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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Transthyretin Amyloid Cardiomyopathy

JACC State-of-the-Art Review

Frederick L. Ruberg, MD,[a] Martha Grogan, MD,[b] Mazen Hanna, MD,[c] Jeffery W. Kelly, PhD,[d] Mathew S. Maurer, MD[e]

ABSTRACT

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an under-recognized cause of heart failure (HF) in older adults, resulting from myocardial deposition of misfolded transthyretin (TTR) or pre-albumin. Characteristic patterns of echocardiography and cardiac magnetic resonance can strongly suggest the disease but are not diagnostic. The diagnosis can be made with noninvasive nuclear imaging when there is no evidence of a monoclonal protein. Amyloid fibril formation results from a destabilizing mutation in hereditary ATTR amyloidosis (hATTR) or from an aging-linked process in wild-type ATTR amyloidosis (wtATTR). Recent studies have suggested that up to 10% to 15% of older adults with HF may have unrecognized wtATTR. Associated features, including carpal tunnel syndrome and lumbar spinal stenosis, raise suspicion and may afford a means for early diagnosis. Previously treatable only by organ transplantation, pharmaceutical therapy that slows or halts ATTR-CM progression and favorably affects clinical outcomes is now available. Early recognition remains essential to afford the best treatment efficacy. (J Am Coll Cardiol 2019;73:2872–91)

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an under-recognized cause of heart failure (HF) in older adults. ATTR is one of the systemic amyloidoses, which are disorders characterized by a misfolded precursor protein that forms cross-β–sheet-rich amyloid fibrils extracellularly in several tissues (1). Although there are >30 known amyloidogenic proteins, cardiac amyloidosis typically arises from misfolded transthyretin (ATTR) or immunoglobulin light-chain aggregation (1). Light-chain amyloidosis (AL) results from misfolding of light-chains secreted by clonal plasma cells (2,3), which involves the heart in 50% to 75% of cases (4). Once believed to be untreatable, contemporary therapies have improved survival for AL (5,6).

ATTR-CM is increasingly being recognized by the cardiology community. The disease is classified by the sequence of the *TTR* gene, either wild-type transthyretin amyloid CM (wtATTR-CM) (no mutation) or hereditary transthyretin amyloid CM (hATTR-CM) (a mutation is present). Recent studies have suggested that the prevalence of wtATTR-CM is substantially higher than previously appreciated in older adults with HF. Furthermore, the most common

From the [a]Section of Cardiovascular Medicine, Department of Medicine, Amyloidosis Center, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts; [b]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; [c]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; [d]Departments of Chemistry and Molecular Medicine, Scripps Research Institute, La Jolla, California; and the [e]Division of Cardiology, Department of Medicine, Center for Advanced Cardiac Care, Columbia University Medical Center, New York, New York. Dr. Ruberg is supported by the National Institutes of Health (NIH) (grants HL139671-01 and AG 050206-02). Dr. Kelly is supported by the NIH (grant DK46335). Dr. Maurer is supported by the NIH (grants R01HL139671-01, R21AG058348 and K24AG036778). Dr. Ruberg has received support from Eidos Therapeutics; and has received consulting fees from Pfizer and GlaxoSmithKline. Dr. Grogan has taken part in clinical trials for Alnylam, Eidos, Pfizer, and Prothena; and has been a consultant to Alnylam, Eidos, Pfizer, Prothena, and Akcea. Dr. Kelly has received consulting, equity, and royalty fees from Pfizer linked to Tafamidis sales; is the founder of Fold Rx and Proteostasis Therapeutics; and has been a consultant, shareholder, and board member of Proteostasis Therapeutics. Dr. Hanna has taken part in clinical trials for Pfizer, Alnylam, and Akcea; and has been a consultant and a member of the Advisory Board for Pfizer, Alnylam, Akcea, and Eidos. Dr. Maurer has received consulting fees from Pfizer, GlaxoSmithKline, EIdos, Prothena, Akcea, and Alnylam; and has received clinical trial funding from Pfizer, Prothena, Eidos, and Alnylam.

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HIGHLIGHTS

- ATTR-CM is an underdiagnosed condition.
- Diagnosing ATTR-CM requires a high index of suspicion and can be made noninvasively with nuclear scintigraphy when there is no evidence of a monoclonal protein.
- Emerging therapies that stabilize TTR have been shown to improve outcomes for patients with ATTR-CM, and TTR silencer therapies are entering late-phase clinical trials.
- Early diagnosis will be critical to afford the best efficacy of therapies.

mutation associated with hATTR-CM (Val122Ile) is present in 3.4% of African Americans, with 1.5 million individuals in the United States being allele carriers (7). Recent advances in nuclear imaging using bone avid radiotracers permit diagnosis of ATTR-CM without a tissue biopsy (8). Contemporary treatment strategies that suppress expression (9,10) or stabilize transthyretin (TTR) (11) have been recently reported to slow or halt disease progression in ATTR polyneuropathy. In addition, strategies that stabilize TTR improve survival in patients with ATTR-CM (12). Advances in noninvasive diagnosis, coupled with concurrent demonstration of efficacy and the anticipated regulatory approval of specific ATTR-CM therapies, has shifted ATTR-CM from a rarely encountered and untreatable "zebra," to a condition that clinicians should consider on a daily basis (**Central Illustration**).

PATHOBIOLOGY OF ATTR

TTR, formerly named pre-albumin, is composed of 4 β-sheet rich monomers that circulate as a tetramer and function as a carrier protein for thyroxine and holo-retinol binding protein (RBP) (13). The native TTR tetramer is secreted from the liver into the blood, with lesser amounts produced by the choroid plexus for cerebral spinal fluid and retinal pigmented epithelial cells for the vitreous of the eye. TTR misfolding and aggregation in these fluids leads to tissue dysfunction and the clinical phenotypes of the ATTR amyloidoses (**Figure 1**) (14).

The *TTR* gene is found on chromosome 18. In hATTR, there are single amino acid mutations in the 127 amino acid sequence that destabilize the heterotetramer, rendering aggregation more efficient. The nomenclature for hATTR places a 1- or 3-letter abbreviation for the normal amino acid at the position indicated followed the amino acid substituted (e.g., Val30Met signifies substitution for valine at position 30 by methionine). Although Val30Met is the commonly used published data nomenclature, this is reported as pV50M in genetic testing reports that include the 20 amino acid signal peptide in the numbering of residues. In wtATTR, the genetic sequence of TTR is normal. It is not clear why the wild-type protein becomes kinetically unstable and aggregates; however, this appears to involve the aging process. Because <5% of TTR carries thyroid hormone, this ligand does not influence the aggregation propensity of TTR (15). In contrast, holo-RBP does bind and stabilize tetrameric TTR, which suggests that low concentrations of holo-RBP may be a risk factor for ATTR-CM (16).

The rate-limiting step of TTR amyloid formation is dissociation of the tetramer into monomers, which possibly involves proteolysis. Subsequently, partial monomer denaturation (17) enables misassembly into several aggregate structures, including amyloid fibrils. In ATTR-CM, one consequence of the aggregation process is cardiac infiltration by rigid, space-occupying TTR amyloid fibrils that lead to stiffness and dysfunction. Nonamyloid aggregates appear to exhibit proteotoxicity in ATTR-CM, as occurs in AL.

DISEASE COURSE AND PROGNOSIS

The natural history of ATTR-CM includes progressive HF, complicated by arrhythmias and conduction system disease (**Table 1**) (18). The clinical course is more variable for those with hATTR-CM compared with those who have wtATTR-CM. hATTR can present as a primary cardiomyopathy or as primary peripheral and autonomic neuropathy, sometimes with vitreous opacities. Not uncommonly, there is a mixed phenotype in hATTR with components of both cardiomyopathy and polyneuropathy (19). The natural history, including age of onset, primary phenotype, and clinical course varies with mutation, fibril type (full length vs. fragments) and within families (20). The presence and extent of cardiac involvement is a major determinant of outcome. Severe autonomic neuropathy may mask the degree of cardiac involvement due to pooling of blood in the splanchnic bed. Although

ABBREVIATIONS AND ACRONYMS

ACC/AHA/HRS = American College of Cardiology/American Heart Association/Heart Rhythm Society

AL = light-chain amyloidosis

ATTR = transthyretin amyloidosis

ATTR-CM = transthyretin amyloid cardiomyopathy

CMR = cardiac magnetic resonance

ECV = extracellular volume fraction

FDA = U.S. Food and Drug Administration

hATTR = hereditary (genetically abnormal) transthyretin amyloidosis

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

ICD = implantable cardioverter-defibrillators

RBP = retinol binding protein 4

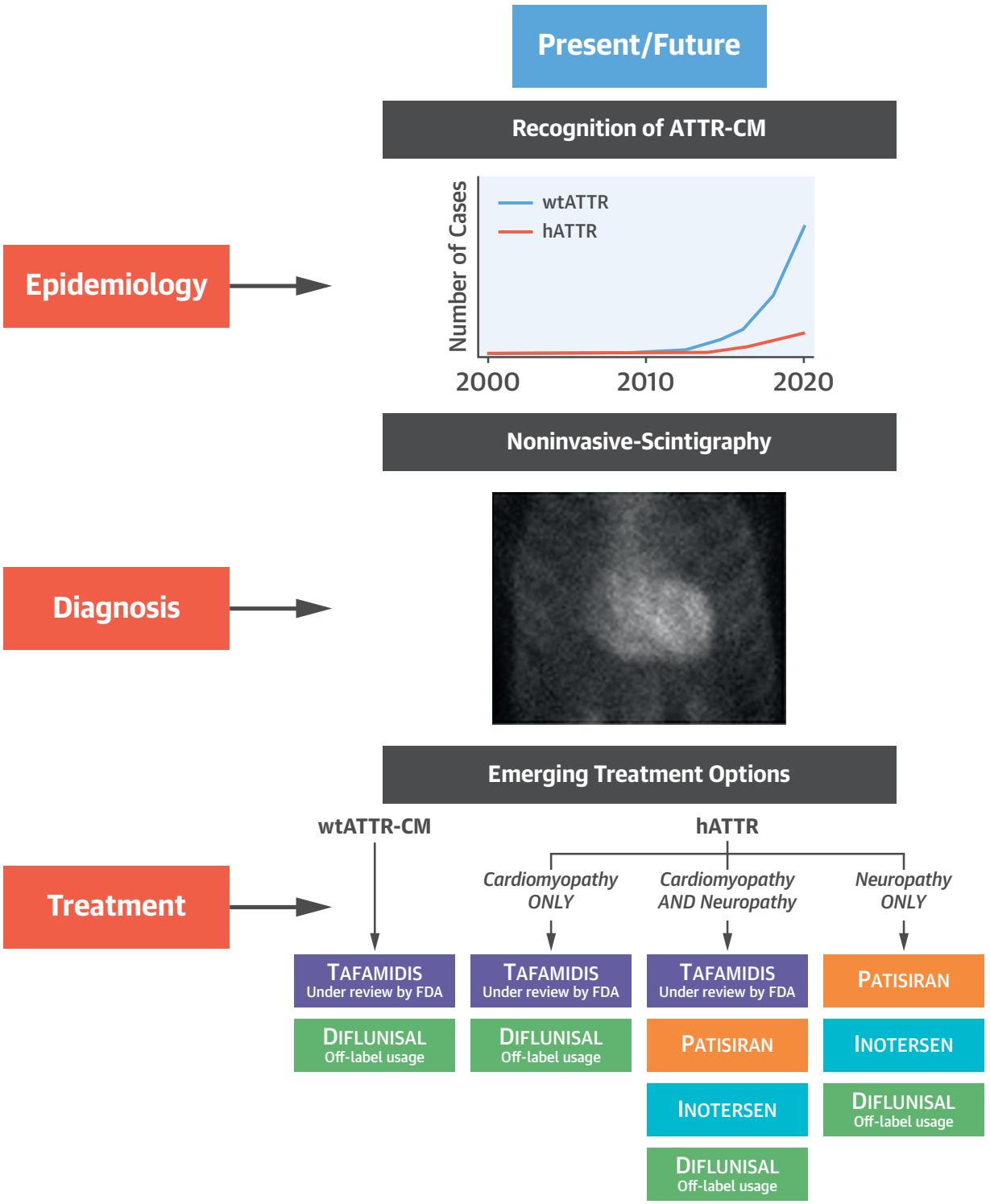
Tc-99m-DPD = technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy

Tc-99m-PYP = technetium-99m pyrophosphate scintigraphy

TTR = transthyretin or pre-albumin

wtATTR = wild-type (genetically normal) transthyretin amyloidosis

CENTRAL ILLUSTRATION **Transthyretin Cardiac Amyloidosis**



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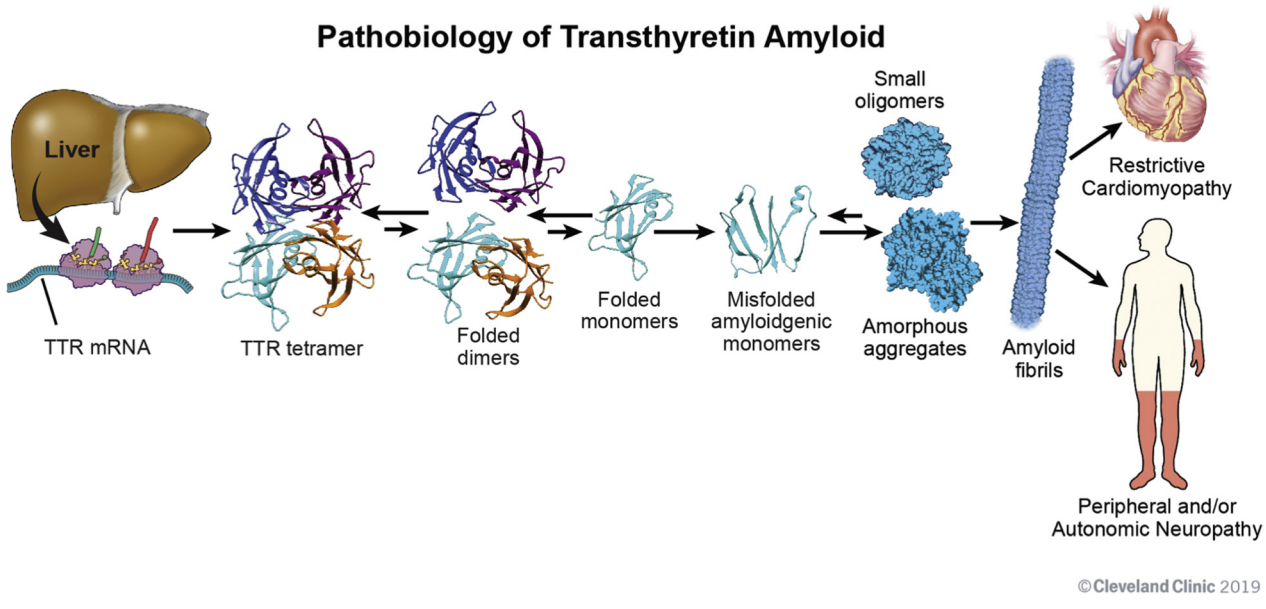
The present and future of transthyretin amyloid cardiomyopathy (ATTR-CM) with respect to epidemiology, diagnostic approach, and treatment. ATTRh = hereditary ATTR; ATTRwt = wild-type ATTR.

FIGURE 1 Pathobiology of ATTR



The mechanism of transthyretin (TTR) protein dissociation, misfolding and aggregation as amyloid fibrils is illustrated with resultant end-organ dysfunction. ATTR = transthyretin amyloid; mRNA = messenger RNA.

both peripheral and autonomic neuropathy can sometimes occur in wtATTR, it is less severe than that in hATTR. Amyloid polyneuropathy can manifest post-heart transplantation in patients with wtATTR-CM (21), perhaps because patients were spared an earlier death from HF. Data also suggest that survival appears worse in hATTR-CM owing to Val122Ile than survival in wtATTR (22–24). Although there is clearly variation in survival with respect to genotype in hATTR, most series have reported a median survival in the range of 8 to 10 years for patients with hATTR polyneuropathy versus 2.5 to 3.5 years in those diagnosed with HF (19).

The phenotype and natural history of wtATTR-CM has been consistent in reported series (25–27). The median survival from diagnosis in untreated patients is consistently approximately 3.5 years but is dependent on the stage of disease. Cardiac biomarkers can be used to risk stratify ATTR-CM patients. The Mayo Clinic wtATTR-CM staging system used thresholds of troponin T and N-terminal pro-B-type natriuretic peptide (>0.05 ng/ml and >3,000 pg/ml, respectively). The 3 stages were defined as: stage I: both biomarker values below threshold; stage II: 1 biomarker above the threshold; and stage III: both biomarkers above the threshold. These 3 stages had a median survival of 66, 42, and 20 months, respectively (27). The ATTR staging system from the U.K. National Amyloidosis Center used N-terminal pro-B-type natriuretic peptide (same threshold of >3,000 pg/ml) and the estimated glomerular filtration rate (<45 ml/min/1.73 m^2) included in both wtATTR-CM and hATTR cohorts and reported a median survival for stage II wtATTR patients of 49 months; patients with hATTR (Val122Ile mutation only) had a survival of 29 months (23). Both studies found that echocardiographic findings, including wall thickness, left ventricular mass, and diastolic function, were not independent predictors of survival. Although cardiac amyloidosis has been associated with a preserved ejection fraction, reduced ejection fraction (<40%) was reported in 30% to 50% of wtATTR-CM cases (18,27). Reduced ejection fraction at diagnosis is more common in Val122Ile hATTR-CM than in wtATTR-CM, which likely reflects a more advanced stage of disease at diagnosis and perhaps accounts for the reduced survival reported in these patients.

In general, ATTR-CM is characterized by years of relative stability despite advanced disease based on imaging, hemodynamics, and reduced functional capacity. This is commonly followed by a significant decline to severe and refractory HF, suggesting that the disease progresses slowly. Accordingly, patients with wtATTR "look much better" clinically than cardiac imaging and invasive hemodynamics would suggest. This is in contrast to AL, in which the

TABLE 1 Disease Course and Prognosis of Hereditary and Wild-Type ATTR-CM

	Hereditary (hATTR-CM)	Wild-Type (wtATTR-CM)
Age of onset	Variable (30–80 yrs) dependent on the mutation	Average 75 yrs, usually >60 yrs
TTR genotype	Abnormal, single nucleotide mutation	Normal
Heritability	Autosomal dominant (50% chance of passage to offspring)	Not known to be heritable
Predominant countries of origin	Val122Ile: U.S., U.K., Western Africa Thr60Ala (Appalachian mutation): U.S., U.K. (predominately Northern part of Republic of Ireland) Val30Met: Sweden, Portugal, Japan Leu111Met: Denmark Ile68Leu: Italy	No known geographic disparities
Prevalence	Val122Ile genotype: 3.4% of African Americans (7) Thr60Ala genotype: ~1% of Northern part of Republic of Ireland (37)	Up to 25% with wtATTR deposits at autopsy 13% in hospitalized HFpEF with wall thickness >12 mm 6%–16% of patients undergoing AVR possibly 1%–3% >75 yrs of age
Median survival after diagnosis without treatment	~2.5 yrs* (Val122Ile)	~3.5 yrs*

*Can be further risk stratified with cardiac biomarker staging systems.

ATTR-CM = transthyretin amyloid cardiomyopathy; AVR = aortic valve replacement; HFpEF = heart failure with preserved ejection fraction.

imaging findings may be subtle despite rapidly progressive HF (18). The discrepancy has been attributed to a more significant direct cardiotoxicity of circulating free light-chains and pre-fibrillar aggregates in AL compared with ATTR. The discrepancy between imaging findings, especially wall thickness and clinical course, highlights the fact that cardiac amyloidosis is not a simple infiltrative disorder and is better characterized as a toxic-infiltrative cardiomyopathy (4).

In addition to HF, the natural history of ATTR-CM commonly includes both conduction system disease and arrhythmias, which may occur years before the onset of HF (18). Conduction system disease is more common in wtATTR-CM than hATTR-CM, with up to one-third of patients requiring permanent pacemakers. Atrial arrhythmias are also more common in wtATTR-CM than in hATTR, occurring in 40% to 60% of patients at diagnosis in recent series (18,25–27) and in almost all patients during the course of the disease. Atrial fibrillation often occurs with a controlled ventricular response because of underlying conduction disease, and, when present, atrial fibrillations becomes persistent in most patients with wtATTR-CM (28). The risk of intracardiac thrombus is increased in all patients with cardiac amyloidosis and may occur even in sinus rhythm (29). Unfortunately, stroke or systemic embolization is the presentation in some patients, usually because of unrecognized atrial fibrillation.

AFFECTED POPULATIONS

OVERVIEW OF GENOTYPES. Wild-type ATTR-CM is almost exclusively a disease of older adults with an average age at diagnosis of 74 years; however, there have been rare individuals diagnosed in their 40s (25–27). In most of the studied cohorts and registries, >90% of patients are men and Caucasian, but whether this relates to a true disease predilection in this population or a referral bias is unknown. In addition to universal cardiac involvement, involvement of soft tissues leads to an increased incidence of bilateral carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture (30,31). Although peripheral and/or autonomic neuropathy are uncommon in wtATTR, neuropathy can be seen in up to 10% of patients (26), but whether this relates to amyloidosis or associated other etiologies also remains undefined.

The delineation between wtATTR and hATTR is critical because of clinical differences in phenotype, prognosis, and implications for screening of family members. In hATTR, each amyloidogenic mutation is believed to have arisen from a genetic founder, with population enrichment of the affected allele in certain geographic regions based on migration patterns. The most common mutation in the United States is Val122Ile (pV142I), which is almost exclusively seen in individuals of west African origin and occurs in 3.4% of African Americans (7). The phenotype is similar to wtATTR-CM in that it causes a late-onset restrictive cardiomyopathy with minimal neuropathy at an average age of onset of 69 years (32). Polyneuropathy is uncommon (33), but has implications based on current drug approval indications (see the Emerging Therapies section). As in wtATTR-CM, there appears to be a male preponderance, with only 25% of reported cases being women (34). The true penetrance of this mutation is unknown and

clearly relates both to the age of ascertainment and the methodology used to define disease. Although a recent report suggested that penetrance may be as low as 10% to 20% (35), this study used a relatively insensitive echocardiographic wall thickness criterion to define disease presence. Furthermore, this study and others demonstrated an association of Val122Ile and HF incidence with advancing age (35,36), which suggested that more sensitive methods could more accurately demonstrate disease penetrance.

The second most common mutation in the United States that causes hATTR-CM is Thr60Ala (pT80A). This variant originates in the Northern part of the Republic of Ireland and causes a mixed phenotype with a high rate of carpal tunnel syndrome (up to 70%), which often presents as the first manifestation (37). Disease onset, particularly of neuropathy, can be earlier (fourth decade of life), with a male predominance of approximately 3:1. Val30Met (pV50M) is the most common worldwide mutation and is the prototype for hATTR polyneuropathy, which is endemic in certain regions of Portugal, Japan, and Sweden. Val30Met has a late-onset variant in nonendemic areas that can present with cardiac symptoms, including heart block and HF. The THAOS (Transthyretin Amyloid Outcome Survey) registry demonstrated that the other important mutations that cause hATTR-CM are Leu111Met and Ile68Leu, which occur in Denmark and Italy, respectively (38).

TTR genetic testing should be performed in all patients with ATTR-CM, regardless of patient age. The results have significant implications for family members at risk; genetic counseling is recommended. The age threshold for testing of offspring of patients with hATTR is an individual decision best addressed through genetic counseling. Once a variant genotype is identified, how to perform surveillance of disease in gene mutation carriers has not yet delineated, although baseline and longitudinal neurological and cardiac assessments are recommended.

OLDER ADULT PATIENTS WITH HF. Wild-type ATTR-CM is undoubtedly the most common type of ATTR-CM, but the true population prevalence of ATTR-CM is unknown. In several autopsy studies, the incidence of wtATTR myocardial deposits increased with age, with a prevalence as high as 20% to 25% in octogenarians and 37% in those >95 years of age (39,40). In an autopsy study of 109 patients with an antemortem diagnosis of HF with preserved ejection fraction (HFpEF), 17% had wtATTR myocardial deposits, with 5% having moderate to severe interstitial deposition that indicated a causative etiology (41). Furthermore, among patients who were >80 years (n = 35), the incidence of wtATTR deposits dramatically increased to 40%, with a striking bias in male patients.

With the advent of bone scintigraphy as a diagnostic tool for the diagnosis of ATTR-CM, approximately 13% of older adult patients hospitalized with HFpEF were shown to have ATTR-CM (42). All were subsequently diagnosed with wtATTR-CM at a mean age of 86 years. In this active ascertainment approach, 50% were women in contrast to previous studies of wtATTR. Furthermore, a study that used scintigraphy demonstrated that among Afro-Caribbean patients admitted with HF, hATTR-CM was identified in 10% of cases as attributable to the Val122Ile mutation (32).

AORTIC STENOSIS. Patients with ATTR-CM and aortic stenosis are demographically similar. Retrospective studies report a prevalence of 6% to 12% of ATTR-CM in patients with severe aortic stenosis (43,44) undergoing surgical valve replacement. The phenomenon of low-flow, low-gradient severe aortic stenosis in older adult patients may be in part explained by co-existent ATTR-CM and restrictive physiology (45). Among 151 consecutive patients >65 years of age referred for transcatheter aortic valve replacement, technetium-99m pyrophosphate (Tc-99m-PYP) imaging revealed that 16% overall and 22% of men had uptake consistent with ATTR-CM, 62% of whom met the criteria for low-flow, low-gradient severe aortic stenosis (46).

HYPERTROPHIC CARDIOMYOPATHY MISDIAGNOSIS. Cardiac amyloidosis can appear phenotypically as hypertrophic cardiomyopathy. Rare patients referred for surgical myectomy are diagnosed with ATTR-CM histologically (47). More commonly, ATTR-CM is confused with nonobstructive hypertrophic cardiomyopathy. Among 298 patients with unexplained left ventricular hypertrophy initially diagnosed as hypertrophic cardiomyopathy, *TTR* genetic testing revealed that 5% harbored a *TTR* mutation with clinical evidence of hATTR-CM using bone scintigraphy and CMR (48). This study did not assess for the presence of wtATTR-CM, which is likely the most common phenocopy of hypertrophic cardiomyopathy in older adults. Finally, asymmetrically increased septal wall thickness can occur in up to 20% to 25% of wtATTR-CM, further confounding diagnosis based on wall thickness (49).

CARPAL TUNNEL SYNDROME. ATTR amyloidosis can lead to deposits in the soft tissues, causing nerve entrapment syndromes, the most common being carpal tunnel syndrome. Deposits in the flexor

retinaculum and tenosynovial tissue within the carpal tunnel occur more often with ATTR than AL and classically present with bilateral symptoms (40). The presence of carpal tunnel syndrome among referred patients with wtATTR-CM is approximately 50% (25,26). The symptoms of carpal tunnel syndrome often precede overt ATTR-CM by an average of 5 to 10 years and are a common initial manifestation (50).

In an effort to facilitate early diagnosis of cardiac amyloidosis, Sperry et al. (51) conducted a prospective study of 98 patients (men: 50 years or older and women: 60 years or older) who underwent carpal tunnel syndrome release surgery for idiopathic carpal tunnel syndrome and examined a small sample of tenosynovium pathologically for amyloid deposits. This study found 10 (10.2%) patients with positive results. Although most of these patients had wtATTR deposits, there were 2 patients diagnosed with hATTR and 2 with AL. One patient with wtATTR deposits was found to have ATTR-CM based upon diagnostic uptake of Tc-99m-PYP scintigraphy.

LUMBAR SPINAL STENOSIS AND OTHER ORTHOPEDIC MANIFESTATIONS. Lumbar spinal stenosis is associated principally with wtATTR-CM. Amyloid deposition causes thickening of the ligamentum flavum, which leads to compression and narrowing of the spinal canal (30). Amyloid deposition in the ligamentum flavum of older patients undergoing spinal stenosis surgery occurs in 45% to 96% of these patients, with an increasing incidence with age (52). Spontaneous rupture of the distal biceps tendon has been reported in 33% of patients with wtATTR-CM (31). A study of patients who underwent other orthopedic surgery for rotator cuff repair found that 38% of tissue samples removed were found to have wtATTR deposits (53), and total knee and hip arthroplasty was 3 to 5 times more common among patients with ATTR amyloidosis than age- and sex-matched controls (54).

DIAGNOSIS

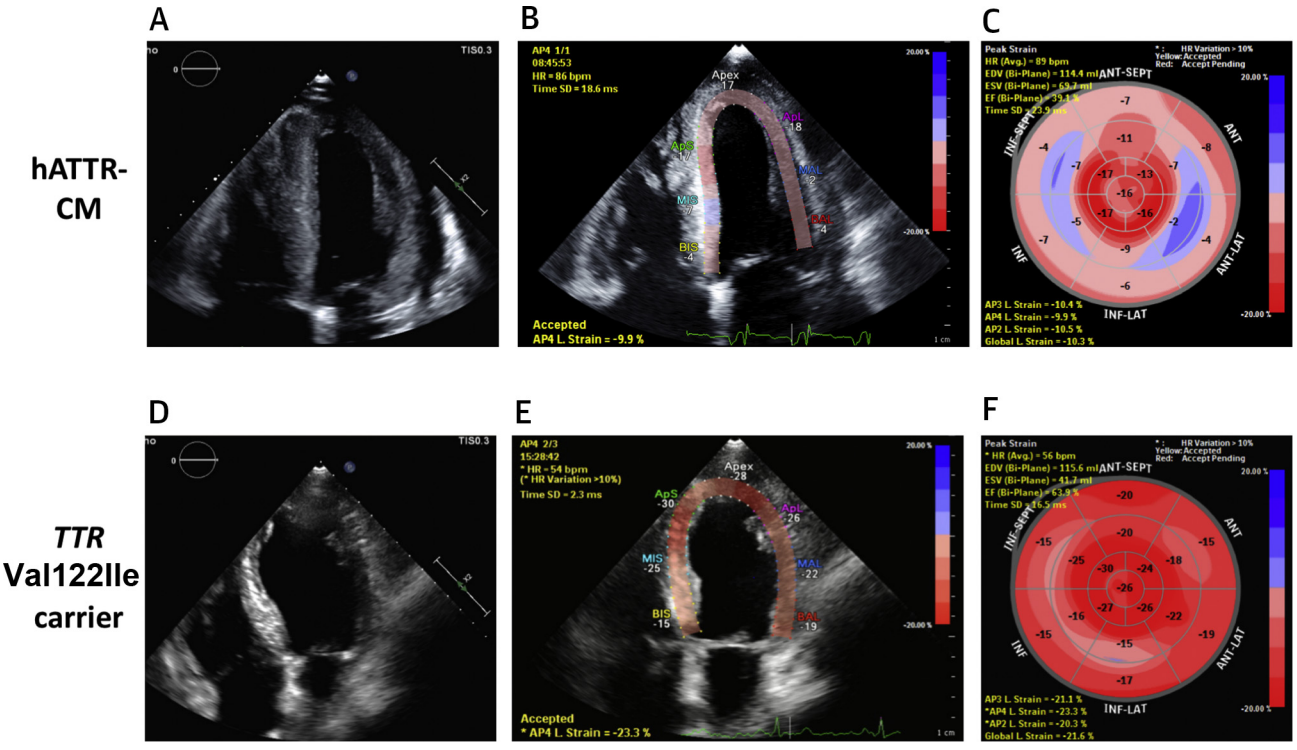
The diagnosis of ATTR-CM poses a challenge to the clinician for a number of reasons. First, the clinical phenotype of wall thickening and HF may be attributed to other common diseases such as hypertensive heart disease, aortic stenosis, or hypertrophic cardiomyopathy. Second, there is a perceived rarity of ATTR-CM related to confusion with the AL type. Third, clinicians are unfamiliar with the appropriate diagnostic algorithm to follow. Finally, the disease was previously believed to be untreatable, which resulted in therapeutic nihilism.

A number of important clinical clues to the presence of ATTR-CM have been described. One clue is a "natural cure" of hypertension: the need for down-titration or discontinuation of antihypertensive therapy. Likewise, the intolerance of β-blockade in newly diagnosed HF should prompt consideration of amyloidosis. A history of HF with carpal tunnel syndrome, lumbar spinal stenosis, and biceps tendon rupture should be actively ascertained. The presence of unexplained peripheral or autonomic neuropathy suggests the possibility of hATTR amyloidosis, but can occur in AL and occasionally in wtATTR.

The presence of increased left ventricular wall thickness in the presence of a low-voltage electrocardiographic pattern can differentiate ATTR-CM from hypertensive or hypertrophic cardiomyopathy. However, only 25% to 40% of patients with ATTR-CM meet low-voltage criteria (18), and in 1 series of hATTR-CM due to Val122Ile, 25% of patients met the criteria for left ventricular hypertrophy (55). There should be heightened clinical suspicion in any patient presenting with low-flow, low-gradient aortic stenosis, or unexplained increased left or right ventricular wall thickness. The currently accepted echocardiographic diagnostic threshold for cardiac amyloidosis is an interventricular septal wall thickness >12 mm, but this does not adjust for sex and is insensitive (56).

Persistent elevation in cardiac biomarkers are commonly observed in ATTR-CM. Although useful for staging of disease and prognosis in wtATTR-CM (27) and hATTR-CM (23), they are also useful for raising suspicion, and, although not specific, values are usually higher in the compensated state than in the average HFpEF patient. Unlike AL, there are no specific circulating biomarkers of ATTR-CM, although the endogenous TTR ligand RBP4 has shown promise (16). Echocardiographic analyses of cardiac deformation, specifically reduced longitudinal systolic strain, is useful in ATTR-CM. There is a distinctive pattern of "apical sparing" in which the left ventricular apical region shows more normal strain compared with progressively worse values at the mid and basal regions (**Figure 2**). Quantification of abnormal ratios of apical to basal strain or apical to basal plus mid-ventricular strain have good diagnostic accuracy (57) for differentiating amyloid heart disease from other etiologies. Similarly, with late gadolinium enhancement CMR, an inability to suppress or "null" the myocardial signal, or the presence of diffuse subendocardial or transmural enhancement patterns suggests amyloidosis (58) with a sensitivity and specificity that approach 85% to 90% (**Figure 3**) (59). CMR parametric imaging using T1 mapping to determine native (noncontrast) myocardial T1 and

FIGURE 2 Echocardiography in ATTR-CM



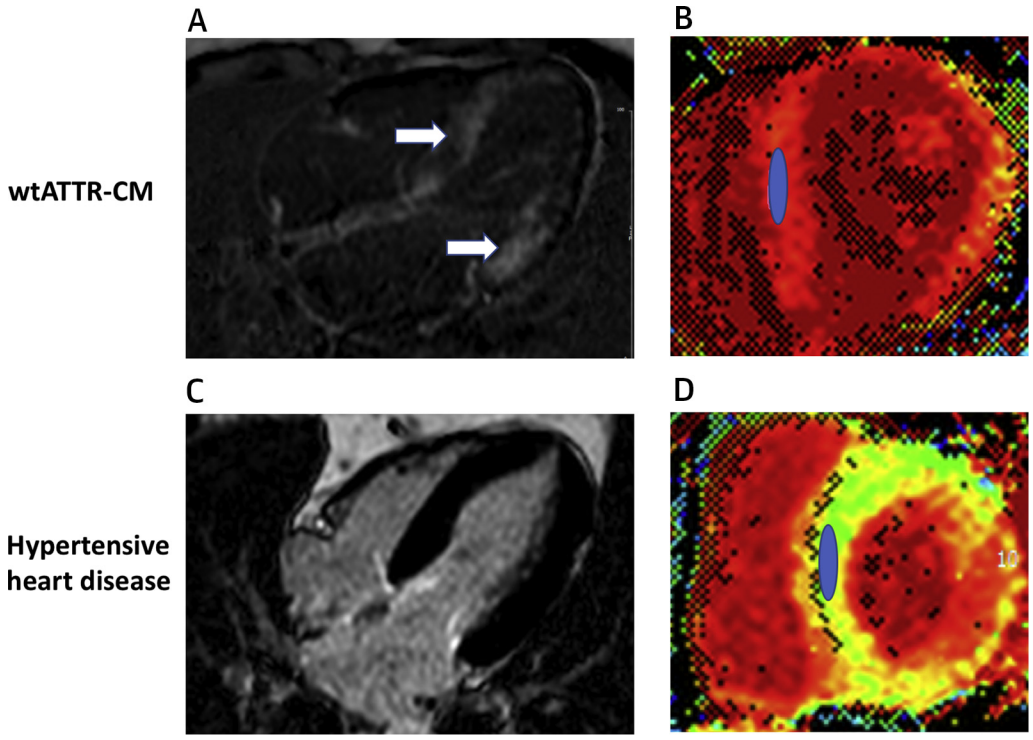
Two patients genopositive for *TTR* Val122Ile. **(A to C)** A 73-year-old male patient. **(A)** Four-chamber view with the **(B)** corresponding longitudinal strain map. **(C)** The map of all myocardial segments. Note the reduced global longitudinal strain (GLS) at −10.3% and apical sparing (>2:1 apical/basal ratio or "cherry on top") pattern. **(D and E)** A 65-year-old male patient with Val122Ile genotype and hypertension (technetium-99m-pyrophosphate scan showing grade 1 uptake). **(F)** The bullseye map shows the absence of apical sparing and GLS is normal at −21.6%. hATTR-CM = hereditary transthyretin amyloid cardiomyopathy.

extracellular volume fraction (ECV) have emerged as even more sensitive and quantitative measures of amyloid deposition in ATTR-CM, with values that are elevated compared with other myocardial processes (58). Although useful for differentiating amyloidosis from non-amyloid diseases, neither echocardiography nor CMR is able to reliably differentiate ATTR-CM from AL (60,61). All of the preceding observations merely suggest the presence of amyloidosis (**Table 2**), necessitating further diagnostic testing for confirmation.

Endomyocardial biopsy remains the gold standard for ATTR-CM diagnosis and is nearly 100% sensitive and specific if biopsy specimens are collected from multiple sites (≥4 are recommended) and tested for amyloid deposits by Congo red staining (62). Definitive identification of the misfolded precursor protein must be determined by either immunohistochemistry (in experienced pathology laboratories) or by the gold standard of laser dissection, tandem mass spectrometry analysis (**Figure 4**) (63). Other tissue biopsies, such as gastrointestinal or abdominal fat aspirate, have varying sensitivity for ATTR-CM, and in the case of wild-type disease, fat aspirate has a sensitivity of only 15% (64).

The only imaging modality that can accurately diagnose ATTR-CM without the need for invasive cardiac biopsy is nuclear scintigraphy using bone-avid radiotracers. Three technetium-labeled radiotracers have been evaluated clinically for ATTR-CM identification. These include Tc-99m- PYP (available in the United States) and Tc-99m−3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or Tc-99m−hydroxymethylene diphosphonate (HMDP), the latter 2 of which are available in Europe. Interest in these radiotracers for amyloidosis identification was rekindled approximately 10 to 15 years ago with initial work showing the capacity of Tc-99m-DPD to identify

FIGURE 3 CMR of ATTR-CM



(A and B) An 82-year-old woman with wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) and **(C and D)** a 76-year-old man with hypertension. **(A and C)** Phase-sensitive inversion recovery late gadolinium enhancement (LGE) images taken in the 4-chamber plane. **(A)** Diffuse LGE **(arrows)** in ATTR-CM, but **(C)** absence of LGE and normal myocardial signal suppression in hypertension. **(B and D)** Corresponding short-axis extracellular volume fraction (ECV) maps taken at the mid-ventricle with regions of interest drawn over the septum. The ECV in **B** was 60% consistent with ATTR-CM, whereas the ECV in **(D)**was 27% (normal). CMR = cardiac magnetic resonance; other abbreviation as in Figure 2.

TABLE 2 Noninvasive Testing Features Suggestive of ATTR-CM

Electrocardiography
Low voltages in context of increased echocardiographic wall thickness
Caution: low voltage seen in <50% of cases with ATTR-CM (18)
Echocardiography
1. Increased LV wall thickness with/without right ventricular wall thickness
2. Apical sparing regional longitudinal strain pattern (>2:1 ratio) or increased LVEF to global longitudinal strain ratio (>4)
Cardiac magnetic resonance imaging
1. Diffuse subendocardial or transmural LGE
2. Increased myocardial native T1
3. Increased extracellular volume fraction (typically >0.4)
4. Inability to suppress myocardial signal with PSIR LGE imaging
Nuclear imaging with bone avid tracers
1. Grade 2 or 3 tracer uptake in conjunction with no evidence of monoclonal gammopathy by serum/urine testing

LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; PSIR = phase-sensitive inversion recovery; other abbreviation as in Table 1.

cardiac amyloidosis (65,66). The mechanism underlying the myocardial retention of these tracers is unknown but has been attributed to the presence of microcalcifications that are more common in ATTR than AL cardiac tissue (20,67). Cardiac tracer uptake is compared with bone uptake of the rib with a simple, semiquantitative scheme developed from grade 0 (no uptake) to grade 3 (cardiac uptake that exceeds rib). Subsequently, studies that used Tc-99m-PYP demonstrated that AL and ATTR-CM could be readily differentiated using the quantitative refinement of a heart to a contralateral chest ratio uptake measurement that exceeds 1.5 (68) (**Figure 5**), and that the test could be reproducibly performed at multiple sites with high accuracy (69). An international collaboration with a large cohort of endomyocardial biopsy proven cases of ATTR-CM concluded that these bone avid tracers conferred 100% specificity for ATTR-CM when grade 2 or 3 uptake was seen in the absence of a monoclonal protein by serum and urine

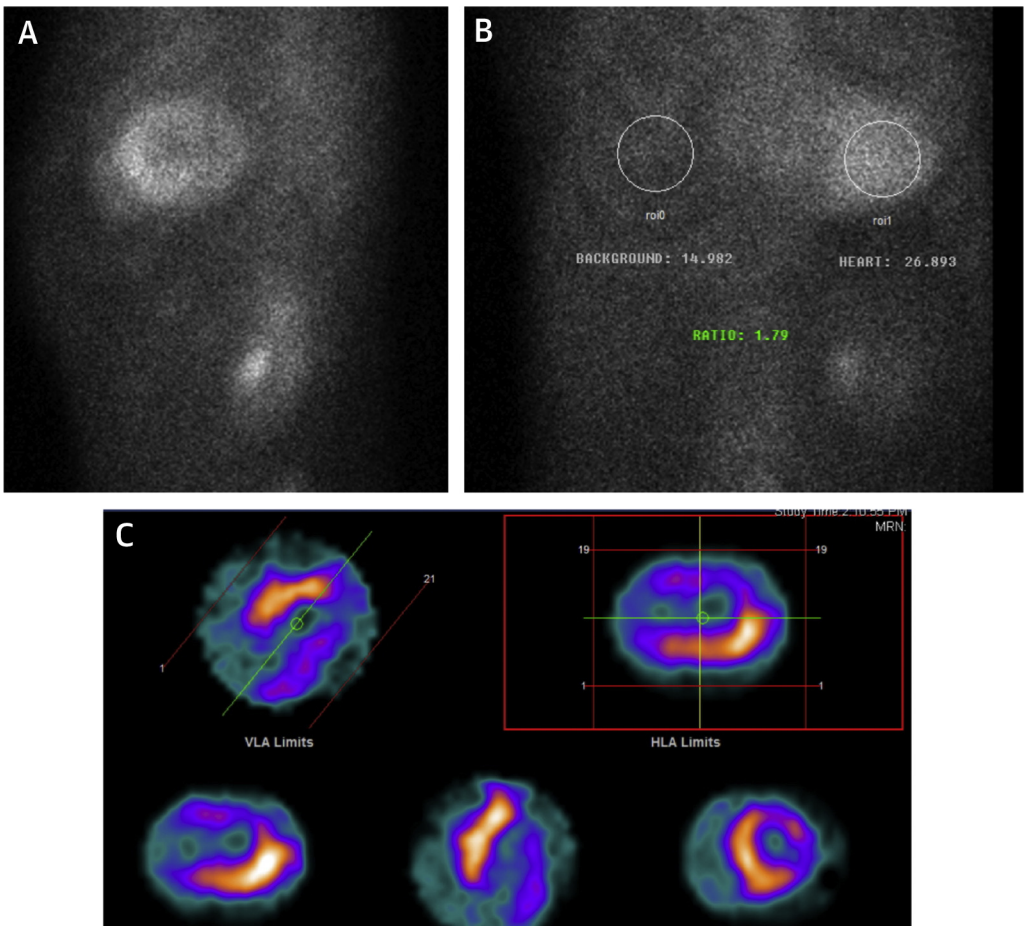
FIGURE 4 Gross and Histopathology of ATTR-CM

(A) Autopsy specimen reveals biventricular thickening, biatrial dilatation, and thickening of both mitral and tricuspid valves. **(B)** Hemotoxylin and eosin staining showing diffuse amyloid deposition. **(C)** Characteristic **apple green** birefringence on polarized light microscopy. **(D)** Immunohistochemistry for typing of amyloid. Mass spectrometry (not illustrated) can also be performed for typing and is considered the gold standard. Abbreviation as in **Figure 2**. Reproduced with permission from Donnelly et al. (100).

testing (8) in patients with HF and typical echocardiographic or CMR findings of amyloidosis. Consequently, the advent of nuclear imaging for nonbiopsy diagnosis of ATTR-CM has affected a change in the clinical approach to this disease, figuring prominently in proposed diagnostic algorithms.

A proposed diagnostic algorithm can be found in **Figure 6**. Tc-99m-PYP or Tc-99m-DPD scintigraphy is combined with serum and urine assessment of AL. There are a number of important caveats. First, AL cannot be diagnosed without a tissue biopsy that shows light-chain amyloid deposits from some organ or site (not necessarily the heart). Second, the historically used screening method to test for AL with serum and urine protein electrophoresis is insensitive, inappropriate, and should be avoided. Serum free light-chains and immunofixation of the serum and urine is the required testing. Third, occasionally, AL cardiac amyloidosis can lead to grade 1 and even higher grades of cardiac uptake on bone scintigraphy. In addition, the coexistence of an unrelated monoclonal gammopathy is common in ATTR-CM (up to 40% to 50% of cases) (70). Thus, the nuclear scan result, regardless of uptake grade, cannot be interpreted as to exclude AL; screening for monoclonal protein must always accompany nuclear scintigraphy in the diagnostic evaluation. In instances when a patient has grade 2 or 3 cardiac uptake on bone scintigraphy but is also found to have an abnormal light-chain ratio or an M protein found on serum and/or urine immunofixation, hematology consultation is required and cardiac biopsy may be necessary.

FIGURE 5 Nuclear Imaging of ATTR-CM With Bone Avid Tracers



(A) A typical patient with ATTR-CM is depicted with grade 3 tracer uptake on planar imaging. **(B)** Increased heart to contralateral chest ratio of 1.79, and **(C)** multiplanar single-photon emission computed tomography showing myocardial (and not blood pool) tracer uptake, with some heterogeneity in uptake intensity. Coronary artery disease was excluded by angiography. HLA = horizontal long axis; VLA = vertical long axis; other abbreviation as in Figure 2.

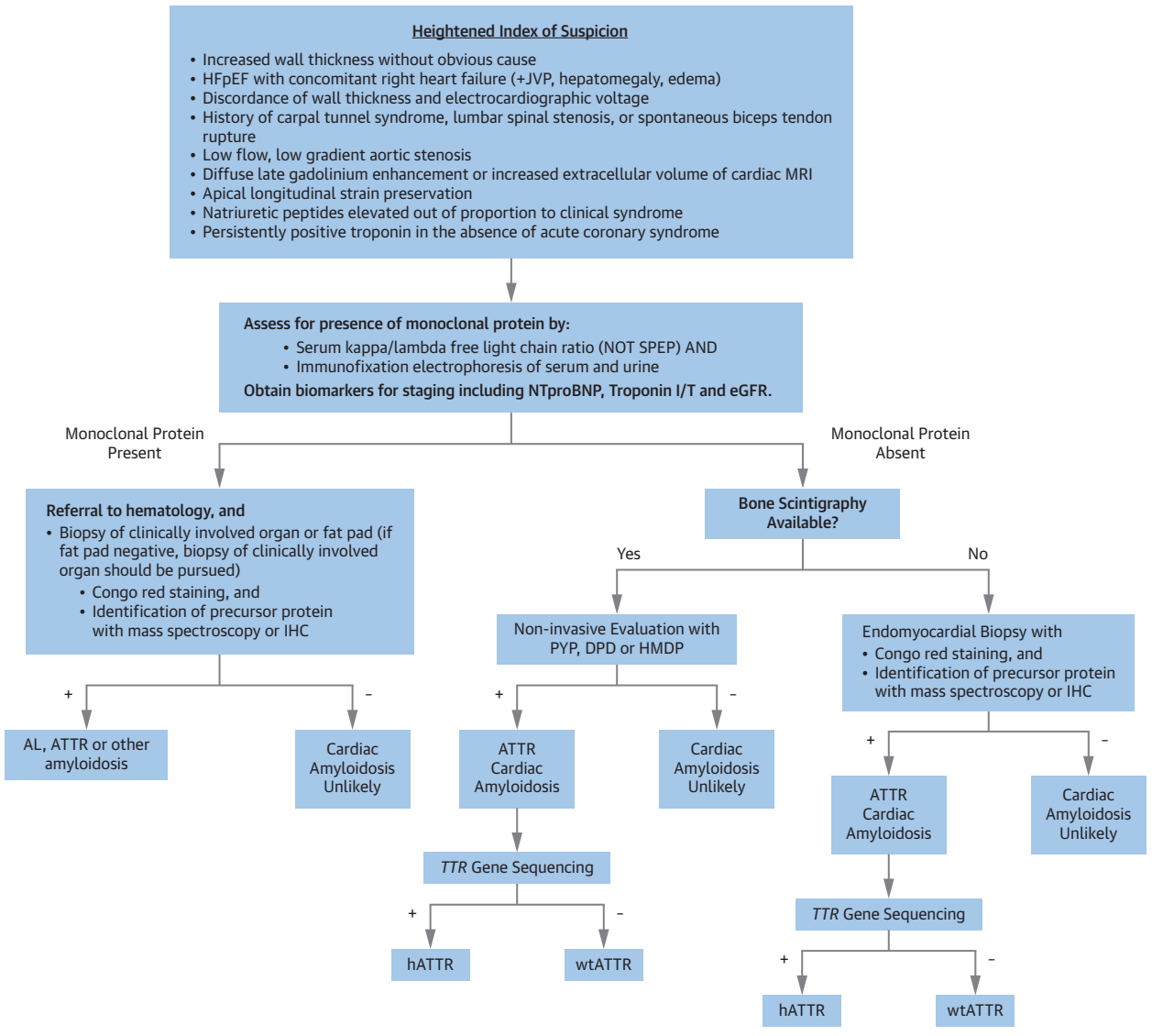
It should be noted that in renal insufficiency, a mildly elevated kappa to lambda ratio may occur, which, in the absence of an M protein on serum and/or urine immunofixation, may not be significant. However, this finding should be discussed with a hematologist. Fourth, low-intensity uptake (grade 1 or sometimes even grade 2) can often be confused for a blood pool signal from the radiotracer, thus acquisition of confirmatory single-photon emission computed tomography together with additional repeat scanning 1 h (or 2 h) later is recommended to demonstrate that the uptake seen is cardiac.

Amyloid-specific molecular imaging agents such as F-18–florbetapir (Amyvid, Eli Lilly, Indianapolis, Indiana) and the C-11–Pittsburgh-B compound that have been developed for imaging of Alzheimer's dementia can identify cardiac amyloidosis, but are not specific for amyloid type (71,72). Although these agents have the potential to similarly diagnose ATTR-CM, none are currently reimbursable by the Centers for Medicare and Medicaid Services nor third party payers.

CLINICAL MANAGEMENT

MEDICAL THERAPY OF HF. Maintenance of euvolemia is central to management of ATTR-CM, with sodium restriction and diuretics. This is challenging because ventricular capacitance is markedly reduced (73), which when coupled with age-related changes in the vascular system and concomitant autonomic dysfunction, enhances load lability.

FIGURE 6 Diagnostic Algorithm for Evaluation of Suspected ATTR-CM



A proposed flow diagram demonstrates the critical requirement to exclude light-chain amyloidosis (AL) by serum and/or urine testing and concomitant use of nuclear scintigraphy to identify the presence of ATTR-CM. It is emphasized that serum free light-chains and serum and/or urine immunofixation electrophoresis are the appropriate tests to exclude a monoclonal gammopathy, which also may be present in patients with ATTR-CM. Nuclear imaging can also be performed concurrent to light-chain assessment, even in the case of a detected monoclonal gammopathy, for additive information. GFR = estimated glomerular filtration rate; hATTR = hereditary ATTR-CM; HFpEF = heart failure with preserved ejection fraction; HMDP = 99mTc-labeled-hydroxymethylene diphosphonate; IHC = immunohistochemistry; JVP = jugular vein pressure; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SPEP = serum protein electrophoresis; Tc-99m-DPD = technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy; Tc-99m-PYP = technetium-99m pyrophosphate scintigraphy; other abbreviations as in Figures 2 and 3.

Thus, with dietary indiscretion, volume overload rapidly ensues. Overly aggressive diuresis is associated with symptomatic hypotension and worsening renal perfusion. Because of circulatory congestion and gut wall edema, loop diuretics with higher bioavailability (torsemide and bumetanide) are preferred and often used in combination with aldosterone antagonists. Non-dihydropyridine calcium channel blockers (e.g., verapamil) should be avoided in patients with ATTR-CM because of previous case reports in patients with AL (74) of high-degree heart block and shock.

There are no guideline-based recommendations for angiotensin-converting enzyme, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitor therapies in cardiac amyloidosis, and such medications may not be well tolerated because of hypotension. Similarly, β-blockers, especially at higher dosages and those with accompanying α-blocking properties, are not well tolerated by patients with cardiac amyloidosis. As cardiac amyloidosis progresses, decline in ventricular capacitance and altered ventricular vascular coupling results in decrements in stroke volume, cardiac output, and hence, blood pressure (73). To maintain adequate organ perfusion, heart rate increases steadily. Accordingly, β-blockers can blunt the compensatory increase in heart rate necessary to maintain adequate cardiac output. Unfortunately, as the disease progresses, decreases in blood pressure and cardiorenal syndrome ensue. Compression stockings and midodrine may be useful in these advanced stages.

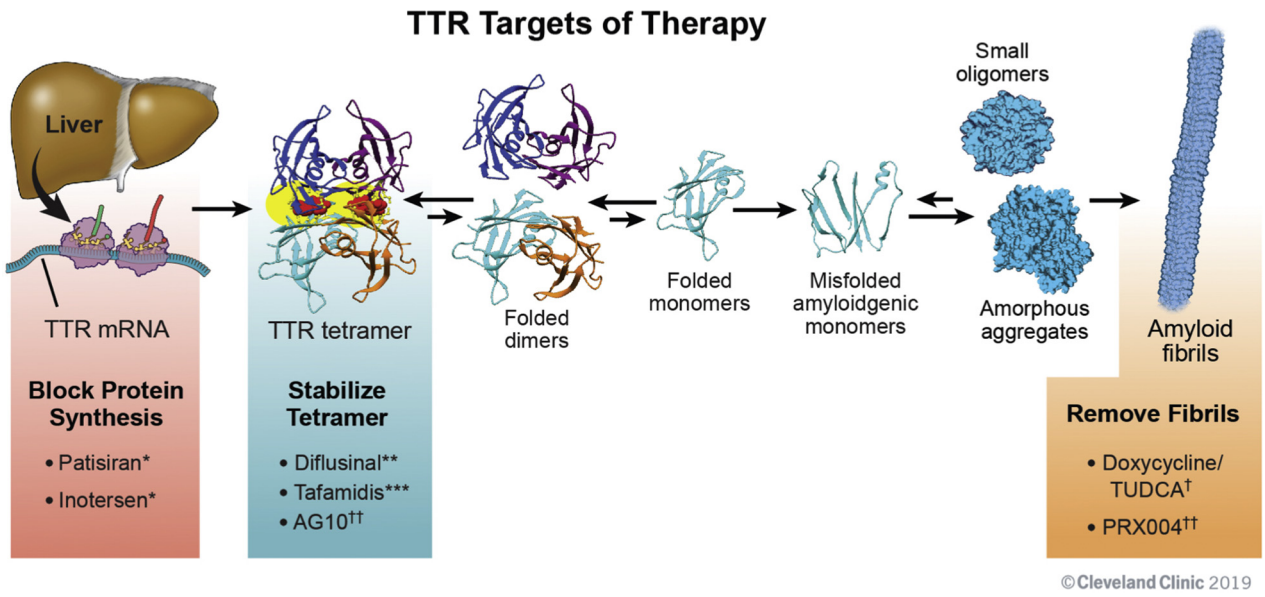
ARRHYTHMIA MANAGEMENT AND PREVENTION. Management of atrial fibrillation is often challenging in patients with cardiac amyloidosis who have a narrow window of "optimal" heart rate. Extreme tachycardia is poorly tolerated, and bradycardia is similarly dangerous due to low stroke volume resulting from severe restrictive hemodynamics. Maintaining sinus rhythm and "atrial kick" in cardiac amyloidosis may be overemphasized because most patients have significantly reduced atrial mechanical function, making the atrial contribution to ventricular filling minimal or absent. Data on the outcomes of catheter ablation in ATTR-CM are limited. In early stage patients, ablation may help maintain sinus rhythm, especially in the setting of atrial flutter (19). However, long-term success of ablation therapies, other than atrioventricular node ablation, is likely less in these patients than in non-amyloid patients. Although antiarrhythmic treatment and cardioversion may be considered in selected patients, it is crucial to exclude intracardiac thrombus, even in patients receiving therapeutic anticoagulation. A recent study found left atrial appendage thrombus in 33% of patients with ATTR-CM who presented for transesophageal echocardiographic cardioversion, with most receiving anticoagulant therapy (75). Amiodarone is the preferred antiarrhythmic agent because of its favorable safety profile in cardiomyopathy and limited data that suggests its safety in ATTR-CM (28). Long-term anticoagulation is preferred once atrial fibrillation is detected in ATTR-CM, regardless of the CHADs-VASc score.

Deposits of TTR amyloid fibrils infiltrate the conduction system, with a significant percentage of patients requiring permanent pacing (18,42). In hATTR, conduction disturbances do not seem to be related to wall thickness and may be related to other factors, such as loss of autonomic nervous control of cardiac function. Due to the high incidence of conduction disturbances, Holter monitoring should be considered when symptoms of syncope, pre-syncope, or palpitations are reported. Indications for permanent pacing should follow the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines (76), with common indications for pacing including sinus node dysfunction, atrioventricular block, and atrial fibrillation with a slow ventricular response.

Patients with ATTR-CM can have markedly reduced stroke volumes and often are pacemaker-dependent. Accordingly, concern has been raised that chronic right ventricular apical pacing can result in left ventricular dyssynchrony, which leads to a further reduction in stroke volume and cardiac output. Some centers favor the use of biventricular pacing when a pacing indication is present. When patients develop worsening HF over time, the lower rate limit on the pacemaker can be increased to help maintain cardiac output. The routine use of automatic implantable cardioverter-defibrillators (ICDs) in patients with ATTR-CM is debatable. If anticipated survival is <1 year, then practice guidelines do not recommend ICD placement for the primary prevention of sudden cardiac death (76). In addition, sudden cardiac death in patients with AL cardiac amyloidosis has often been attributed to electromechanical dissociation rather than to a primary arrhythmic cause (77), further arguing against ICD use in this population. Although several small series have reported successful defibrillation in individual patients with ICDs (78,79), an overall survival benefit from ICD therapy has not been demonstrated. Thus, there are currently no clear indications for primary prevention ICD implantation in ATTR-CM. Secondary prevention is reasonable as per ACC/AHA/HRS guidelines. Careful risk and/or benefit analysis is recommended for patients who might benefit from an ICD, which include those with outpatient telemetry monitoring who demonstrate a high burden of nonsustained ventricular tachycardia or sustained ventricular tachycardia, and patients listed for heart transplantation (78). The decision to implant a secondary prevention ICD should be individualized.

ORGAN TRANSPLANTATION. Although liver transplantation has been used to treat hATTR by removing

FIGURE 7 Therapies Available or in Development to Treat ATTR-CM



Therapeutic strategies for ATTR-CM are illustrated with agents either presently approved, under review, or in development. *TTR silencers patisiran and inotersen are not presently approved for ATTR-CM but rather for hATTR polyneuropathy (with or without cardiomyopathy). **Diflunisal may be used off-label in selected patients with ATTR-CM but only with careful monitoring. ***The agent tafamidis is undergoing U.S. Food and Drug Administration review for an ATTR-CM indication. †Combination of doxycycline and tauro-deoxycholic acid (TUDCA) can be used in conjunction with other strategies and is being evaluated in a clinical trial. ††AG10, a TTR stabilizer, and PRX004, a monoclonal antibody that binds and potentially removes ATTR deposits, are both in development. Abbreviations as in Figures 1, 2, and 6.

mutant TTR from blood, progression of disease may occur as a result of wild-type TTR deposition on pre-existing mutant ATTR deposits (80). Liver transplantation to treat hATTR has dramatically decreased with the advent of TTR stabilizers and is not indicated for wtATTR-CM. For patients with advanced ATTR-CM, both hereditary and wild-type, orthotopic heart transplantation (with combined liver transplantation in some variants of hATTR) is an option in selected patients (81). However, heart transplantation is not a viable option for most patients with ATTR-CM because of the shortage of donor organs, the advanced age of most affected individuals, and other factors.

AVAILABLE AND EMERGING TTR-SPECIFIC THERAPIES. There are numerous pharmacological strategies under development (Figure 7) to ameliorate the ATTR amyloidoses, including: 1) TTR mRNA knockdown and/or silencing; 2) TTR stabilization; and 3) TTR amyloid fibril disruption and/or extraction. The first of these strategies has led to development of the U.S. Food and Drug Administration (FDA)–approved drugs patisiran and inotersen for hATTR polyneuropathy, but not for ATTR-CM. The stabilizer tafamidis is undergoing accelerated review for ATTR-CM.

PRESENTLY UNDER REGULATORY REVIEW FOR ATTR-CM. Tafamidis. Tafamidis binds the thyroxine-binding sites of TTR with high affinity and selectivity, slowing dissociation of TTR tetramers into monomers, which inhibits aggregation. Tafamidis was shown to slow the progression of peripheral neurological impairment in ATTR polyneuropathy (82), leading to its approval for the treatment of stage 1 and 2 hATTR polyneuropathy in numerous countries.

Phase II data showed that tafamidis meglumine (20 mg daily) stabilized TTR in ATTR-CM (83). The 30-month ATTR-ACT (ATTR-CM Phase 3 Clinical Trial) study (84) compared tafamidis meglumine (20 or 80 mg) with placebo in 441 subjects with ATTR-CM due to wtATTR or hATTR (12). The primary analysis used the Finkelstein-Schoenfeld method (85), which is a hierarchical rank-sum analysis in which all-cause mortality was first assessed, followed by the rates of cardiovascular hospitalizations. The primary endpoint was achieved with a win ratio (the number of pairs of treated patient "wins" divided by number of pairs of placebo patient wins) of 1.70 (95% confidence interval: 1.26 to 2.29; $p = 0.0006$). In more traditional time-to-first event analyses,

tafamidis treatment resulted in lower all-cause mortality than placebo, with a 13.4% absolute difference in mortality and a 32% relative risk reduction in cardiovascular hospitalizations. This translated into a number needed to treat of 7.5 to prevent 1 death after 2.5 years of treatment. Tafamidis treatment resulted in a lower rate of decline in the 6-min walk test ($p < 0.001$) and in the Kansas City Cardiomyopathy Questionnaire score ($p < 0.001$). Tafamidis was well tolerated with the incidence and types of adverse events not differing from placebo. Across 11 prespecified subgroups, the point estimates for the hazard ratios favored tafamidis over placebo, except for the subjects in New York Heart Association functional class III at baseline, for whom the rates of cardiovascular-related hospitalizations were higher among patients who received tafamidis. These data highlighted the importance of early diagnosis to optimize the benefit from tafamidis therapy. Tafamidis was awarded Breakthrough designation by the FDA in May 2018 and approval for treating ATTR-CM is anticipated by July 2019. However, cost may prove be a significant obstacle to widespread use.

AVAILABLE FOR OFF-LABEL USE, EFFECTIVE IN ATTR POLYNEUROPATHY, WITH LIMITED DATA IN ATTR-CM. Diflunisal. Diflunisal is an nonsteroidal anti-inflammatory drug that has been repurposed as a TTR kinetic stabilizer; it binds within the 2 thyroxine binding sites. In a phase III, randomized, placebo controlled trial of patients with hATTR polyneuropathy resulting from a diverse number of mutations, diflunisal (250 mg orally twice daily) was well tolerated. Although there was significant attrition of subjects, which required multiple imputation, data nonetheless demonstrated that diflunisal improved symptoms of neuropathy versus placebo (11).

The experience with diflunisal in ATTR-CM has been limited to open-label, single-center studies (86–89). Diflunisal (250 mg orally twice daily) was generally well tolerated, with side effects in a minority of subjects, including thrombocytopenia and renal dysfunction. Diflunisal was associated with a survival benefit similar to tafamidis in 1 nonrandomized ATTR-CM study (89). Despite its application in patients with concomitant use of oral anticoagulants, significant bleeding has not been reported, although studies have included highly selected patients. The dose administered for TTR stabilization is lower than the dose for anti-inflammatory benefits, which perhaps explains the low toxicity observed. Because of the encouraging safety profile, coupled with the potential efficacy and low cost, especially in comparison to other disease-modifying agents, use of diflunisal could be considered for selected patients with ATTR-CM. In general, we restrict its use to subjects without significant renal dysfunction (e.g., estimated glomerular filtration rate of >45 ml/min/1.73 m^2), who do not have evidence of thrombocytopenia, are not volume overloaded, or on a high-dose diuretic, and who have no evidence of recent renal or hemodynamic instability. We also advise discontinuation of other nonsteroidal anti-inflammatory drugs and recommend administration of a proton pump inhibitor. Significant toxicity can be avoided with careful attention to renal function, volume status, and monitoring for gastrointestinal bleeding.

THERAPIES PRESENTLY APPROVED FOR ATTR POLYNEUROPATHY, WITH LIMITED DATA IN ATTR-CM. Patisiran. Patisiran is a small-interfering RNA that specifically targets TTR mRNA, which leads to its degradation and lowering of TTR protein levels. Phase I and phase II studies of patisiran in healthy volunteers and in patients with hATTR polyneuropathy showed a dose-dependent and robust mean reduction in serum TTR levels of up to 90% (90). The APOLLO (A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran [ALN-TTR02] in Transthyretin [TTR]-Mediated Polyneuropathy [Familial Amyloidotic Polyneuropathy-FAP]) trial successfully tested the hypothesis that by reducing the precursor protein in hATTR amyloidosis, improvement in the modified Neuropathy Impairment Score would be achieved (9). The modified Neuropathy Impairment Score +7 is an aggregate score that combines a combination of sensory, motor, and autonomic neuropathy measurements. A total of 225 patients with hATTR polyneuropathy (43% of whom had the Val30Met mutation) underwent randomization in a 2:1 fashion to receive patisiran ($n = 148$) or placebo ($n = 77$) at a dose of 0.3 mg/kg every 3 weeks for 18 months, along with pre-medication to minimize the risk of infusion-related reactions. The study excluded patients in New York Association functional class III or IV HF. Patisiran therapy was effective, with a highly significant difference in the change in the modified Neuropathy Impairment Score +7 after 18 months. In addition, the Norfolk Quality of Life-Diabetic Neuropathy score showed a significant benefit with patisiran. Mild or moderate infusion-related reactions occurred in approximately 20% of the patients who received patisiran and 10% of those who received placebo, with similar other

TABLE 3 Emerging Therapies for ATTR-CM

Drug Name	Mechanism of Action	Indication	Route of Administration	Dose	Common, Serious or Potential Side Effects	Concomitant Therapy	Monitoring	Approval
Patisiran	Silencer	Neuropathy	IV	0.3 mg/kg q 3 weeks up to 30 mg	Infusion-related reactions Vitamin A deficiency	With IV infusion: IV corticosteroid (e.g., dexamethasone 10 mg, or equivalent) Oral acetaminophen (500 mg) IV H1 blocker (e.g., diphenhydramine 50 mg, or equivalent) IV H2 blocker (e.g., ranitidine 50 mg, or equivalent) Daily vitamin A supplements	None	Approved in United States and Europe
Inotersen	Silencer	Neuropathy	Subcutaneous	284 mg q week	Thrombocytopenia/ glomerulonephritis, requiring testing before treatment and monitoring during therapy Infusion site reactions, fever Vitamin A deficiency	Daily vitamin A supplements	Weekly platelet counts Every 2 weeks measures of serum creatinine, eGFR urinalysis, and UPCR	Approved in United States and Europe
Tafamidis meglumine	Stabilizer	Neuropathy	Oral	20 mg	Reported in hATTR polyneuropathy; Diarrhea UTI Vaginal infection Stomach ache or abdominal pain	None	None	In Europe and Japan
		Cardiomyopathy		20 mg or 80 mg	Side effects were less common than with placebo in cardiomyopathy			Anticipated 2019
Tafamidis free salt	Stabilizer	Cardiomyopathy	Oral	61 mg	Unknown	None	None	Anticipated 2019
Diflunisal	Stabilizer	Neuropathy Cardiomyopathy	Oral	250 mg PO BID	Related to NSAID properties: Bleeding Hypertension Fluid Retention Renal dysfunction	Proton pump inhibitor	Monitor renal function, platelet count, hemoglobin 1 week after initiation and then every 3-6 months	Approved in United States and Europe, off-label usage

BID = twice daily; eGFR = estimated glomerular filtration rate; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = orally; UPCR = urine protein to creatinine ratio; UTI = urinary tract infection; other abbreviation as in Table 1.

adverse event incidence and severity (9). These data led to the FDA approval of patisiran in August 2018 for the treatment of hATTR polyneuropathy.

In a pre-specified cardiac subpopulation of the APOLLO trial that included patients with a baseline left ventricular wall thickness ≥13 mm without a history of hypertension or aortic valve disease (n = 126; 56% of the overall population), patisiran reduced mean left ventricular wall thickness, increased end-diastolic volume, improved global longitudinal strain (particularly at the base), and increased cardiac output at month 18 compared with placebo (91). Although the myocardial effects took 18 months to be observed, the lowering of N-terminal pro-B-type natriuretic peptide occurred as early as 9 months and persisted during 18 months of therapy. In a post hoc exploratory analysis, the exposure-adjusted rates of cardiac hospitalizations and/or all-cause death were lower with patisiran than with placebo. Of the subjects who died, 7 deaths in the patisiran group (4.7%) were possibly related to HF (cause characterized as sudden cardiac death or HF), whereas there was only 1 such death in the placebo group (with 2:1 randomization). Also, atrioventricular block that required pacemaker support was observed in 4 of 148 patients in the patisiran group (2.7%) versus 0 of 77 patients in the placebo group (91).

Inotersen. Inotersen is a 2′-O-methoxyethyl-modified antisense oligodeoxynucleotide that lowers hepatic production of TTR. NEURO-TTR (A Phase 2/3

Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients With Familial Amyloid Polyneuropathy) was a phase III trial in adults with stage 1 or 2 hATTR polyneuropathy who received inotersen (300 mg subcutaneously weekly) or placebo in a 2:1 randomization. The primary endpoint included change in the modified Neuropathy Impairment Score +7 and a co-primary endpoint of the change in the Norfolk Quality of Life-Diabetic Neuropathy questionnaire. Both primary efficacy assessments favored inotersen. Five deaths occurred in the inotersen group and none in the placebo group. The most frequent serious adverse events in the inotersen group were glomerulonephritis (3%) and thrombocytopenia (3%), with 1 death associated with thrombocytopenia (10). Inotersen was approved by the FDA in October 2018 for hATTR polyneuropathy with a Risk Evaluation and Mitigation Strategy that includes weekly monitoring of platelet counts and monitoring of renal function and urinary protein every 2 weeks.

An open-label study of inotersen in 22 patients with ATTR-CM, 15 of whom had completed 12 months of follow-up, demonstrated stabilization of disease as measured by left ventricular wall thickness, left ventricular mass, 6-min walk test, and echocardiographic global systolic strain (92).

Both knockdown therapies (antisense oligodeoxynucleotide and RNA interference) demonstrated cardiac effects after 15 to 18 months of therapy, later than the 8 to 9 months when neurological improvement was observed. The safety and efficacy of patisiran, inotersen, and other TTR silencing therapies in patients with ATTR-CM are the focus of upcoming clinical trials.

ROLE AND COST EFFECTIVENESS OF THERAPIES. Both patisiran and inotersen are approved for hATTR polyneuropathy with or without cardiac involvement but not for ATTR-CM without polyneuropathy. The Institute for Clinical and Economic Review conducted a clinical evidence review using the PICOTS (Population, Intervention[s] of interest, Comparator intervention[s], key Outcomes, Time horizon, and Setting of interest) framework (93) and applied its framework for an ultra-rare disease, with the assumption that <10,000 individuals would be eligible for treatment with these drugs. The report by the Institute for Clinical and Economic Review found that both inotersen and patisiran provided a substantial net health benefit compared with best supportive care alone, but current pricing far exceeded commonly cited thresholds for cost-effectiveness. They noted that at the net price of $345,000 per year, both therapies exceeded commonly cited thresholds for cost-effectiveness of $50,000 to $150,000 per quality-adjusted life year (QALY) gained. Furthermore, they noted that both agents would need to be discounted by ≥90% to reach threshold prices. Although the cost of diflunisal is minimal in comparison to silencers, the cost of tafamidis is unknown because it has yet to be approved.

THERAPEUTIC CHOICES AND COMBINATION THERAPY. Clinicians may soon have the enviable dilemma of choosing among several disease-modifying therapies for ATTR-CM. Although selection of a particular therapy for an individual patient will always remain complex and best addressed through a process of shared decision making, there are differences in available treatments (**Table 3**) that may guide choices. In addition, therapies shown to be effective have been tested in patients with symptomatic disease and thus are not indicated for asymptomatic carriers of *TTR* mutations. For such patients, many amyloidosis experts have been offering asymptomatic carriers diflunisal when they approach an age at which disease is likely to penetrate or if they demonstrate tissue evidence of amyloidosis by biopsy or myocardial retention of a bone scintigraphy agent.

TTR silencers, including patisiran and inotersen, have been not been approved for hATTR-CM without neuropathy. As noted, although patients with coexistent cardiac involvement were included in these trials, patients with New York Heart Association functional class III and IV were excluded. Thus, for most patients with ATTR-CM who cardiovascular clinicians encounter, including those with wtATTR-CM and hATTR-CM due to Val122Ile, these agents are not approved, and because of their current high cost, may not be reimbursed by third party payers. In the less common instance of hATTR polyneuropathy with cardiomyopathy, the choice between which silencer therapy to initiate is difficult to make in the absence of data directly comparing these agents. Finally, with the emergence of these effective therapies, critically unanswered questions arise regarding the usefulness of therapeutic change in nonresponders or in the role of combination silencer and stabilizer therapy.

INVESTIGATIONAL APPROACHES. Stabilization. AG-10 is a potent and selective kinetic stabilizer of TTR (94) that has been shown in a phase II study of 49 subjects with ATTR-CM to stabilize TTR at

28 days (95). A phase III study of AG10 in ATTR-CM is expected to initiate soon. The cathecol-O-methyltransferase inhibitor tolcopone, an FDA-approved Parkinson's disease therapeutic, also functions as a TTR protein stabilizer and is presently under investigation in ATTR amyloidosis (96).

Resorption and/or disruption. Antibody-mediated removal of amyloid deposits is an area of active development (97); however, clinical data using this approach have currently resulted in cessation of product development because of futility or toxicity. An antibody that targets TTR residues 89 to 97 (PRX-004; Prothena Biosciences, San Francisco, California) (98) has entered into phase I trials in patients with hATTR amyloidosis.

Gene editing and/or seeding inhibitors. CRISPR/Cas9 technology is in pre-clinical development to silence expression of TTR, as are TTR fibril capping agents (99).

CONCLUSIONS

ATTR-CM affects a growing population of patients encountered in clinical practice. With the advent of contemporary noninvasive imaging techniques, providers now have the tools required to facilitate earlier diagnosis of ATTR-CM. The emergence of effective therapies for ATTR-CM will likely translate into improved outcomes, but for such therapies to be most effective, early identification of affected individuals is critical.

ADDRESS FOR CORRESPONDENCE: Dr. Mathew S. Maurer, Clinical Cardiovascular Research Laboratory for the Elderly, Columbia University Irving Medical Center, Allen Hospital of New York Presbyterian, 5141 Broadway, 3 Field West, Room 035, New York, New York 10034. E-mail: msm10@cumc.columbia.edu. Twitter: @ColumbiaMed.

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