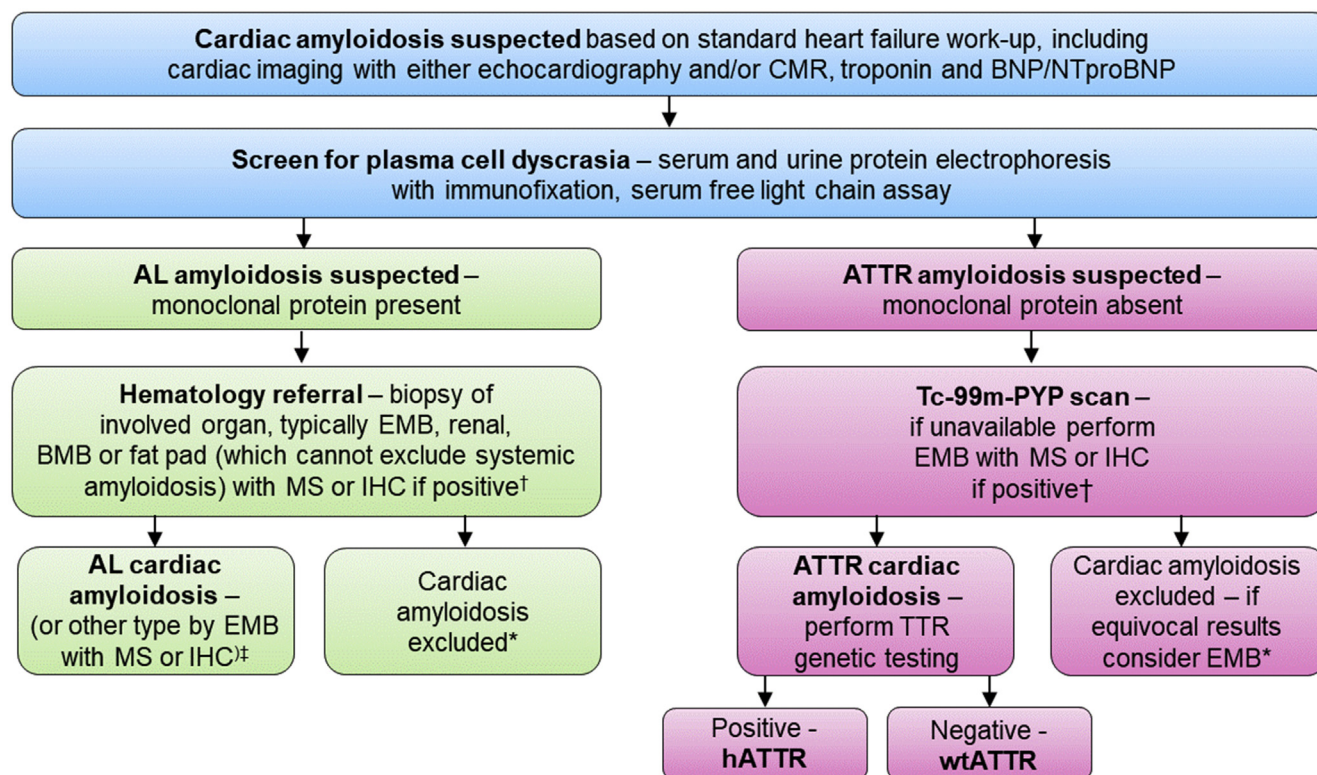
3. We recommend that serum and urine protein electrophoresis with immunofixation and sFLC assay be performed in all patients with suspected cardiac amyloidosis to evaluate for possible AL amyloidosis or other plasma cell dyscrasia (Strong Recommendation, Moderate-Quality Evidence).

Cardiac imaging plays a critical role in the diagnostic evaluation of patients with suspected cardiac amyloidosis (Fig. 4). Conventional echocardiographic findings associated with cardiac amyloidosis include a small or normal LV chamber size, increased biventricular wall thickness and cardiac valve thickness, diastolic dysfunction, and small pericardial effusion. Each of these findings is nonspecific and

might not be present, particularly in the early stages. In the absence of another cause, increased LV wall thickness  $> 1.2$  cm warrants further investigation and consideration of an infiltrative disorder.<sup>14</sup> Increased LV wall thickness is typically symmetrical, however asymmetric patterns have also been reported.<sup>15</sup> LVEF is typically preserved, however might be reduced, which might be a late finding and more commonly occurs in wtATTR. Diastolic dysfunction is expected, but restrictive physiology by Doppler assessment might be a relatively late finding. LV longitudinal systolic strain measurement using speckle-tracking echocardiography showing reduced global longitudinal strain with apical sparing (base to apical gradient) is a relatively more specific finding and can be helpful for differentiating cardiac amyloidosis from other causes of increased LV wall thickness.<sup>13,16</sup>

Cardiovascular magnetic resonance imaging (CMR) is highly valuable for the evaluation of suspected cardiac amyloidosis, because of its superior spatial resolution and tissue characterization capabilities. Findings associated with cardiac amyloidosis include late gadolinium enhancement (LGE) in a diffuse transmural or subendocardial pattern, although other patterns might be present.<sup>14</sup> Although a subendocardial LGE pattern might be more prevalent with AL and a transmural pattern with ATTR, respectively, CMR cannot reliably differentiate subtype.<sup>17</sup> Elevated native (noncontrast) T1 mapping time and post contrast extracellular volume expansion are highly sensitive





**Figure 3.** Diagnostic algorithm for the evaluation of suspected cardiac amyloidosis. \* Endomyocardial biopsy should be performed if noninvasive evaluation is equivocal or negative despite a high index of clinical suspicion. † Tissue biopsy analysis includes Congo red staining for amyloid deposits. ‡ A diagnosis of AL cardiac amyloidosis should prompt urgent hematology referral. AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; BMB, bone marrow biopsy; BNP, B-type natriuretic peptide; CMR, cardiovascular magnetic resonance imaging; EMB, endomyocardial biopsy; hATTR, hereditary transthyretin amyloidosis; IHC, immunohistochemistry; MS, mass spectrometry; NTproBNP, N-terminal pro-B-type natriuretic peptide; PYP, pyrophosphate; wtATTR, wild type transthyretin amyloidosis.

## RECOMMENDATION

- We recommend echocardiography with longitudinal LV strain measurement, or CMR with LGE and T1 mapping imaging be performed in all patients with suspected cardiac amyloidosis to evaluate for characteristic features of cardiac amyloidosis or alternative causes of HF (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** Although findings on echocardiography and/or CMR might be highly consistent with cardiac amyloid infiltration, in isolation these tests are generally not considered confirmatory of the diagnosis, and neither test can reliably differentiate subtype. The choice of echocardiography and/or CMR should take into account local availability, expertise, and contraindications to CMR including advanced renal dysfunction for LGE imaging.

**Values and preferences.** In the setting of a subtype-confirmed diagnosis of systemic amyloidosis (AL or ATTR) on the basis of noncardiac tissue biopsy, characteristic findings on echocardiography and/or CMR combined with clinical and serum biomarker assessment might be sufficient to conclude the presence of cardiac involvement without the need for further testing.

quantitative techniques associated with cardiac amyloid deposition.<sup>18,19</sup>

Nuclear scintigraphy with bone-seeking radiotracer has a high level of diagnostic accuracy for confirming ATTR cardiac amyloidosis in the absence of monoclonal protein.<sup>20,21</sup> In the presence of a positive result, defined as grade 2 or higher uptake (greater than or equal to bone uptake), or a heart to contralateral lung uptake ratio  $\geq 1.5$ , a diagnosis of ATTR cardiac amyloidosis can be made without the need for tissue biopsy after monoclonal protein has been excluded.<sup>21</sup> <sup>99m</sup>Tc-labelled compounds including pyrophosphate, 3,3-diphosphono-1,2-propanodicarboxylic acid, and hydroxymethylene-diphosphonate are all highly sensitive for this indication, even for early stage disease,<sup>14</sup> although only <sup>99m</sup>Tc-pyrophosphate is available in Canada. The use of single-photon emission computed tomography imaging is recommended for all patients in conjunction with planar imaging, and can help differentiate myocardial uptake from overlying bone or blood pool signal. Single-photon emission computed tomography can also help differentiate the regional myocardial uptake seen in patients with a history of myocardial infarction from the diffuse myocardial uptake typical of ATTR, improving diagnostic accuracy in this setting.<sup>14</sup>

**RECOMMENDATION**

5. We recommend performance of nuclear scintigraphy with bone-seeking radiotracer (if available) to evaluate for cardiac involvement when ATTR cardiac amyloidosis is suspected after exclusion of AL (Strong Recommendation, Moderate-Quality Evidence).

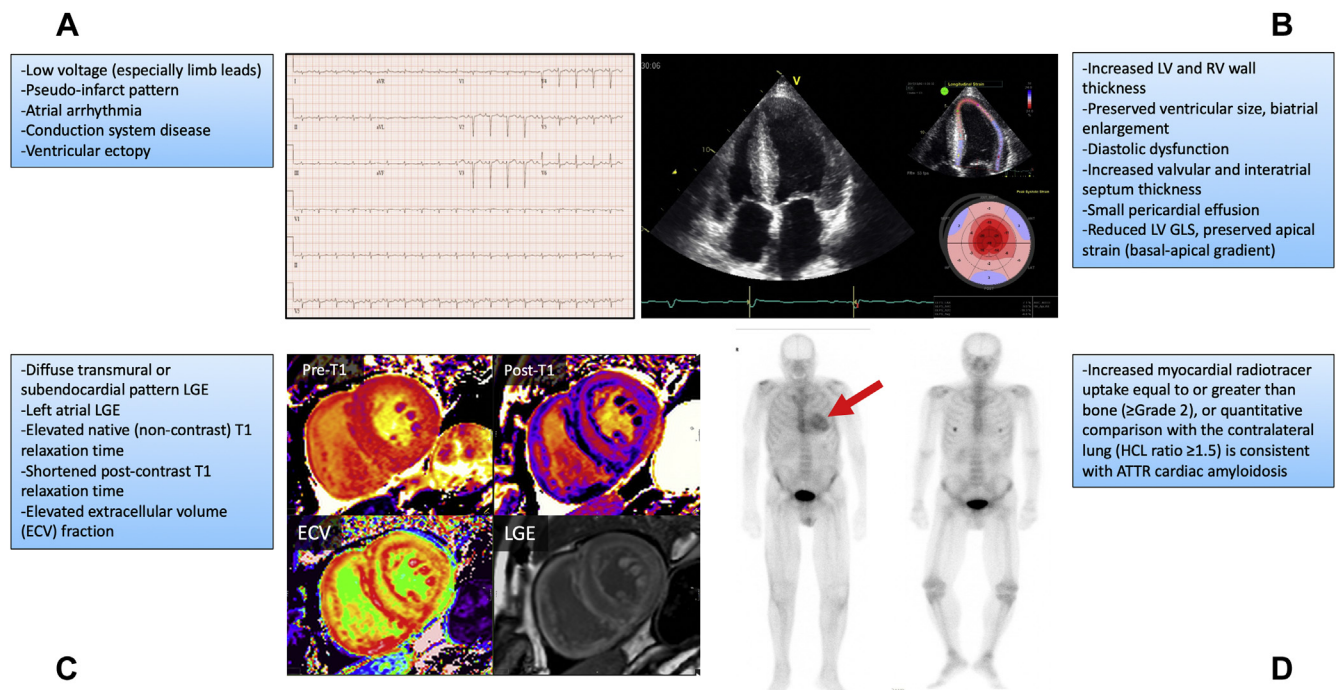
**Practical tip.** Patients with AL cardiac amyloidosis (or other rare non-ATTR subtypes) might have radiotracer uptake by nuclear scintigraphy, and a positive scan does not exclude AL. Serum and urine screening for monoclonal protein (as described earlier) is required for all patients with suspected cardiac amyloidosis.

Endomyocardial biopsy remains the diagnostic gold standard for all subtypes and should be performed when noninvasive evaluation yields equivocal results or clinical suspicion remains high despite a negative workup. Biopsy samples should be stained with Congo red, with amyloid deposits showing green birefringence when viewed under polarized light.<sup>7</sup> Identification of subtype requires immunohistochemistry, immunofluorescence, or laser microdissection with mass spectrometry, the latter of which is now more commonly

used to identify the misfolded precursor protein.<sup>22</sup> These techniques are not widely available and should only be performed in laboratories with significant expertise. The diagnosis of AL amyloidosis requires tissue biopsy confirmation. Patients with monoclonal protein identified using screening tests often undergo bone marrow biopsy to exclude concurrent multiple myeloma, which might stain positive for amyloid deposits. Biopsy of remote sites (such as abdominal fat pad, rectum, colon, or other soft tissue) have variable diagnostic yield but might obviate the need for endomyocardial biopsy when positive and combined with imaging evidence of cardiac involvement. Direct biopsy of a clinically involved organ has the highest sensitivity.

**RECOMMENDATION**

6. We recommend the performance of endomyocardial biopsy for diagnosis and subtyping with mass spectrometry or immunohistochemistry/immunofluorescence (if available) when the existing diagnostic workup for cardiac amyloidosis is equivocal or discordant with clinical suspicion (Strong Recommendation, Low-Quality Evidence).



**Figure 4.** Findings on cardiovascular investigations associated with cardiac amyloidosis along with representative examples. **(A)** Typical electrocardiogram findings and representative example. **(B)** Echocardiogram findings, with imaging from the apical 4-chamber view (**left image**) showing biventricular wall thickening, preserved ventricular size, valve thickening, and biatrial enlargement, with longitudinal strain measurement on speckle-tracking echocardiography (**top right**) showing preserved apical strain with impaired basal and middle segment values (**bottom right**). **(C)** Cardiovascular magnetic resonance imaging findings with representative examples showing diffuse elevation in native T1 (no contrast; Pre-T1) mapping (**top left**), reduction in post contrast T1 (Post-T1) mapping (**top right**), increased extracellular volume (ECV; **bottom left**), and subendocardial late gadolinium enhancement (LGE) of the left and right ventricles (**bottom right**). **(D)** <sup>99m</sup>Tc-pyrophosphate nuclear scintigraphy showing increased myocardial uptake in a patient with transthyretin cardiac amyloidosis (**red arrow, left panel**) and absent myocardial uptake in a patient without this diagnosis (**right panel**). GLS, global longitudinal strain; HCL, heart/contralateral lung ratio; LV, left ventricular; RV, right ventricular. Cardiovascular magnetic resonance images in **(C)** provided courtesy of Dr James White, University of Calgary, and nuclear scintigraphy images in **(D)** provided courtesy of Dr Denise Chan, University of Calgary.

**Practical tip.** Abdominal fat pad aspirate/biopsy and bone marrow biopsy are less invasive approaches for detecting systemic amyloidosis compared with biopsy of organs with suspected involvement, however, have a relatively lower diagnostic yield. The reported yield of abdominal fat pad biopsy in cardiac amyloidosis ranges from 15% to 84%, depending on subtype, and is highest for AL.<sup>23</sup> A negative result does not exclude the diagnosis in patients with suspected cardiac amyloidosis.

When ATTR is confirmed, genetic sequencing to differentiate hATTR from wtATTR should be performed. This has relevance for prognostic assessment, the likelihood of extracardiac involvement, the need for family member screening, and eligibility for novel ATTR-targeted therapies. When a TTR gene mutation is identified, referral for genetic counselling is recommended.

**RECOMMENDATION**

7. For patients with a diagnosis of ATTR cardiac amyloidosis, we recommend the performance of genetic testing to differentiate hATTR from wtATTR (Strong Recommendation, Moderate-Quality Evidence).

**Management of Cardiac Amyloidosis**

The management of cardiac amyloidosis can be divided into 2 parallel pathways (Fig. 5): (1) management of end-organ sequelae, including HF and arrhythmias; and (2) prevention of further amyloid deposition with disease-modifying therapies.

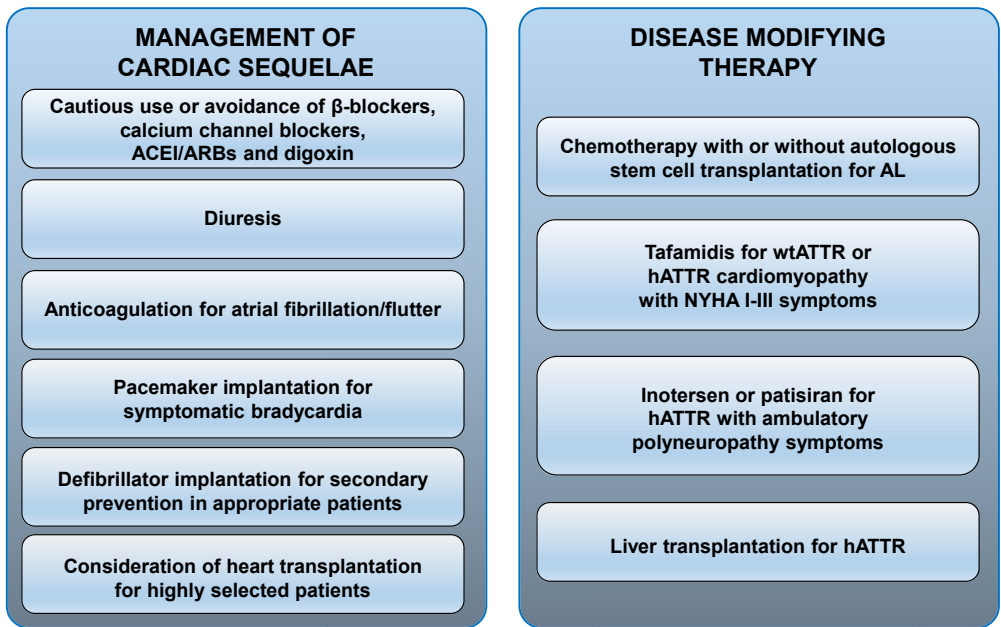
**Management of HF symptoms**

The physiology of cardiac amyloidosis involves progression to restrictive cardiomyopathy coupled with variable degrees of autonomic dysfunction. These factors often lead to poor tolerability of many common agents used to treat HF, including  $\beta$ -blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and digoxin. Although data regarding the safety and efficacy of traditional HF therapies are limited, dietary sodium restriction and diuresis (using loop diuretics, mineralocorticoid receptor antagonists, and thiazide diuretics as needed) are considered the mainstay of HF supportive management.

**Practical tip.**  $\beta$ -Blockers, ACE inhibitors, and angiotensin receptor blockers are frequently poorly tolerated by patients with cardiac amyloidosis, and if indicated should be used with considerable caution. Furthermore, limited data and reports suggest an increased risk of local toxicity with digoxin and calcium channel blockers<sup>24,25</sup> and these medications should be similarly used with caution or avoided altogether if possible.

**Advanced HF therapies**

In cardiac amyloidosis patients with refractory HF symptoms, advanced therapies may be considered. Contemporary data series indicate that outcomes after heart transplantation in carefully selected patients with ATTR and AL are similar to those in other patients.<sup>26,27</sup> Long-term outcomes, particularly for AL patients, have not been reported in the modern era. Selection criteria have been published by several institutions and typically involve exclusion of clinically relevant extracardiac involvement.<sup>28,29</sup> In AL patients, autologous stem cell transplantation (ASCT) has been performed after successful heart transplantation, although some centres reserve this



**Figure 5.** Parallel management pathways in cardiac amyloidosis. ACEI, angiotensin converting enzyme inhibitor; AL, light chain amyloidosis; ARB, angiotensin receptor blocker; hATTR, hereditary transthyretin amyloidosis; NYHA, New York Heart Association; wtATTR, wild type transthyretin amyloidosis.



approach for patients in whom adequate light chain control cannot be achieved with chemotherapy alone.<sup>28,29</sup> Liver transplantation can be performed as a disease-modifying therapy for hATTR by halting production of mutant TTR protein, and this approach has been more commonly used to treat familial amyloid polyneuropathy. Heart-liver transplantation (combined or sequentially) has been performed with success in patients with hATTR with cardiac involvement.<sup>30</sup> The advent of effective TTR-targeted medical therapies might reduce the need for liver transplantation in this setting. The use of durable LV assist devices has not been well studied in cardiac amyloidosis, however, small case series suggest that outcomes might be inferior compared with patients with dilated cardiomyopathy, particularly when LV size is small.<sup>31</sup> To date, consensus criteria to improve patient selection are lacking and the role of LV assist device therapy for cardiac amyloidosis remains uncertain.

## RECOMMENDATION

8. We recommend that heart transplantation be considered for select patients with advanced HF due to cardiac amyloidosis, in whom significant extracardiac manifestations are absent and the risk of disease progression is considered low and/or amenable to disease-modifying therapy (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** Although older reports identified poor outcomes among cardiac amyloidosis patients who received heart transplants, contemporary reports generally indicate similar short- and intermediate-term outcomes to other heart transplant recipients. This is likely because of advances in light chain-directed therapy in AL and improved patient selection.

## Arrhythmias and thromboembolic risk

Atrial arrhythmias are common in patients with cardiac amyloidosis. There are no data to inform the choice between a rate or rhythm control strategy. Traditional rate controlling medications are often poorly tolerated and amiodarone might be the best tolerated agent. The long-term efficacy of rhythm control strategies, including left atrial catheter ablation, is uncertain although might be poor because of diffuse atrial amyloid deposition.<sup>32</sup> Cardiac amyloidosis patients with AF are at a particularly high risk of left atrial thrombus and thromboembolic events.<sup>33</sup> Left atrial thrombus has been reported in patients receiving therapeutic anticoagulation and in patients in sinus rhythm.<sup>33,34</sup> There are no data to support a specific anticoagulation strategy.

## RECOMMENDATION

9. In the absence of contraindications, we recommend therapeutic anticoagulation in patients with cardiac amyloidosis and AF, regardless of calculated risk of stroke or systemic embolism (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** Cardiac amyloidosis appears to be associated with a particularly high rate of left atrial thrombus, stroke, and systemic embolism. This risk is not captured by risk scores such as CHADS<sub>2</sub>65 or CHA<sub>2</sub>DS<sub>2</sub>-VASc.

**Practical tip.** There are no data to inform the choice between warfarin and direct oral anticoagulants, which might be preferable because of the ease of administration and relatively lower risk of intracranial hemorrhage shown in other cardiovascular disease populations.

**Practical tip.** In patients with cardiac amyloidosis, high rates of left atrial thrombus have been reported on imaging and at autopsy, even in patients with adequate durations of therapeutic anticoagulation or with brief durations of AF. Thrombus has also been reported in patients in sinus rhythm. Transesophageal echocardiography should be considered before cardioversion in stable patients, regardless of duration of arrhythmia or anticoagulation.

Conduction system disease is also highly prevalent in patients with cardiac amyloidosis. A high rate of progression to complete heart block has been reported in hATTR patients undergoing prophylactic pacemaker implantation,<sup>35</sup> and case series have reported improved symptoms after pacemaker implantation for bradycardia.<sup>36</sup> The use of cardiac resynchronization therapy has not been examined. Cardiac amyloidosis patients are also at a high risk of sudden cardiac death. This might be mediated by ventricular arrhythmias, bradyarrhythmias (commonly complete heart block), or pulseless electrical activity.<sup>37</sup> It has not been shown that device therapy (pacemaker and/or implantable cardioverter-defibrillator [ICD]) improves survival. Nonetheless, appropriate shocks have been reported in up to 32% of cardiac amyloidosis patients who received ICDs,<sup>38</sup> most for secondary prevention indications. Clear criteria for primary prevention device therapy have not been identified.

**Practical tip.** Although there is a high rate of progression of conduction system disease in patients with cardiac amyloidosis, evidence does not support the routine prophylactic use of pacemakers in patients who do not otherwise meet standard guideline indications. Although a large proportion of deaths might be preceded by bradycardia, including complete heart block, it is not known whether pacemakers improve survival.

**Practical tip.** Criteria for primary prevention ICDs have not been clearly identified. In particular, there is no evidence showing benefit of ICDs for primary prevention of sudden cardiac arrest/death in cardiac amyloidosis patients with LVEF ≤ 35%. We suggest that ICDs be offered to patients with standard indications for secondary prevention, and that an individualized approach be used for primary prevention.

## Disease-modifying therapy

In AL, disease progression is attenuated by suppression of abnormal free light chain production. Untreated, AL cardiac amyloidosis is a rapidly progressive disease with a dismal prognosis. Timely diagnosis and initiation of therapy is

essential for good outcomes. Although a comprehensive discussion of AL-directed therapies is beyond the scope of this document, management typically consists of chemotherapy with consideration for ASCT in eligible patients.

In ATTR, disease progression can be slowed or prevented by novel TTR-targeted therapies (Fig. 6). Tafamidis is an oral TTR stabilizer that binds to TTR tetramers in circulation and prevents their breakdown into unstable amyloidogenic monomers. In the Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), 441 patients with ATTR cardiomyopathy (76% wtATTR, 24% hATTR) and New York Heart Association (NYHA) functional class I-III symptoms were randomized to tafamidis or placebo.<sup>39</sup> Over 30 months, tafamidis was associated with a 32% reduction in mortality and a 30% reduction in cardiovascular hospitalization. Tafamidis was well tolerated, and was also associated with improved quality of life and 6-minute walk distance scores compared with placebo.

## RECOMMENDATION

10. We recommend tafamidis (if available) for patients with ATTR cardiac amyloidosis and NYHA class I-III symptoms (Strong Recommendation, High-Quality Evidence).

**Practical tip.** The ATTR-ACT trial included patients with NTproBNP levels > 600 pg/mL and excluded patients with NYHA class IV symptoms or severe functional disability, measured using a 6-minute walk distance < 100 m, representing criteria that should be considered when determining eligibility for treatment.

**Practical tip.** Subgroup analysis from the ATTR-ACT trial suggested that the reduction in cardiovascular hospitalization associated with tafamidis is greatest for patients with NYHA class I-II symptoms.

Inotersen and patisiran are TTR RNA silencing agents that prevent the hepatic production of TTR protein. Inotersen is an antisense oligonucleotide and patisiran is a small interfering RNA molecule. Both agents have been studied in phase III clinical trials involving ambulatory patients with hATTR and polyneuropathy symptoms. In the Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy (NEURO-TTR) trial, 172 patients were randomized to subcutaneous inotersen or placebo.<sup>40</sup> After 15 months, patients randomized to inotersen had significantly better neurologic function and quality of life compared with placebo. In the A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (APOLLO) trial, 225 patients were randomized to intravenous patisiran or placebo.<sup>41</sup> Over 18 months, neurologic function and quality of life for patients in the patisiran arm were improved compared with placebo. Neither of these agents has been tested in patients with wtATTR, and neither trial confirmed the presence of cardiac involvement with biopsy or scintigraphy. A prespecified subgroup analysis of 126 APOLLO patients with unexplained LV wall thickening suggestive of cardiac amyloidosis showed reductions in mean LV wall thickness, global longitudinal

## RECOMMENDATION

11. We recommend treatment with a TTR RNA silencing agent (patisiran or inotersen) for patients with hATTR amyloidosis with ambulatory polyneuropathy (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** To date, randomized placebo-controlled clinical trials of TTR silencers have only included patients with hATTR polyneuropathy and have examined their efficacy with respect to neurologic outcomes. Cardiac outcomes have not been rigorously studied in patients receiving TTR silencers, and cardiac subpopulations in trials of these agents did not undergo testing to confirm cardiac involvement.

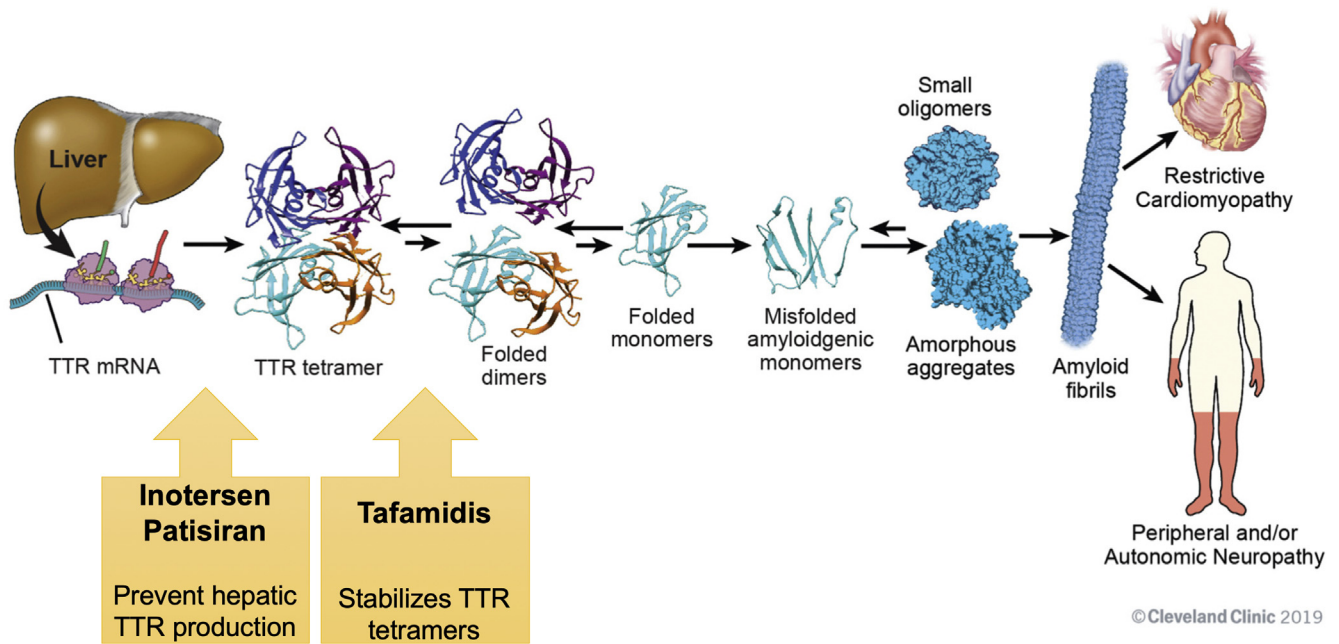
strain, and NTproBNP, and a trend toward lower rates of mortality and cardiac hospitalizations among patients randomized to patisiran compared with placebo.<sup>42</sup>

**Practical tip.** In hATTR patients with a mixed phenotype (polyneuropathy and cardiomyopathy), the decision to use tafamidis or a TTR silencer should be individualized and is best undertaken by a multidisciplinary team including a cardiologist and a neurologist, considering variables including availability, toxicity profile, ease of administration, and dominant phenotype. The efficacy and safety of combination therapy with tafamidis and TTR silencing therapy has not been evaluated.

Other potentially disease-modifying agents that have been examined in limited off-label studies in patients with cardiac amyloidosis (Supplemental Table S1) include: diflunisal,<sup>43</sup> combination doxycycline and either tauroursodeoxycholic acid (TUDCA) or ursodeoxycholic acid (ursodiol),<sup>44</sup> and epigallocatechin 3-gallate (EGCG; green tea extract).<sup>45</sup> Diflunisal is a nonsteroidal anti-inflammatory drug that stabilizes TTR, has shown benefit for treatment of hATTR polyneuropathy, and is generally well tolerated except in patients with significant renal insufficiency or those at high risk for decompensated HF. The latter 2 therapies have shown amyloid fibril inhibition or degradation properties *in vivo* and might have efficacy for patients with either AL or ATTR. Although none of these therapies have been rigorously tested, they might represent a therapeutic alternative for patients for whom approved therapies are not available. The safety and efficacy of combination therapies involving these agents have not been evaluated.

## Follow-up and monitoring

As disease-modifying therapy evolves, it has become increasingly important to develop methods for measuring response to therapy. In AL amyloidosis, cardiac response to therapy is defined by changes in cardiac biomarkers, NYHA class, and imaging parameters.<sup>46</sup> The use of such biomarkers is less well defined in patients with ATTR. Imaging parameters that might prove useful in AL and/or ATTR include changes in LV wall thickness and global longitudinal strain using echocardiography and changes in LV mass, T1 mapping, and extracellular volume values in CMR.<sup>6,14,46</sup> Further studies are needed to define optimal surveillance strategies.



**Figure 6.** Disease-modifying therapies for transthyretin amyloidosis. TTR, transthyretin. Modified from Ruberg et al.<sup>6</sup> with permission from Elsevier.

## RECOMMENDATION

12. We recommend that serial imaging with echocardiography or CMR in addition to measuring BNP/NTproBNP levels be used to monitor cardiac disease progression and/or response to therapy in patients with cardiac amyloidosis (Strong Recommendation, Low-Quality Evidence).

**Practical tip.** The optimal monitoring frequency of serial cardiac imaging using echocardiography or CMR is uncertain, with most reports suggesting a range between every 6-48 months, and/or in the setting of clinical deterioration. A comprehensive approach to interpreting imaging findings integrated with clinical and serum biomarker data is suggested. Nuclear scintigraphy with bone-seeking radiotracer is presently not recommended to monitor disease progression and/or response to therapy.

## Considerations for Clinical Care

Amyloidosis is a multisystem disease and patients frequently have complex management considerations. The diagnosis is associated with a high level of anxiety in many patients, in part because of confusion around different disease subtypes and lengthy delays to diagnosis because of low physician awareness. Patients with wtATTR are also typically older and might have a significant comorbid disease burden, further complicating their care.

Amyloidosis is considered a rare disease. Many specialists will have limited exposure and might not have access to subspecialty consultation, novel therapies, or clinical trial opportunities. Where possible, the centralization of care among specialists with expertise in amyloidosis might have

significant benefits. In particular, it might be beneficial for ATTR patients to be followed in a setting with access to neuromuscular disease experts to enable decision-making regarding TTR-targeted therapy. The patient complexity suggests that support from nursing and pharmacy is likely to be beneficial.

## RECOMMENDATION

13. We recommend that comprehensive interdisciplinary management be offered to patients with established cardiac amyloidosis (Strong Recommendation, Very Low-Quality Evidence).

**Values and preferences.** Care provided by multidisciplinary teams has not been rigorously studied. Centres with access to multidisciplinary care should consider patient referral to appropriate subspecialty services to ensure adequate management of multisystem disease and access to novel therapies and clinical trials, which are more likely to be offered in these settings. This might not be feasible in many centres.

The prognosis of cardiac amyloidosis at the time of diagnosis can vary widely, dependent on subtype and the extent of cardiac and extracardiac involvement. Cardiac troponin and natriuretic peptide levels are among the strongest predictors of survival in AL amyloidosis<sup>47,48</sup> and ATTR.<sup>49,50</sup> In AL amyloidosis, a staging system involving cardiac biomarkers developed at the Mayo Clinic, and subsequently revised to incorporate sFLC levels, has been validated and is widely used to risk-stratify patients and identify those who might be eligible for ASCT.<sup>48</sup> For ATTR cardiomyopathy, staging systems have also been developed,<sup>49,50</sup> although they are not as widely used as the Mayo Clinic system for AL.

## RECOMMENDATION

14. We recommend that a validated, serum biomarker-based staging system, inclusive of troponin and/or BNP/NTproBNP, be used to risk-stratify patients with cardiac amyloidosis (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** The revised Mayo Clinic staging system is well validated and widely used to risk-stratify patients with AL amyloidosis (Supplemental Table S2). Staging systems for ATTR cardiomyopathy have not been as well validated and no single system is used consistently, however serum biomarker-based ATTR-specific staging systems have been developed. Multiple cardiac imaging parameters have also shown prognostic utility for patients with cardiac amyloidosis. A comprehensive approach to interpreting imaging findings integrated with clinical and serum biomarker data is suggested.

Outcomes among patients with cardiac amyloidosis are improving with continued development of novel AL- and ATTR-targeted therapies. The prognosis, particularly when diagnosed at an early stage, is now much improved compared with previous eras. Nonetheless, patients with advanced cardiac amyloidosis and those who fail to respond to disease-modifying therapy still have a poor prognosis and impaired quality of life. Early referral for palliative care support in this setting might be beneficial.

## Conclusions

Approaches for the diagnostic evaluation and management of patients with cardiac amyloidosis have improved substantially in recent years. The evolution of disease-modifying therapies for AL and ATTR has led to an enhanced awareness of these disorders and the importance of early recognition and diagnosis. A high index of suspicion for the clinical clues that might accompany cardiac amyloidosis in addition to knowledge of the disease-specific considerations for management are now imperative for clinicians managing common cardiovascular disorders. This position statement is intended to provide clinicians with an overview of key elements for assessment and management, and facilitate early recognition, diagnosis, and implementation of appropriate therapy. Furthermore, development of new targeted therapies remains ongoing for both subtypes, including chemotherapeutic agents for AL, TTR stabilizers and silencers for ATTR, and amyloid fibril-degrading agents for both. These advancements bring new questions regarding optimal management approaches, including (but not limited to) serial monitoring strategies and optimal timing and efficacy for potential combination use of disease-modifying therapies. This exciting and rapidly changing landscape promises hope for further improvement in outcomes for cardiac amyloidosis patients.

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### Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at [www.onlinecjc.ca](http://www.onlinecjc.ca) and at <https://doi.org/10.1016/j.cjca.2019.12.034>.