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EXPERT CONSENSUS DECISION PATHWAY

2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the American Association of Neuromuscular & Electrodiagnostic Medicine, Heart Failure Society of America, and International Society of Amyloidosis. The American Academy of Neurology affirms the value of this statement.

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PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, health policy statements, appropriate use criteria) to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence may be new and evolving or where sufficient data may be more limited. Despite this, numerous care gaps continue to exist, highlighting the need for more streamlined and efficient processes to implement best practices in service to improved patient care.

Central to the ACC's strategic plan is the generation of "actionable knowledge"—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has evolved from developing isolated documents to developing integrated "solution sets." Solution sets are groups of closely related activities, policy, mobile applications, decision support, and other tools necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of the solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated content will be refined over time to best match changing evidence and member needs.

Expert consensus decision pathways (ECDPs) represent a key component of solution sets. The methodology for ECDPs is grounded in assembling a group of clinical experts to develop content that addresses key questions facing our members across a range of high-value clinical topics.[1] This content is used to inform the development of various tools that accelerate real-time use of clinical policy at the point of care. They are not intended to provide a single correct answer; rather, they encourage clinicians to ask questions and consider important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as stand-alone policy.

Nicole M. Bhave, MD, FACC
Chair, ACC Solution Set Oversight Committee

1. INTRODUCTION

1.1. Overview of amyloidosis

The systemic amyloidoses are a broad spectrum of diseases that result from misfolding of proteins that aggregate into β-sheet amyloid fibrils. Over 35 amyloidogenic precursor proteins have been identified that give rise to diseases characterized by extracellular deposition of insoluble amyloid fibrils throughout various tissues and

organs.[2] In cardiac amyloidosis, amyloid fibrils accumulate in the interstitial space between cardiac myocytes, precipitating cellular injury and impairing compliance. Advanced cardiac amyloidosis is physiologically characterized as a restrictive cardiomyopathy (CM).

The nomenclature for systemic amyloidosis includes an "A" for amyloid followed by an abbreviation of the protein that misfolds. The vast majority of encountered cases of amyloid CM will be caused by misfolding of 1 of 2 proteins: 1) monoclonal immunoglobulin light chain produced in bone-marrow plasma cell disorders; and 2) transthyretin (abbreviated TTR), also known as prealbumin, a thyroxine and retinol (vitamin A) transport protein produced by the liver (the organ principally responsible for generating circulating TTR), choroid plexus, and retinal pigmented epithelium. As such, the abbreviation for the associated amyloid CMs are termed AL-CM and ATTR-CM, respectively. Rare causes of cardiac amyloidosis include serum amyloid A amyloidosis (AA), hereditary apolipoprotein A-1, and apolipoprotein A-4 amyloidosis. AA amyloidosis in particular may be suggested based on a history of chronic inflammatory disease, such as rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease, chronic infections, and familial periodic fever syndromes (such as familial Mediterranean fever).

TTR misfolding and aggregation appear to increase with aging (through as of yet incompletely characterized mechanisms), as autopsy series of patients over 80 years of age indicate that 25% harbor TTR amyloid deposits (but not all to a degree that clinically manifests).[3,4] Misfolding and aggregation of TTR in ATTR-CM occurs in the context of genetically normal (wild-type) protein, formerly referred to as "senile" or "age-related" ATTR-CM and now more accurately characterized as wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM). Alternatively, ATTR caused by substitution or deletion mutations rendering TTR prone to misfolding was formerly referred to as "familial" ATTR-CM and now is more accurately termed variant transthyretin amyloid cardiomyopathy (ATTRv-CM).[2] There are over 130 known *TTR* variants associated with ATTR amyloidosis of which the most common in the United States is the substitution of isoleucine for valine at position 122 of the protein sequence (reported as pV142I or Val122Ile or V122I). The prevalence of the Val122Ile variant has been reproducibly shown to be 3.5% in the self-identified U.S. Black population, corresponding to approximately 1.5 million carriers.[5]

Clinical recognition and diagnosis of cardiac amyloidosis at an early stage of the disease is critical, affording an affected patient the widest array of treatment options that have a favorable impact on survival and/or prevent potentially irreversible loss of physical function and quality of life. Several recent critical advances in the diagnostic approach, coupled with approval of effective therapies and widespread engagement by societies, regulatory bodies, and advocacy organizations, have elevated cardiac amyloidosis to a position of diagnostic prominence.[6] First, imaging techniques and monoclonal light chain testing now allow for accurate noninvasive diagnosis of ATTR-CM in the proper clinical context[7] without the need for confirmatory endomyocardial biopsies. Second, observational studies indicate that ATTR-CM may be under-recognized in a significant proportion of patients with heart failure (HF).[8,9] Third, with important advances in the treatment of both ATTR-CM[10] and AL-CM,[11] timely diagnosis will allow prompt implementation of therapeutic interventions that may improve survival, physical function, and/or quality of life.

AL amyloidosis is likely a rare disease with, as of 2015, an estimated annual incidence of 1 in 75,000 to 100,000 and a prevalence of 1 in 25,000.[12] Approximately 75% of patients with AL have some degree of cardiac involvement.[13] Although ATTR-CM was historically also considered a rare condition and precise estimates of its incidence and prevalence are not available, evidence is accumulating, both through direct ascertainment by sensitive imaging[14] or indirectly through biobank analyses,[15] that the disease is considerably more common than previously assumed.

1.2. Pitfalls and delays in diagnosis of cardiac amyloidosis

The majority of patients with ATTR-CM do not receive a timely diagnosis. In a survey of patients with ATTR-CM, diagnosis was made within 6 months of symptom onset in only 35% of those with ATTRv and 46% of those with ATTRwt. Many patients see more than 5 physicians before receiving a correct diagnosis because of the perceived disease rarity, overlap with other more "common" diseases, and the seemingly disconnected constellation of clinical findings, including musculoskeletal, neurologic, gastrointestinal (GI), and renal manifestations.[16,17]

In addition, the cardiac manifestations do not always readily signal a diagnosis of amyloidosis. The increased left ventricular wall thickness may be mistaken for hypertensive heart disease, concentric hypertrophy from aortic stenosis (AS), hypertrophic CM, or other infiltrative CMs, such as Fabry disease. In fact, ATTR-CM has been subsequently diagnosed in 16% of patients with AS undergoing valve replacement[8,18] and in 13% of patients initially diagnosed with heart failure with preserved ejection fraction (HFpEF).[9] These findings indicate that a patient who presents with dyspnea attributed to AS or HFpEF may have a concomitant diagnosis of cardiac amyloidosis. Thus, the diagnostic evaluation should not end with an assumption that AS or HFpEF alone is responsible for the patient's presentation.

1.3. The need for a multidisciplinary approach to cardiac amyloidosis

Even if cardiac amyloidosis is suspected, pitfalls in the diagnostic algorithm may result in misdiagnosis, with potentially catastrophic consequences given the marked differences in treatment approaches and prognoses for untreated AL-CM vs ATTR-CM. Median survival from diagnosis in untreated patients is 3.6 to 4.8 years for ATTRwt-CM, 2.6 years for ATTRv-CM due to Val122Ile, and 5.8 years for ATTRv-CM due to other variants.[17,19,20] With advances in management, survival of treated AL-CM varies by degree of heart impairment and has increased from 0.3 to 2.2 years[21] to as long as >10 years.[22,23] As cardiac involvement governs survival in patients with cardiac amyloidosis, selected patients with advanced HF may warrant transplant consideration. With refinements in patient selection and management, survival after heart transplantation has improved[24] up to a median of 10.2 years in the current era for patients with amyloid CM.[25] Therefore, patients are living longer, and most transition from acute to chronic management of their amyloid disease.

Multidisciplinary collaboration starts with an understanding of when specialized diagnostic expertise is warranted, specifically regarding the interpretation of the monoclonal light chain testing results, performance and interpretation of cardiac scintigraphy scans, and the indications for and interpretation of biopsies and genetic testing. Specialized cardiac expertise in management may also be warranted regarding HF management; the indications for and contraindications to advanced HF therapies, such as heart transplantation and mechanical circulatory support; and the role of palliative care.

Because amyloid fibrils deposit in extracardiac organ systems, multidisciplinary collaboration across specialties is requisite to optimize care. Patients with cardiac amyloidosis often have extracardiac manifestations involving the kidney, nervous system, GI tract, and musculoskeletal system that can lead to significant morbidity and impairment to quality of life. Because patients with amyloidosis are often followed by multiple specialists, it is essential to have a designated primary clinician to coordinate care among specialists. This is most commonly the cardiologist for patients with ATTR-CM and the hematologist for patients with AL-CM.

Multidisciplinary collaborative models are already used in other diseases characterized by both cardiac and significant extracardiac manifestations, such as sarcoidosis,[26,27] neuromuscular diseases,[28] and carcinoid syndrome.[29] Creating such a model for amyloidosis may offer a structure that would benefit other conditions: when specific triggers for collaboration with relevant specialists are identified, multidisciplinary models used for amyloidosis could be scaled and operationalized for other cardiac conditions with multisystem manifestations, such as HF with renal, pulmonary, and hepatic involvement.

With these points in mind, the purpose of this ECDP is to provide practical and timely guidance on the diagnosis and management of cardiac amyloidosis with an emphasis on the pitfalls in diagnosis and the role of multidisciplinary collaboration in optimizing management.

2. METHODS

The ACC created the Heart House Roundtables, a structured format of interactive discussion among a broad group of stakeholders, to address high-value topics and issues that clinicians and patients face daily, such as the diagnosis and management of cardiac amyloidosis.[30] The planning committee for the Cardiac Amyloidosis roundtable was led by Michelle M. Kittleson, MD, PhD, FACC, and Frederick L. Ruberg, MD, FACC. To accommodate the multiple perspectives necessary to synthesize and construct new therapeutic frameworks for patients with amyloidosis, this roundtable was designed to include experts in diverse medical specialties, such as cardiology, genetics, health care disparities, hematology, orthopedic surgery, pathology, and pharmacoeconomics, while also involving physicians, nurses, and advanced practice providers.

Recognizing the significant impact of trials and approved medications, discussions focused on the real-world challenges faced in working toward the accurate diagnosis and appropriate management of cardiac amyloidosis for improved patient outcomes. As a result, the ACC saw an opportunity to provide guidance to bridge a communication gap between cardiovascular clinicians and other specialists who jointly manage patients with amyloidosis. To support this effort, a writing committee of multidisciplinary experts was convened in 2022 to develop an ECDP providing guidance on the diagnosis and management of cardiac amyloidosis as well as the identification of extracardiac manifestations and timely referral to relevant specialists. For this update, the writing committee convened in mid-2022 via conference calls attended only by writing committee members and ACC staff. Differences were resolved by consensus among the group, and no portions of the ECDP required administrative decision overrides. The work of the writing committee was supported only by the ACC and did not have any commercial support. Writing committee members were all unpaid volunteers.

The invited writing group participants represent broad expertise in the care of the patient with amyloidosis.

A review of outstanding questions was facilitated. Subsequent writing assignments were configured according to areas of expertise. E-mail correspondence was used to edit contributed content. Conference calls of the writing committee were confidential and were attended only by committee members and ACC staff.

The ACC and the Solution Set Oversight Committee recognize the importance of avoiding real or perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI Policy in determining what constitutes a relevant relationship, with additional vetting by the Solution Set Oversight Committee.

ECDP writing groups must be chaired or cochaired by an individual with no relevant RWI. Although vice chairs and writing group members may have relevant RWI, overall writing group participants with RWI must constitute <50% of the total group. Relevant disclosures for the writing group and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2. To ensure complete transparency, a comprehensive list of disclosure information for the writing group, including relationships not pertinent to this document, is available in a Supplemental Appendix. Writing group members are discouraged from acquiring relevant RWI throughout the writing process.

Every ECDP undergoes a formal peer review process consistent with ACC policy, and includes a public comment period to obtain further feedback. Following reconciliation of all comments, ECDPs are then vetted and approved for publication by the Clinical Policy Approval Committee.

3. ASSUMPTIONS AND DEFINITIONS

To facilitate interpretation of the recommendations provided in this ECDP, specific assumptions were made by the writing committee, as specified in Section 3.1.

3.1. General clinical assumptions

1. The principal focus of this effort, including ECDP considerations, applies to patients with or at risk for cardiac amyloidosis.
2. The writing committee endorses the evidence-based approach to HF management recommended in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[6]
3. These algorithms assume the treating clinician will seek input as needed from a pharmacist, a cardiologist, an HF specialist, hematologist, neurologist, gastroenterologist, nephrologist, palliative care specialist, an individual with genetics expertise, and/or an amyloidosis referral center to guide clinical management.
4. Optimal patient care decisions should properly reflect the patient's preferences and priorities as well as those of the managing clinician. A shared-decision model regarding care decisions is appropriate, particularly when clinical equipoise exists in areas of treatment uncertainty.
5. This ECDP is not intended to supersede good clinical judgement. The treating clinician should seek input as needed from relevant experts (eg, pharmacists, cardiologists, endocrinologists).
6. This ECDP is based on the best data currently available. New information is being generated rapidly (eg, trials of additional agents and including other patient populations), and as these data become available, they will influence the considerations made here. Clinicians should be careful to incorporate relevant information published after this ECDP.
7. Although implementing relevant portions of these recommendations in the acute inpatient setting may be reasonable, this ECDP is primarily focused on management in the outpatient ambulatory setting.

3.2. Definitions

Cardiac amyloidosis: a restrictive CM resulting from the deposition of amyloid fibrils in the myocardial interstitium. The 2 most common types are AL amyloidosis, where the amyloid fibrils are composed of monoclonal immunoglobulin light chains, and ATTR amyloidosis, where the amyloid fibrils are composed of the transthyretin protein and can occur in the context of variant or wild-type *TTR* genetics, resulting in AL cardiac amyloidosis, ATTRv cardiac amyloidosis, or ATTRwt cardiac amyloidosis, respectively.

GDMT: Guideline-directed medical therapy, representing treatment options supported for use by clinical practice guidelines.

Heart failure: defined per the criteria outlined in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[6] An HF event, including hospitalization, is defined by the criteria outlined by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials.[31]

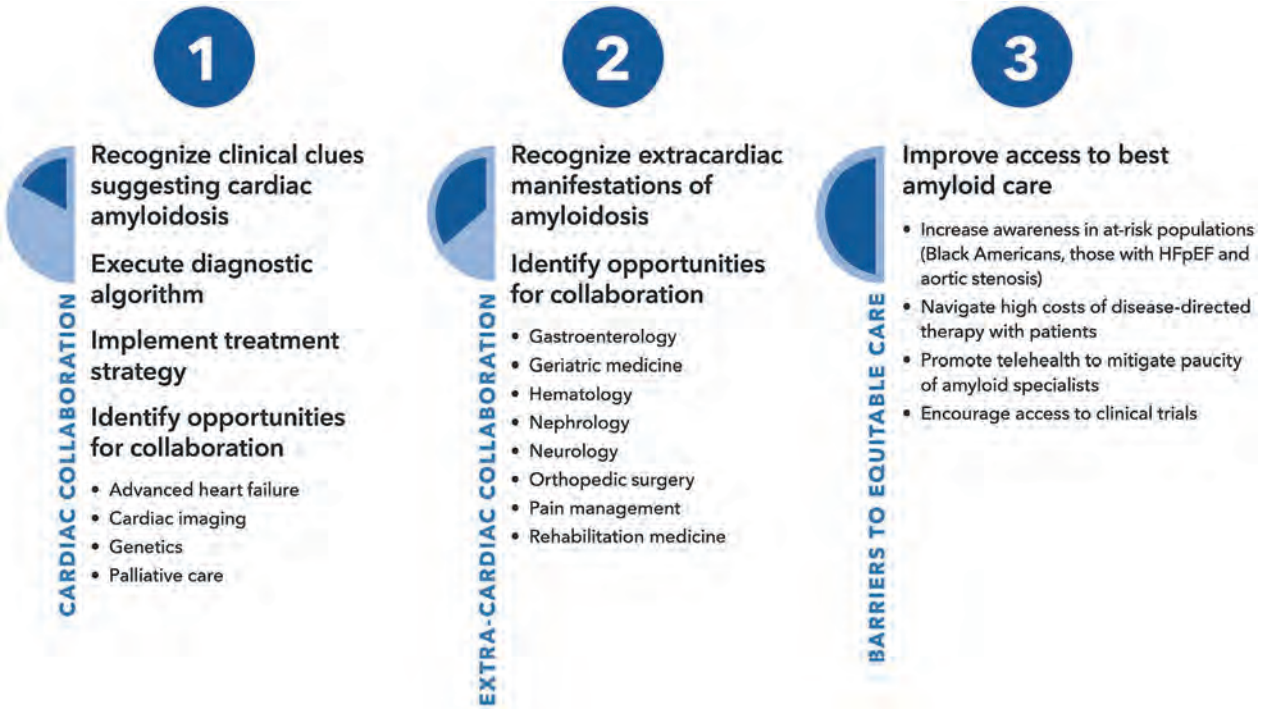
Heart failure with reduced ejection fraction (HFrEF): clinical diagnosis of HF and left ventricular ejection fraction (EF) ≤40%.[6]

Heart failure with mildly reduced EF: clinical diagnosis of HF and left ventricular EF 41% to 49%.[6]

Heart failure with preserved ejection fraction (HFpEF): clinical diagnosis of HF and left ventricular EF ≥50%.[6]

Monoclonal protein screen: serum kappa and lambda free light chains, serum immunofixation electrophoresis

FIGURE 1 Summary Graphic



HFpEF = heart failure with preserved ejection fraction.

(SIFE), and urine immunofixation electrophoresis (UIFE), which, when taken together, have >99% sensitivity for the identification of AL amyloidosis.[32]

New York Heart Association (NYHA) functional classification:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- Class IV: Unable to perform any physical activity without symptoms of HF or symptoms of HF at rest.

4. PATHWAY SUMMARY GRAPHIC

The multidisciplinary care of amyloidosis involves 3 steps (Figure 1). The first step is identifying what general cardiologists should know about the diagnosis and management of cardiac amyloidosis and what decisions require consultation with a cardiac amyloid specialist. The second step is recognizing the relevant extracardiac manifestations and when to establish multidisciplinary collaboration. The third step is to understand barriers to equitable care, future directions, and unanswered questions.

5. DESCRIPTION, RATIONALE, AND IMPLICATION OF PATHWAY

Cardiovascular specialists should: 1) be aware of the clinical clues that suggest a diagnosis of cardiac amyloidosis; 2) identify the diagnostic algorithm for cardiac amyloidosis, including the role of the monoclonal protein screen, bone scintigraphy, and/or genetic testing and/or biopsy; 3) avoid diagnostic pitfalls of the monoclonal protein screen, bone scintigraphy, and biopsy; 4) implement a treatment plan with specific attention to the roles of traditional HF medications and arrhythmia management; 5) recognize the extracardiac manifestations and need for timely referral to appropriate specialists; and 6) understand the unmet needs and future directions in the field.

Thus, essential components of the multidisciplinary care of patients with cardiac amyloidosis comprise 3 steps around which this EDCP document is organized (Figure 1):

- Step 1: identify what every cardiologist should know about the diagnosis and management of cardiac

TABLE 1 Clues Suggesting a Diagnosis of Cardiac Amyloidosis

Cardiac Manifestations	Extracardiac Manifestations
Clinical	**Musculoskeletal**
■ Fatigue	■ Bilateral carpal tunnel syndrome
■ Heart failure symptoms	■ Lumbar/cervical spinal stenosis
■ Family history of heart failure	■ Spontaneous biceps tendon rupture
Electrical	■ Hip or knee replacement
■ Conduction system disease/pacemaker	**Neurologic**
■ Atrial fibrillation	■ Peripheral neuropathy
■ Pseudoinfarct pattern	■ Family history of neuropathy
■ Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging	■ Autonomic dysfunction
Imaging	■ Intolerance to vasodilating antihypertensive medications
■ Increased left ventricular wall thickness	■ Orthostatic hypotension
■ Grade 2 or worse diastolic function	■ Gastroparesis
■ Abnormal longitudinal strain with apical sparing	■ Urinary incontinence
■ Diffuse subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging with increased extracellular volume fraction	■ Erectile dysfunction
Laboratories	**Renal**
■ Persistent low-level troponin elevation	■ Nephrotic syndrome
■ Elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide	

amyloidosis and what diagnostic and management decisions require consultation with a cardiac amyloid specialist;

- Step 2: recognize the relevant extracardiac manifestations and how and when to establish multidisciplinary collaborations for the care of these patients;
- Step 3: understand the future directions and unanswered questions in the care of patients with cardiac amyloidosis.

6. STEP 1: COLLABORATION BETWEEN GENERAL CARDIOLOGISTS AND AMYLOID SPECIALISTS

6.1. Diagnosis

6.1.1. The role of the general cardiologist

6.1.1.1. An iterative process of diagnosis

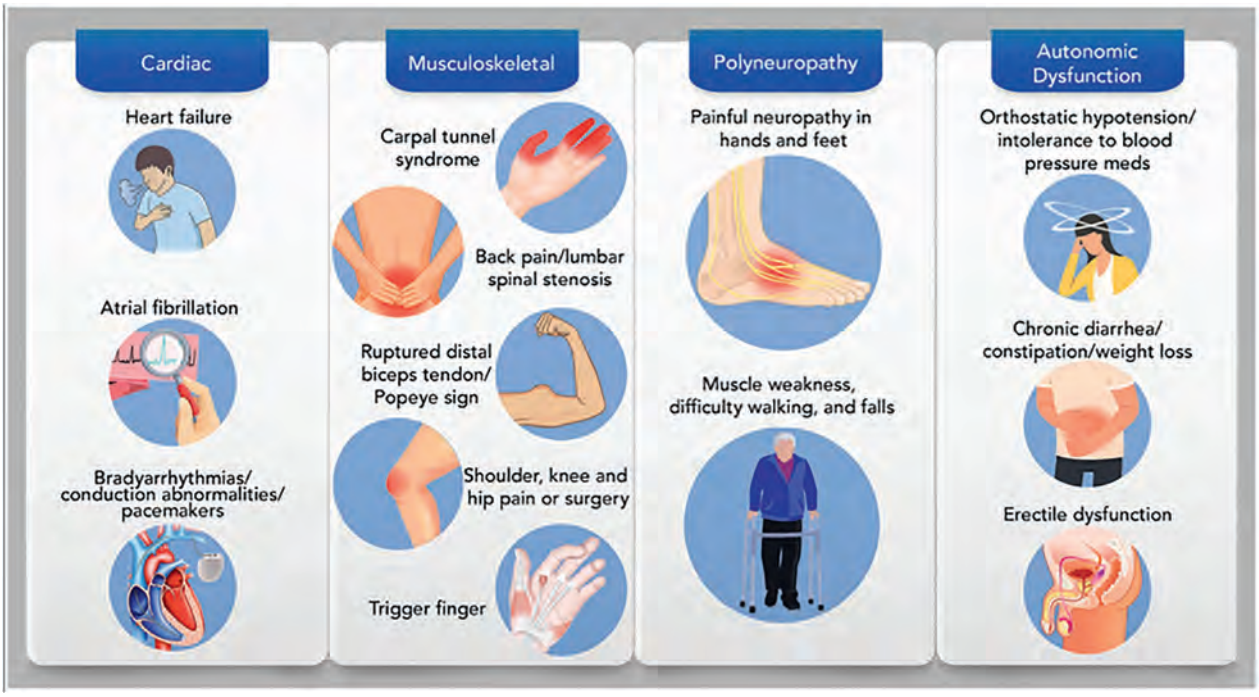
The diagnosis of cardiac amyloidosis requires the clinician to be mindful of clinical features (clues or "red flags") that are associated with the cardiac amyloidosis phenotype as well as the diagnostic tools that assist in identifying the disease.[33-35] First and foremost, diagnosis of cardiac amyloidosis requires a high index of suspicion because the diagnosis cannot be established on the basis of routine testing alone. Specific laboratory and imaging tests are required and may not be ordered without an appropriate index of suspicion.[34] Once cardiac amyloidosis is suspected, the goal is to obtain an early and rapid diagnosis as early initiation of therapy can prevent further amyloid deposition and further end-organ damage.[33,36]

Cardiac amyloidosis clinical clues/red flags can be broadly divided into cardiac features (ie, increased left ventricular wall thickness in the absence of hypertension or valvular heart disease, HF symptoms, diastolic dysfunction, atrial fibrillation [AF], conduction system disease, elevated cardiac biomarkers) and extracardiac manifestations (ie, history of carpal tunnel syndrome, spinal stenosis, hip or knee replacement, prior shoulder surgery, proteinuria, or peripheral/autonomic neuropathy) (Table 1 and Figure 2).[33-35]

Cardiac manifestations alone are insufficient to conclusively distinguish AL from ATTR amyloidosis because there is considerable overlap of clinical, imaging, and electrocardiographic features. As covered in more detail in Section 7.4, there are some pathognomonic extracardiac manifestations of AL amyloidosis, including macroglossia/submandibular gland enlargement from soft tissue involvement and periorbital purpura from capillary fragility and acquired Factor X deficiency.[37] In contrast, musculoskeletal manifestations, such as spontaneous biceps tendon rupture and spinal stenosis, are unique to ATTR amyloidosis.[38,39] Of the organ systems that are affected by both AL and ATTR amyloidosis, CM, GI involvement, peripheral neuropathy, and orthostatic hypotension are common.[40]

The cardiac amyloidosis diagnostic process begins with clinical history/examination, electrocardiogram (ECG), and transthoracic echocardiogram.[34] Discordance between QRS voltage and wall thickness seen on echocardiogram is a well-recognized feature.[33,42] However, the lack of low QRS voltage on ECG by commonly applied criteria is only present in about 30% of patients with cardiac amyloidosis, and thus its absence does not exclude the diagnosis.[42] Echocardiographic diagnostic clues include increased left ventricular wall thickness (above the sex-specific upper limit of normal and typically ≥1.2 cm) as well as other features such as atrioventricular valve/right ventricle free wall/interatrial septum thickening, diastolic dysfunction, decreased mitral annular systolic velocity (s'), biatrial enlargement,

FIGURE 2 **Clinical Manifestations of Cardiac Amyloidosis***



*Reproduced with permission from Nativi-Nicolau et al.[41]

and decreased global longitudinal strain with relative apical sparing.[33,34,43,44]

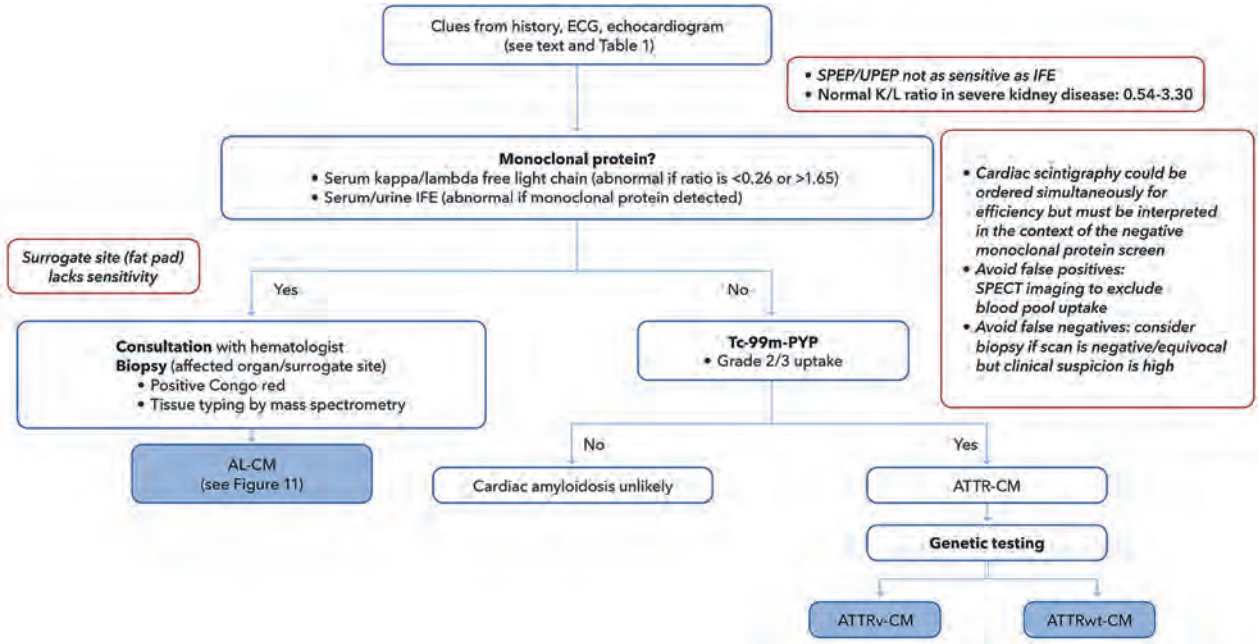
Cardiac magnetic resonance (CMR) imaging provides detailed cardiac tissue characterization, allowing for differentiation of cardiac amyloidosis from other forms of CM associated with increased left ventricular wall thickness and preserved EF.[43,44] Expansion of the extracellular volume, abnormal gadolinium contrast kinetics, and diffuse late gadolinium enhancement are characteristic CMR features of cardiac amyloidosis.[43,44] CMR is very useful to exclude amyloidosis in suspected cases; however, it is important to note that CMR is neither necessary nor sufficient for establishing the diagnosis of cardiac amyloidosis as a standalone test and cannot distinguish between AL-CM and ATTR-CM.[45,46] Cardiac involvement can be inferred, however, with characteristic CMR findings in the context of a proven extracardiac tissue biopsy showing amyloid deposits, although the type of cardiac amyloidosis (AL or ATTR) cannot be determined from CMR alone. CMR is also useful to establish other diagnoses when there are findings suggestive of other infiltrative/inflammatory or restrictive CMs, including sarcoidosis, hemochromatosis, or Fabry disease, as well as hypertrophic CM, myocarditis, or constrictive pericarditis.[44,47]

6.1.1.2. Noninvasive and invasive diagnostic pathways

The cardiac amyloidosis diagnostic algorithm should always begin with a monoclonal protein screen to assess for the presence of a plasma cell disorder and, therefore, supportive evidence for AL-CM (**Figure 3**). Although cardiac scintigraphy has emerged as a cornerstone of noninvasive ATTR-CM diagnosis, cardiac uptake that is consistent with ATTR-CM (grade 2 or 3 uptake) may be present in over 10% of patients with AL-CM.[7,48,49] Thus, the obligate first decision point in choosing the appropriate diagnostic pathway is *based on the presence or absence of a monoclonal protein.*[33,50,51] A diagnostic pitfall would be to interpret a cardiac scintigraphy scan without a concomitant monoclonal protein screen; a scintigraphy scan alone is neither appropriate nor valid for distinguishing ATTR-CM from AL-CM.

AL amyloidosis can be essentially excluded by obtaining a monoclonal protein screen comprising 3 laboratory tests: serum free light chain (sFLC) assay, SIFE, and UIFE.[50] The sFLC assay measures the relative proportion

FIGURE 3 Diagnostic Algorithm for Cardiac Amyloidosis



AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM = amyloid transthyretin cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; ECG = electrocardiogram; IFE = immunofixation electrophoresis; K/L = kappa/lambda; PYP = pyrophosphate; SPECT = single-photon emission computed tomography; SPEP/UPEP = serum/urine protein electrophoresis.

of kappa and lambda light chains (with monoclonality assumed by an abnormal ratio), whereas SIFE/UIFE assesses for the presence of a monoclonal protein.[52] If no monoclonal protein is identified by SIFE/UIFE and the sFLC ratio is in the normal range, then AL amyloidosis has been excluded with a negative predictive value of ~99%.[32,34] An important diagnostic pitfall of the monoclonal protein screen is that serum/urine protein electrophoresis (SPEP/UPEP) should not be used to exclude a monoclonal protein given its lower accuracy relative to immunofixation for AL amyloidosis.[50] If a monoclonal protein is present by immunofixation and/or an abnormal sFLC ratio is found, the noninvasive diagnostic pathway is no longer an option and biopsy of the involved organ is preferred.[35,36]

Technetium-based compounds (pyrophosphate [Tc-PYP], diphosphono-1,2-propanodicarboxylic acid [Tc-DPD], and hydroxymethylene diphosphonate [Tc-HMDP]), originally used in bone imaging, have emerged as an important imaging tool in the diagnosis of ATTR-CM.[10] In the United States, Tc-PYP is the predominantly used radiotracer, while Tc-HMDP (also known as HDP) is also available. However, technetium 99m-methyl diphosphonate is not an acceptable tracer for the diagnosis of ATTR-CM.[53]

Cardiac scintigraphy with Tc-PYP requires intravenous injection of the radiopharmaceutical followed by the acquisition of planar and single-photon emission computed tomography (SPECT) or SPECT/computed tomography images at 1 or 3 hours after injection.[6,47] The radiotracers can persist in the ventricular cavity, producing an uptake signal that can be mistaken for myocardial uptake on planar imaging. A diagnostic pitfall would be to perform planar imaging alone. This increases the risk that blood pool radiotracer uptake will be mistaken for myocardial uptake; hence, subsequent SPECT images must be acquired if uptake is present to distinguish myocardial uptake from the blood pool radiotracer signal.[43,44,50]

The 2022 shortage of Tc-PYP because of supply-chain disruptions also engendered significant inequities of care because some centers had available radiotracer and others did not. Diagnostic performance studies of Tc-PYP and other radiotracers available in the United States, such as Tc-HMDP, will be important to validate interchangeable use and permit continued new ATTR-CM diagnoses to be made noninvasively.[54]

A qualitative and quantitative scoring system has been developed to make the diagnosis of ATTR-CM based on the uptake of these radiotracers.[43,44,46,50] It is important

to note that diagnostic performance of these radiotracers was established in referral populations with high disease prevalence; thus, translation to a lower-likelihood population will likely be associated with diminished accuracy leading to false positives. Furthermore, the rapid implementation of Tc-PYP imaging has led to increasing case ascertainment for ATTR-CM but with some pitfalls: 1) the risk of misinterpretation if a monoclonal protein screen is not also ordered; 2) the recognition that there can be false-negative Tc-PYP scans and further investigation is warranted if the clinical suspicion is high[10]; and 3) the possibility of false-positive Tc-PYP scans when planar imaging alone (and not SPECT) is acquired.[55]

Before the advent of cardiac scintigraphy, the diagnosis of cardiac amyloidosis could only be made by histologic confirmation of amyloid deposits via tissue biopsy. An additional benefit of obtaining tissue is that it allows for immunohistologic determination or proteomic analysis of the amyloidogenic precursor protein at the amino-acid level through mass spectrometry. Endomyocardial biopsy should be performed (if other tissue biopsy does not confirm amyloid) in the following scenarios[34]: 1) high clinical suspicion of cardiac amyloidosis in a patient with a monoclonal protein by immunofixation electrophoresis (IFE) and/or an abnormal sFLC K/L ratio above the upper range of normal; 2) high clinical suspicion for cardiac amyloidosis despite negative or equivocal Tc-PYP imaging; or 3) cardiac scintigraphy is unavailable.

Genetic testing (*TTR* gene sequencing) to establish the presence or absence of a *TTR* variant performed in concert with genetic counseling is essential to the complete evaluation of ATTR-CM. Distinguishing ATTRv from ATTRwt in the patient assists not only with cascade testing of at-risk relatives but also may inform treatment strategy, as mRNA silencers are currently only approved for use in the context of ATTRv-associated neuropathy.

6.1.2. The role of the cardiac amyloid specialist

There are no current established competencies for a cardiac amyloid specialist, although generally such specialists will be those who have completed a fellowship in advanced heart failure and transplant cardiology (AHFTC) or advanced cardiac imaging. The 2017 ACC/AHA/HFSA/ISHLT/ACP Advanced Training Statement on Advanced Heart Failure and Transplant Cardiology noted that trainees should have familiarity with cardiac amyloidosis.[56] The 2020 ACC/HFSA/ISHLT Lifelong Learning Statement for Advanced Heart Failure and Transplant Cardiology Specialists[57] further emphasized that all AHFTC specialists should know the pathophysiology, clinical presentation, diagnostic criteria, methods of risk stratification, and management of patients with amyloidosis. However, the document notes that the skill to manage patients with HF from cardiac amyloidosis is reserved for selected AHFTC specialists based on practice focus. How this focus is achieved, whether by participating in a yearlong fellowship not accredited by the American Council for Graduate Medical Education or by self-directed application and management of patients with amyloidosis, is currently not established.

6.1.2.1. Light chain interpretation

The ratio of kappa and lambda free light chains, rather than the absolute levels, should be used for diagnostic and disease-monitoring purposes. This is particularly true in the setting of kidney dysfunction because of the effect of reduced glomerular filtration rate (GFR) on the circulating concentrations of free light chains. Normal bone marrow produces approximately twice as many kappa as lambda free light chains (FLCs), and clearance occurs by 2 mechanisms: the kidneys and the reticuloendothelial system. Although the reticuloendothelial system clears kappa and lambda FLCs at the same rate, the kidneys clear kappa much more efficiently than lambda, thus overcoming the extra kappa FLC production by the bone marrow.

However, as the GFR drops, renal clearance contributes less to sFLC levels, and the K/L ratio reflects the higher levels of kappa production by the bone marrow rather than the more efficient kappa clearance by the kidneys. Thus, in chronic kidney disease, higher K/L ratios are common[50,52] However, in such cases, SIFE and UIFE are normal and AL amyloidosis is uncommon.[58] In contrast, a low K/L ratio is never normal because it indicates a lambda monoclonal process and should always prompt further investigation.[59]

A recent publication with data from over 75,000 participants defined reference sFLC ratio ranges associated with degrees of renal impairment based upon estimated glomerular filtration rates (eGFRs) calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[60] Consider that a normal K/L ratio is 0.26 to 1.65 in the setting of normal kidney function. If the GFR is 45 to 59 mL/min/1.73 m^2, then a sFLC K/L ratio of 0.46 to 2.62 may be considered normal. If the GFR is 30 to 44 mL/min/1.73 m^2, then a ratio of 0.48 to 3.38 may be considered normal.[60] In the most extreme cases, when the GFR is $<$30 mL/min/1.73 m^2, a ratio of 0.54 to 3.30 may be considered normal.[60] When the monoclonal protein screen is abnormal or borderline abnormal, collaboration with a hematologist is warranted to exclude AL amyloidosis or other paraprotein-mediated disorders, as discussed in detail in Section 7.4.[52]

There is a rare entity of heavy-chain amyloidosis that may be suggested by an abnormal monoclonal protein screen. The diagnosis can be established by immunofluorescence staining of biopsy tissue with anti-heavy-chain antibodies. The clinical characteristics and course of

heavy-chain amyloidosis are generally similar to those of AL amyloidosis.[61]

6.1.2.2. The role of biopsy in diagnosis

In patients with suspected AL amyloidosis, standard evaluation includes tissue biopsy to demonstrate the presence of amyloid and, in many cases, to determine the type of amyloid. If a patient has biopsy-proven AL amyloidosis (from an extracardiac tissue source) and imaging features consistent with cardiac amyloidosis, endomyocardial biopsy is not typically pursued, although concomitant AL/ATTR cardiac amyloidosis has been described and thus, if suspected, cardiac biopsy is appropriate.[62]

In patients with suspected cardiac amyloidosis and an abnormal monoclonal protein screen, endomyocardial biopsy may be required to make the diagnosis. A common diagnostic pitfall is choice of biopsy site. Although biopsy of the involved organ (most commonly heart or kidney) is more invasive than biopsy of a surrogate site such as the abdominal fat pad, the latter offers varying sensitivity: 84% for AL-CM, 45% for ATTRv-CM, and 15% for ATTRwt-CM.[62,63] Furthermore, the reported sensitivity noted is for multisystemic disease; sensitivity will likely be lower in patients earlier in the disease course. Thus, although helpful if positive, a negative fat pad biopsy excludes neither AL-CM nor ATTR-CM, and biopsy of an affected organ is often needed to establish the diagnosis.[62]

The amyloid precursor protein may be identified on biopsy by immunohistochemistry or immunogold immunoelectron microscopy in experienced centers, although mass spectrometry-based analysis (liquid chromatography with tandem mass spectrometry [LC-MS/MS]) of the biopsy is the gold standard for tissue diagnosis, with a reported sensitivity of 88% and specificity of 96%.[64] This is described in detail in Section 7.4.2.2.

6.1.2.3. Diagnosis of rarer forms of amyloidosis

To date, cardiac amyloidosis has been described from 9 types of precursor proteins.[35] Greater than 90% to 95% of all cardiac amyloidosis arises from 1 of 2 proteins: AL and ATTR. Positive uptake on Tc-DPD imaging has been seen in rare forms of amyloidosis, including AA, apolipoprotein A1, apolipoprotein A4, and beta2-microglobulin amyloidosis, whereas false negative scans are observed in amyloidosis due to the Phe64Leu variant of *TTR*. Clinical clues (such as family history and dialysis status) may help to identify these patients, although histologic assessment via biopsy is required for these rare forms of amyloidosis, if suspected clinically.[35]

6.2. Treatment

6.2.1. The role of the general cardiologist in the management of cardiac amyloidosis

6.2.1.1. Tafamidis

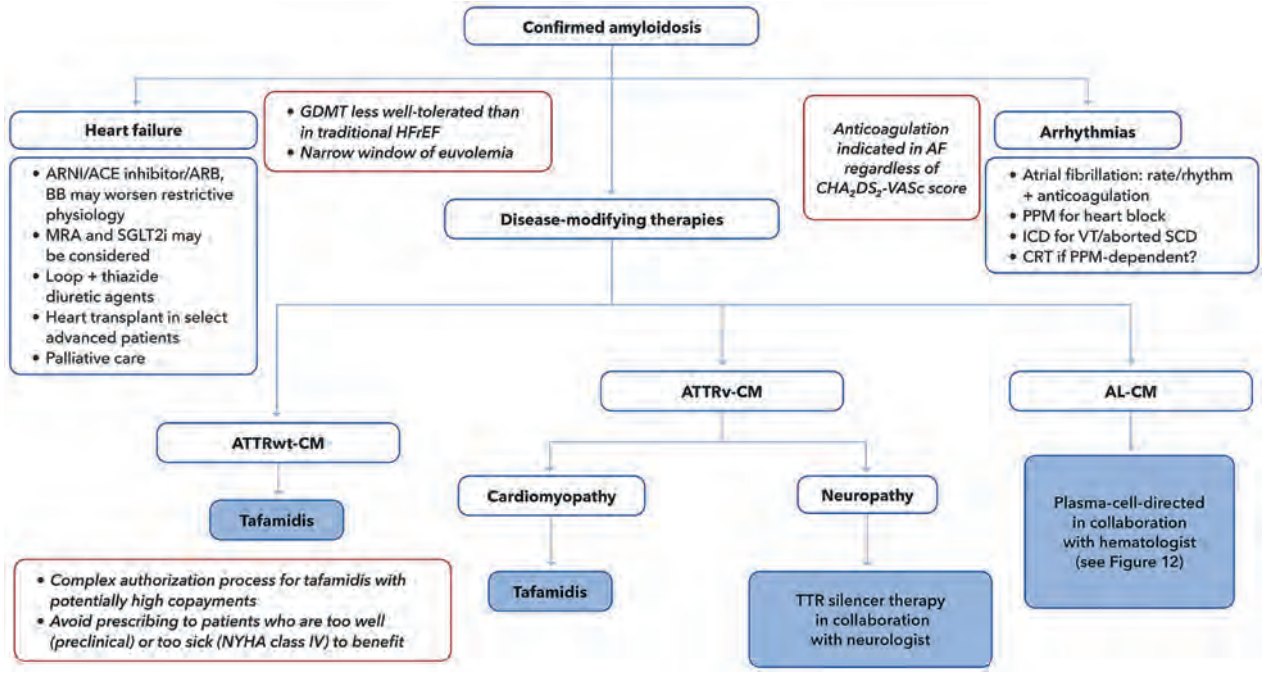
As of 2022, tafamidis is the only medication approved by the U.S. Food and Drug Administration (FDA) for treatment of ATTR cardiac amyloidosis. It acts as a TTR stabilizer, slowing the dissociation of TTR and thus fibril formation and cardiac deposition (**Figure 4**). Early diagnosis is crucial because tafamidis delays progression of disease but will not necessarily result in its regression. The FDA-approved dosages are tafamidis 61 mg or tafamidis meglumine 80 mg.

In the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) study, tafamidis compared with placebo demonstrated reductions in all-cause mortality and cardiovascular-related hospitalizations. Benefits were consistent across prespecified subgroups, including stratification by ATTRwt vs ATTRv status and NYHA functional class I or II vs III, with the exception of higher cardiovascular hospitalization rates in NYHA functional class III participants who received tafamidis.[10] The increased hospitalization rate was proposed to be driven by longer survival and exposure time in an advanced disease state, underscoring the importance of early diagnosis and treatment initiation. A subsequent prespecified analysis from ATTR-ACT supported benefit from tafamidis, regardless of variant or wild-type status, with reductions in mortality and functional decline.[65] Additionally, tafamidis slows the decline in patient-reported quality-of-life metrics,[66] and the mortality benefit was evident up to 58 months in the long-term extension of patients on continuous tafamidis compared with those initially on placebo who transitioned to tafamidis.[67]

Tafamidis has a favorable side-effect profile. In ATTR-ACT, adverse events were mild to moderate in severity, and permanent discontinuation occurred more frequently in the placebo group.[10] In real-world practice, safety monitoring has not been required. For this reason, the major driver for starting treatment is whether a patient will meaningfully benefit (clinically relevant disease without competing life-limiting comorbidity) and whether it is affordable.

As discussed in detail in Section 8.1, the predominant barrier is risk for cost due to the high original list price of $225,000 annually. A cost-effectiveness analysis estimated a cost of $880,000 per quality-adjusted life-year gained and that a 92.6% price reduction would be needed to make tafamidis meet established thresholds for cost-effectiveness.[68] With clinical implementation, a single-center experience showed that financially tenable

FIGURE 4 **Overview of Management of Cardiac Amyloidosis**



AF = atrial fibrillation; ARNI/ACE inhibitor/ARB = renin-angiotensin system inhibitors; AL-CM = amyloid monoclonal immunoglobulin light chain; ATTR = amyloid transthyretin; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; BB = beta-blocker; CRT = cardiac resynchronization therapy; HFrEF = heart failure with reduced ejection fraction; GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association; PPM = permanent pacemaker; SCD = sudden cardiac death; SGLT2i = sodium glucose cotransporter 2 inhibitor; TTR = transthyretin; VT = ventricular tachycardia.

tafamidis administration for individual patients frequently relies on copayment assistance programs.[69] Thus, one barrier to prescription of tafamidis by general cardiologists includes the availability of and difficulty navigating the copayment assistance programs and authorization process.

Another barrier to prescribing tafamidis may be the lack of data regarding the appropriate patient population who will benefit. Although not included in the approved labeling, uncertainty exists regarding the efficacy of tafamidis early along the disease continuum, including asymptomatic genetic carriers without clinically -evident cardiac amyloidosis or those with localized, noncardiac disease, such deposits identified at the time of carpal tunnel surgery.[70] Furthermore, some patients with advanced disease may not benefit from tafamidis, such as those excluded from the ATTR-ACT trial, including patients with NYHA functional class IV status and advanced HF, or those of advanced age (90 years or older), although use in such patients should be based on an individualized shared decision-making discussion.[10]

The utility and frequency of longitudinal assessments of quality of life and exercise capacity in patients being treated with tafamidis has not been established, although early evidence suggests that treatment can improve exercise capacity, as defined by cardiopulmonary exercise testing, in approximately 50% of treated patients.[71] Continuation of therapy among those with evidence of worsening disease should be a decision made following a shared discussion of costs and benefits.

Although there are alternatives to tafamidis, they lack a similar evidence base and are not as well tolerated. The chemical structure of tafamidis is similar to that of the nonsteroidal anti-inflammatory drug (NSAID) diflunisal, which itself functions as an effective TTR stabilizer. Although tafamidis should remain the first-line agent in the treatment of ATTR-CM as the only available approved drug, the cost of diflunisal is approximately $25 to $50 per month, rendering it an alternative option for those who are “too well” or those patients who cannot afford tafamidis. Whereas diflunisal was superior to placebo in slowing neurologic disease progression in the randomized, placebo-controlled trial of ATTR polyneuropathy,[72] only limited retrospective data inform its use in ATTR-CM. Evidence from small studies suggests that diflunisal may slow the progression of echocardiographic decline

and prolong survival in ATTR-CM.[73] As an NSAID, diflunisal must be administered with care and avoided in those with impaired kidney function (typically eGFR <45 mL/min/1.73 m^2) or a history of gastric bleeding; caution should be exercised for those with recent HF decompensation or on high-dose diuretic agents.[74]

6.2.1.2. Volume management and guideline-directed medical therapy

Volume management is the mainstay of therapy in cardiac amyloidosis, with many patients presenting with predominant right-sided HF symptoms. Loop diuretic agents and sequential nephron blockade with mineralocorticoid receptor antagonists should be considered. Recognizing that these patients have a narrow euvolemic window due to diastolic dysfunction or, in advanced cases, restrictive physiology (**Figure 4**), thiazide diuretic agents (such as metolazone) should be used with caution due to the greater risk of overdiuresis, hyponatremia, hypokalemia, and kidney dysfunction. Kidney function is closely linked to outcomes in ATTR-CM, with eGFR a component of a commonly-used risk model for staging of ATTR-CM,[19] and progressive increases in diuretic agent dose are associated with poor outcomes.[75] In AL amyloidosis, direct kidney deposition can impair kidney function and contribute to diuretic agent resistance.

Expert consensus documents caution against the use of standard HF guideline-directed medical therapy in cardiac amyloidosis.[6,34,35] Physiological changes include alterations in the pressure-volume relationships with abnormal passive ventricular filling and altered ventricular-vascular coupling,[76] resulting in reduced stroke volume, greater dependence on heart rate to maintain cardiac output, and inability to augment cardiac output in response to vasodilation. For this reason, beta-blockers should be used with caution in patients with cardiac amyloidosis; even at low doses, they can be poorly tolerated,[77] and discontinuation may improve outcomes.[78]

Angiotensin receptor-neprilysin inhibitors, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may be poorly tolerated due to vasodilation, particularly in patients with underlying autonomic orthostatic hypotension, although data specific to cardiac amyloidosis is limited. Conversely, regarding mineralocorticoid antagonists, a recent retrospective analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial with a cohort enriched for amyloidosis based on echocardiographic features (but not confirmed cases) observed benefit with spironolactone, with a reduction in the combined endpoint of cardiovascular death, HF hospitalization, or aborted cardiac arrest.[79] Last, although recent trials have shown benefit of sodium glucose cotransporter inhibitors for HFpEF[80] and there is theoretical benefit, there is insufficient evidence regarding their efficacy (or harm) in cardiac amyloidosis.

6.2.1.3. Management of AF

The reported prevalence of AF in cardiac amyloidosis is variable but may be as high as 56% in AL amyloidosis and 70% in ATTR-CM.[81] A pitfall in the management of AF is the lack of recognition of the high risk of thromboembolism (**Figure 4**). The risk for intracardiac thrombus may be as high as 33% in cardiac amyloidosis and can be present even in those on chronic anticoagulation.[82] Hence, consensus statements and guidelines recommend anticoagulation when AF is present, regardless of the CHA_2DS_2-VASc risk score.[6] Additionally, transesophageal echocardiography to evaluate for left atrial appendage thrombus is necessary before cardioversion, regardless of the duration of anticoagulation before the procedure.[82] There is insufficient randomized clinical trial evidence to inform the use of direct oral anticoagulants vs warfarin in cardiac amyloidosis, although the former offer ease of administration and have been widely used as first-line anticoagulation strategies in AL-CM and ATTR-CM since their approval.

Although left atrial appendage closure devices can be considered in those with contraindications to anticoagulation, data is lacking. Generally, ventricular response rates in AF tend not to be elevated, although at times additional heart-rate-lowering agents, such as low-dose beta-blockade, may be effective if tolerated without hypotension. For patients with refractory AF with difficult-to-manage heart rates or tachy-brady syndrome, atrioventricular junctional ablation with permanent pacemaker placement may be a reasonable last option. Although digoxin has historically been believed to be contraindicated in cardiac amyloidosis due to in vitro evidence of binding to amyloid fibrils,[83] more recent data suggests it may be used for rate control of AF with close monitoring.[84,85] Rhythm control can be considered if the patient remains symptomatic despite attempts at rate control, and amiodarone is generally well tolerated as a first-line agent.[81] Published data for catheter ablation in cardiac amyloidosis has suggested higher success rates in those with earlier-stage disease.[86]

6.2.2. The role of the cardiac amyloid specialist in the management of amyloidosis

6.2.2.1. Specific clinical scenarios warranting specialist evaluation

There are a number of clinical scenarios where collaboration with a cardiologist with expertise in cardiac amyloidosis would be useful, as outlined in the following discussion. Cardiac amyloid specialists can also connect patients with advocacy groups, such as the Amyloid

TABLE 2 Phase 3 Clinical Trials in ATTR-CM

Trial Name	Intervention	Endpoints	Study Progress
ATTRIBUTE-CM NCT03860935	Acoramidis (TTR stabilizer)	Hierarchical combination of all-cause mortality, frequency of CV-related hospitalization, and change from baseline to month 30 of treatment in the total distance walked in 6 min	Enrollment completed November 2020 Did not meet primary 12-mo endpoint of change in 6-min walk distance; 30-mo endpoint of all-cause mortality and CV-related hospitalization is ongoing
CARDIO-TTRansform NCT04136171	Eplontersen (TTR silencer, antisense oligonucleotide)	Composite of CV mortality and recurrent CV clinical events up to week 140	Enrollment completed mid-2022
HELIOS-B NCT04153149	Vutrisiran (TTR silencer, small interfering RNA)	Composite of all-cause mortality recurrent CV events (CV hospitalizations and urgent HF visits) at 30-36 mo	Enrollment completed August 2021
APOLLO-B NCT03997383	Patisiran (TTR silencer, small interfering RNA)	6-min walk distance at 12 mo	Met 12-mo primary endpoint: improvement in 6-min walk test Met 12-mo first secondary endpoint: improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary No difference in secondary composite endpoint: win ratio for change in 6-min walk test, death, and CV hospitalization at 12 mo

APOLLO-B = A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy; ATTRIBUTE-CM = Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; CARDIO-TTRansform = A Study to Evaluate the Efficacy and Safety of Eplontersen in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy; CV = cardiovascular; HELIOS-B = A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; HF = heart failure; TTR = transthyretin.

Research Consortium, Amyloidosis Support Groups, and the Amyloidosis Foundation, that provide outreach and education to inform and empower patients, families, and caregivers.

Progressive HF: For patients with cardiac amyloidosis and progressive HF despite volume optimization, referral to a specialist should be considered. This may be beneficial for individualizing guideline-directed medical therapy and to evaluate potential roles of advanced HF therapies (discussed in detail in Section 7.6).

Conduction disease: Conduction disease is prevalent in patients with cardiac amyloidosis, frequently involving the His-Purkinje system in both AL-CM and ATTR-CM.[81,87,88] Hence, there should be close monitoring for the need for a permanent pacemaker and appropriate referral to electrophysiology. In cases of pacemaker dependence or a high degree of anticipated pacing, cardiac resynchronization therapy may be considered, although the benefit has not been established.

Risk stratification for ventricular arrhythmias: Nonsustained ventricular arrhythmias are very common in both AL-CM and ATTR-CM, but it is not clear if they are predictors of subsequent sudden cardiac death. Although some studies have demonstrated appropriate implantable cardioverter-defibrillator therapies in cardiac amyloidosis,[89,90] none have convincingly shown improved survival. Current guidelines state that there is insufficient data to provide recommendations beyond standard indications for use of implantable cardioverter-defibrillators as primary prevention in cardiac amyloidosis[91] and that individualized decision-making is necessary.[92]

Transcatheter aortic valve replacement: Concurrent AS is a recognized comorbidity in cardiac amyloidosis, particularly in ATTRwt, and dual pathology is frequently found in older patients. Up to 16% of patients with AS undergoing transcatheter aortic valve replacement may have ATTR-CM.[8] Emerging data suggests that aortic valve intervention confers both symptom palliation and survival benefit relative to medical management in patients with cardiac amyloidosis[93,94]; hence, the presence of cardiac amyloidosis should not preclude referral to structural interventional cardiology.

6.2.2.2. Access to clinical trials

An important reason to refer a patient to a cardiac amyloid specialist is access to clinical trials of newer agents that may improve quality of life and survival. Particularly for a condition like ATTR-CM, where there is only one currently-approved disease-directed therapy, clinical trials may allow patients access to better treatment options.

A comprehensive review of clinical trials is beyond the scope of this document, but important ongoing trials in ATTR-CM are summarized in **Table 2**. Acoramidis is a novel TTR stabilizer currently in a phase 3 clinical trial. It did not meet its primary 12-month endpoint of change in 6-minute walk distance, but the study will continue to assess the 30-month endpoint of all-cause mortality and cardiovascular hospitalizations. TTR silencers are FDA-approved for ATTRv polyneuropathy, with ongoing trials

for ATTR-CM. Patisiran and vutrisiran are small interfering RNA therapeutics,[95,96] and inotersen is an antisense oligonucleotide therapeutic.[97] Acting upstream of TTR stabilizers, TTR silencers are theoretically synergistic with stabilizers, but data are lacking on combination therapy.

In vitro TTR disrupters (doxycycline with tauroursodeoxycholic acid[98] or epiallocatechin-3-gallate in green tea[99]) would be ideal if effective as they theoretically reverse amyloid deposition in affected organs. However, data are limited, particularly in the era of tafamidis, and these agents are no longer recommended as standard-of-care. A number of different antifibril antibodies have been developed for immune system-triggered amyloid resorption but, to date, these agents either remain in clinical trials or have failed to meet study endpoints.

An emerging therapy is gene editing leveraging clustered regularly interspaced short palindromic repeats and the associated Cas9 endonuclease (CRISPR-Cas9) complex, resulting in permanent modification of genomic DNA. The early experience in 6 patients with ATTRv, as part of a phase 1 clinical study, showed durable knockout of TTR after a single infusion. At day 28 after administration, there was sustained 87% mean knockdown of TTR in the group that received the highest dose. In short-term follow-up, there were no major adverse events.[100]

7. STEP 2: COLLABORATION BETWEEN CARDIOLOGISTS AND OTHER SPECIALISTS

It is essential for cardiologists to be aware of the extracardiac manifestations of cardiac amyloidosis because the varied extracardiac manifestations may offer clinical clues to diagnosis and may contribute to patients' morbidity and decrements in quality of life. Furthermore, multidisciplinary collaboration may be required for diagnostic purposes as well, for example, with geneticists, genetic counselors, or other clinicians with genetics expertise to best perform and interpret the results of genetic testing, or with hematologists to interpret the results of plasma cell disorder testing.

The next section will focus on the necessary decision pathways involved in initiating multidisciplinary collaborations with genetic experts, nephrologists, hematologists, gastroenterologists, neurologists, advanced heart failure cardiologists, and palliative care specialists.

7.1. Genetics

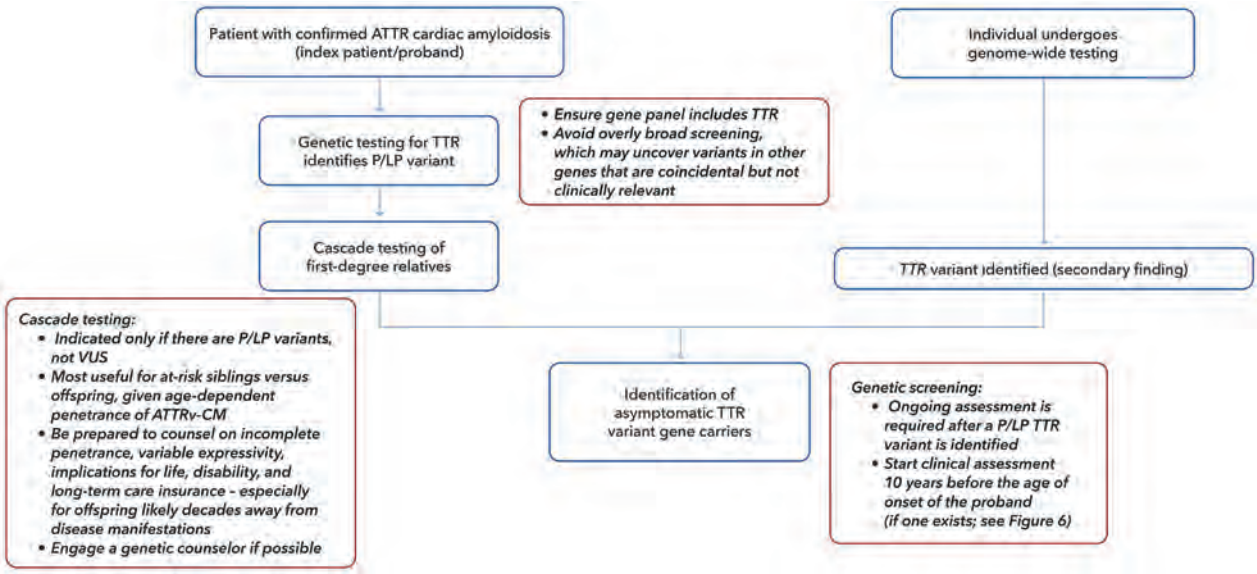
Human TTR is encoded by the single-copy gene *TTR* on chromosome 18.[101] *TTR* spans about 7 kB and contains 4 exons and 3 introns.[101] Over 130 human *TTR* variants have been identified, and the most common variants are shown in Table 3.[102] The hereditary form of ATTR-CM is caused by variants in the TTR gene (*TTR*) and is transmitted as an

TABLE 3 Genetic and Clinical Characteristics of *TTR* Variants Known to Cause Heritable Amyloidosis

Variant	Frequency	Penetrance	Typical Age of Onset (y)	Cardiac Phenotype	Neurologic Phenotype	Race and/or Nationality	Country/Location
Val122Ile	3.5% in Blacks	37.4% with carpal tunnel syndrome, polyneuropathy, cardiomyopathy, or heart failure by age 75 y[103]	Late 60s	+++	+	Black and Caribbean Hispanics/West African ancestry	Worldwide
Val30Met (early onset)	Most common variant currently worldwide	>90%	<40	+	+++	Portuguese, Japanese, Swedish	Portugal, Sweden, Japan, Brazil, Cyprus, and Majorca
Val30Met (late onset)	1 per million in Japan	>60%	>50	++	++	Worldwide	Worldwide
Thr60Ala	1% in County Donegal, Ireland.	>90%	>50	+++	++	Irish	Ireland, England, United States
Leu111Met	<1% of all *TTR* variants	>90%	30-40	+++	+	Danish	Denmark
Ile68Leu	<1% of all *TTR* variants	>90%	55	+++	+	Italian, German	Italy, Germany
Ser77Tyr	<1% of all *TTR* variants	>90%	55	++	++	French, German, American	United States, France, Spain
Glu89Gln	<1% of all *TTR* variants	>90%	55	++	++	Italian	Italy
Gly47Glu	<1% of all *TTR* variants	>90%	45	++	+++	Italian	Italy, German
Ile84Ser	<1% of all *TTR* variants	Unknown	40	++	+++	Swiss, German	United States
Phe64Leu	<1% of all *TTR* variants	Unknown	>50	++	+++	Italian	Italy, United States
Leu58His	<1% of all *TTR* variants	Unknown	>50	++	+++	German	United States, Germany
Ser50Arg	<1% of all *TTR* variants	Unknown	>40	++	+++	Asian, Mexican	Japan, Mexico
Gly47Ala	<1% of all *TTR* variants	Unknown	>40	+	+++	German, Italian, French, Mexico	Germany, Italy, France
Val20Ile	<1% of all *TTR* variants	Unknown	60s	++	+	German[104]	Germany

+ = less common; ++ = common; +++ = more common.

FIGURE 5 **Process and Pitfalls of Genetic Testing**



ATTR = amyloid transthyretin; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; P/LP = pathogenic/likely pathogenic; TTR = transthyretin; VUS = variants of unknown significance.

autosomal-dominant disease, where only 1 copy of the variant is needed to cause disease.

Most variants that cause ATTR are rare and penetrant, where penetrance is defined as the likelihood that an individual carrying a variant will show evidence of the condition. In contrast, one common variant encountered in the United States,[105] the Val122Ile variant, is present in 3.5% of individuals (1 in 29) who self-identify as Black (**Table 3**). This variant affects individuals of West African ancestry[106] who are most often Black or African American or are Hispanic from Caribbean, Central, or South American countries.[15] Given its prevalence, there are ~1.5 million allele carriers of the Val122Ile variant in the United States, although its penetrance, as discussed later, remains unknown.

7.1.1. Indications for genetic testing

Genetic testing for suspected ATTR amyloidosis is indicated in individuals with clinical evidence to support a *TTR*-related phenotype (**Figure 5**). Assuming this individual is the first member of a family to be identified, such a patient is known as the proband (or index patient). Genetic testing for a specific condition is only recommended for individuals who have a phenotype established to have a genetic basis, and the gene panel is recommended to be constrained to those genes that have a known association with the condition under evaluation.[107,108]

This parsimonious approach is best because the probability of finding a relevant variant that is disease-associated is much higher for individuals with that phenotype and mitigates the countervailing concern of finding undue numbers of variants of uncertain significance (VUS). If a pathogenic (P) or likely pathogenic (LP) variant is identified in *TTR* (or another CM gene), cascade testing of at-risk first-degree relatives should be considered.[108,109] Variants of uncertain significance (VUS) are not considered appropriate for cascade testing.

The age-dependent penetrance of TTR-related amyloid, which, in most cases, becomes clinically evident in the seventh, eighth, and ninth decades of life, highlights that the potential benefits of cascade genetic testing will have greater immediate relevance for at-risk siblings of a proband than for their younger at-risk offspring. Moreover, cascade testing of individuals several decades before their presumptive age of onset should only be undertaken after counseling of the individual regarding both possible benefits and harms of testing.[108,109]

7.1.2. Choosing the appropriate gene panel

Clinical genetic testing for *TTR* is now widely available and is commonly included in panels of several dozen

TABLE 4 Essential Components of the Genetic Testing Process

Minimal Clinical Competence—All Providers Offering Clinical Genetic Testing
■ Obtain a 3-generation (or greater) family history for the phenotype of interest.
■ Assess the pedigree for patterns for inheritance (dominant, recessive, X-linked), and identify possible at-risk family members depending upon inheritance patterns.
■ Decide, within the context of patient choice, if clinical genetic testing is warranted based on the phenotype, the pedigree, and the clinical needs of the patient.
■ Provide pretest counseling if testing is warranted, including issues of life insurance or other issues not covered by GINA.
■ Select an appropriate testing panel, accounting for insurance coverage and clinical coverage for a differential diagnosis based upon the proband phenotype.
■ Discuss genetic testing results with the patient (P, LP, VUS), and counsel the patient on possible cascade clinical and genetic testing implications for at-risk family members.
■ Offer therapeutic options for the patient/family based on testing results.
Clinical Competence Associated With Certified Genetics Professionals
■ Assist with in-depth family communications: ■ Arrange clinical evaluations and genetic testing as indicated. ■ Counsel at-risk family members.
■ Explain employment and insurance implications of genetic testing.
■ Assess for complex modes of inheritance.
■ Provide explanations regarding age of onset, penetrance, and expressivity.

GINA = Genetic Information Nondiscrimination Act; LP = likely pathogenic; P = pathogenic; VUS = variant of uncertain significance.

genes known to cause CMs. Gene panels are organized by phenotype (arrhythmogenic right ventricular, restrictive, hypertrophic, and dilated CM, or a pan-CM panel inclusive of all CMs). Neuropathy gene panels follow the same logic, with specific types of neuropathies including different genes. However, the genes present on testing panels offered by different companies vary considerably. If *TTR* variant testing is desired, it is essential to ensure that *TTR* is present on the testing panel.

Because the phenotype of increased wall thickness, often interpreted as left ventricular hypertrophy (LVH), is commonly associated with ATTR-CM, *TTR* is included on virtually all hypertrophic CM gene panels as well as those for restrictive and dilated CM. However, if a *TTR* variant is identified in a patient otherwise rigorously classified as having idiopathic dilated CM (specifically, with nonsyndromic left ventricular enlargement associated with left ventricular systolic dysfunction), a *TTR* variant may be coincidental but not causal, and further specific testing for ATTR-CM, such as by nuclear imaging or endomyocardial biopsy, may be required.[110] Thus, another diagnostic pitfall is to ensure that genetic testing is being performed in the appropriate clinical context because pretest probability will guide interpretation of results, especially given incomplete penetrance and variable expressivity. A final diagnostic pitfall would be to assume that a normal *TTR* genotype in an at-risk patient excludes ATTR amyloidosis.

7.1.3. Challenges in genetic screening

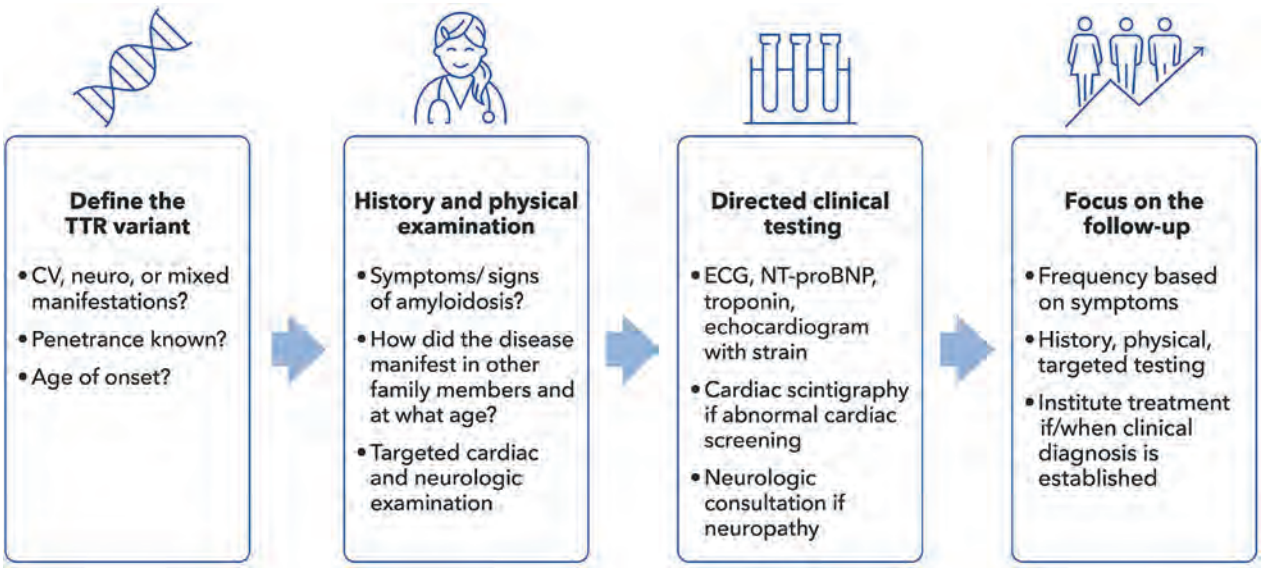
One of the major challenges of genetic screening is that all *TTR* variants show incomplete penetrance and variable expressivity. Amyloidosis commonly displays incomplete penetrance, where an individual may carry a relevant variant but not show any evidence of the associated phenotype, although the penetrance of TTR is well established as age-dependent. The biological mechanisms for the age-dependent penetrance of TTR-associated amyloidosis remain largely unknown, and factors that contribute to penetrance are poorly defined but may include inflammation, whether inheritance is maternal or paternal, and other factors.[111-113] Men have been reported to have more penetrant TTR-associated disease, although the reasons for this are unknown.[114,115]

Amyloidosis also exhibits variable expressivity (different from penetrance), as the disease phenotype can manifest differently in individuals who share the same genotype. For example, in TTR-associated amyloidosis, there may be differences in the extent and clinical findings of CM vs neuropathy with a specific *TTR* variant.

Understanding the implications of the age-dependent incomplete penetrance and variable expressivity of *TTR* variants is key to providing the most insightful clinical care. Some variants are associated with a much earlier age of onset, and ATTRwt is associated with an older mean age of onset.[105] However, a pitfall of genetic testing is to assume that age alone is a valid discriminator of ATTRwt vs ATTRv disease. This is not the case; all individuals with ATTR-CM should undergo genetic testing regardless of age at presentation, given the variable expressivity and the implications for at-risk relatives as well as differences in disease-modifying therapies (the TTR silencers patisiran and vutrisiran [small interfering RNAs] and inotersen [antisense oligonucleotide] are only approved by the FDA for use in ATTRv neuropathy).

The penetrance of TTR-associated amyloidosis with the Val122Ile variant was reported to be as low as 8% based on echocardiographic features,[116] although its clinical penetrance is likely higher.[117] More sensitive autopsy studies of myocardial tissue from individuals over 60 years of age have shown that the pathologic penetrance of the Val122Ile variant was complete (eg, 100% of the myocardial tissue specimens examined).[118] Epidemiologic studies have demonstrated that the Val122Ile variant has been associated with an increased risk of HF after controlling for relevant risk factors,[116,119] highlighting the importance of this variant beyond a fully clinically-evident amyloid CM.

FIGURE 6 Management of Asymptomatic *TTR* Variant Gene Carriers



CV = cardiovascular; ECG = electrocardiogram; neuro = neurologic; NT-proBNP = N-terminal pro-B-type natriuretic peptide; *TTR* = transthyretin.

7.1.4. Multidisciplinary collaboration: the role of genetic counselors

For busy cardiovascular clinicians, covering key aspects[120] of counseling for heritable diseases (**Table 4**) is time-consuming and may be optimally accomplished with collaboration from genetic counselors, who can provide more comprehensive services beyond assistance with testing within a counseling framework.[108] Importantly, those undergoing testing should be informed that their genetic test results cannot be used to determine eligibility for health insurance based on the Genetic Information Nondiscrimination Act (GINA). However, it is also critical to inform patients in pretest counseling that GINA does not offer eligibility protection for life, disability, or long-term care insurance, which could be denied based on a positive test result.

7.1.5. Management of asymptomatic *TTR* variant gene carriers

There are 2 types of individuals who may be identified as asymptomatic carriers of a pathogenic *TTR* variant: first-degree relatives of affected individuals identified through cascade testing and/or individuals who undergo genome-wide testing for other reasons.[108] Under the latter testing scenario, rare variants, including some considered pathogenic, may be identified without an associated phenotype. Due to the increased use of clinical exome or genome testing, the American College of Medical Genetics and Genomics has recommended that established pathogenic and likely pathogenic variants of select actionable genes beyond those targeted by the phenotype of interest be returned to individuals undergoing clinical exome or genome sequencing.[121] Such findings are referred to as secondary findings—variants serendipitously identified and associated with an actionable phenotype, but not associated with the reason that the testing was initiated. A substantial fraction of genes on the American College of Medical Genetics and Genomics secondary findings gene list[122] are CM, channelopathy, and aortopathy genes due to the presentation of these phenotypes with sudden death from arrhythmia or aortic rupture and the availability of interventions to prevent life-threatening disease. *TTR* has been added to this list[122] due to its prevalence in African Americans, its association with systemic amyloidosis and increased risk of HF, and possible therapeutic intervention.

Consensus statements have recommended ongoing assessment for disease penetrance in asymptomatic gene carriers approximately 10 years before the age of onset in the proband.[123,124] A proposed framework for following and managing these asymptomatic gene carriers is provided in **Figure 6**. Key aspects of care include knowledge regarding specific *TTR* variants, performing a thorough directed history and physical examination, implementing relevant clinical testing, and ensuring long-term follow-up.

When assessing the impact of a specific *TTR* variant, the following questions are important: How does the variant typically manifest disease (eg, cardiac, neurologic,

or mixed phenotype)? What is the usual penetrance? At what age does the expected phenotype become clinically detectable? **Table 3** is a useful resource in this regard.

Components of a thorough and directed history and physical examination include assessment of symptoms and signs relative to those of the proband and other affected relatives and determining insight into penetrance and expressivity from evaluation of an extended pedigree. A targeted cardiac and neurologic examination is required, with engagement of colleagues from relevant disciplines as signs and symptoms dictate.

Necessary clinical testing will include, at a bare minimum, a screening ECG, cardiac biomarkers (natriuretic peptide and troponin), and an echocardiogram, ideally with strain imaging. If there are symptoms or abnormal laboratory or imaging tests, cardiac scintigraphy or CMR may be warranted. If there is evidence of neurologic involvement, such as peripheral neuropathy (numbness, paresthesia, imbalance), autonomic dysfunction (orthostatic hypotension, GI symptoms), or carpal tunnel syndrome, then neurology consultation may be warranted for a complete neurologic examination, measurement of the Neurologic Impairment Score (NIS), use of questionnaires to define symptom severity (eg, Small-Fiber Neuropathy and Symptom Inventory Questionnaire [SFN-SIQ], Autonomic Symptom Profile [ASP], or Composite Autonomic Symptom Score [COMPASS]), neurophysiological assessments, such as electromyography (EMG) with nerve conduction studies, sympathetic skin response and quantitative sensory testing, and, possibly, autonomic function tests, including postural blood pressure monitoring, sudomotor testing, and heart rate (R-R) variability.

Finally, fostering a long-term relationship with asymptomatic gene carriers is essential. If no clinical evidence of *TTR* amyloidosis is found, repeat clinical testing is reasonable every 3 to 5 years in the absence of symptoms or sooner if symptoms arise or as the predicted age of disease onset approaches. Notably, such screening recommendations are based primarily on expert opinion; studies designed to more formally establish screening intervals are needed. All patients should be counseled on the usual presenting symptoms, with instructions to return before the next scheduled screening visit if new symptoms arise.

7.2. Neurology

7.2.1. Neurologic manifestations of AL and ATTR cardiac amyloidosis

Patients with either AL amyloid or ATTRv amyloidosis may develop polyneuropathy. Polyneuropathy is observed in 17% to 35% of patients with AL amyloidosis,[125-127] and in ATTRv, the presence of peripheral neuropathy varies with the variant. For patients in the endemic region of Northern Portugal with the Val30Met variant, over 80% develop peripheral neuropathy by age 50 years. In contrast, for patients with the Val122Ile variant, which is predominantly associated with CM, the prevalence of polyneuropathy is unclear but estimated at about 10%. ATTRwt, in turn, predominantly causes CM, but approximately 30% of patients may have a polyneuropathy that may (or may not) be attributable to amyloidosis.[128-130]

Amyloid neuropathy is often initially a small-fiber neuropathy, causing sensory loss and pain in the toes and feet. It is rapidly progressive (15-20× more rapid than diabetic neuropathy) and unusual in that autonomic dysfunction is often an initial or early manifestation of the polyneuropathy.[131] Left untreated, the neuropathy progresses to large-fiber neuropathy with increasing weakness, gait dysfunction, and eventually loss of ambulation. Neuropathy associated with ATTRwt is usually milder and autonomic dysfunction is much less prominent than with ATTRv.[128-130]

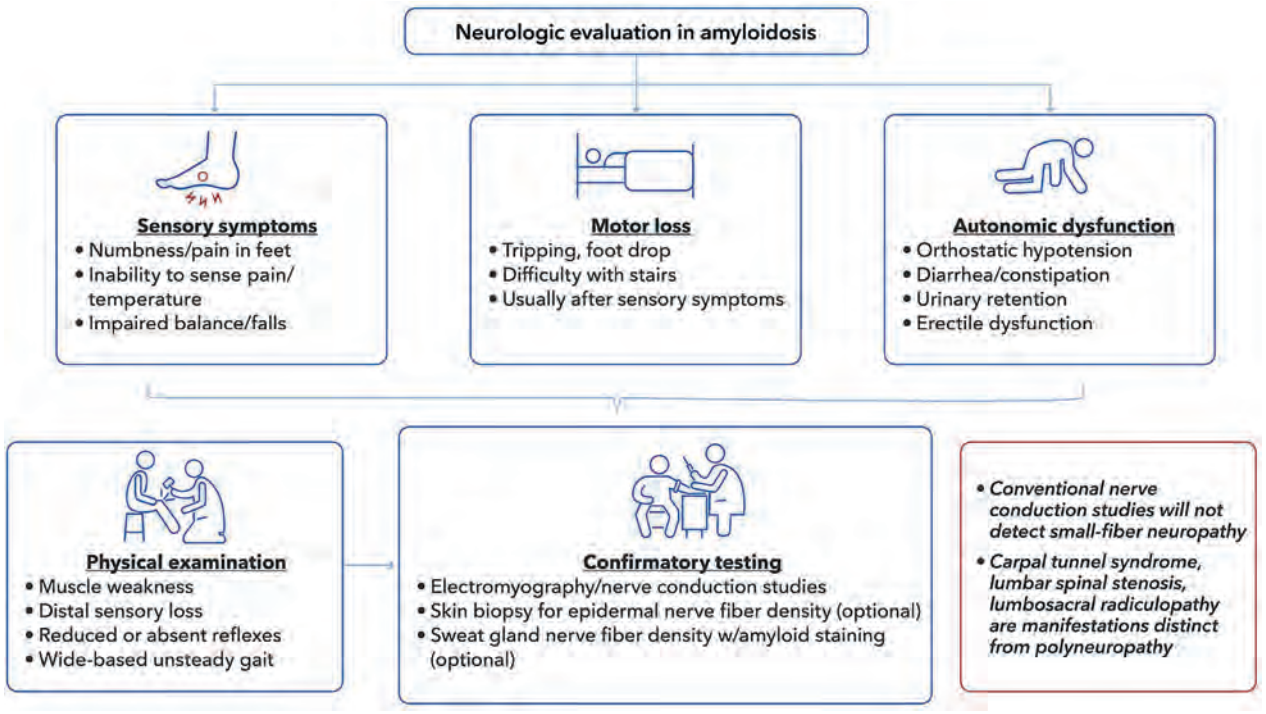
7.2.2. Multidisciplinary collaboration: when to involve a neurologist

Manifestations that may prompt a consultation with a neurologist are outlined in **Figure 7**, as well as evaluation strategies. Symptoms of polyneuropathy typically begin symmetrically with numbness, paresthesia, or pain in the toes and feet. These symptoms are worse at the end of the day or at nighttime. As symptoms progress, the fingertips may be involved next. Muscle weakness also begins distally, with weakness first in the toe extensors and then in the ankle dorsiflexors, and proprioceptive sensory loss in the feet causes gait imbalance. Autonomic symptoms may include orthostatic hypotension, alternating diarrhea and constipation and night diarrhea, urinary retention, and sexual dysfunction.

On physical examination, there may be muscle weakness, more prominently distally, sensory loss distally, reduced or absent reflexes, and a wide-based unsteady gait. Confirmatory tests for polyneuropathy include nerve conduction studies and electromyography.[132] However, when patients have only small-fiber neuropathy, this will not be detected by conventional nerve conduction studies, and a skin biopsy to determine epidermal nerve fiber density may be performed to confirm a small-fiber neuropathy.[133] Sweat gland nerve fiber density[134] may also be examined, as well as Congo red staining for amyloid.

The modified NIS + 7 scale was specifically designed to assess polyneuropathy impairment in patients with ATTRv amyloidosis,[135] and has been the primary endpoint in the 2 landmark trials of TTR silencers for ATTRv neuropathy.[95,97] The modified NIS + 7 uses highly standardized, quantitative, and referenced assessments to quantify muscle weakness, muscle stretch reflexes,

FIGURE 7 Manifestations and Evaluation of Amyloid Polyneuropathy



sensory loss, and autonomic impairment. Physicians using this scale in clinical trials should be specifically trained and monitored to minimize variability, and thus, it is not practical for use in clinical settings. In clinical settings, the course of ATTRv amyloid polyneuropathy may be followed with the familial amyloid polyneuropathy (FAP) score. FAP stage 1 is the ability to walk unassisted; FAP stage 2 is the ability to walk with assistance, with a cane or a walker; and FAP stage 3 is when patients are wheelchair- or bed-bound.

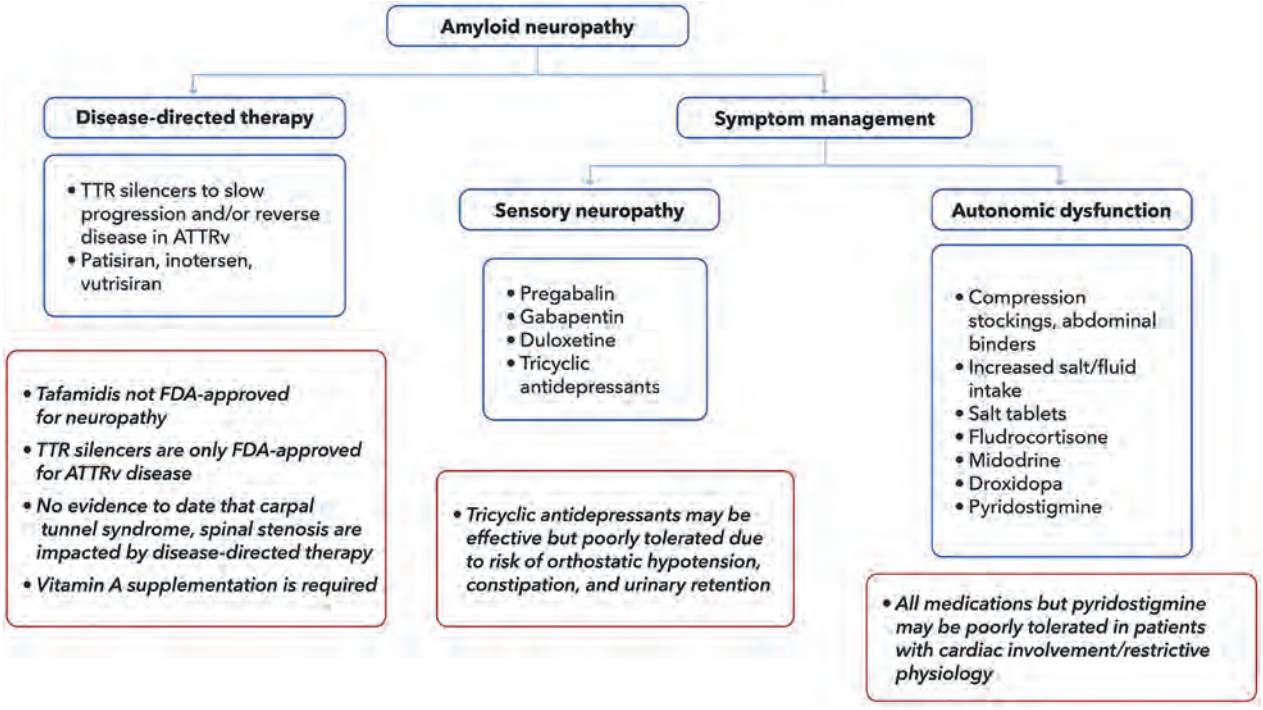
Other neurologic syndromes that are common with amyloidosis are carpal tunnel syndrome and lumbar stenosis or lumbosacral radiculopathy. These syndromes are distinct from polyneuropathy; however, they can cause a similar pattern of numbness, pain, and weakness and may be confused with polyneuropathy. Carpal tunnel syndrome often precedes the polyneuropathy in patients by many years. The classic symptom of lumbar stenosis is neurogenic claudication with numbness, pain, or weakness in the legs after walking a short distance, which persists with standing but is relieved by sitting or lying down. This is the opposite of the precipitating factors in polyneuropathy symptoms, which are usually worse when lying in bed and improve with walking.

7.2.3. Management of amyloid neuropathy

Management is summarized in **Figure 8** and medications are detailed in **Table 5**. There are currently 3 medications that are approved by the FDA for ATTRv polyneuropathy (tafamidis is also approved in Europe for polyneuropathy). TTR silencers act by blocking the translation of RNA to synthesize the protein transthyretin. Patisiran and vutrisiran are small interfering RNAs,[95,96] and inotersen is an antisense oligonucleotide.[97]

These 3 TTR silencers reduce progression of the polyneuropathy compared with placebo, and some patients had improvement in measures of neuropathy impairment or neuropathy quality of life. In pivotal trials, on average at the cohort level, the 3 silencers resulted in stabilization or reversal of disease progression (in terms of neuropathy and quality of life) relative to patients' pretreatment baseline.[95-97,136] Early diagnosis and treatment is important because patients treated earlier have better measures of neuropathy impairment and quality of life than those whose treatment is delayed by 1 year or more.[137] Of note, as the normal function of transthyretin is to transport retinol, daily supplementation with vitamin A 3,000 IU is needed when these medications are prescribed. With patisiran, infusion-related reactions may occur, and premedication is recommended with corticosteroid,

FIGURE 8 **Management of Amyloid Neuropathy**



ATTRv = variant transthyretin amyloidosis; FDA = U.S. Food and Drug Administration; TTR = transthyretin.

acetaminophen, and antihistamines (H1 and H2 blockers) at least 60 minutes before the infusion. Inotersen can result in injection-site reactions as well as thrombocytopenia and glomerulonephritis. Because of this, platelet counts should be followed weekly, and serum creatinine and the urine protein-creatinine ratio should be followed every 2 weeks.

Diflunisal and tafamidis are TTR stabilizers which also slow the progression of ATTRv polyneuropathy.[72,138] However, although approved for ATTR-CM, tafamidis does not have approval from the FDA for treatment of ATTRv polyneuropathy. Diflunisal was demonstrated effective in ATTRv polyneuropathy to slow disease progression but is not FDA approved for this indication.[72]

In conjunction with disease-directed therapy, symptomatic management is important for patients with peripheral neuropathy and may include physical therapy, medications for neuropathic pain, and treatment of autonomic disorders. Pregabalin, gabapentin, and duloxetine may be beneficial for neuropathic pain. Tricyclic antidepressants, which are commonly used for neuropathic pain, may have increased side effects in many patients with amyloid neuropathy who also may have orthostatic hypotension or other autonomic symptoms, such as urinary retention, erectile dysfunction, or constipation.[139] It is important to note, however, that older patients with amyloidosis are at greater risk for side effects of these medications. Along with consultation with a geriatric specialist, the Beers Criteria from the American Geriatric Society is a helpful guide that outlines potentially inappropriate medication use in older adults.[140]

Orthostatic hypotension may improve with increased fluid intake, salt tablets, fludrocortisone, midodrine, or droxidopa, although these interventions may be poorly tolerated in patients with heart failure from cardiac involvement. Pyridostigmine is another option for orthostatic hypotension without the risks of fluid retention or supine hypertension.[141] Compression with knee- or thigh-high compression socks or stockings, and abdominal binders (in patients who can tolerate them) can be helpful without the risk of drug side effects or interactions.

Currently, there is no evidence that TTR stabilizers or silencers are beneficial in polyneuropathy associated with ATTRwt amyloidosis. There is also currently no evidence that these medications are beneficial for carpal tunnel syndrome or lumbar stenosis associated with

TABLE 5 Medications for Treatment of Neurologic Manifestations of Cardiac Amyloidosis

Agent	Dosing	Maximum Dosage	Precautions	Adverse Effects
Disease-modifying therapy				
TTR silencers				
Patisiran (small interfering RNA)	0.3 mg/kg every 3 wk, IV (for patients weighing 100 kg or more, the recommended dosage is 30 mg)	30 mg every 3 wk	Premedication with dexamethasone 10 mg IV, acetaminophen 500 mg, diphenhydramine 50 mg, famotidine 20 mg; requires vitamin A supplementation 3,000 IU daily; only approved for use in ATTRv polyneuropathy	Infusion-related reactions
Inotersen (antisense oligonucleotide)	284 mg once a wk, SC	Fixed dose	Requires vitamin A supplementation 3,000 IU daily; check platelet count weekly and serum creatinine, eGFR, and UPCR every 2 wk; only approved for use in ATTRv polyneuropathy	Thrombocytopenia, glomerulonephritis, injection-related reactions
Vutrisiran (small interfering RNA)	25 mg every 3 mo, SC	same	Requires vitamin A supplementation 3,000 IU daily; only approved for use in ATTRv polyneuropathy	Arthralgias
Neuropathic pain				
Pregabalin	75 mg twice daily; after 4-7 d, increase by same dosage to goal of 300 mg/d as necessary to 600 mg/d	600 mg/d (split twice a day)	Kidney insufficiency (dosage adjust); psychiatric disease or addiction history (euphoria risk)	Sedation, dizziness, confusion, edema, euphoria, weight gain (Schedule V controlled substance)
Gabapentin	300 mg at bedtime, increase every 4-7 d by 300-mg increments, initially to 3 times/d and then to goal of 1,800 mg/d and as necessary to 3,600 mg/d	3,600 mg/d (split 3 times/d)	Kidney insufficiency (dosage adjust)	Sedation, dizziness, confusion, edema, weight gain
Tricyclic antidepressants: amitriptyline, nortriptyline	10-25 mg at bedtime, increase every 4-7 d to goal of 100 mg at bedtime	150 mg/d	Risk of serotonin syndrome; caution if cardiac disease or dysrhythmia history	Sedation, dry mouth, orthostatic hypotension, confusion, weight gain, urinary retention, constipation, blurred vision
Selective serotonin–noradrenaline reuptake inhibitors: Duloxetine	20-30 mg once daily, then increase weekly by same dosage to goal of 60 mg/d	120 mg/d (split twice a day)	Risk of serotonin syndrome; increased bleeding risk (care with anticoagulants), withdrawal syndromes with abrupt discontinuation, caution with hepatic failure	Sedation, fatigue, nausea, hyperhidrosis, dizziness, modest hypertension
Orthostatic hypotension				
Sympathomimetic agents				
Midodrine	2.5 mg 3 times daily, titrated to symptoms and blood pressure	10 mg 3 times daily	May be poorly tolerated in HF	Supine hypertension; itching (especially scalp itching) due to pilomotor activation; urinary retention; and headaches
Droxidopa	100 mg 3 times daily, titrated to symptoms and blood pressure	600 mg 3 times daily	May be poorly tolerated in HF	Supine hypertension, headaches, dizziness, and nausea
Pyridostigmine	30 mg 2 or 3 times daily, titrated to symptoms and blood pressure	60 mg 3 times daily	Less likely to cause supine hypertension	Increased salivation, lacrimation, diarrhea, urinary urgency, sweating, and bradycardia
Agents to increase blood volume				
Salt tablets	1 or 2 tablets (600-1,200 mg) once or twice daily	600 mg 4 times/d	Poorly tolerated in HF	Supine hypertension, edema
Fludrocortisone	0.2 mg loading dose followed by 0.1 mg/d	1.0 mg/d	Poorly tolerated in HF	Supine hypertension, hypokalemia, and edema

Information from Watson et al.[139] and Freeman et al.[142]

ATTRv = variant transthyretin amyloidosis; eGFR = estimated glomerular filtration rate; HF = heart failure; IV = intravenous; SC = subcutaneous; UPCR = urine protein-creatinine ratio.

TABLE 6 Neurologic Contraindications to Heart Transplantation in Cardiac Amyloidosis

Severe peripheral neuropathy with resulting inability to ambulate (FAP Stage 3)
Severe autonomic dysfunction with:
■ Orthostatic hypotension that requires medications to raise the blood pressure (midodrine and/or droxidopa) that cannot be weaned
■ Malnutrition and wasting, as reflected in a modified body mass index[a] <600 kg/m^2·g/L
■ Urinary retention requiring catheterization

[a]Modified body mass index defined as body mass index × serum albumin.
FAP = familial amyloid polyneuropathy.

amyloidosis. In these situations, treatment involves physical therapy, braces, or surgical intervention.

7.2.4. Neurologic contraindications to heart transplantation

Amyloid polyneuropathy, if severe, may be a contraindication to heart transplant especially when the neurologic involvement does not improve after heart transplantation and may in fact progress.[143] The International Society of Heart and Lung Transplantation guidelines note that severe extracardiac amyloid organ dysfunction should be considered a contraindication to heart transplantation (Class 2A, Level of Evidence: B).[144]

Although the International Society of Heart and Lung Transplantation guidelines do not provide details about neurologic evaluation or contraindications, for patients with significant neurologic symptoms, an evaluation by a neurologist with expertise in peripheral neuropathy is recommended to identify significant neurologic impairment that would hamper post-transplantation rehabilitation efforts and/or have a significant impact on quality of life. Table 6 outlines generally accepted neurologic contraindications to heart transplantation in patients with cardiac amyloidosis.

7.3. Gastroenterology

7.3.1. GI manifestations of AL and ATTR amyloidosis

Amyloidosis can affect GI function via multiple potential mechanisms. Mucosal involvement may lead to malabsorption or protein-losing enteropathy, neuropathic involvement may present primarily as GI dysmotility, and vascular involvement may present with ischemia and bleeding. Small intestinal bacterial overgrowth and obstructive symptoms may also manifest.

Even without direct mucosal deposition, amyloidosis can result in profound GI symptoms through polyneuropathy involving the enteric nervous system with resultant dysautonomia. The most common reported GI symptoms of amyloidosis include early satiety, weight loss, abdominal pain, nausea, constipation, and diarrhea.[145-147]

Although GI symptoms and clinical presentation may vary based on the pattern of amyloid deposition, it is not well established if the degree of GI tract infiltration correlates with the degree of GI symptoms. For example, GI symptoms are reported in up to 60% of patients with AL amyloidosis,[148] but biopsy-confirmed GI involvement is reported far less frequently, in 3% to 15% of patients in 3 large retrospective analyses.[148-150] In an analysis of THAOS (Transthyretin Amyloidosis Outcomes Survey), 63% of patients with ATTRv amyloidosis reported GI symptoms at enrollment, most commonly unintentional weight loss and early satiety. In a postmortem examination of patients with ATTR amyloidosis, about 40% had pathologic evidence of amyloid deposits in the GI tract.[151] GI symptoms were more predominant in patients with neuropathic variants. Notably, patients with predominantly ATTRwt amyloidosis with cardiac involvement did not have an increase in GI manifestations with the rate of reported symptoms comparable to that of the general population.[147]

7.3.2. Diagnosis of GI amyloid involvement

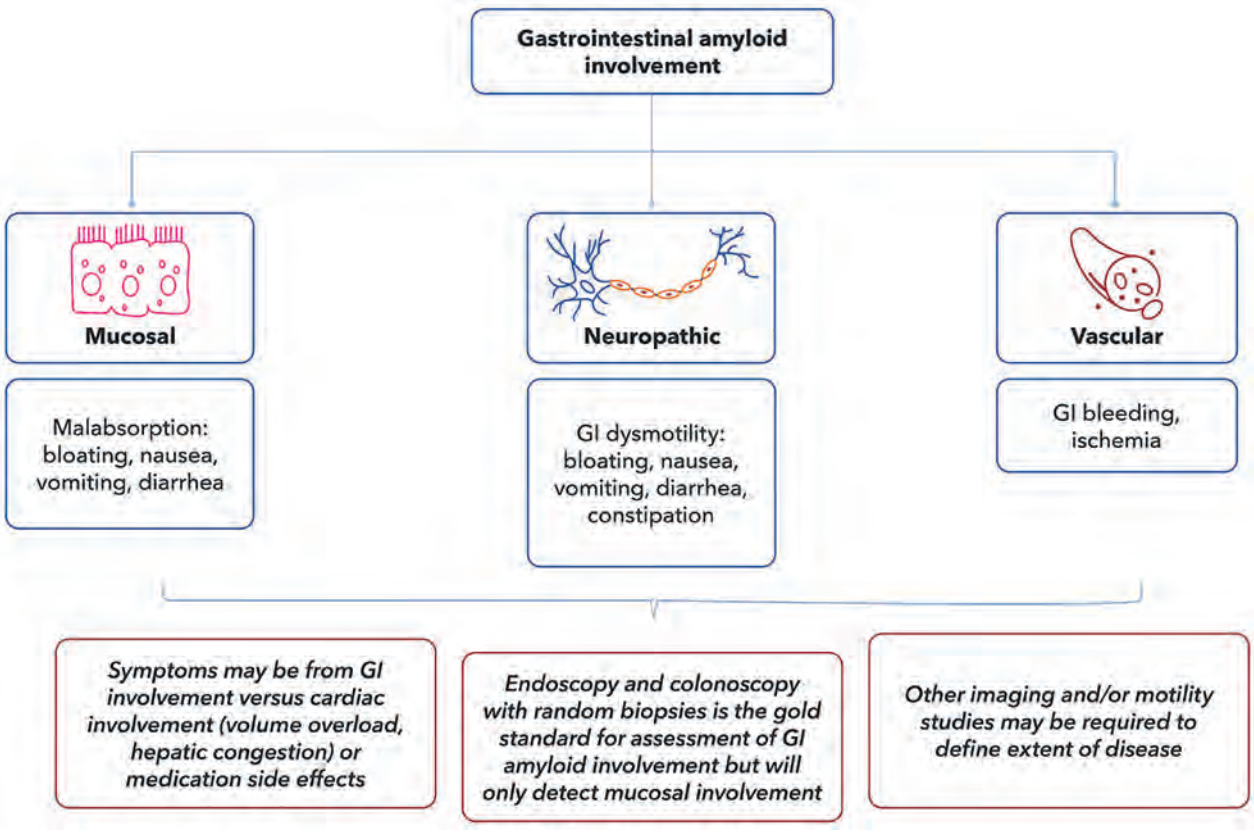
It can be difficult to ascertain if GI symptoms in patients with amyloidosis result from GI amyloid involvement, autonomic neuropathy, or unrelated entities. For example, patients with cardiac amyloidosis can have volume overload with resultant hepatic congestion causing abdominal pain and nausea. In addition, abdominal pain, nausea, diarrhea, and constipation are common side effects from many medications.

Thus, diagnosis of amyloidosis in the context of GI symptoms can be challenging (Figure 9). Objective markers of nutritional status and body mass index (BMI) can be nonspecific because they are affected by non-GI etiologies and may not represent direct effects of GI amyloid deposition. The modified body mass index (mBMI) (serum albumin multiplied by BMI) can be useful to assess for malnutrition in patients with amyloidosis, although the source of the malnutrition (autonomic involvement, advanced HF, and/or direct GI amyloid infiltration) may not be clear. Because conventional BMI does not reflect fluid accumulation that can occur in amyloidosis and falsely elevates BMI, mBMI is a more accurate measure of malnutrition status. An mBMI <600 kg/m^2·g/L is a marker of poor nutritional status and poor prognosis in cardiac amyloidosis.[152]

The gold standard for GI involvement is endoscopic biopsy with Congo red staining; however, this approach will demonstrate mucosal amyloid deposition only and cannot identify instances of primarily neuropathic or muscular involvement.

Despite these caveats, endoscopy and colonoscopy with random biopsy acquisition is generally performed in the case of established amyloidosis with suspected GI

FIGURE 9 Evaluation and Manifestations of GI Amyloid Involvement



GI = gastrointestinal.

involvement. Although management, outlined later, is supportive and not amyloid-specific, biopsies serve 2 purposes: 1) risk stratification to assess the degree of extracardiac manifestations if the patient is undergoing heart transplant evaluation (Section 7.6.3); and 2) to exclude other causes of GI symptoms. When submitting endoscopic biopsy samples to pathology, it is important to specify that Congo red staining be used because a diagnosis of amyloidosis may be missed based on standard histological findings alone. Limited data suggest that the diagnostic yield of biopsies may be highest in the duodenum,[153] but biopsies are typically performed throughout the GI tract and will target any areas of mucosal irregularity or regions of the GI tract most implicated by symptoms.

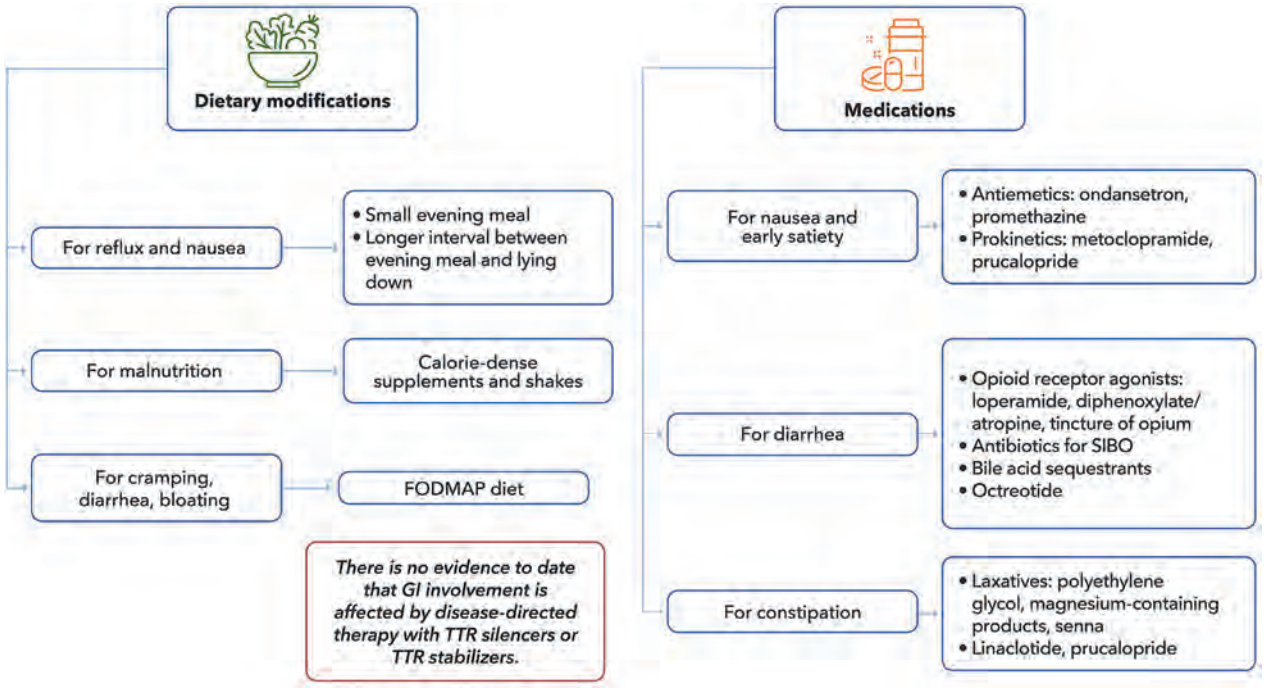
In affected patients, there may also be a role for imaging or motility studies to exclude other processes and tailor management. Cross-sectional imaging, fluoroscopy, breath testing, or manometry may all be helpful on a case-by-case basis; however, none of these will have findings pathognomonic for amyloidosis. Hepatic involvement in AL amyloidosis can be diagnosed either by direct biopsy or inferred through the presence of hepatomegaly and an elevated alkaline phosphatase level in an already-diagnosed patient. Hepatic amyloid deposition is reported in approximately 15% to 20% of patients with AL amyloidosis; however, in most cases, this is a marker of more widespread systemic amyloid distribution rather than a dominant cause of symptoms.[148]

7.3.3. Management of GI amyloid involvement

Therapy for GI amyloidosis generally consists of supportive therapy to alleviate symptoms (**Figure 10 and Table 7**). Collaboration with a geriatric specialist and/or review of potentially inappropriate medications by the Beers Criteria from the American Geriatrics society may be helpful to avoid harmful polypharmacy. None of the treatments detailed later will affect amyloid deposition, so it is reasonable to target treatment to symptoms without waiting for a definitive diagnosis of amyloidosis.

Given the overlay between diet and GI symptoms, dietary modification is always a reasonable first step,

FIGURE 10 Management of GI Amyloidosis



FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI = gastrointestinal; SIBO = small intestine bacterial overgrowth; TTR = transthyretin.

and collaboration with a nutritionist is helpful. Because symptoms may arise from slow gastric emptying and/or gastroesophageal reflux, eating a small evening meal, having a predominantly liquid meal (which will have faster gastric transit), and lengthening the time between dinner and lying in bed may all mitigate symptoms of nausea, vomiting, and abdominal pain. Calorie-rich supplements and shakes may be useful to combat weight loss from malabsorption. A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) aims to reduce consumption of gas-producing foods and may relieve cramping, diarrhea, and bloating and reduce uncontrollable bowel movements after eating, likely related to an exaggerated gastrocolic reflex.

Medications may also be used to target the various GI manifestations of amyloidosis. Nausea and early satiety may stem from dysmotility and can be treated with antiemetics (such as ondansetron and promethazine) or prokinetics (such as metoclopramide or prucalopride). Diarrhea may stem from malabsorption, small intestinal bacterial overgrowth, and/or dysmotility/neuropathy and can be treated with opioid receptor agonists (loperamide, diphenoxylate/atropine, tincture of opium), antibiotics (rifaximin), bile salt binding agents, or octreotide. Constipation is typically a result of dysmotility and can be treated with either over-the-counter or prescription laxatives (including polyethylene glycol, magnesium-containing products, senna, linaclotide, and prucalopride). Weight loss and malnutrition are often multifactorial but can be treated with nutritional supplements and, in rare cases, parenteral nutrition. In addition, endoscopic therapies, such as dilation or bleeding control, may have roles in individual patients with obstructive or vascular manifestations.

In contrast to these palliative, symptom-directed therapies, there is currently no strong evidence that disease-modifying therapies for amyloidosis, such as the TTR stabilizer tafamidis or the TTR silencers patisiran, inotersen, or vutrisiran, have an impact on GI involvement or symptoms. However, a survey-based assessment of patients with ATTRv neuropathy receiving patisiran noted improvement in diarrhea,[157] and there is optimism that long-term therapy with ATTR-specific medications may lead to gradual improvement in overall GI function.

TABLE 7 Medications for Gastrointestinal Involvement of Cardiac Amyloidosis

Medication	Dosing	Adverse Effects
Nausea and early satiety		
Antiemetics		
Ondansetron	4-8 mg every 4-8 h	Headache, fatigue, malaise, constipation
Promethazine	12.5-25 mg every 4-6 h	Extrapyramidal side effects, tardive dyskinesias, neuroleptic malignant syndrome, hyperprolactinemia, QT prolongation
Prokinetics		
Metoclopramide	10-20 mg every 6-8 h	Sedation, anxiety, mood disturbances, sleep disruption, dystonic reactions, tardive dyskinesia, galactorrhea, sexual dysfunction
Prucalopride	2 mg daily	Headache, abdominal pain, nausea, and diarrhea were observed
Diarrhea		
Opiate-receptor antagonists		
Loperamide	2-4 mg 4 times daily	Dry mouth, bloating, nausea, vomiting, constipation
Diphenoxylate atropine	2.5-5 mg 4 times daily	Drowsiness, dizziness, headache, blurred vision, dry mouth, loss of appetite
Tincture of opium	2-20 drops 4 times daily	Nausea, vomiting, lightheadedness, dizziness, drowsiness, constipation
Treatment of small intestine bacterial overgrowth		
Metronidazole	250 mg 3 times daily	Dizziness, headache, stomach upset, nausea, vomiting, loss of appetite, diarrhea, constipation, or metallic taste
Rifaximin	550 mg 3 times daily	Nausea, stomach pain, dizziness, excessive tiredness, headache, muscle tightening, joint pain
Ciprofloxacin	500 mg twice daily	Nausea, vomiting, stomach pain, heartburn, diarrhea
Bile salt binding agents		
Cholestyramine	4 g 1-4 times daily	Constipation, bloating, vomiting, diarrhea
Colesevelam	625 mg up to 6 times daily	Constipation, bloating, vomiting, diarrhea
Colestipol	4 g 1-4 times daily	Constipation, bloating, vomiting, diarrhea
Somatostatin analog		
Octreotide	50-250 mcg 3 times daily (subcutaneously)	Constipation, bloating, vomiting, diarrhea
Constipation		
Laxatives		
Osmotic laxative: polyethylene glycol	17 g daily	Diarrhea or distension
Saline laxatives: magnesium citrate or magnesium sulfate		Caution in patients with cardiovascular diseases, kidney impairment, and hypertension
Stimulant laxatives: senna		Cramping and diarrhea, reduction over time
Secretory agents: linaclotide	145 μg daily	Diarrhea, which may occur during the first 4 weeks of therapy

Compiled from Singh et al,[154] Hammer et al,[155] and Włodarczyk et al.[156]

7.3.4. Triggers for referral to a gastroenterologist

Many of the initial therapies for GI amyloid can be used without involving a gastroenterologist; however, there are situations where referral to a gastroenterologist experienced in amyloidosis would be reasonable (Table 8). Collaboration with a gastroenterologist is useful for diagnosing and treating significant nausea, vomiting, diarrhea, constipation, weight loss, and GI bleeding, including performing specialized testing.

Collaboration with a gastroenterologist is also essential to determine if the GI manifestations of amyloidosis contraindicate heart transplantation. GI involvement with malabsorption and significant malnutrition are relative contraindications to heart transplant, with the strength of that contraindication being directly linked to symptom severity.

7.4. Hematologic manifestations and management

7.4.1. Overview of AL amyloidosis

AL amyloidosis is a protein misfolding disorder with an associated plasma cell or B cell lymphoproliferative disorder. Misfolded immunoglobulin light chains form deposits in various organs, causing architectural disruption or direct cytotoxicity and resulting in organ dysfunction, failure, and death.[13,158]

AL amyloidosis is most commonly caused by subtle indolent B-cell (bone marrow plasma cell) clones that

TABLE 8 Indications to Refer to Gastroenterology

Symptoms not responding to dietary adjustments or over-the-counter supportive medications
Significant malnutrition or unexplained weight loss
Unusual or unexplained GI symptoms
Need for endoscopy/colonoscopy for biopsies to assess amyloid deposition
Need for additional testing/procedures to exclude other conditions that may mimic amyloidosis symptoms
Diagnosis and management of amyloid GI complications, including malabsorption, small intestinal bacterial overgrowth, severe nausea, vomiting, diarrhea, constipation, and GI bleeding
Assess for potential GI contraindications to heart transplantation

GI = gastrointestinal.

produce an immunoglobulin light chain lambda isotype in 75% to 80% of cases and a kappa isotype in the remaining cases. The B-cell hematologic malignancy multiple myeloma is similar to AL amyloidosis in that it also represents a clonal expansion, but the plasma cell burden in multiple myeloma is generally higher and amyloid deposition is an uncommon clinical feature. That said, approximately 10% to 15% of patients with multiple myeloma also have AL amyloidosis,[159] and 10% of AL amyloidosis cases are associated with multiple myeloma.[160] This association is important to recognize because the anti-plasma cell therapies used to treat AL amyloidosis are derived from treatments for multiple myeloma.

7.4.2. Clinical manifestations of AL amyloidosis as distinct from ATTR amyloidosis

The mechanisms that underlie organ tropism, the deposition of amyloid fibrils in specific organs and not others, are poorly understood. The heart and the kidneys are the 2 most frequently affected organs in systemic AL amyloidosis, by restrictive CM and proteinuria, respectively. However, AL amyloidosis also involves soft tissues, the liver and GI tract, the autonomic and peripheral nervous systems, and lymph nodes as well.

Clinical manifestations most often observed in AL amyloidosis include macroglossia/submandibular gland enlargement from soft tissue involvement and periorbital purpura and coagulopathy from acquired factor X deficiency.[37] In contrast, musculoskeletal manifestations, such as biceps tendon rupture and spinal stenosis, are most often indicative of ATTR amyloidosis.[38,39] Organ systems that are affected by both AL and ATTR amyloidosis include the heart, GI tract, and nervous system.

7.4.3. Collaboration between hematologists and cardiologists in AL amyloidosis

There are multiple indications for collaboration between cardiologists and hematologists in the management of patients with presumed or established AL amyloidosis. These include: 1) interpretation and evaluation of abnormal monoclonal protein screens; 2) monitoring for cardiotoxicity of AL amyloidosis therapies; 3) assessment of cardiovascular fitness for high-dose melphalan with autologous stem cell transplantation treatment regimens; and 4) identification of candidacy for heart transplantation and post-transplant management.

7.4.4. Hematologist-directed diagnosis of AL amyloidosis

7.4.4.1. Interpretation of the monoclonal protein screen

In about 10% to 40% of patients with ATTR-CM, there will be evidence of a plasma cell dyscrasia with presence of a monoclonal light chain in serum or urine without evidence of AL amyloidosis or multiple myeloma.[161-163] The abnormal monoclonal protein screen may be a sign of concomitant monoclonal gammopathy of uncertain significance (MGUS), AL amyloidosis, or multiple myeloma. In fact, the prevalence of MGUS increases with age, affecting approximately 5% of patients older than age 70 years; therefore, it stands to reason that older patients, including those with ATTR-CM, may also have concomitant MGUS.[164] The abnormal screen may also be spurious in some cases because associated kidney dysfunction results in disproportionate urinary loss of lambda light chains[59,60,165,166] as outlined in detail in Section 6.1.2.1. However, in these cases, IFE does not demonstrate a monoclonal protein.

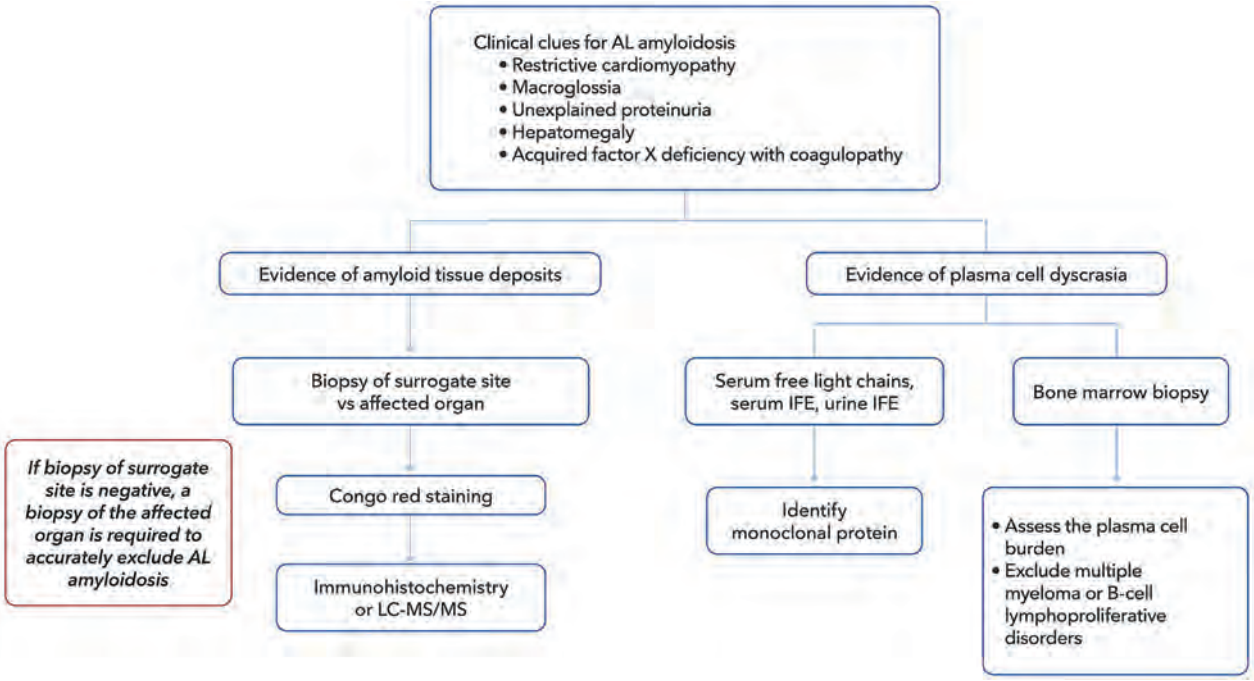
Whenever monoclonal protein testing is abnormal, it is useful to collaborate with a hematologist to ascertain whether the findings are spurious due to kidney dysfunction, a true MGUS, AL amyloidosis, or multiple myeloma. At that point, the hematologist can guide the evaluation, as outlined later.

7.4.4.2. Diagnostic approach to AL amyloidosis

As noted in Section 6.1, the diagnosis of amyloidosis is often delayed due to the nonspecific and vague symptoms. AL amyloidosis in particular should be considered in patients with a seemingly disparate constellation of any of the following signs/symptoms, including unexplained proteinuria, restrictive CM, peripheral neuropathy with autonomic features or bilateral carpal tunnel syndrome, hepatomegaly, or acquired factor X deficiency with coagulopathy. Furthermore, any patient with a monoclonal gammopathy or multiple myeloma with typical cardiac features of AL-CM or atypical manifestations like macroglossia or periorbital ecchymoses should undergo evaluation for AL amyloidosis (**Figure 11**).

Unlike diagnosis of ATTR-CM, which can be made without tissue biopsy, the diagnosis of AL amyloidosis requires both: 1) demonstration of tissue amyloid deposits; and 2) evidence of a plasma cell dyscrasia (or

FIGURE 11 Diagnosis of AL Amyloidosis



AL = amyloid monoclonal immunoglobulin light chain; IFE = immunofixation electrophoresis; LC-MS/MS = liquid chromatography with tandem mass spectrometry.

rarely, B-cell lymphoma) by monoclonal protein screen and bone marrow biopsy. Notably, the sensitivity of finding amyloid deposits in the bone marrow in systemic AL amyloidosis is 69%.[167] However, it is important that typing by mass spectrometry be performed, given that over 10% of patients with a monoclonal gammopathy can have ATTR deposits in the bone marrow.[168] Fine-needle aspiration of abdominal fat as a surrogate organ site is a simple, less-invasive, office-based procedure with excellent but not total sensitivity for AL amyloidosis (84% for AL-CM; 45% for ATTRv-CM; and 15% for ATTRwt-CM).[62,63] Thus, there are 2 approaches to tissue biopsy if AL amyloidosis, in particular, is suspected: 1) biopsy of the affected organ; or 2) bone marrow and/or abdominal fat aspiration first and, if negative for Congo red staining, proceed to biopsy of the affected organ to fully exclude the diagnosis of AL amyloidosis. In situations of suspected concomitant systemic AL and ATTR cardiac amyloidosis (such as MGUS in the context of abnormal nuclear scintigraphy), cardiac biopsy is the preferred route to definitively establish the cardiac pathology.

If amyloid deposits are detected in biopsies by Congo red staining, the next step is to determine the precursor protein. This may be performed by immunohistochemistry or immunogold immunoelectron microscopy in experienced centers, but mass spectrometry-based analysis (LC-MS/MS) of the biopsy is the gold standard for tissue diagnosis, with a reported sensitivity of 88% and specificity of 96%.[64] Although LC-MS/MS is not widely available, pathological samples demonstrating positive Congo red staining can be transferred to an experienced reference laboratory for LC-MS/MS to establish the identity of the amyloidogenic protein. It is particularly important that tissue biopsy precursor typing is performed in the common clinical scenario of MGUS with suspected ATTR cardiac amyloidosis, as Congo red staining alone is insufficient.

Once a tissue diagnosis of amyloidosis has been established, confirmation of AL amyloidosis requires demonstration of a plasma cell disorder by: 1) identification of a monoclonal light chain in the blood or urine (which may be done first, as noted in Section 6.1.1.2, as part of the diagnostic algorithm to exclude AL amyloidosis before performing a Tc-PYP scan to assess for ATTR amyloidosis); and 2) bone marrow biopsy showing clonal proliferation of lambda or kappa-producing plasma cells (or B cells). As noted in Section 6.1.1.2, an accurate monoclonal protein screen requires sFLC, SIFE, and UIFE. Importantly, SPEP/UPEP should not be used to exclude a monoclonal protein in suspected AL amyloidosis, given

its lower sensitivity relative to IFE and the low level of monoclonal protein in AL amyloidosis (unlike myeloma).[50]

Even if a monoclonal immunoglobulin light chain is identified in the serum or urine, a bone marrow biopsy is mandatory to assess the plasma cell burden as evidence for multiple myeloma while ruling out other, less-common disorders that can be associated with AL amyloidosis, such as B-cell lymphoproliferative disorders (eg, Waldenström macroglobulinemia, chronic lymphocytic leukemia, or non-Hodgkin lymphoma) that warrant different management strategies.

7.4.5. Hematologist-directed treatment of AL amyloidosis

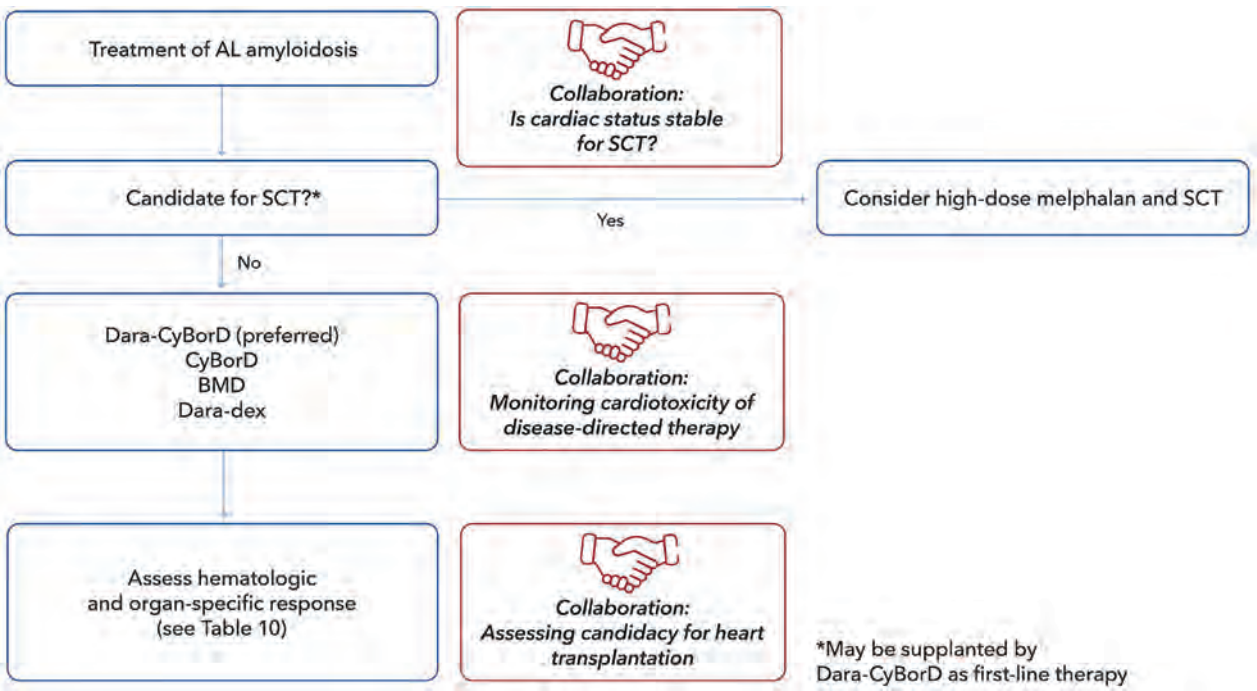
Because AL amyloidosis most commonly results from a clonal plasma cell disorder, the primary treatment uses chemotherapy and/or immunotherapy to target the aberrant plasma cells, eradicate the underlying clone, and decrease amyloid precursor protein production, thereby limiting further organ damage and allowing for regression of tissue amyloid deposits (**Figure 12**). The goal of treatment of AL amyloidosis is to eradicate the pathological plasma cells and remove the affected light chain from the circulation. Management of AL amyloidosis is derived from anti-plasma-cell multiple myeloma therapies.[158]

As patients with AL amyloidosis are considered at higher risk than those with myeloma for treatment-related toxicity due to systemic organ involvement,[169,170] the choice of specific regimens must balance treatment efficacy, toxicity, and tolerability.[171] In contrast to therapies for malignancies such as breast cancer with known significant cardiotoxicity (such as anthracycline-based chemotherapy or monoclonal antibodies against human epidermal growth factor receptor 2), there are no absolute contraindications to the use of plasma cell-directed therapies based on EF or cardiac status in AL-CM. However, as noted in **Table 9**, collaboration with a cardiologist is important when patients are receiving therapies to monitor for cardiac decompensation, most commonly decompensated HF, atrial arrhythmias, or thromboembolism. Collaboration with specialists in geriatrics and palliative care may also be helpful to review the goals, values, and preferences of patients.

7.4.5.1. High-dose melphalan chemotherapy with autologous stem cell transplantation in AL amyloidosis

Before the recent advent and FDA approval of highly effective plasma-cell-directed therapies (eg, daratumumab with bortezomib, cyclophosphamide, and dexamethasone[11]), the standard of care in AL amyloidosis

FIGURE 12 Management of AL Amyloidosis



AL = light-chain amyloidosis; BMD = bortezomib-melphalan-dexamethasone; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; Dara = daratumumab; dex = dexamethasone; SCT = stem cell transplantation.

TABLE 9 Therapies for AL Amyloidosis and Cardiac Toxicities

Agent	Toxicity

Corticosteroids	■ Dexamethasone
	■ Prednisone
	  ■ Peripheral edema
	  ■ Pulmonary edema
	  ■ Fluid overload

Proteasome inhibitors	■ Bortezomib[172]
	  ■ Grade 3 HF in 6.4%
	  ■ >10% decrease in LVEF in 23%
	■ Carfilzomib[173]
	  ■ Dyspnea, LVEF reduction, pulmonary hypertension in 36%
	■ Ixazomib[174]
	  ■ 15% with grade 3 fatigue, dyspnea, skin rash
	  ■ Grade 3 HF in 10%

Immunomodulatory agents	■ Thalidomide
	  ■ bradycardia
	■ Lenalidomide[175]
	  ■ Paradoxical increase in cardiac biomarkers, 86% with >30% increase in BNP
	  ■ Kidney dysfunction in 66% at a median of 44 days, 10% required kidney replacement therapy
	■ Pomalidomide[176]
	  ■ Paradoxical increase in BNP in 88.8%
	  ■ Kidney dysfunction in 26%
	■ With all agents, patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (eg, hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

Melphalan	■ No cardiotoxicity directly related to melphalan
Cyclophosphamide	■ Myocarditis, myopericarditis, pericardial effusion, including cardiac tamponade, and heart failure ■ Supraventricular arrhythmias (including AF and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) ■ Risk of cardiotoxicity may be increased with high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment to the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents
Daratumumab	■ Cardiac failure in 12%, grade 3-4 in 6% ■ Cardiac arrhythmia in 8%, grade 3-4 in 2% ■ AF in 6%, grade 3-4 in 2%

Compiled from Hughes et al.[177]

AF = atrial fibrillation; BNP = B-type natriuretic peptide; HF = heart failure; LVEF = left ventricular ejection fraction.

in the United States had been high-dose melphalan followed by autologous stem cell transplantation (HDM/SCT) for highly selected patients, which offers the possibility of long-lasting remission and high organ response rates. Patients deemed eligible for HDM/SCT are selected based on their assessed risk for adverse outcomes (morbidity and mortality), and cardiac involvement is a major determinant of risk. That said, treatment-related mortality with HDM/SCT in experienced centers is approximately 3%, with expected very good partial hematological response or better (see later discussion for hematologic response grading) in about 70% of patients and a median survival of over 15 years in those patients achieving a complete response.[178] With this approach, therapy with 2 to 4 cycles of a bortezomib-based regimen is administered for induction in all transplant-eligible patients with bone-marrow plasma cell percentages >10%.[179]

There are no standard established eligibility criteria for SCT, and cardiac evaluation will vary by treating specialty center. When a cardiologist performs an evaluation to determine if a patient is a candidate for SCT, it is important to consider how the patient will handle fluid shifts and potential infections associated with fever, tachycardia, and hypotension. Generally, an EF <40% is considered a contraindication to SCT, given the risk of hemodynamically significant decompensation.[180]

Thus, many patients with AL-CM are not candidates for SCT due to advanced cardiac and other organ involvement, and only about 25% of newly diagnosed AL amyloidosis patients are usually eligible for this intensive treatment.[22] For these patients, recent advances in plasma cell-directed therapies offer great promise.

7.4.4.3.2. Non-SCT therapies for AL amyloidosis

The landmark ANDROMEDA (A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination With Cyclophosphamide, Bortezomib and Dexamethasone [CyBorD] Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light-chain [AL] Amyloidosis) study (NCT03201965) was a phase 3 trial of daratumumab (an anti-CD38 monoclonal antibody) in combination with cyclophosphamide, bortezomib, and dexamethasone (CyBorD or VCd) in patients with newly-diagnosed AL amyloidosis. There was an unprecedented high rate of deep hematologic responses with very good partial responses or better in 78.5% of patients who received daratumumab plus CyBorD vs 49.2% of patients who received CyBorD alone.[11] Based on this, daratumumab was approved by the FDA and the European Medicines Agency for treatment of newly-diagnosed AL amyloidosis. Daratumumab remains the only agent approved for treatment of AL amyloidosis.

Thus, daratumumab-CyBorD has now emerged as the standard of care for newly diagnosed AL amyloidosis. It may become the preferred induction therapy before HDM/SCT and offers great promise to the majority of patients who may not be candidates for SCT.[181]

Regimens used for patients who are not candidates for SCT comprise bortezomib-based regimens in combination with dexamethasone and an alkylating agent. The most common regimens are CyBorD[182] and bortezomib-melphalan-dexamethasone.[183] Patients with advanced cardiac involvement with N-terminal pro-B-type natriuretic peptide (NT-proBNP) >8,500 pg/mL may receive the single agent daratumumab and a minimal dose of dexamethasone to minimize potential cardiotoxicity (as planned in A Study of Daratumumab Monotherapy in

TABLE 10 Criteria for Hematologic and Organ Response to Treatment in AL Amyloidosis

Hematologic response	
CR—complete response	Both criteria must be met: ■ Absence of amyloidogenic light chains (either free and/or as part of a complete immunoglobulin), defined by negative SIFE and UIFE *and* ■ Either a FLC ratio within the reference range or an uninvolved FLC concentration greater than the involved FLC concentration with or without an abnormal FLC ratio
VGPR—very good partial response	dFLC <40 mg/L
PR—partial response	dFLC decrease ≥50%
NR—no response	dFLC decrease <50%
Organ response	
Cardiac response	Decrease in NT-proBNP by >30% and <300 ng/L (if baseline NT-proBNP >650 ng/L)
Renal response	At least 30% decrease in proteinuria or drop below 0.5 g/24 h, in the absence of kidney progression, defined as a >25% decrease in eGFR
Hepatic response	50% decrease in abnormal alkaline phosphatase value or decrease in radiographic liver size by ≥2 cm

dFLC = difference between involved and uninvolved FLC; eGFR = estimated glomerular filtration rate; FLC = free light chain; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SIFE = serum immunofixation electrophoresis; UIFE = urine immunofixation electrophoresis.

Previously Untreated Patients With Stage 3B Light Chain [AL] Amyloidosis by the European Myeloma Network: NCT04131309).

7.4.4.3.3. Assessing response to therapy in AL amyloidosis

Response to plasma-cell-directed therapy is monitored in 2 ways: 1) hematologic response of sFLC; and 2) organ response. Depending on the affected organs, assessment may include serum troponin, NT-proBNP, electrocardiography and echocardiography, creatinine, 24-hour UPEP, and liver enzymes.[184]

Various hematologic and organ-specific response criteria involving circulating or urinary biomarkers have been adopted. Generally, a hematologic response is observed within 3 to 6 months of treatment initiation and defined by the magnitude of light chain reduction, as noted in **Table 10**. Organ-specific response to treatment is generally observed 6 to 12 months after a hematologic response.

For patients whose disease relapses after or is refractory to initial therapy (autologous SCT or a bortezomib-based regimen), options include daratumumab (if not used in first-line regimens) or immunomodulatory-based regimens, including lenalidomide, pomalidomide, and thalidomide. Given the potential for cardiac and kidney toxicity, daratumumab is generally preferred. Other potential agents for relapsed disease include ixazomib, an oral proteasome inhibitor,[185] as well as venetoclax, which blocks the antiapoptotic B-cell lymphoma-2 protein that facilitates programmed cell death and provides a high hematologic response in relapsed/refractory disease in patients with the t(11;14) cytogenetic alteration.[186] Relapsed/refractory patients should be enrolled in clinical trials whenever possible.

7.4.4.4. Hematologic contraindications to heart transplantation

Systemic AL amyloidosis is a multisystem disease. As with other extracardiac manifestations of cardiac amyloidosis, the potential contraindications related to AL amyloidosis include assessment of criteria that would have an impact on post-transplant survival or quality of life. As survival after heart transplantation is approximately 75% at 5 years and 50% at 10 years,[187] any condition with a lower rate of survival would be considered a contraindication. Thus, when the cardiologist collaborates with the hematologist to determine whether the AL amyloidosis is a contraindication to heart transplantation in a patient with advanced HF who is otherwise eligible, the hematologist should assess AL-amyloid-related survival against these metrics.[188]

If the projected survival from AL amyloidosis is deemed to be <75% at 5 years and/or <50% at 10 years, then the risk of transplantation would be prohibitive. This may be true if there are high-risk cytogenetic findings, such as t(11;14),[189] that suggest a higher likelihood of plasma cell disease resistant to standard treatment or multiple myeloma. Ideally, a very good partial or complete hematologic response would be achieved before transplant consideration; however, this may not be essential in the context of newer, more efficacious plasma-cell-directed therapies.[11] Still, potential contraindications related to the extracardiac manifestations, both GI and neurologic, must be considered, as outlined in Sections 7.2 and 7.3 and summarized in Section 7.6.3.

The need for deep and prolonged suppression of the amyloidogenic light chains following heart transplantation to prevent amyloid recurrence makes highly effective anti-plasma-cell treatment an important component of the pathway. Limited data on patient outcomes as well as the additional risks and interaction of chemotherapy with cardiac immunosuppression, potential cardiac toxicity, or higher risk of organ rejection from immunomodulatory-based regimens are important considerations in decisions about the choice of anti-plasma-cell therapy following heart transplantation.[190] All patients undergoing consideration for a heart transplant should also be assessed by an experienced team for eligibility for SCT (given its high rate of inducing a deep and sustained hematologic response). Suitability for sequential heart transplantation followed by SCT should be a consideration in the selection of candidates for a heart transplant.

7.5. Nephrology

7.5.1. Kidney manifestations AL and ATTR amyloidosis

In AL amyloidosis, the kidney is one of the most common sites of amyloid deposition, with involvement in approximately 70% of patients. Kidney involvement in AL amyloidosis is usually characterized by nephrotic syndrome and progressive loss of kidney function.[191] Nephrotic syndrome can be severe, with high-grade proteinuria, marked hypoalbuminemia, and anasarca. In a small proportion of patients, amyloid deposition is limited to the kidney interstitial compartment and/or vasculature. These individuals typically have reduced kidney function but minimal proteinuria.

Although direct kidney involvement in ATTR amyloidosis has been demonstrated with several TTR mutations, including Val30Met, Val30Ala, Phe33Cys, Gly47Glu, and Val142Ile as well as with ATTRwt, the involvement is usually subclinical. In the vast majority of patients with ATTR amyloidosis, the associated kidney disease is due to cardiorenal syndrome, which also frequently occurs in AL-CM.[192-194] Autonomic nervous system involvement, which can occur in both AL and ATTR disease, can also contribute to hemodynamically-mediated kidney impairment (Figure 13).

7.5.2. Challenges in assessment of kidney function in cardiac amyloidosis

Because patients with systemic amyloidosis often have muscle wasting, using the serum creatinine concentration to estimate kidney function, as is usually done in clinical practice, can result in overestimation of the GFR. Serum concentrations of cystatin C, a marker of kidney function that is independent of muscle mass, cystatin C-based GFR estimating equations, and determination of creatinine clearance with 24-hour urine collection can provide better indications of kidney function when muscle mass is reduced.[195]

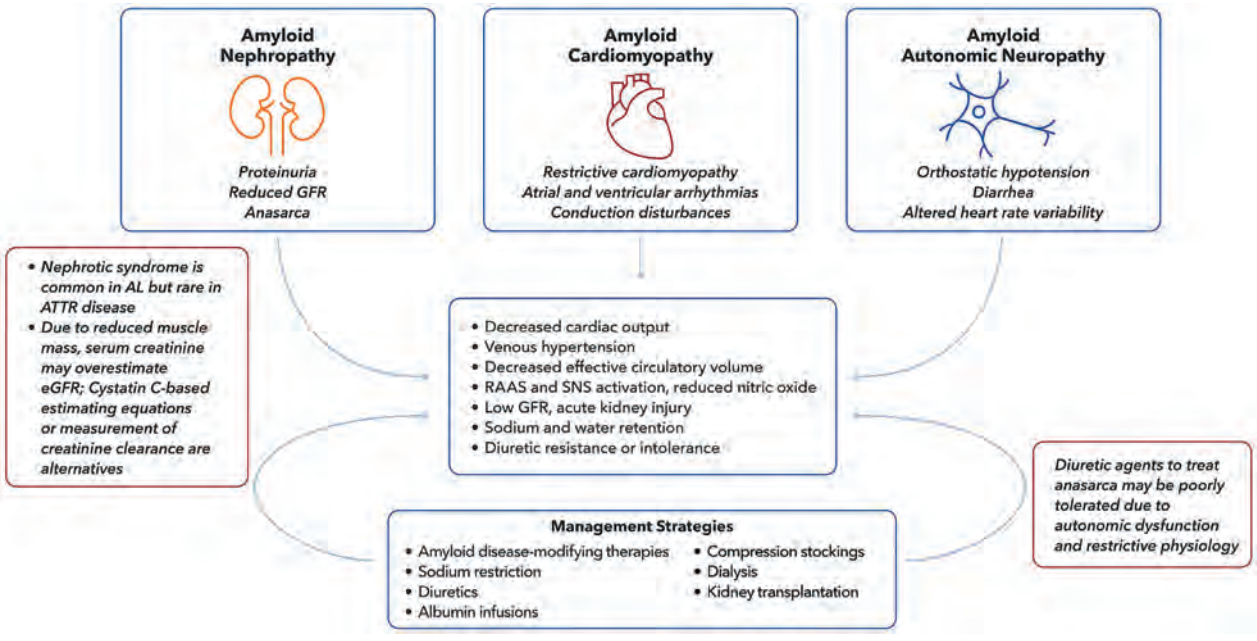
7.5.3. Management of kidney manifestations of amyloidosis

7.5.3.1. Impact of treatment of AL and ATTR amyloidosis

In AL amyloidosis, eradication of the amyloidogenic light chain with anti-plasma-cell therapy often leads to improvement in the kidney manifestations of the disease. In distinction to the cardiac manifestations of AL amyloidosis where abnormalities frequently persist, proteinuria typically decreases progressively over many months to several years after a hematologic complete response or very good partial response and can resolve fully if the hematologic response is sustained.[196-198] Although GFR usually does not improve, kidney function often stabilizes after amyloidogenic light chain production is halted.

If kidney function declines despite laboratory studies indicating eradication of the amyloidogenic light chain, it may be difficult to determine whether the deterioration in kidney function reflects ongoing amyloid deposition that is not evident by clinically-available studies, is the result

FIGURE 13 Interplay of Factors Influencing Kidney Function in Cardiac Amyloidosis



AL = amyloid monoclonal immunoglobulin light chain; ATTR = amyloid transthyretin; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; RAAS = renin-aldosterone-angiotensin system; SNS = sympathetic nervous system.

of prior injury from amyloid deposition, or is related to the toxicities of treatment. A kidney biopsy is usually not helpful in this setting because amyloid persists in tissue, and it is not possible to distinguish new amyloid from pre-existing deposits.[199]

In ATTR-CM, the impact of the TTR stabilizer tafamidis specifically on kidney outcomes has not been established. One would expect that if tafamidis results in improved hemodynamic conditions, then kidney impairment would also improve; however, kidney outcomes with tafamidis have not been specifically studied.

The use of diflunisal, an NSAID and TTR stabilizer, is not generally recommended for patients with significant kidney impairment (typically, eGFR <45 mL/min/1.73 m^2) or volume overload due to the potential deleterious effects of NSAIDs on kidney hemodynamic conditions, potassium excretion, and sodium excretion.[72]

The TTR silencer inotersen, approved for use in patients with ATTRv-associated polyneuropathy, was associated with the development of crescentic glomerulonephritis in 3 of 112 patients (3%) who received active therapy in the phase 3 trial for ATTRv polyneuropathy.[97] This has not been observed with patisiran or vutrisiran, and the mechanism for this unexpected complication is not known.

7.5.3.2. Supportive management of kidney dysfunction

Supportive management for amyloidosis-associated nephrotic syndrome is similar to approaches used for nephrotic syndrome from other glomerulopathies. This includes dietary sodium restriction; loop diuretic agents, sometimes administered in combination with a thiazide diuretic agent such as metolazone; and compression stockings to reduce peripheral edema and increase the tolerability of diuretic agents, which can be challenging in the setting of autonomic neuropathy or CM.

Because of greater bioavailability, orally administered torsemide or bumetanide or intravenously administered loop diuretic agents may be more effective than oral furosemide for patients with significant intestinal wall edema. By increasing the delivery of the loop diuretic agent to the tubular lumen or by increasing intravascular oncotic pressure, intravenous infusions of albumin can facilitate diuresis when there is marked hypoalbuminemia (eg, serum albumin <1.5-2 g/dL).

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be used for their antiproteinuric effects if the blood pressure is not prohibitively low. Although there is a role for sodium glucose cotransporter 2 inhibitors in slowing the decline of kidney dysfunction in patients with chronic kidney disease[200] and in HFrEF,[201] this class of drugs has not been studied in the setting of amyloid-associated kidney dysfunction. The management of volume overload due to nephrotic syndrome or in the setting of cardiorenal syndrome requires a balance between efforts to remove excess fluid and resulting alterations in hemodynamic variables that reduce kidney perfusion and GFR.

TABLE 11 Contributions of Nephrologists to the Care of Patients With Cardiac Amyloidosis

Managing nephrotic syndrome
Managing chronic kidney disease
Interpreting serum free light chain concentrations in kidney impairment
Interpretating cardiac biomarkers in kidney impairment
Addressing kidney effects of anti–plasma-cell therapies; risk-stratifying for stem cell transplantation
Dosing drugs based on kidney function
Determining need for kidney biopsy and assessing implications of biopsy findings
Assessing suitability for kidney transplantation
Preparing for initiation of dialysis and modality selection

Lipid-lowering medications can have some effect on nephrotic syndrome–associated hyperlipidemia; however, many patients with amyloidosis continue to have markedly elevated levels of cholesterol and triglycerides despite the use of such agents. Anticoagulation to prevent thromboembolic complications is generally not recommended specifically for amyloidosis-associated nephrotic syndrome in the absence of other indications.

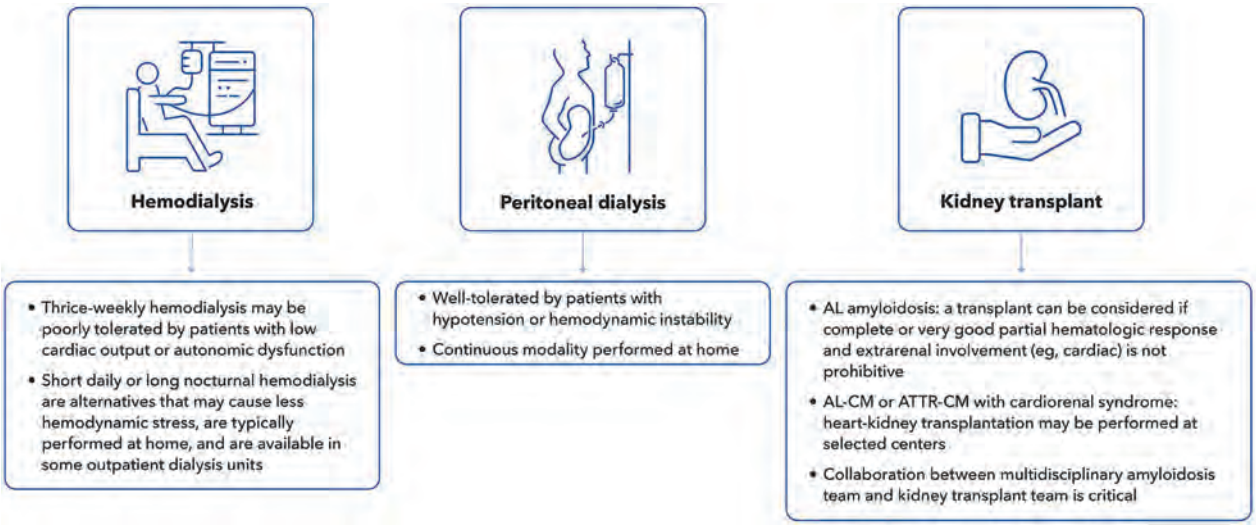
7.5.3.3. Role of nephrologists in the multidisciplinary care of patients with amyloidosis

Nephrologists provide important contributions to the multidisciplinary care for patients with AL or ATTR amyloidosis who have either amyloid nephropathy or reduced kidney function due to amyloid CM (Table 11). Input from nephrologists is particularly important for managing nephrotic syndrome, cardiorenal syndrome, metabolic complications of chronic kidney disease, and nephrotoxic effects of treatments for amyloidosis, such as lenalidomide-associated acute kidney injury, proteosome inhibitor–associated thrombotic microangiopathy or interstitial nephritis, or acute kidney injury associated with autologous STC.[202-206]

Nephrologists also should be involved in decisions about the need for a kidney biopsy and interpretation of biopsy findings and the preparation for kidney replacement therapy, including the assessment of suitability for kidney transplantation.

For patients with AL or ATTR disease who progress to end-stage kidney disease, kidney replacement therapy can be provided with hemodialysis, peritoneal dialysis, or, in selected patients, kidney transplantation (Figure 14). For patients with severe CM, peritoneal dialysis, short daily hemodialysis, or long nocturnal hemodialysis may be better tolerated from a hemodynamic standpoint than conventional thrice-weekly hemodialysis.

FIGURE 14 Kidney Replacement Therapy for Patients With Cardiac Amyloidosis



AL = amyloid monoclonal immunoglobulin light chain; AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTR-CM = amyloid transthyretin cardiomyopathy.

Kidney transplantation can be considered for patients with AL amyloidosis who progress to end-stage kidney disease if they have had a complete or very good partial hematologic response with anti-plasma-cell therapy and if their cardiac disease and other extrakidney manifestations of amyloidosis are not prohibitive.[207,208] Kidney transplantation may also be performed in patients with cardiorenal syndrome who are undergoing heart transplantation for ATTR-CM.

7.6. Advanced HF

Cardiac involvement is the single most important prognostic indicator in patients with amyloidosis. An overview of the identification of advanced HF and management options is shown in **Figure 15**.

7.6.1. Markers of poor prognosis in cardiac amyloidosis

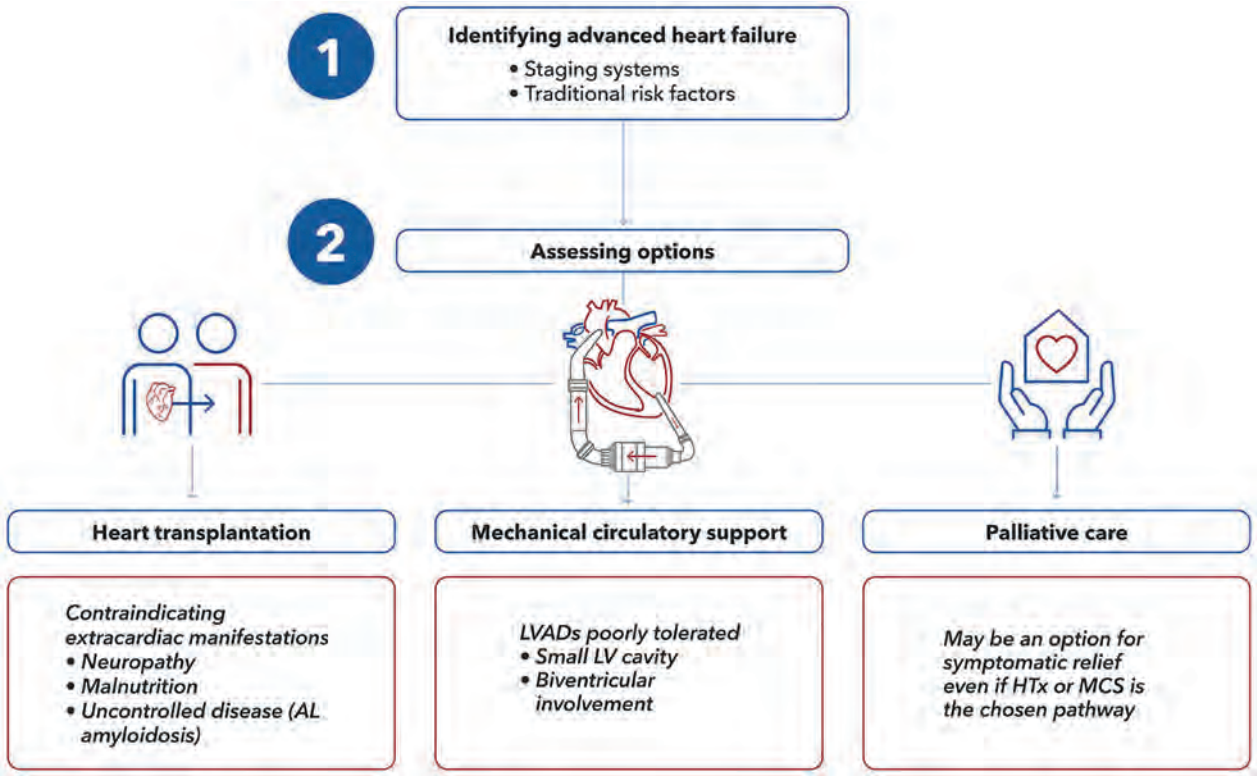
The ability to reliably estimate survival in cardiac amyloidosis: 1) enhances the clinician's ability to counsel patients on the likelihood of response to treatment and overall survival; and 2) allows appropriate and timely triage to advanced HF therapies in appropriate candidates. Cardiac prognostication includes laboratory and clinical signs and symptoms of advanced HF. The prognostic value of ECG and imaging parameters is not well established.

For both AL-CM and ATTR-CM, troponin and NT-proBNP are powerful indicators of disease burden and prognosis.[209,210] Multiple staging systems have been developed that rely predominantly on these biomarkers (**Table 12**).[20,21,211,212] There are additional biomarkers that are uniquely prognostic for the type of amyloidosis: free light chains (dFLC) and kidney function for AL-CM and ATTR-CM, respectively.[19,212]

Simply put, the worse the marker, the poorer the prognosis. However, there are limitations to the use of these staging systems for prognostication. First, the staging systems were developed before current effective therapies that improve survival were available, such as daratumumab for AL amyloidosis and tafamidis for TTR amyloidosis.[10,11,67] Second, reliance on staging systems alone for prognostication may identify those patients who are either too well or too sick for advanced HF therapies. For example, the median survival in the more severe cohort from all staging systems for ATTR-CM is still roughly 2 years, which may identify patients too well for advanced HF therapies. However, those patients with worsening kidney function from cardiorenal syndrome may have worse prognoses, whereas those with eGFR <45 mL/min/1.73 m^2 observe only a moderate reduction in survival from the UK staging system for ATTR amyloidosis.

Ultimately, traditional markers of poor prognosis in HF may be required to best identify those candidates who are limited enough from a cardiac standpoint but still have acceptable extracardiac function for advanced HF therapies. In both AL-CM and ATTR-CM, the combination of peak Vo_2 <13 mL/kg/min coupled with NT-proBNP ≥1,800 ng/L predicted an increase in all-cause death or HF hospitalization.[214] In AL-CM, older age, NYHA functional

FIGURE 15 Advanced Heart Failure Identification and Management Options



AL = amyloid light chain; HTx = heart transplantation; LV = left ventricular; LVAD = left ventricular assist device; MCS = mechanical circulatory support.

class III-IV, and systolic blood pressure <100 mm Hg have also been associated with worse survival.[211,215] In ATTR-CM, increasing diuretic agent dose and worse NYHA functional class were independent risk factors for worse survival, providing incremental value to existing ATTR-CM staging scores.[75]

7.6.2. Indications for heart transplantation

In select patients with ATTR-CM and AL-CM with advanced/stage D HF, heart transplantation may be an option,[216] and the current adult donor allocation system provides priority as Status 4 to amyloid CM, given the lack of durable mechanical circulatory support (MCS) support options.[144] The traditional signs of advanced HF apply in patients with cardiac amyloidosis and should be recognized as triggers for a discussion of prognosis and advanced HF therapies that incorporates the patient's goals, values, and preferences (Table 13). Identification of advanced HF in cardiac amyloidosis, however, may be more challenging because the symptoms of low-output HF, such as fatigue and GI symptoms, may be more subtle nonspecific, and be attributed to other disease states.

The most important lesson in advanced HF in cardiac amyloidosis, in particular, is that there is no single test to identify those patients who may be candidates for advanced HF therapies. The individual patient's trajectory and multiple factors from the history, physical examination, laboratory testing, and imaging studies must be considered together in context to identify those at greatest risk of future decompensation and who will derive the greatest benefit from advanced therapies.

7.6.3. Contraindications to heart transplantation

As multiorgan amyloid infiltration is common, the contraindications to heart transplantation in patients with cardiac amyloidosis center around the degree of extracardiac involvement and the impact of this involvement on post-transplant morbidity and mortality (Table 14). In both AL-CM and ATTR-CM, as in all potential heart transplant candidates, the presence of frailty as a multidimensional concept may influence outcomes.[217]

In AL-CM, it is critical to screen for the presence of significant extracardiac organ involvement, including high-grade albuminuria, significant hepatic infiltration,

TABLE 12 Staging Systems for Cardiac Amyloidosis

	Mayo Staging System[20]	UK Staging System[19]	Mayo 2004[21]	Mayo 2004 With European Modification[213]	Mayo 2012[212]	Boston University[22]
Population	ATTRwt-CM	ATTRwt-CM and ATTRv-CM	AL-CM	AL-CM	AL-CM	AL-CM
Parameters and thresholds	■ TnT ≤0.05 ng/mL ■ NT-proBNP ≤3,000 pg/mL	■ NT-proBNP ≤3,000 pg/mL ■ eGFR ≥45 mL/min	■ Troponin: ■ TnT ≥0.035 mcg/L or ■ TnI ≥0.1 mcg/L Or ■ High-sensitivity TnT ≥50 ng/L ■ BNP: ■ NT-proBNP ≥332 ng/L	■ Troponin: ■ TnT ≥0.035 mcg/L Or ■ TnI ≥0.1 mcg/L Or ■ High-sensitivity TnT ≥50 ng/L ■ BNP: ■ NT-proBNP ≥332 ng/L	■ Troponin ■ TnT ≥0.025 mcg/L Or ■ High-sensitivity TnT ≥40 ng/L ■ BNP ■ NT-proBNP ≥1,800 ng/L or ■ BNP ≥400 ng/L ■ dFLC ≥18 mg/dL	■ BNP >81 pg/mL ■ TnI >0.1 ng/mL
Median survival						
Stage I: no parameters above threshold	66 mo	69.2 mo	26.4-27.2 mo	Median survival not reached; 60% survival at 10 y	94.1 mo	Median survival not reached; >12 y
Stage II: 1 parameter above threshold	40 mo	46.7 mo	10.5-11.1 mo	49 mo	40.3 mo	113 mo
Stage III: 2 parameters above threshold	20 mo	24.1 mo	3.5-4.1 mo		14 mo	52 mo
Stage IIIA: 2 parameters above threshold and NT-proBNP <8,500 ng/mL	N/A	N/A	N/A	14 mo	N/A	
Stage IIIB: 2 parameters above threshold and NT-proBNP ≥8,500 ng/mL	N/A	N/A	N/A	5 mo	N/A	12 mo (if BNP >700 mg/mL)
Stage IV: 3 parameters above threshold	N/A	N/A	N/A	N/A	5.8 mo	N/A

AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; BNP = B-type natriuretic peptide; dFLC = difference between involved and uninvolved free light chain; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TnI = troponin I; TnT = troponin T.

significant GI involvement with malnutrition, pulmonary amyloidosis with exudative effusions,[218,219] and significant peripheral neuropathy with autonomic dysfunction. The presence of multiple myeloma in the setting of AL amyloidosis and response to administered plasma-cell-directed therapies will also affect transplant candidacy, as discussed in Section 7.4.[220,221] All patients undergoing consideration for a heart transplant should also be assessed by an experienced team for eligibility for SCT (given its high rate of inducing a deep and sustained hematologic response)—suitability for sequential heart transplantation followed by SCT should be a consideration in selection of suitable candidates for a heart transplant.

For ATTR-CM, potentially contraindicating extracardiac involvement includes GI involvement and autonomic neuropathy. GI involvement can result in malnutrition with risk for infection and poor wound healing. Disabling neuropathy will not improve after cardiac transplantation and may significantly impair rehabilitation efforts and quality of life. In ATTRwt-CM in particular, an age of 70 years or more may be prohibitive at some centers, although it may not be if extracardiac organ function is otherwise intact. For ATTRv-CM, heart-liver transplantation has traditionally been considered in patients at risk for neuropathy because neuropathy may progress with heart transplantation alone. However, the criteria for heart transplantation alone vs heart-liver transplantation are not well defined,[144] especially with the advent of TTR silencer therapy, which may have a role after heart transplantation. TTR-specific therapy, including tafamidis or a silencing agent (in patients with ATTRv-CM) should be prescribed following heart transplantation if coexistent neuropathy attributable to amyloidosis is present.[222]

7.6.4. Mechanical circulatory support

Despite the increasing use of heart transplantation for patients with cardiac amyloidosis, there is extremely high wait list mortality, particularly in patients with AL

TABLE 13 Clinical Indicators of Stage D/Advanced Heart Failure Relevant to Cardiac Amyloidosis

Repeated hospitalizations or emergency department visits for HF in the past 12 mo
Need for intravenous inotropic therapy
Persistent NYHA functional class III to IV symptoms despite therapy
Severely reduced exercise capacity (peak Vo_2, <14 mL/kg/min or <50% predicted, 6-min walk test distance <300 m, or inability to walk 1 block on level ground because of dyspnea or fatigue)
Recent need to escalate diuretic agents to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d or use of supplemental metolazone therapy
Refractory clinical congestion
Progressive deterioration in kidney or hepatic function
Worsening right HF or secondary pulmonary hypertension
Frequent SBP ≤90 mm Hg
Cardiac cachexia
Persistent hyponatremia (serum sodium <134 mEq/L)
Refractory or recurrent ventricular arrhythmias; frequent implantable cardioverter-defibrillator shocks
Adapted from ACC 2022 guidelines with modifications[6]

ACC = American College of Cardiology; HF = heart failure; NYHA = New York Heart Association; SBP = systolic blood pressure; Vo_2 = oxygen consumption.

TABLE 14 Extracardiac Contraindications to Heart Transplantation in Cardiac Amyloidosis

Frailty	Fried frailty phenotype ≥3 criteria[217] ■ Weakness ■ Slowness ■ Exhaustion ■ Low physical activity ■ Unintentional weight loss
Autonomic neuropathy	Severe symptomatic orthostasis requiring midodrine and/or droxidopa
Peripheral neuropathy	Symptoms severe enough to limit ambulation
Pulmonary disease	Symptomatic pulmonary involvement (pleural effusions, pleural involvement, parenchymal nodules)[219]
GI tract disease	Modified BMI <600 $kg/m^2 \cdot g/L$[152] GI bleeding, malabsorption
Kidney disease	Proteinuria ≥500 mg/d
Hematologic disease	Light chains not responsive to therapy High-risk cytogenetics[189] Multiple myeloma

BMI = body mass index; GI = gastrointestinal.

amyloidosis,[188,223] and it may be necessary to consider durable MCS as a bridge to transplantation.

Barriers to the successful use of durable MCS devices include the small left ventricular cavity and biventricular involvement. The small left ventricular cavity makes left ventricular assist device (LVAD) cannula placement more challenging with a higher risk for suction events.[224] In fact, when patients with cardiac amyloidosis who underwent LVAD implantation were stratified by left ventricular size, those with larger cavities (left ventricular end-diastolic diameter >46 mm) had markedly improved post-LVAD survival,[225] and surgical debulking for LVAD placement (in a small case series) may be useful.[226]

A second challenge arises from the fact that patients with cardiac amyloidosis typically have evidence of biventricular dysfunction, resulting in the risk of right ventricular failure when LVADs are placed. In this situation, a durable biventricular assist device such as the total artificial heart may be placed with acceptable outcomes, as found in a small, single-center analysis.[227] However, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) data indicate worse survival in all patients with cardiac amyloidosis and MCS compared with those with dilated CM and nonamyloid restrictive CM, regardless of whether an LVAD or biventricular MCS was used, and with a high burden of early adverse events.[228]

Another concern for the use of durable MCS in patients with amyloidosis is the risk of infection in those patients with AL amyloidosis upon receiving plasma cell-directed therapies.[221]

Temporary MCS, such as the intra-aortic balloon pump[229] or a percutaneous microaxial catheter-based pump, may be a suitable alternative as bridge to transplantation in patients with cardiac amyloidosis.[229] An axillary approach allows for ambulation while the patient awaits transplantation and can be used in patients meeting hemodynamic criteria to achieve status 2 for timely transplantation.

7.6.5. Palliative care

7.6.5.1. Role of palliative care specialist

The international Association for Hospice and Palliative care defines palliative care as the active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life. Palliative care aims to improve the quality of life of patients, families, and caregivers.[230] Although there is little specific literature on palliative medicine in amyloidosis, the approach is similar to that for any life-threatening disease. Specialty palliative care intervention should be tailored to the patient and caregiver goals, values, and preferences (**Figure 16**).[230]

7.6.5.2. Timing of palliative care intervention

For AL-CM patients, symptoms secondary to the disease process and/or plasma cell-directed therapies can be

FIGURE 16 Palliative Care Interventions

overwhelming. For patients with ATTRv-CM, symptoms are dependent on genotype, ranging from minimal to none in those diagnosed by screening to debilitating in others. Symptoms of ATTRwt-CM can range from minimal to those of advanced HF and are often coupled with the decrement in quality of life that occurs as part of advanced age.

In addition to palliative care specialists, collaboration with geriatricians offers significant benefits in the recognition and management of multiple geriatric syndromes such as polypharmacy, cognitive impairment, or social isolation. Geriatricians have particular expertise in managing older adults with multiple chronic conditions and working across specialties and disciplines to ensure that care is aligned with what matters to the older person.

Because cardiac amyloidosis will inevitably progress in many patients, with increased symptom burden, worsening quality of life, and complex care needs, it is also useful to engage in collaboration with specialists in palliative care. Patients with cardiac amyloidosis should

be referred to the palliative care team at any stage of their disease when any of the physical symptoms, such as intractable HF, neuropathy, orthostasis, GI distress, or emotional/spiritual distress, are interfering with their quality of life.[231]

8. STEP 2: UNMET NEEDS AND FUTURE DIRECTIONS IN MULTIDISCIPLINARY CARE

There are numerous barriers to equitable care in patients with cardiac amyloidosis, summarized in Figure 17 and described in detail in the following discussion.

8.1. The costs and approval processes of novel amyloid therapies

Before 2018, the only available treatment for ATTRv disease was liver transplantation to eliminate the source of variant TTR production. For patients with ATTR-CM, heart transplantation (to remove the end-product of TTR deposition) was the only disease-specific treatment but was infrequently pursued because of the advanced age of presentation in the case of ATTRwt-CM and the necessity for multiorgan (heart and liver) transplantation in ATTRv-CM.

The recently approved and emerging treatments for ATTR amyloidosis exemplify the best of modern medicine: advancements in basic science can be used to develop targeted disease-specific treatments. The currently approved pharmacologic treatments for ATTR that use novel *TTR* gene silencing approaches to suppress TTR protein production or TTR stabilization to prevent TTR tetramer dissociation into fibrils represent breakthrough treatments when compared with the historical treatments of solid organ transplantation.

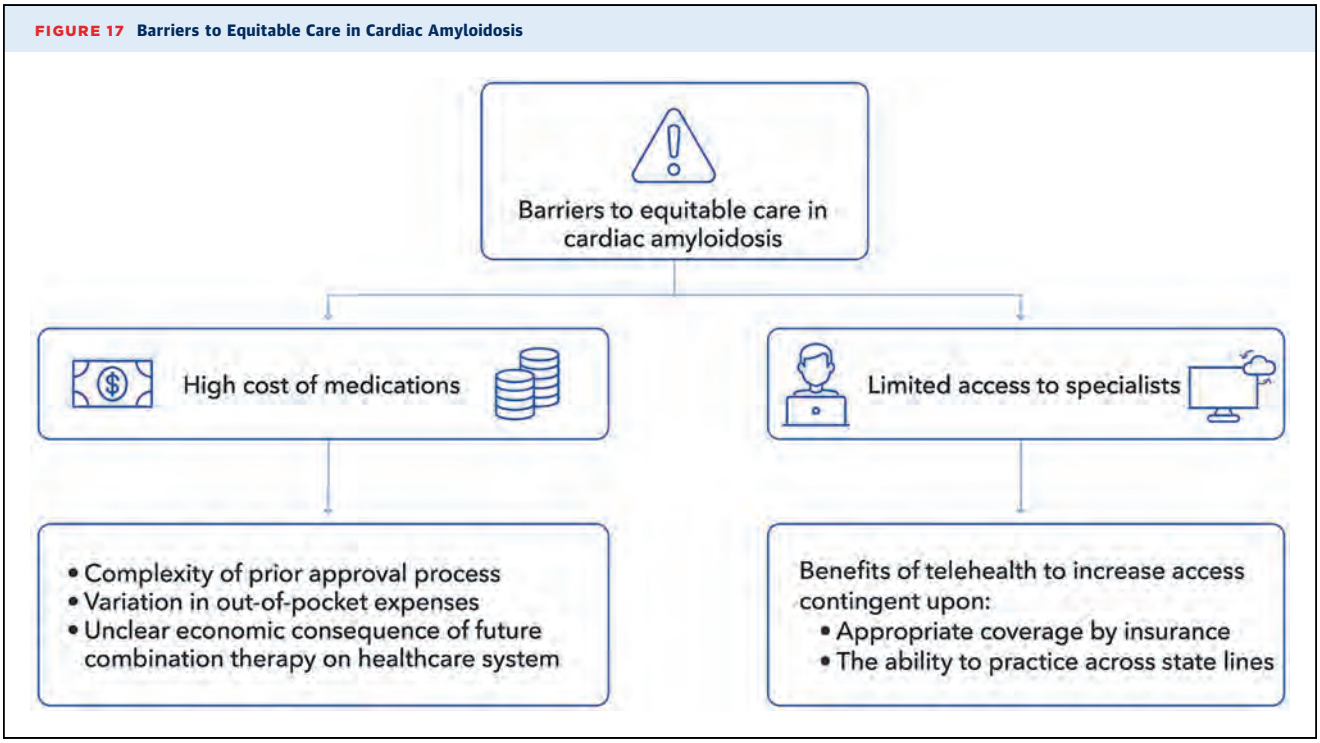
In contrast to solid organ transplantation, where limitations in the donor supply require strict selection criteria to determine eligibility, these novel pharmacologic treatments in theory should be widely available to broad cohorts of patients. Unfortunately, the current pricing of the approved ATTR disease-specific treatments has the potential to limit patient access and adoption of these novel therapeutics.

Globally, there are countries where national review boards have not approved some of these ATTR disease-specific treatments due to concerns of cost-effectiveness and limited resources. In the United States, patisiran, inotersen, and vutrisiran are FDA-approved for the treatment of ATTRv polyneuropathy, and tafamidis is FDA-approved for the treatment of ATTR-CM (irrespective of *TTR* genotype). As a result, most commercial and government-sponsored insurance plans do cover these agents in the appropriately selected patient populations, but there is considerable variability in terms of prior authorization requirements, time to approval, and patient out-of-pocket costs.

8.1.1. Complexity of prescription process

Due to these complexities, navigating the multistep process from drug prescription to administration often requires multidisciplinary clinical teams (including pharmacy professionals and nurses) experienced in the

FIGURE 17 Barriers to Equitable Care in Cardiac Amyloidosis



nuances of the prior authorization process and the logistics of patient assistance programs to offset the potentially high out-of-pocket expenses.

This creates a significant burden for both patients and the medical team. From a patient standpoint, there is anxiety around the list price "sticker shock" of these new treatments and concern about delays in navigating the hurdles of prior authorizations and financial assistance. From the medical perspective, many large amyloidosis referral centers have one or more nonphysician staff members (usually nurses or pharmacists) dedicated solely to the considerable time required to navigate this process.

Such coordination of expertise is often only financially feasible in larger academic practices or integrated health systems, whereas smaller health systems and community practices struggle as the logistics of therapy initiation require hours of uncompensated staff time. Furthermore, the reimbursement model for multidisciplinary care requires reassessment so that team members can be compensated for the time and effort expended to provide comprehensive care.

8.1.2. Financial incentives to 340B centers

In an attempt to ensure equitable patient access to costly medications, Congress enacted Section 340B of the Public Health Service Act in 1992, which requires drug manufacturers to offer significantly discounted prices to qualifying 340B centers, including community health centers, safety-net hospitals, and critical access hospitals that serve uninsured, underinsured, low-income, or undocumented immigrant patients.

The original intent was that these 340B centers could charge patients with insurance the list price of these medications and use the revenue (known as the "340B spread") to cover the uncompensated expenses that resulted from the care and monitoring of these vulnerable populations. However, in a somewhat contradictory fashion, the use of more expensive medications by 340B centers is incentivized in that the 340B spread is larger, and there has been a dramatic increase in the number of 340B centers in the last 20 years—including some with lesser commitments to uncompensated care.[232,233]

As noted earlier, many large health systems and academic medical centers qualify as 340B centers and have used revenue from the 340B spread to develop more general medication access teams to help patients navigate the high cost of amyloid therapies along with other new cardiovascular drugs, such as angiotensin receptor-neprilysin inhibitors, direct oral anticoagulants, sodium glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and proprotein convertase subtilisin/kexin type 9 inhibitors. Although such arrangements have the potential to improve patient access to lifesaving medications, it will be important to ensure that financial incentives align to ensure equitable and cost-effective care for all patients.

8.1.3. Variations in out-of-pocket expenses

In the United States, there is considerable variability in the out-of-pocket expenses of ATTR-CM disease-modifying therapies based on the patient's health insurance plan and prescription drug benefit. In general, commercially insured patients (meaning those patients who are not on government-funded insurance like Medicare or Medicaid) are eligible to receive a variety of direct-to-consumer copayment assistance programs from pharmaceutical companies.

As a result, most commercially insured patients can eventually obtain disease-modifying ATTR therapy with manageable out-of-pocket expenses.[69,234] However, for patients with government funded-insurance such as Medicare or Medicaid, these direct-to-consumer copay assistance programs are illegal due to antikickback statutes. This is particularly relevant because the overwhelming majority of patients with ATTRwt-CM are over 65 years of age and use the Medicare Part D prescription drug benefit.

Given its high cost, the average annual out-of-pocket cost for tafamidis could approach $18,000 per year, more than half of which occurs after the catastrophic coverage threshold.[34] This annual out-of-pocket expense would reset every calendar year for the entire duration of treatment—which is currently presumed to be lifelong—and can result in a significant financial burden as most patients on Medicare are retired and on fixed incomes.

To add further complexity, an intravenous therapy such as patisiran that cannot be self-administered falls under the Medicare Part B benefit. As such, it may paradoxically require a minimal out-of-pocket copayment from the patient ($0-$35 per infusion, depending on the Medicare supplement plan) but have tremendous expense to the health care system, with a wholesale price of $34,000 (based on the maximum dose of 30 mg) per infusion and a billable amount 1.5 to 2.5 times higher than this amount when accounting for compounding, administration, and health care professional services fees.[235]

As drug-manufacturer-to-consumer direct copay assistance is not allowed for Medicare (or Medicaid) patients, pharmaceutical companies have partnered with independent patient assistance foundations to provide grants to cover out-of-pocket medication expenses for select diseases, including amyloidosis. These third-party foundation grants are most often awarded based on annual income limits (usually 500% of the Federal Poverty Level, which, in 2022, is $67,950 for an individual and $91,550 for a 2-person household living in the contiguous United States).[236]

Beyond these grants to foundations, pharmaceutical manufacturers are allowed to provide free drug to patients (including those who are uninsured and those on government-sponsored insurance programs), and there are patients who have directly appealed and are receiving free medication from the manufacturers. However, the lack of transparency as to who is eligible for free drug and the psychological stress engendered by whether a patient's annual renewal for free drug will be approved by the manufacturer creates significant anxiety for both patients and their clinical providers.

8.1.4. Economic burden to the health care system

Finally, beyond the financial implications for an individual patient, the potential economic burden in terms of overall health care expenditures is significant. Tafamidis was the single most expensive cardiovascular drug ever approved in the United States when it received FDA approval in May 2019 as a breakthrough drug for a rare disease. A recent cost-effectiveness analysis suggested a high incremental cost-effectiveness ratio of $880,000 per quality-adjusted life-year gained and that over a 90% price reduction would be needed to make tafamidis cost-effective at the generally accepted threshold of $100,000 per quality-adjusted life year.[68]

In addition, it is increasingly clear that ATTR-CM (particularly ATTRwt) is not as rare a disease as initially suspected, with an estimated 120,000 patients in the United States.[68] Treatment of all eligible patients in the United States is estimated to increase annual health care spending by $32.3 billion.[68] Thus, based on 2020 list prices and current cost-effectiveness analysis, the most recent AHA/ACC/HFSA heart failure guidelines provided a Class 1 recommendation for the treatment of select ATTR-CM patients with tafamidis, but stated that tafamidis treatment provided low economic value.[6] A similar analysis by the Institute for Clinical and Economical Review in 2018 concluded that patisiran (at that point, inotersen had not yet been approved), although clinically effective, provided "low long-term value" for the expenditure required.[237] That stated, cost alone should not be a reason to withhold treatment, as the value to the individual patient with respect to symptom improvement and survival afforded by these novel agents is not easily quantifiable and has not been studied as of yet. Such cost-effectiveness analyses serve to contextualize these novel agents in the landscape of approved therapeutics and provide impetus to reconsider pricing.

8.1.5. Consequences of future combination therapy for TTR amyloidosis

It is possible that the optimal therapeutic approach for ATTR-CM will involve administration of *TTR* silencing and stabilizing agents concurrently. Such a strategy will clearly result in higher cost per patient. Thus, determination of a favorable or unfavorable response to therapy is imperative to select from available treatments or combinations of treatments.

Treatment efficacy will likely be determined by a combination of circulating markers (prealbumin, cardiac troponins, natriuretic peptides, kidney function), imaging markers (the best candidates appear to be echocardiographic global longitudinal strain and CMR extracellular volume fraction),[238] as well as conventional HF metrics (functional status, hospitalizations, and survival).

8.2. Telehealth in the care of patients with amyloidosis

8.2.1. Telehealth is an increasing need

As elaborated in this ECDP, the diagnosis and treatment of ATTR-CM is best accomplished by a multidisciplinary care model predicated upon collaboration between primary care providers, cardiologists in the community, and amyloid specialists at referral centers. The initial diagnostic studies for ATTR-CM, including echocardiography and laboratory evaluation for the presence of a plasma cell disorder, are widely available, and there is increasing availability of Tc-PYP imaging capacity at many hospitals and large cardiology practices throughout the United States.

However, because of the large volume of patients who will be considered and tested for suspected ATTR-CM, equivocal scan results and abnormalities in their screening labs for a plasma cell disorder will necessitate a substantial number of referrals to experienced amyloid specialists. Furthermore, such referrals to specialized centers could result in inequities in care because patients in geographically rural areas or with limited socioeconomic resources may be unable to travel to access these amyloid specialists.

8.2.2. Challenges to telehealth implementation

The recent expanded utilization of telehealth, necessitated by the COVID-19 pandemic, appears to be a promising strategy to improve access to amyloidosis specialists. In theory, an amyloidosis specialist in partnership with local clinicians could provide virtual consultations for patients with inconclusive initial testing and help strategize the subsequent diagnostic and therapeutic plans without the need for geographic travel.

However, it would be essential that insurance payers continue to recognize the clinical providers' time for these telehealth services in terms of medical visit billing. In addition, reducing barriers to telehealth, such as revising state medical licensing rules to allow for practice across state lines, would improve patient access, particularly for patients in less populated or geographically

isolated states that may not have an in-state amyloid specialist. Furthermore, an updated online database of qualified and accessible amyloidosis specialists could empower clinicians and patients to reach out for assistance and/or self-refer for specialized care.

8.2.3. The need for ongoing clinical trials

Finally, there are numerous unanswered questions in our understanding of ATTR-CM, as outlined in a number of scientific society statements.[34,239] To advance the field, amyloid specialists and their patients will need to continue to participate in a variety of clinical research efforts such as participation in industry-sponsored multicenter clinical trials, implementation studies, and pragmatic trials, including large registries. Broad access to such clinical research will ensure that an appropriate diversity of patients and disease types are studied, ensure equitability, and will be a critical component for the care of our current and future patients with ATTR-CM.

9. DISCUSSION AND IMPLICATIONS OF PATHWAY

The paradigm of care for the cardiac amyloidosis patient is evolving, and that evolution is reflected in this ECDP. As recently as 10 to 15 years ago, because of its perceived rarity, cardiac amyloidosis was not routinely considered as a diagnosis to explain the etiology of HF and increased left ventricular wall thickness on echocardiogram. The advent of an accurate, noninvasive imaging means to diagnose ATTR cardiac amyloidosis facilitated enhanced recognition of ATTR amyloidosis and its prevalence among patients with HFpEF and AS. Testing for ATTR amyloidosis has identified unrecognized cases of AL amyloidosis. Finally, the development of effective therapies to improve survival in patients with both AL and ATTR amyloidosis now renders an understanding of the diagnosis and management of cardiac amyloidosis paramount for every cardiovascular specialist.

Not only is cardiac amyloidosis more common than previously thought and the subtleties of diagnosis important to recognize, but the multisystem manifestations require attention and appropriate referral to skilled subspecialists. For example, although the noninvasive diagnosis of ATTR cardiac amyloidosis appears potentially straightforward, there are diagnostic pitfalls enumerated herein that may result in misdiagnosis, with catastrophic consequences for the patient.

Thus, cardiovascular specialists need to incorporate the appropriate index of suspicion, accurate diagnostic algorithms, timely identification of multisystem involvement with appropriate multidisciplinary collaboration, and disease management strategies to optimize outcomes in patients with amyloidosis.

This ECDP and associated treatment algorithms should be used in concert with established guidelines for the management of HF. Although intended to facilitate clinical decision-making, the information provided in this ECDP should complement rather than supersede good clinical judgement. The treatment of patients with amyloidosis is complex. It involves physicians and advanced-practice providers across a wide array of specialties, including primary care, cardiology, nephrology, hematology, neurology, gastroenterology, and palliative care. It also involves associated providers such as nurses, pharmacists, dieticians, and geneticists. In this manner, optimal care reflects the wholistic potential of a team-based approach.

Ultimately, the primary goals of care for all patients with cardiac amyloidosis are improved survival and maximized quality of life through each patient's individual disease journey. Achieving these important goals requires a team-based approach to achieve optimal outcomes. We anticipate that the algorithms proposed here will continue to evolve as new evidence emerges but that the overarching and now attainable goal of improving cardiovascular outcomes in patients with cardiac amyloidosis will remain consistent.

PRESIDENT AND STAFF

REFERENCES

1. Januzzi JL Jr, Ahmad T, Binder LG, et al. 2019 methodology for creating expert consensus decision pathways: a report of the American College of Cardiology. *J Am Coll Cardiol*. 2019;74:1138-1150.

2. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) Nomenclature Committee. *Amyloid*. 2020;27:217-222.

3. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40:232-239.

4. Cornwell GG 3rd, Murdoch WL, Kyle RA, et al. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. *Am J Med*. 1983;75:618–623.

5. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19:733–742.

6. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421.

7. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin Amyloidosis. *Circulation*. 2016;133:2404–2412.

8. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38:2879–2887.

9. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015;36:2585–2594.

10. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016.

11. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *N Engl J Med*. 2021;385:46–58.

12. Quock TP, Yan T, Chang E, et al. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv*. 2018;2:1046–1053.

13. Merlini G, Dispenzieri A, Sanchorawala V, et al. Systemic immunoglobulin light chain amyloidosis. *Nat Rev Dis Primers*. 2018;4:38.

14. AbouEzzeddine OF, Davies DR, Scott CG, et al. Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2021;6:1267–1274.

15. Damrauer SM, Chaudhary K, Cho JH, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African or Hispanic/Latino ancestry. *JAMA*. 2019;322:2191–2202.

16. Lousada I, Comenzo RL, Landau H, et al. Patient experience with hereditary and senile systemic amyloidoses: a survey from the Amyloidosis Research Consortium. *Orphanet J Rare Dis*. 2015;10(Suppl 1):P22.

17. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140:16–26.

18. Longhi S, Lorenzini M, Gagliardi C, et al. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac amyloidosis. *J Am Coll Cardiol Img*. 2016;9:325–327.

19. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2018;39:2799–2806.

20. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol*. 2016;68:1014–1020.

21. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22:3751–3757.

22. Lilleness B, Ruberg FL, Mussinelli R, et al. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. *Blood*. 2019;133:215–223.

23. Barrett CD, Dobos K, Liedtke M, et al. A changing landscape of mortality for systemic light chain amyloidosis. *J Am Coll Cardiol HF*. 2019;7:958–966.

24. Davis MK, Lee PH, Witteles RM. Changing outcomes after heart transplantation in patients with amyloid cardiomyopathy. *J Heart Lung Transplant*. 2015;34:658–666.

25. Ohiomoba RO, Youmans QR, Ezema A, et al. Cardiac transplantation outcomes in patients with amyloid cardiomyopathy. *Am Heart J*. 2021;236:13–21.

26. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201:e26–e51.

27. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1305–1323.

28. Feingold B, Mahle WT, Auerbach S, et al. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e200–e231.

29. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. *J Am Coll Cardiol*. 2017;69:1288–1304.

30. Morris PB, Kovacs RJ, Allen LA, et al. 2019 methodology for Heart House Roundtables: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2019;74:1116–1137.

31. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66:403–469.

32. Muchtar E, Gertz MA, Kyle RA, et al. A modern primer on light chain amyloidosis in 592 patients with mass spectrometry-verified typing. *Mayo Clin Proc*. 2019;94:472–483.

33. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *J Am Coll Cardiol HF*. 2019;7:709–716.

34. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–e22.

35. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42:1554–1568.

36. Ruberg FL, Grogan M, Hanna M, et al. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872–2891.

37. Hoffman JE, Dempsey NG, Sanchorawala V. Systemic amyloidosis caused by monoclonal immunoglobulins: soft tissue and vascular involvement. *Hematol Oncol Clin North Am*. 2020;34:1099–1113.

38. Westermark P, Westermark GT, Suhr OB, et al. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. *Ups J Med Sci*. 2014;119:223–228.

39. Geller HI, Singh A, Alexander KM, et al. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. *JAMA*. 2017;318:962–963.

40. Gertz M, Adams D, Ando Y, et al. Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. *BMC Family Practice*. 2020;21:198.

41. Nativi-Nicolau J, Karam C, Khella S, et al. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. *Heart Fail Rev*. 2022;27(3):785–793.

42. Cyrille NB, Goldsmith J, Alvarez J, et al. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. *Am J Cardiol*. 2014;114:1089–1093.

43. Dorbala S, Ando Y, Bokhari S, et al. 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. *J Nucl Cardiol*. 2019;26:2065–2123.

44. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 2 of 2-diagnostic criteria and appropriate utilization. *J Nucl Cardiol*. 2020;27:659–673.

45. Brownrigg J, Lorenzini M, Lumley M, et al. Diagnostic performance of imaging investigations in detecting and differentiating cardiac amyloidosis: a systematic review and meta-analysis. *ESC Heart Fail*. 2019;6:1041–1051.

46. Dorbala S, Cuddy S, Falk RH. How to image cardiac amyloidosis: a practical approach. *J Am Coll Cardiol Img*. 2020;13:1368–1383.

47. Dorbala S, Ando Y, Bokhari S, et al. 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. *Circ Cardiovasc Imaging*. 2021;14:e000029.

48. Quarta CC, Zheng J, Hutt D, et al. 99mTc-DPD scintigraphy in immunoglobulin light chain (AL) cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging*. 2021;22:1304–1311.

49. Sidiqi MH, McPhail ED, Theis JD, et al. Two types of amyloidosis presenting in a single patient: a case series. *Blood Cancer J*. 2019;9:30.

50. Hanna M, Ruberg FL, Maurer MS, et al. Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: *JACC* review topic of the week. *J Am Coll Cardiol*. 2020;75:2851–2862.

51. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail*. 2019;12:e006075.

52. Witteles RM, Liedtke M. Avoiding catastrophe: understanding free light chain testing in the evaluation of ATTR amyloidosis. *Circ Heart Fail*. 2021;14:e008225.

53. Cuscaden C, Ramsay SC, Prasad S, et al. Estimation of prevalence of transthyretin (ATTR) cardiac amyloidosis in an Australian subpopulation using bone scans with echocardiography and clinical correlation. *J Nucl Cardiol*. 2021;28:2845–2856.

54. Miller EJ, Campisi R, Shah NR, et al. Radiopharmaceutical supply disruptions and the use of (99m)Tc-hydroxymethylene diphosphonate as an alternative to (99m)Tc-pyrophosphate for the diagnosis of transthyretin cardiac amyloidosis: an ASNC information statement. *J Nucl Cardiol*. 2022:1–13.

55. Poterucha TJ, Elias P, Ruberg FL, et al. False positive 99mTc-pyrophosphate scanning leading to inappropriate tafamidis prescriptions. *J Am Coll Cardiol Img*. 2021;14:2042–2044.

56. Jessup M, Drazner MH, Book W, et al. 2017 ACC/AHA/HFSA/ISHLT/ACP advanced training statement on advanced heart failure and transplant cardiology (revision of the ACCF/AHA/ACP/HFSA/ISHLT 2010 clinical competence statement on management of patients with advanced heart failure and cardiac transplant): a report of the ACC Competency Management Committee. *J Am Coll Cardiol*. 2017;69:2977–3001.

57. Yancy CW, Drazner MH, Coffin ST, et al. 2020 ACC/HFSA/ISHLT lifelong learning statement for advanced heart failure and transplant cardiology specialists: a report of the ACC Competency Management Committee. *J Am Coll Cardiol*. 2020;75:1212–1230.

58. Alreshq R, Cozzolino M, Lilleness B, et al. Light chain testing abnormalities among patients with transthyretin amyloid cardiomyopathy referred for technetium-99m pyrophosphate imaging. *Am J Cardiol*. 2022;181:105–112.

59. Hutchison CA, Harding S, Hewins P, et al. Quantitative assessment of serum and urinary polyclonal free light chains in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1684–1690.

60. Long TE, Indridason OS, Palsson R, et al. Defining new reference intervals for serum free light chains in individuals with chronic kidney disease: results of the iStopMM study. *Blood Cancer J*. 2022;12:133.

61. Eulitz M, Weiss DT, Solomon A. Immunoglobulin heavy-chain-associated amyloidosis. *Proc Natl Acad Sci U S A*. 1990;87:6542–6546.

62. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017;38:1905–1908.

63. Witteles RM, Liedtke M. AL Amyloidosis for the Cardiologist and Oncologist: Epidemiology, Diagnosis, and Management. *J Am Coll Cardiol CardioOnc*. 2019;1:117–130.

64. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114:4957–4959.

65. Rapezzi C, Elliott P, Damy T, et al. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. *J Am Coll Cardiol HF*. 2021;9:115–123.

66. Hanna M, Damy T, Grogan M, et al. Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the tafamidis in transthyretin cardiomyopathy clinical trial). *Am J Cardiol*. 2021;141:98–105.

67. Elliott P, Drachman BM, Gottlieb SS, et al. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2022;15:e008193.

68. Kazi DS, Bellows BK, Baron SJ, et al. Cost-effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation*. 2020;141:1214–1224.

69. Masri A, Chen H, Wong C, et al. Initial experience prescribing commercial tafamidis, the most expensive cardiac medication in history. *JAMA Cardiol*. 2020;5:1066–1067.

70. Westin O, Fosbøl EL, Maurer MS, et al. Screening for cardiac amyloidosis 5 to 15 years after surgery for bilateral carpal tunnel syndrome. *J Am Coll Cardiol*. 2022;80:967–977.

71. Eslam RB, Öztürk B, Rettl R, et al. Impact of tafamidis and optimal background treatment on physical performance in patients with transthyretin amyloid cardiomyopathy. *Circ Heart Fail*. 2022;15:e008381.

72. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310:2658–2667.

73. Siddiqi OK, Mints YY, Berk JL, et al. Diflunisal treatment is associated with improved survival for patients with early stage wild-type transthyretin (ATTR) amyloid cardiomyopathy: the Boston University Amyloidosis Center experience. *Amyloid*. 2022;29:71–78.

74. Ibrahim M, Saint Croix GR, Lacy S, et al. The use of diflunisal for transthyretin cardiac amyloidosis: a review. *Heart Fail Rev*. 2022;27:517–524.

75. Cheng RK, Levy WC, Vasbinder A, et al. Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *J Am Coll Cardiol CardioOnc*. 2020;2:414–424.

76. Bhuiyan T, Helmke S, Patel AR, et al. Pressure-volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail*. 2011;4:121–128.

77. Aimo A, Vergaro G, Castiglione V, et al. Safety and tolerability of neurohormonal antagonism in cardiac amyloidosis. *Eur J Intern Med*. 2020;80:66–72.

78. Cheng RK, Vasbinder A, Levy WC, et al. Lack of association between neurohormonal blockade and survival in transthyretin cardiac amyloidosis. *J Am Heart Assoc*. 2021;10:e022859.

79. Sperry BW, Hanna M, Shah SJ, et al. Spironolactone in patients with an echocardiographic HFpEF phenotype suggestive of cardiac amyloidosis: results from TOPCAT. *J Am Coll Cardiol HF*. 2021;9:795–802.

80. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

81. Giancaterino S, Urey MA, Darden D, et al. Management of arrhythmias in cardiac amyloidosis. *J Am Coll Cardiol EP*. 2020;6:351–361.

82. El-Am EA, Dispenzieri A, Melduni RM, et al. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol*. 2019;73:589–597.

83. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation*. 1981;63:1285–1288.

84. Muchtar E, Gertz MA, Kumar SK, et al. Digoxin use in systemic light-chain (AL) amyloidosis: contraindicated or cautious use? *Amyloid*. 2018;25:86–92.

85. Donnelly JP, Sperry BW, Gabrovsek A, et al. Digoxin use in cardiac amyloidosis. *Am J Cardiol*. 2020;133:134–138.

86. Donnellan E, Wazni O, Kanj M, et al. Atrial fibrillation ablation in patients with transthyretin cardiac amyloidosis. *Europace*. 2020;22:259–264.

87. Reisinger J, Dubrey SW, Lavalley M, et al. Electrophysiologic abnormalities in AL (primary) amyloidosis with cardiac involvement. *J Am Coll Cardiol*. 1997;30:1046–1051.

88. Barbhaiya CR, Kumar S, Baldinger SH, et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm*. 2016;13:383–390.

89. Lin G, Dispenzieri A, Kyle R, et al. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol*. 2013;24:793–798.

90. Hamon D, Algalarrondo V, Gandjbakhch E, et al. Outcome and incidence of appropriate implantable cardioverter-defibrillator therapy in patients with cardiac amyloidosis. *Int J Cardiol*. 2016;222:562–568.

91. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793–2867.

92. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72:e91–e220.

93. Scully PR, Patel KP, Treibel TA, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J*. 2020;41:2759–2767.

94. Nitsche C, Scully PR, Patel KP, et al. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol*. 2021;77:128–139.

95. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:11–21.

96. Adams D, Tournev IL, Taylor MS, et al. HELIOS-A: 9-month results from the phase 3 study of vutrisiran in patients with hereditary transthyretin-mediated

amyloidosis with polyneuropathy (1234). *Neurology*. 2021;96:1234.

97. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22-31.

98. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid*. 2012;19(Suppl 1):34-36.

99. aus dem Siepen F, Bauer R, Aurich M, et al. Green tea extract as a treatment for patients with wild-type transthyretin amyloidosis: an observational study. *Drug Des Devel Ther*. 2015;9:6319-6325.

100. Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N Engl J Med*. 2021;385:493-502.

101. Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. *Annu Rev Nutr*. 1994;14:495-533.

102. Mutations in Hereditary Amyloidosis. Accessed October 2022. http://www.amyloidosismutations.com/

103. Parker MM, Damrauer SM, Tcheandjieu C, et al. Association of the transthyretin variant V122I with polyneuropathy among individuals of African ancestry. *Sci Rep*. 2021;11:11645.

104. Bauer R, Dikow N, Brauer A, et al. The "Wagshurst study": p.Val40Ile transthyretin gene variant causes late-onset cardiomyopathy. *Amyloid*. 2014;21:267-275.

105. Maurer MS, Hanna M, Grogan M, et al. Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161-172.

106. Jacobson DR, Alexander AA, Tagoe C, et al. The prevalence and distribution of the amyloidogenic transthyretin (TTR) V122I allele in Africa. *Mol Genet Genomic Med*. 2016;4:548-556.

107. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405-424.

108. Musunuru K, Hershberger RE, Day SM, et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2020;13:e000067.

109. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2018;20:899-909.

110. Trachtenberg BH, Jimenez J, Morris AA, et al. TTR variants in patients with dilated cardiomyopathy: an investigation of the DCM Precision Medicine Study. *Genet Med*. 2022;24:1495-1502.

111. Plante-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol*. 2011;10:1086-1097.

112. Gorram F, Olsson M, Alarcon F, et al. New data on the genetic profile and penetrance of hereditary Val30Met transthyretin amyloidosis in Sweden. *Amyloid*. 2021;28:84-90.

113. Kurian SM, Novais M, Whisenant T, et al. Peripheral blood cell gene expression diagnostic for identifying symptomatic transthyretin amyloidosis patients: male and female specific signatures. *Theranostics*. 2016;6:1792-1809.

114. Campbell CM, LoRusso S, Dispenzieri A, et al. Sex differences in wild-type transthyretin amyloidosis: an analysis from the transthyretin amyloidosis outcomes survey (THAOS). *Cardiol Ther*. 2022;11(3):393-405.

115. Caponetti AG, Rapezzi C, Gagliardi C, et al. Sex-related risk of cardiac involvement in hereditary transthyretin amyloidosis: insights from THAOS. *J Am Coll Cardiol HF*. 2021;9:736-746.

116. Quarta CC, Buxbaum JN, Shah AM, et al. The amyloidogenic V122I transthyretin variant in elderly Black Americans. *N Engl J Med*. 2015;372:21-29.

117. Carry BJ, Young K, Fielden S, et al. Genomic screening for pathogenic transthyretin variants finds evidence of underdiagnosed amyloid cardiomyopathy from health records. *J Am Coll Cardiol CardioOnc*. 2021;3:550-561.

118. Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med*. 1997;336:466-473.

119. Parcha V, Malla G, Ivin MR, et al. Association of transthyretin Val122Ile variant with incident heart failure among black individuals. *JAMA*. 2022;327:1368-1378.

120. Mital S, Musunuru K, Garg V, et al. Enhancing literacy in cardiovascular genetics: a scientific statement from the American Heart Association. *Circ Cardiovasc Genet*. 2016;9:448-467.

121. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23:1391-1398.

122. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2022;24:1407-1414.

123. Conceicao I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. *Amyloid*. 2019;26:3-9.

124. Gillmore JD, Reilly MM, Coats CJ, et al. Clinical and genetic evaluation of people with or at risk of hereditary ATTR amyloidosis: an expert opinion and consensus on best practice in Ireland and the UK. *Adv Ther*. 2022;39:2292-2301.

125. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32:45-59.

126. Duston MA, Skinner M, Anderson J, et al. Peripheral neuropathy as an early marker of AL amyloidosis. *Arch Intern Med*. 1989;149:358-360.

127. Matsuda M, Gono T, Morita H, et al. Peripheral nerve involvement in primary systemic AL amyloidosis: a clinical and electrophysiological study. *Eur J Neurol*. 2011;18:604-610.

128. Wajnsztajn Yungher F, Kim A, Boehme A, et al. Peripheral neuropathy symptoms in wild type transthyretin amyloidosis. *J Peripher Nerv Syst*. 2020;25:265-272.

129. Kleefeld F, Scherret E, Knebel F, et al. Same same, but different? The neurological presentation of wildtype transthyretin (ATTRwt) amyloidosis. *Amyloid*. 2022;29:92-101.

130. Russell A, Hahn C, Chhibber S, et al. Utility of neuropathy screening for wild-type transthyretin amyloidosis patients. *Can J Neurol Sci*. 2021;48:607-615.

131. Wang AK, Fealey RD, Gehrking TL, et al. Patterns of neuropathy and autonomic failure in patients with amyloidosis. *Mayo Clin Proc*. 2008;83:1226-1230.

132. England JD, Gronseth GS, Franklin G, et al. Distal symmetrical polyneuropathy: definition for clinical research. *Muscle Nerve*. 2005;31:113-123.

133. England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2009;72:177-184.

134. Gibbons CH, Illigens BM, Wang N, et al. Quantification of sweat gland innervation: a clinical-pathologic correlation. *Neurology*. 2009;72:1479-1486.

135. Dyck PJB, Gonzalez-Duarte A, Obici L, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: from NIS to mNIS+7. *J Neurol Sci*. 2019;405:116424.

136. Adams D, Polydefkis M, Gonzalez-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol*. 2021;20:49-59.

137. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol*. 2020;27:1374-1381.

138. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79:785-792.

139. Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. *Mayo Clin Proc*. 2015;90:940-951.

140. 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67:674-694.

141. Singer W, Opfer-Gehrking TL, McPhee BR, et al. Acetylcholinesterase inhibition: a novel approach in the treatment of neurogenic orthostatic hypotension. *J Neurol Neurosurg Psychiatry*. 2003;74:1294-1298.

142. Freeman R, Abuzinadah AR, Gibbons C, et al. Orthostatic hypotension: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72:1294-1309.

143. Batra J, Rosenblum H, Cappelli F, et al. Racial differences in Val122Ile-associated transthyretin cardiac amyloidosis. *J Card Fail*. 2022;28:950-959.

144. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35:1-23.

145. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. *Am J Gastroenterol*. 2008;103:776–787.

146. Syed U, Ching Companioni RA, Alkhawam H, et al. Amyloidosis of the gastrointestinal tract and the liver: clinical context, diagnosis and management. *Eur J Gastroenterol Hepatol*. 2016;28:1109–1121.

147. Wixner J, Mundayat R, Karayal ON, et al. THAOS: gastrointestinal manifestations of transthyretin amyloidosis - common complications of a rare disease. *Orphanet J Rare Dis*. 2014;9:61.

148. Rosenzweig M, Kastritis E. Liver and gastrointestinal involvement: update. *Hematol Oncol Clin North Am*. 2020;34:e1–e13.

149. Lim AY, Lee JH, Jung KS, et al. Clinical features and outcomes of systemic amyloidosis with gastrointestinal involvement: a single-center experience. *Korean J Intern Med*. 2015;30:496–505.

150. Yen T, Chen FW, Witteles RM, et al. Clinical implications of gastrointestinal symptoms in systemic amyloidosis. *Neurogastroenterol Motil*. 2018;30:e13229.

151. Ueda M, Horibata Y, Shono M, et al. Clinicopathological features of senile systemic amyloidosis: an ante- and post-mortem study. *Mod Pathol*. 2011;24:1533–1544.

152. Suhr O, Danielsson A, Holmgren G, et al. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med*. 1994;235:479–485.

153. Iida T, Yamano H, Nakase H. Systemic amyloidosis with gastrointestinal involvement: diagnosis from endoscopic and histological views. *J Gastroenterol Hepatol*. 2018;33:583–590.

154. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. *Therap Adv Gastroenterol*. 2016;9:98–112.

155. Hammer HF. Management of chronic diarrhea in primary care: the gastroenterologists' advice. *Dig Dis*. 2021;39:615–621.

156. Włodarczyk J, Waśniewska A, Fichna J, et al. Current overview on clinical management of chronic constipation. *J Clin Med*. 2021;10:1738.

157. Obici L, Gonzalez-Duarte A, Waddington-Cruz M, et al. Impact of patisiran, an RNAi therapeutic, on diarrhea symptoms in patients with hereditary transthyretin-mediated amyloidosis. *Am J Gastroenterol*. 2020;115:s1657.

158. Lyon AR, Lopez-Fernandez T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43:4229–4361.

159. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003;349:583–596.

160. Siragusa S, Morice W, Gertz MA, et al. Asymptomatic immunoglobulin light chain amyloidosis (AL) at the time of diagnostic bone marrow biopsy in newly diagnosed patients with multiple myeloma and smoldering myeloma. A series of 144 cases and a review of the literature. *Ann Hematol*. 2011;90:101–106.

161. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). *Amyloid*. 2018;25:62–67.

162. Geller HI, Singh A, Mirto TM, et al. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. *Mayo Clin Proc*. 2017;92:1800–1805.

163. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc*. 2013;2:e000098.

164. Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2018;378:241–249.

165. Molina-Andújar A, Robles P, Cibeira MT, et al. The renal range of the κ/λ sFLC ratio: best strategy to evaluate multiple myeloma in patients with chronic kidney disease. *BMC Nephrol*. 2020;21:111.

166. Xu B, Tang Y, Zhou J, et al. Disease spectrum of abnormal serum free light chain ratio and its diagnostic significance. *Oncotarget*. 2017;8:82268–82279.

167. Muchtar E, Dispenzieri A, Lacy MQ, et al. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. *Ann Med*. 2017;49:545–551.

168. Chiu A, Dasari S, Kurtin PJ, et al. Bone marrow amyloid: a comprehensive analysis of 1,469 samples, including amyloid type, clinical features, and morphologic distribution. *Amyloid*. 2022;29:156–164.

169. Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. *Blood Advances*. 2019;3:3002–3009.

170. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. *Br J Haematol*. 2008;140:365–377.

171. Palladini G, Merlini G. How I treat AL amyloidosis. *Blood*. 2022;139:2918–2930.

172. Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. *Blood*. 2009;114:1489–1497.

173. Cohen AD, Landau H, Scott EC, et al. Safety and efficacy of carfilzomib (CFZ) in previously-treated systemic light-chain (AL) amyloidosis. *Blood*. 2016;128:645.

174. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood*. 2017;130:597–605.

175. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood*. 2007;109:492–496.

176. Sanchorawala V, Shelton AC, Lo S, et al. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. *Blood*. 2016;128:1059–1062.

177. Hughes DM, Staron A, Sanchorawala V. A pharmacist's review of the treatment of systemic light chain amyloidosis. *J Oncol Pharm Pract*. 2021;27:187–198.

178. Sanchorawala V, Sun F, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. *Blood*. 2015;126:2345–2347.

179. Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. *Amyloid*. 2022;29:1–7.

180. Hemu M, Zimmerman A, Kalra D, et al. Pretransplant cardiac evaluation using novel technology. *J Clin Med*. 2019;8:690.

181. Staron A, Zheng L, Doros G, et al. Marked progress in AL amyloidosis survival: a 40-year longitudinal natural history study. *Blood Cancer J*. 2021;11:139.

182. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. *Blood*. 2019;134:2271–2280.

183. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, melphalan, and dexamethasone for light-chain amyloidosis. *J Clin Oncol*. 2020;38:3252–3260.

184. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia*. 2012;26:2317–2325.

185. Dispenzieri A, Kastritis E, Wechalekar AD, et al. A randomized phase 3 study of ixazomib-dexamethasone versus physician's choice in relapsed or refractory AL amyloidosis. *Leukemia*. 2022;36:225–235.

186. Premkumar VJ, Lentzsch S, Pan S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. *Blood Cancer J*. 2021;11:10.

187. Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38:1056–1066.

188. Gray Gilstrap L, Niehaus E, Malhotra R, et al. Predictors of survival to orthotopic heart transplant in patients with light chain amyloidosis. *J Heart Lung Transplant*. 2014;33:149–156.

189. Bochtler T, Hegenbart U, Kunz C, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. *Blood*. 2016;128:594–602.

190. Qualls DA, Lewis GD, Sanchorawala V, et al. Orthotopic heart transplant rejection in association with immunomodulatory therapy for AL amyloidosis: A case series and review of the literature. *Am J Transplant*. 2019;19:3185–3190.

191. Dember LM. Amyloidosis-associated kidney disease. *J Am Soc Nephrol*. 2006;17:3458–3471.

192. Connors LH, Lim A, Prokaeva T, et al. Tabulation of human transthyretin (TTR) variants, 2003. *Amyloid*. 2003;10:160–184.

193. Fenoglio R, Baldovino S, Barreca A, et al. Renal involvement in transthyretin amyloidosis: the double presentation of transthyretin amyloidosis deposition disease. *Nephron*. 2022:1–8.

194. Law S, Fontana M, Gillmore JD. Advances in diagnosis and treatment of cardiac and renal amyloidosis. *Cardiol Clin*. 2021;39:389–402.

195. Inker LA, Levey AS. New equations for estimating the GFR without race. Reply. . *N Engl J Med*. 2022;386:1672–1673.

196. Dember LM, Sanchorawala V, Seldin DC, et al. Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on al amyloidosis-associated renal disease. *Ann Intern Med*. 2001;134:746–753.

197. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. *Blood*. 2011;118:4346–4352.

198. Leung N, Dispenzieri A, Fervenza FC, et al. Renal response after high-dose melphalan and stem cell transplantation is a favorable marker in patients with primary systemic amyloidosis. *Am J Kidney Dis*. 2005;46:270–277.

199. Angel-Korman A, Jaberi A, Sanchorawala V, et al. The utility of repeat kidney biopsy in systemic immunoglobulin light chain amyloidosis. *Amyloid*. 2020;27:17–24.

200. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383:1436–1446.

201. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;143:298–309.

202. Specter R, Sanchorawala V, Seldin DC, et al. Kidney dysfunction during lenalidomide treatment for AL amyloidosis. *Nephrol Dial Transplant*. 2011;26:881–886.

203. Terao T, Tsushima T, Miura D, et al. Carfilzomib-induced thrombotic microangiopathy is underestimated in clinical practice: a report of five patients and literature review. *Leuk Lymphoma*. 2022;63:1102–1110.

204. Cheungpasitporn W, Leung N, Rajkumar SV, et al. Bortezomib-induced acute interstitial nephritis. *Nephrol Dial Transplant*. 2015;30:1225–1229.

205. Fadia A, Casserly LF, Sanchorawala V, et al. Incidence and outcome of acute renal failure complicating autologous stem cell transplantation for AL amyloidosis. *Kidney Int*. 2003;63:1868–1873.

206. Nader R, Zhen A, Angel-Korman A, et al. Predictors and outcomes of acute kidney injury during autologous stem cell transplantation in AL amyloidosis. *Nephrol Dial Transplant*. 2022;37:1281–1288.

207. Angel-Korman A, Havasi A. Kidney transplantation in systemic amyloidosis. *Transplantation*. 2020;104:2035–2047.

208. Havasi A, Heybeli C, Leung N, et al. Outcomes of renal transplantation in patients with AL amyloidosis: an international collaboration through The International Kidney and Monoclonal Gammopathy Research Group. *Blood Cancer J*. 2022;12:119.

209. Dispenzieri A, Kyle RA, Gertz MA, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. *Lancet*. 2003;361:1787–1789.

210. Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation*. 2003;107:2440–2445.

211. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood*. 2013;121:3420–3427.

212. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol*. 2012;30:989–995.

213. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015;126:612–615.

214. Nicol M, Deney A, Lairez O, et al. Prognostic value of cardiopulmonary exercise testing in cardiac amyloidosis. *Eur J Heart Fail*. 2021;23:231–239.

215. Nuvolone M, Milani P, Palladini G, et al. Management of the elderly patient with AL amyloidosis. *Eur J Intern Med*. 2018;58:48–56.

216. Kristen AV, Kreusser MM, Blum P, et al. Improved outcomes after heart transplantation for cardiac amyloidosis in the modern era. *J Heart Lung Transplant*. 2018;37:611–618.

217. Jha SR, Hannu MK, Chang S, et al. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. *Transplantation*. 2016;100:429–436.

218. Tada L, Anjum H, Linville WK, et al. Recurrent pleural effusions occurring in association with primary pulmonary amyloidosis. *Case Rep Pulmonol*. 2015;2015:421201.

219. Berk JL. Pleural effusions in systemic amyloidosis. *Curr Opin Pulm Med*. 2005;11:324–328.

220. Theodorakakou F, Fotiou D, Dimopoulos MA, et al. Solid organ transplantation in amyloidosis. *Acta Haematol*. 2020;143:352–364.

221. Witteles RM. Cardiac transplantation and mechanical circulatory support in amyloidosis. *J Am Coll Cardiol CardioOnc*. 2021;3:516–521.

222. Griffin JM, Baughan E, Rosenblum H, et al. Surveillance for disease progression of transthyretin amyloidosis after heart transplantation in the era of novel disease modifying therapies. *J Heart Lung Transplant*. 2022;41:199–207.

223. Maurer MS, Raina A, Hesdorffer C, et al. Cardiac transplantation using extended-donor criteria organs for systemic amyloidosis complicated by heart failure. *Transplantation*. 2007;83:539–545.

224. Swiecicki PL, Edwards BS, Kushwaha SS, et al. Left ventricular device implantation for advanced cardiac amyloidosis. *J Heart Lung Transplant*. 2013;32:563–568.

225. Grupper A, Park SJ, Pereira NL, et al. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: improving outcomes for a lethal disease. *J Heart Lung Transplant*. 2015;34:1042–1049.

226. Randhawa VK, Gabrovsek A, Soltesz EG, et al. A case series of cardiac amyloidosis patients supported by continuous-flow left ventricular assist device. *ESC Heart Fail*. 2021;8:4353–4356.

227. Kittleson MM, Cole RM, Patel J, et al. Mechanical circulatory support for cardiac amyloidosis. *Clin Transplant*. 2019:e13663.

228. Michelis KC, Zhong L, Tang WHW, et al. Durable mechanical circulatory support in patients with amyloid cardiomyopathy: insights from INTERMACS. *Circ Heart Fail*. 2020;13:e007931.

229. Bhimaraj A, Agrawal T, Duran A, et al. Percutaneous left axillary artery placement of intra-aortic balloon pump in advanced heart failure patients. *J Am Coll Cardiol HF*. 2020;8:313–323.

230. Radbruch L, De Lima L, Knaul F, et al. Redefining palliative care-a new consensus-based definition. *J Pain Symptom Manage*. 2020;60:754–764.

231. Tsukanov J, Fabbro ED. Palliative care and symptom management in amyloidosis: a review. *Curr Probl Cancer*. 2016;40:220–228.

232. Marcus JL, Killelea A, Krakower DS. Perverse incentives - HIV prevention and the 340B drug pricing program. *N Engl J Med*. 2022;386:2064–2066.

233. Nikpay S, Buntin M, Conti RM. Diversity of participants in the 340B drug pricing program for US hospitals. *JAMA Intern Med*. 2018;178:1124–1127.

234. Cuddy SAM, Coyle ML, Falk RH. Initial monthly cost of tafamidis-the real price for patients. *JAMA Cardiol*. 2020;5:847–848.

235. Chen H, Chandrashekar P, Fischer K, et al. Navigating the complex web of prescribing amyloidosis therapeutics: a primer. *J Am Heart Assoc*. 2022;11:e023895.

236. U.S. Department of Health and Human Services. Annual update of the HHS Poverty Guidelines. Federal Register. Accessed June 24, 2022. https://www.federalregister.gov/documents/2022/01/21/2022-01166/annual-update-of-the-hhs-poverty-guidelines

237. Institute for Clinical and Economical Review. Inotersen and patisiran for hereditary transthyretin amyloidosis: effectiveness and value final evidence report. Accessed June 24, 2022. http://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_Amyloidosis_Final_Evidence_Report_101718.pdf

238. Patel RK, Fontana M, Ruberg FL. Cardiac amyloidosis: multimodal imaging of disease activity and response to treatment. *Circ Cardiovasc Imaging*. 2021;14:e009025.

239. Rapezzi C, Aimo A, Serenelli M, et al. Critical comparison of documents from scientific societies on cardiac amyloidosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79:1288–1303.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)— 2023 ACC EXPERT CONSENSUS DECISION PATHWAY ON COMPREHENSIVE MULTIDISCIPLINARY CARE FOR THE PATIENT WITH CARDIAC AMYLOIDOSIS

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APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2023 ACC EXPERT CONSENSUS DECISION PATHWAY ON COMPREHENSIVE MULTIDISCIPLINARY CARE FOR THE PATIENT WITH CARDIAC AMYLOIDOSIS

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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APPENDIX 2. CONTINUED

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ACC = American College of Cardiology; AHA = American Heart Association.

APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
AF = atrial fibrillation
AL = amyloid monoclonal immunoglobulin light chain
AL-CM = amyloid monoclonal immunoglobulin light chain cardiomyopathy
AS = aortic stenosis
ATTR = amyloid transthyretin
ATTR-CM = amyloid transthyretin cardiomyopathy
CM = cardiomyopathy
CMR = cardiac magnetic resonance
ECDP = Expert Consensus Decision Pathways
FDA = Food and Drug Administration
GI = gastrointestinal
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
LVAD = left ventricular assist device
MCS = mechanical circulatory support
NYHA = New York Heart Association
PYP = pyrophosphate
SCT = stem cell transplantation
sFLC = serum free light chain