ANNUAL REVIEWS

Annual Review of Medicine

Cardiac Amyloidosis: Overlooked, Underappreciated, and Treatable

Jonah Rubin and Mathew S. Maurer

Clinical Cardiovascular Research Laboratory for the Elderly, Columbia University Irving Medical Center, Allen Hospital of NewYork-Presbyterian Hospital, New York, NY 10032, USA; email: yonahrubin@gmail.com, msm10@cumc.columbia.edu

Annu. Rev. Med. 2020. 71:203–19

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-052918-020140

Keywords

cardiac amyloidosis, transthyretin, light chain, aging, heart failure, cardiomyopathy

Abstract

Cardiac amyloidosis (CA) is an infiltrative and restrictive cardiomyopathy that leads to heart failure, reduced quality of life, and death. The disease has two main subtypes, transthyretin cardiac amyloidosis (ATTR-CA) and immunoglobulin light chain cardiac amyloidosis (AL-CA), characterized by the nature of the infiltrating protein. ATTR-CA is further subdivided into wild-type (ATTRwt-CA) and variant (ATTRv-CA) based on the presence or absence of a mutation in the transthyretin gene. CA is significantly underdiagnosed and increasingly recognized as a cause of heart failure with preserved ejection fraction. Advances in diagnosis that employ nuclear scintigraphy to diagnose ATTR-CA without a biopsy and the emergence of effective treatments, including transthyretin stabilizers and silencers, have changed the landscape of this field and render early and accurate diagnosis critical. This review summarizes the epidemiology, pathophysiology, diagnosis, prognosis, and management of CA with an emphasis on the significance of recent developments and suggested future directions.

INTRODUCTION

CA: cardiac amyloidosis

ATTR: transthyretin

AL-CA: immunoglobulin light chain cardiac amyloidosis

ATTRwt-CA: wild-type transthyretin cardiac amyloidosis

ATTRv-CA: variant transthyretin cardiac amyloidosis

HFpEF: heart failure with preserved ejection fraction

Cardiac amyloidosis (CA) causes a restrictive cardiomyopathy and heart failure, conduction disease, reduced quality of life, and death. The disease is categorized into two subtypes, transthyretin cardiac amyloidosis (ATTR-CA) and immunoglobulin light chain cardiac amyloidosis (AL-CA), characterized by the precursor protein that forms amyloid and infiltrates the myocardium. ATTR-CA can be caused by normal transthyretin protein, a condition previously called senile or age-related CA and now referred to as wild-type transthyretin CA (ATTRwt-CA); alternatively, it can be caused by transthyretin harboring mutations, a condition previously called familial CA and now referred to as variant transthyretin CA (ATTRv-CA) (1). Major differences between these types of CA are outlined in **Table 1**. ATTRwt-CA is more common than previously realized, specifically among older adults with heart failure with preserved ejection fraction (HFpEF). Recent advances in therapeutic options render accurate and early diagnosis critical. Delayed diagnosis of AL-CA is associated with higher mortality over the short term (2).

Diagnosis of CA requires a heightened index of clinical suspicion and awareness of clinical clues suggestive of CA. One survey of patients with AL-CA found that for over 30% of affected individuals, obtaining the accurate diagnosis had taken more than a year and at least five physicians (4). Our goal is to reduce the time to diagnosis by elucidating clues for recognizing CA, clarifying common misconceptions, and highlighting recent advances.

EPIDEMIOLOGY

ATTRwt-CA is typically diagnosed at 70–75 years of age, with a striking male predominance (>90%) (5, 6), often after the disease has already reached advanced stages. While the exact prevalence of ATTR-CA is unknown, autopsy studies have revealed ATTR in 25% of subjects over 80–85 years of age (7, 8). Use of nuclear scintigraphy has enabled broader evaluation and has detected ATTRwt-CA more frequently than expected. ATTR-CA was found in 13% of 120 patients admitted with HFpEF (9) and in 16% of 151 patients with severe calcific aortic stenosis

Table 1 Typical presenting features of subtypes of cardiac amyloidosis (partially adapted from 3)

	Feature	AL-CA	ATTRwt-CA	ATTRv-CA
Epidemiology	Age at diagnosis	5th to 9th decade	7th to 10th decade	3rd to 8th decade
	Gender	Roughly equal male:female	Very significant male predominance	Male predominance
Biology	Involved protein	Immunoglobulin light chain	Transthyretin	Transthyretin
	Genetic cause	None	None	Autosomal dominant inheritance
	Extracardiac involvement	Nerves, kidney, liver, gastrointestinal tract, skin, tongue/soft tissue	Carpal tunnel, lumbar spine, gastrointestinal tract	Nerves
Prognosis		Depends on stage Median survival 4–6 months with advanced heart failure	Depends on stage Median survival 2–6 years in the absence of treatment	Depends on mutation and stage Median survival 3–12 years
Potential therapy		Antiplasma cell therapy, autologous stem cell transplant	Tafamidis, diflunisal	Inotersen, patisiran, tafamidis, diflunisal

Abbreviations: AL-CA, immunoglobulin light chain cardiac amyloidosis; ATTRv-CA, variant transthyretin cardiac amyloidosis; ATTRwt-CA wild-type transthyretin cardiac amyloidosis.

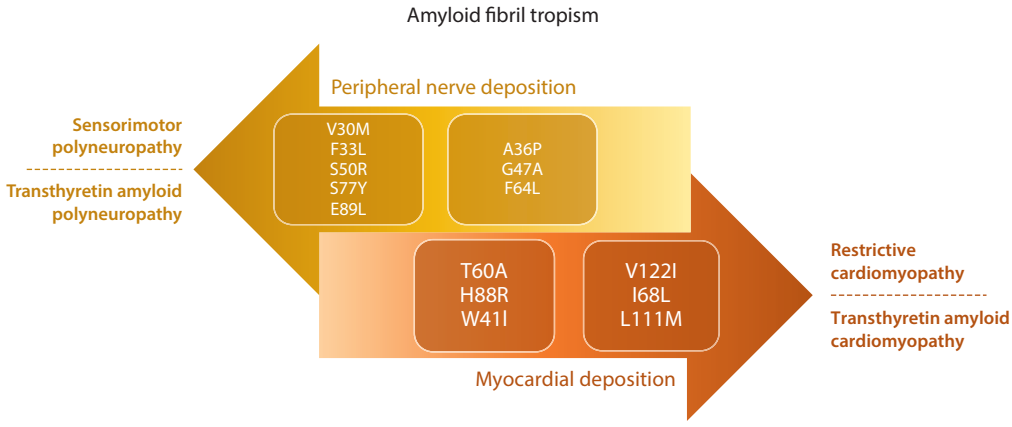


Figure 1

Cardiac versus neurologic involvement in transthyretin variant amyloidosis. Nerve versus myocardial tropism of transthyretin amyloidosis differs by mutation, with significant overlap, as depicted here.

undergoing transcatheter aortic valve replacement (10). Up to 5% of patients suspected of having hypertrophic cardiomyopathy actually have ATTR-CA (11), and up to 3% of adult males >75 years of age have ATTR-CA based on scintigraphy (12).

Patients with ATTRv-CA are typically diagnosed at a younger age than those with ATTRwt-CA. More than 130 amyloidogenic mutations have been identified and can cause a predominantly cardiomyopathic, neuropathic, or mixed phenotype (**Figure 1**). Val122Ile, present in 3.4% of African Americans (13), is the most common mutation in the United States, followed by Thr60Ala (the Appalachian mutation), which is found in individuals of Irish descent (14, 15).

AL-CA typically presents at an earlier age than ATTRwt-CA and occurs only slightly more frequently among men than among women (16). Its exact prevalence is unknown, but it is significantly less common than ATTR-CA. The incidence of immunoglobulin light chain amyloidosis is approximately 10 to 12 per million person-years (17), and about 50% of cases have cardiac involvement (18).

PATHOPHYSIOLOGY

CA is caused by cumulative myocardial deposition of insoluble amyloid that causes chamber stiffening, conduction disturbances, impaired diastolic function initially, and HFpEF that can progress to a reduced ejection fraction (EF).

Transthyretin (alternatively, prealbumin) is a tetrameric protein mainly produced in the liver that transports thyroid hormone and retinol (hence its name: "trans" for transporter, "thy" for thyroid hormone, and "retin" for retinol). With aging, or a destabilizing mutation, the tetramer dissociates into monomers or oligomers that misfold and aggregate into amyloid fibrils (**Figure 2*a***).

In AL-CA, bone marrow plasma cells secrete excess monoclonal immunoglobulin light chains, which similarly misfold and aggregate into amyloid fibrils (**Figure 2*b***). Light chains also activate the p38 mitogen-activated protein (MAP) kinase signaling pathway, upregulating natriuretic peptide production (20, 21). Thus, elevated brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP) reflect light chain toxicity to cardiomyocytes in addition to increased filling pressures, rendering AL-CA a "toxic and infiltrative" cardiomyopathy (21). Light chain amyloidosis can affect multiple organs, including the kidney (nephrotic syndrome in approximately 30% of patients), nerves (peripheral and autonomic neuropathy in approximately

EF: ejection fraction

BNP: brain natriuretic peptide

NT-proBNP: N-terminal probrain natriuretic peptide

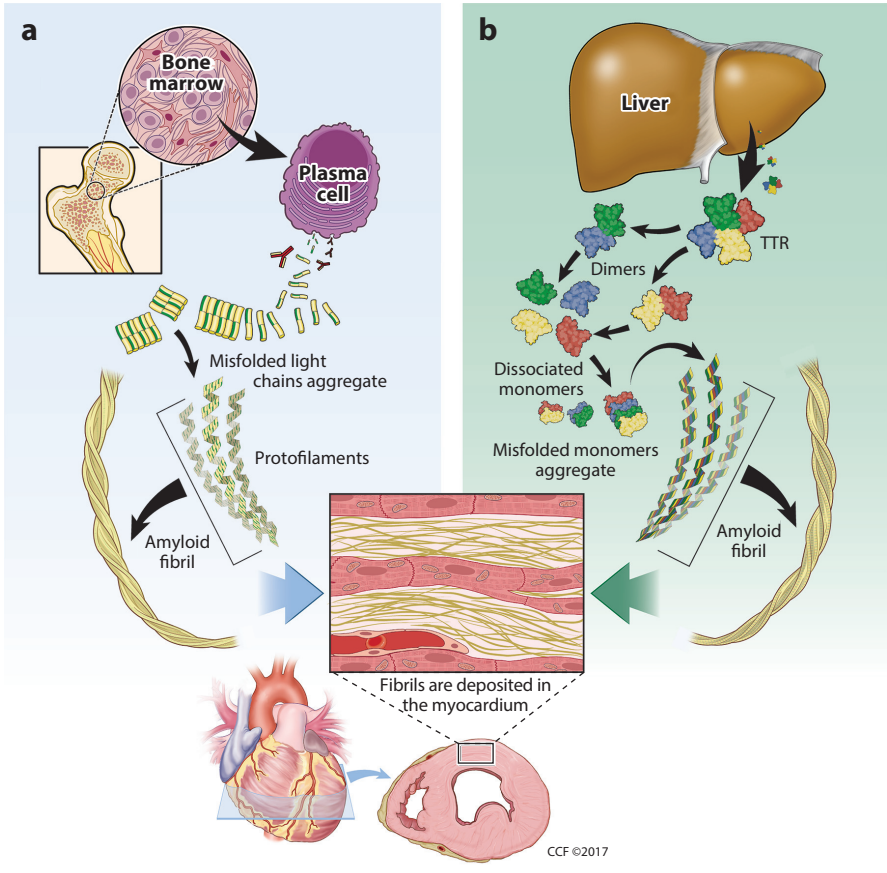


Figure 2

Mechanism of development of immunoglobulin light chain cardiac amyloidosis (AL-CA) and transthyretin cardiac amyloidosis (ATTR-CA). (*a*) A plasma cell originating from the bone marrow produces excess monoclonal light chains, which aggregate into amyloid fibrils and deposit in the myocardium, leading to AL-CA. (*b*) Transthyretin (TTR), a tetrameric protein produced by the liver, dissociates into its monomers, which aggregate into amyloid fibrils that deposit in the myocardium, leading to ATTR-CA. Reprinted from Reference 19 with permission. Copyright © 2017 Cleveland Clinic Foundation. All rights reserved.

12–17%, sometimes with gastric dysmotility), gastrointestinal tract (present in most patients but symptomatic in approximately 1%), and rarely the liver (22).

Diffuse amyloid deposition causes both atrial dysfunction and ventricular wall hypertrophy with resultant declines in ventricular end diastolic capacitance, stroke volume, and cardiac output. Infiltration of the conduction system causes arrhythmias such as atrial fibrillation, which eventually occurs in nearly all patients with CA and is associated with intracardiac thrombosis (23–25) and heart block.

DIAGNOSIS

Transthyretin Cardiac Amyloidosis

Previously, definitive diagnosis of ATTR-CA often required an endomyocardial biopsy staining positive with Congo Red, with confirmatory testing for ATTR via immunohistochemistry or

mass spectroscopy. Endomyocardial biopsy is highly sensitive and specific (nearly 100% for each) and is considered the gold standard for diagnosis. However, given its invasive nature, biopsy was performed only when there was significant suspicion of CA. Furthermore, performance and interpretation of the pathologic results require specific expertise. Diagnosis was therefore often significantly delayed.

SPEP/UPEP with IFE: serum/urine protein electrophoresis with immunofixation

Recently, bone nuclear scintigraphy emerged as a noninvasive diagnostic test that is 92% sensitive and 95% specific for ATTR-CA (26–28) in the absence of monoclonal gammopathy. A nuclear radiotracer, ^{99m}Tc-PYP in the United States and ^{99m}Tc-DPD or ^{99m}Tc-HMDP elsewhere, is used. One to three hours after injection, thoracic or whole-body planar images coupled with single photon emission computed tomography (SPECT) images are obtained and interpreted with one of two methods. One is the semiquantitative scoring system, which grades radiotracer uptake in the myocardium compared to rib. No myocardial uptake with normal rib uptake is grade 0. Myocardial uptake less than, equal to, or greater than rib uptake is scored as grades 1, 2, or 3, respectively. Grades 2–3 are diagnostic of ATTR-CA. The second method, the quantitative scoring system, compares a circular region of interest over the heart (H) to the contralateral lung (CL) field. An H/CL uptake ratio $\geq$1.5 is also diagnostic of ATTR-CA. The radiotracer washes out over time, such that a positive test using the H/CL ratio would be $\geq$1.3 at 3 h after injection. A common cause of a false positive scan is AL-CA, and thus scintigraphy must be coupled with lab testing for AL-CA as described below. Once ATTR-CA is diagnosed, genetic testing is employed to subtype it as either wild-type or hereditary.

Immunoglobulin Light Chain Cardiac Amyloidosis

AL-CA cannot be diagnosed without a biopsy, and yield is highest when the affected organ is biopsied. Pathologic confirmation of immunoglobulin light chain amyloid in extracardiac tissue with cardiac imaging consistent with CA is often sufficient to establish a diagnosis, but notably, the sensitivity of a fat pad biopsy is 70–80% at best, even in advanced disease (29). Thus, when clinical suspicion is high and a fat pad biopsy is negative, an endomyocardial biopsy or biopsy of a clinically affected organ should be considered. Lab testing must include serum and urine protein electrophoresis with immunofixation (SPEP/UPEP with IFE) as well as kappa and lambda serum free light chains. Together, these tests are 99% sensitive for a monoclonal plasma cell dyscrasia indicative of AL-CA (30). However, presence of a monoclonal gammopathy does not confirm AL-CA, as up to 20–40% of patients with ATTR-CA have a monoclonal gammopathy of undetermined significance, further confounding the diagnosis (31, 32). In these cases, nuclear scintigraphy is insufficient for diagnosis, and biopsy is required (**Figure 3**).

"Red Flags" and Associated Syndromes

Misconceptions about CA (**Table 2**) and its varied presentations contribute to its underdiagnosis. The phenotypic heterogeneity in ATTRv amyloidosis varies with each mutation, patient gender, endemic or nonendemic region, age of onset (33), type of fibril fragment (34), presence of inflammation, and other factors (35). The heart is affected in most cases but is rarely the only affected organ. Therefore, awareness of "red flags" suggestive of amyloidosis can enhance one's index of appropriate clinical suspicion and enable earlier diagnosis of CA.

ATTRwt amyloidosis that subsequently causes ATTR-CA is often preceded, several years before onset, by orthopedic clues including carpal tunnel syndrome (36), lumbar spinal stenosis (37), hip and knee arthroplasty (38), and biceps tendon rupture (39). ATTRv amyloid often causes sensorimotor polyneuropathy, particularly with a predominantly neuropathic mutation such as Val30Met. Notably, there are predominant cardiac phenotypes caused by known mutations

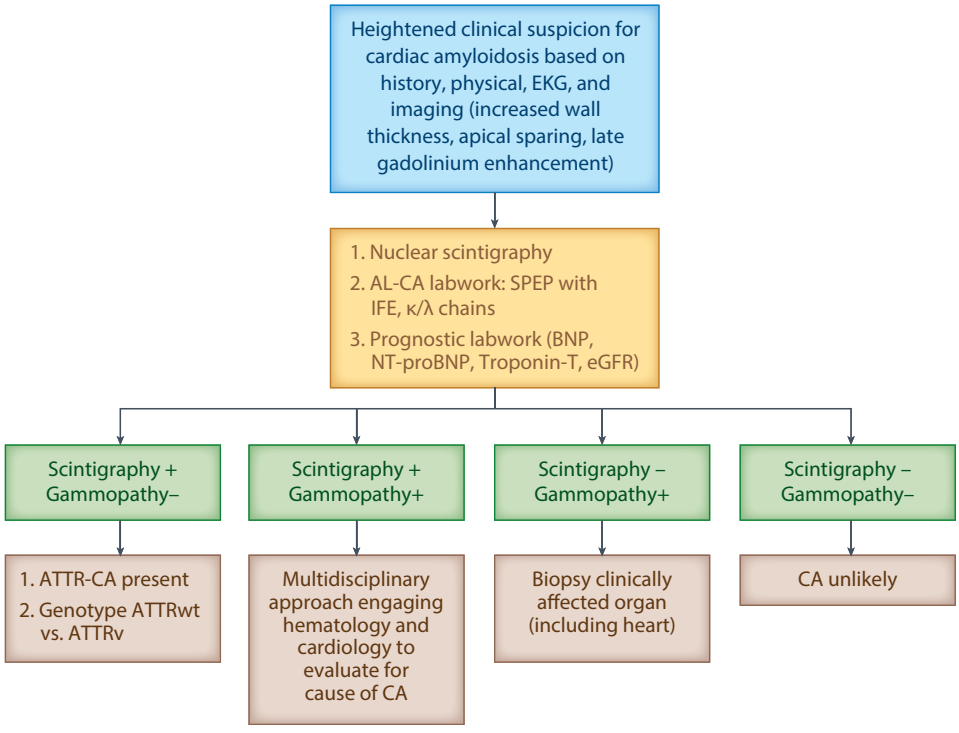


Figure 3

Basic algorithmic approach to diagnosis of CA. Abbreviations: AL-CA, immunoglobulin light chain cardiac amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BNP, brain natriuretic peptide; CA, cardiac amyloidosis; eGFR, estimated glomerular filtration rate; EKG, electrocardiogram; NT-proBNP, N-terminal probrain natriuretic peptide; SPEP with IF, serum protein electrophoresis with immunofixation.

Table 2 Clarification of common misconceptions about cardiac amyloidosis

Misconception	Correction
CA is rare	ATTR-CA, particularly ATTRwt-CA, is not rare
Nuclear scintigraphy can definitively diagnose CA	Nuclear scintigraphy can be used to diagnose ATTR-CA but not AL-CA
Patients with CA will often have low voltage on EKG	Low voltage on EKG is not sensitive for CA. Rather than looking at EKG voltage alone, clinicians are encouraged to integrate EKG voltage and the wall thickness on echocardiography and calculate a voltage:mass ratio
Fat pad biopsy is very sensitive for detecting AL amyloidosis	Fat pad biopsy has a sensitivity for detecting AL amyloidosis up to 80% and is dependent on extent of disease, 45% in ATTRv and only 15% in ATTRwt
Patients with CA and a monoclonal gammopathy must have AL-CA	Patients with ATTR-CA may have a concomitant monoclonal gammopathy of undetermined significance, which does not reflect underlying light chain amyloidosis. Therefore, in patients suspected to have CA with monoclonal proteins, ATTR-CA is still possible and, given the epidemiology, is more likely than AL-CA
CA is not treatable	Both ATTR-CA and AL-CA are treatable

Abbreviations: AL, amyloid light chain; ATTR, amyloid transthyretin; ATTRv, transthyretin variant; ATTRwt, transthyretin wild-type; CA, cardiac amyloidosis; EKG, electrocardiogram.

including Val122Ile (40), Leu111Met in Denmark (41), and Ile68Leu in Italy (42). Other mutations, including Thr60Ala (43), cause a mixed phenotype with both cardiac and neurologic involvement (44). Other possible neurologic symptoms include autonomic dysfunction presenting as orthostatic hypotension, erectile dysfunction, gastrointestinal motility disorders (with resultant nausea, alternating diarrhea and constipation, and dumping syndrome), or urinary retention. Cardiac arrhythmias may precede symptomatic heart failure.

Macroglossia and periorbital purpura are specific, not sensitive, signs for AL amyloidosis and are rarely seen in ATTR-CA. Hepatomegaly and peripheral neuropathy also commonly occur in AL-CA, but their presence is neither sensitive nor specific. AL amyloidosis can cause nephrotic syndrome and should be considered in a patient with undifferentiated cardiac hypertrophy and proteinuria.

Cardiac Testing

Diffuse low voltage on electrocardiogram (EKG) is commonly reported in CA but is not sensitive (<30%) and manifests as disease progresses. Therefore, low voltage is specific and prognostic but not helpful for early identification (45). Evidence of pseudoinfarction, pathologic Q waves in the absence of a previous infarct or wall motion abnormality, is a more sensitive EKG finding and is present in up to 70% of patients with CA (45). A low voltage-to-mass ratio is the hallmark of infiltrative cardiomyopathy and is more sensitive than low voltage in isolation (46). By indexing voltage to mass, thus accounting for increased mass from amyloid deposition, even seemingly normal voltage may prove relatively low, suggesting CA.

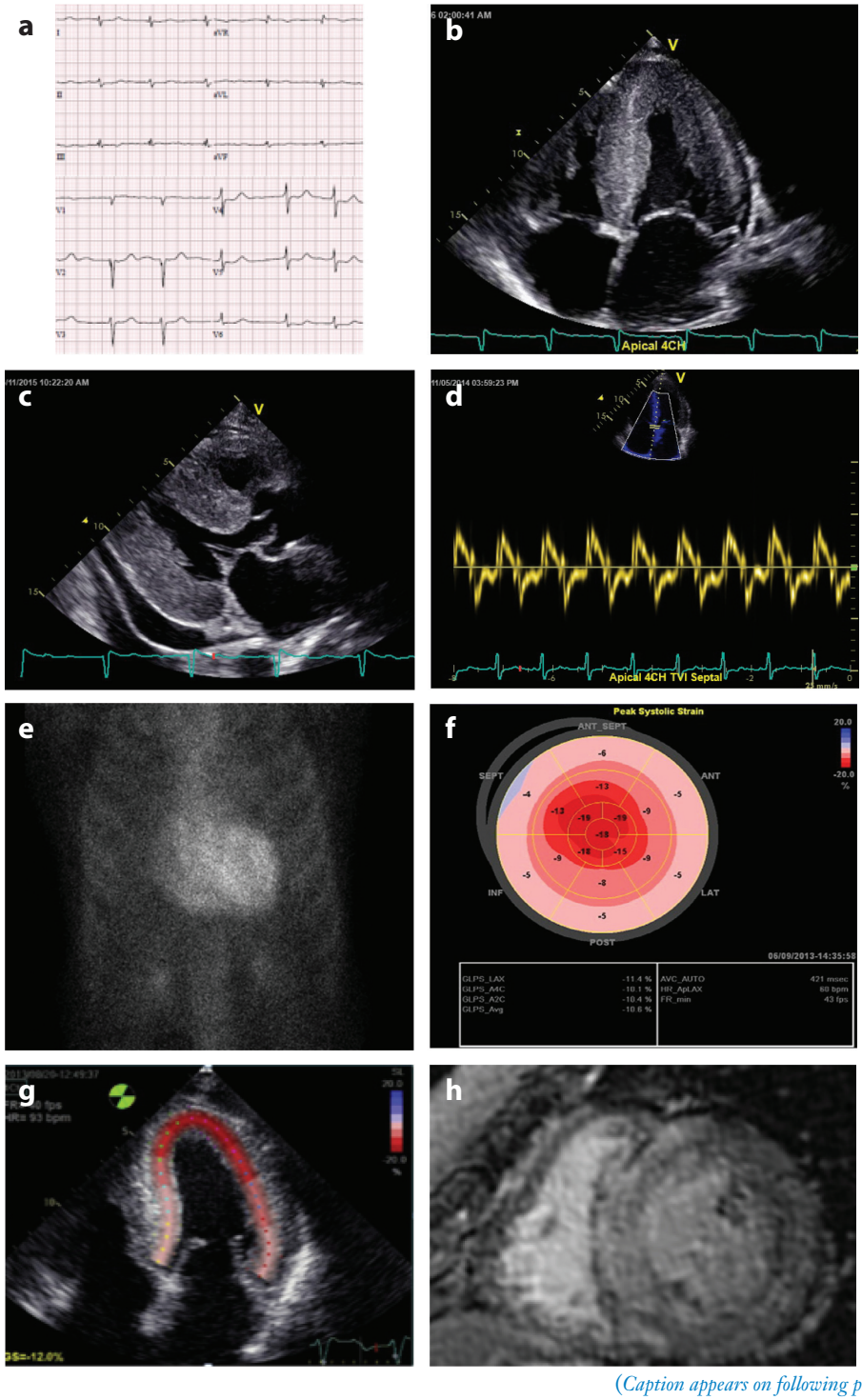
On echocardiogram, amyloid causes thickened ventricles (left ventricular wall thickness ≥12 mm), left atrial enlargement, and diastolic dysfunction (steep deceleration time, low tissue Doppler velocity at the mitral annulus or E′, and an elevated E/e′ ratio) (47). Other findings include valve and interatrial septal thickening, apical sparing using global longitudinal strain (48), and reduced mitral annular plane systolic excursion (49) (see **Figure 4**). The echogenicity of amyloid protein may result in a speckled appearance of the myocardium, though the specificity of this finding is low with harmonic imaging. EF is typically initially preserved because although the stroke volume declines, so does the end-diastolic volume, with a concomitant reduction in cardiac output and hence blood pressure over time. A novel volumetric analogue of strain, the myocardial contraction fraction (MCF), indexes myocardial volume to stroke volume, thereby revealing abnormalities in myocardial shortening that are masked by the presence of a preserved EF (50). Indeed, MCF is demonstrably reduced in CA and more strongly associated with mortality than is EF in both AL-CA (51) and ATTR-CA (52).

Cardiac magnetic resonance (CMR) imaging is more expensive and less widely available than echocardiography, but provides higher resolution and better imaging of the myocardium. Late gadolinium enhancement of the left ventricle and atria is a feature of CA, often present before changes on echocardiography indicative of CA, and progresses from a subendocardial to a diffuse myocardial pattern with advancing amyloid infiltration (**Figure 4**). CMR cannot reliably distinguish AL-CA from ATTR-CA. CMR measurement of extracellular volume is emerging as a potential measure to track progression of CA over time and response to therapy.

STAGING AND PROGNOSIS

Biomarkers

Troponin, BNP, and NT-proBNP have been studied extensively for their diagnostic and prognostic utility in AL-CA, and data are emerging in ATTR-CA. Elevated natriuretic peptide indicates



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

Testing and imaging for cardiac amyloidosis. (*a*) Electrocardiogram with diffusely low voltage and poor R wave progression consistent with pseudoinfarction. (*b*) Four-chamber apical view demonstrating thickened ventricular walls and atrial septum, small ventricular chambers and dilated atria. (*c*) Parasternal view demonstrating thickened left and right ventricular walls, dilated left atria and a pericardial effusion. (*d*) Septal tissue Doppler velocities showing low (<5 cm/s) S and E′ velocities and a restrictive filling pattern. (*e*) Nuclear scintigraphy demonstrating significant radiotracer uptake in the myocardium compatible with a grade 3 scan. (*f*) Polar map of regional strain showing global reduction in strain, with regional variation and apical preservation but reduced basal strain. This appearance is often described as "cherry on top." (*g*) Speckled strain on apical four-chamber view demonstrating apical preservation of strain. (*h*) Magnetic resonance image demonstrating thickened ventricular walls and diffuse delayed enhancement. MRI figure courtesy of Dr. Andrew Einstein.

cardiac involvement in AL amyloidosis (53); higher values are associated with worse prognosis, and significant reduction after plasma cell therapy is associated with improved survival (54). Natriuretic peptides are elevated in ATTR-CA as well, but not to the same degree as in AL-CA for the same degree of wall thickening, which is attributable to the toxicity of light chains. Higher troponin also portends poorer prognosis in both AL-CA and ATTR-CA (5).

Staging Systems

Several staging systems have been proposed for prognostication of CA. The original Mayo staging system for AL-CA utilizes both troponin (troponin-T < 0.035 μg/L or troponin-I < 0.1 μg/L) and NT-proBNP (<322 ng/L), and defines stages I, II, and III based on whether both, one, or neither of these markers are below the threshold (55). These stages predict a median survival of 27.2, 11.1, and 4.1 months, respectively.

A more recently revised and validated staging system introduced the difference between involved and uninvolved free light chains (FLC-diff), eliminated troponin-I, and changed the cutoffs for troponin-T and NT-proBNP. FLC-diff (≥18 mg/dl), troponin-T (≥0.025 ng/ml), and NT-proBNP (≥1,800 pg/ml) were used to define stages I, II, III, and IV, based on whether none, one, two, or all three factors were above the threshold, and correlated with a median overall survival of 94, 40, 14, and 6 months, respectively (56). Another staging system utilizing BNP instead of NT-proBNP was recently described (57).

A staging system for ATTRwt-CA stratifies patients into three stages based only on troponin-T (<0.05 ng/ml) and NT-proBNP (<3,000 pg/ml) (6). Stages I, II, and III are defined as having both, one, or neither of the markers below the threshold, with a median survival of 66, 40 and 20 months, respectively. Age, EF, and pericardial effusion were also multivariate predictors of mortality. A more recent study of both ATTRwt-CA and ATTRv-CA proposed substituting troponin-T with estimated glomerular filtration rate (eGFR) of 45 ml/min (58). Median survival was 69, 47, and 24 months in stages I, II, and III, respectively, with longer survival in ATTRwt-CA than in ATTRv-CA (59).

MANAGEMENT

General Management of Cardiac Amyloidosis

Heart failure management in CA requires maintaining euvolemia via sodium restriction and judicious diuretic use. This is particularly challenging in CA because of concomitant age-related changes in ventricular coupling and autonomic dysfunction resulting in load lability and hypotension. Several commonly used medications are also relatively contraindicated in CA. Beta blockers may prevent the increased heart rate that physiologically compensates for diminishing

FLC-diff: difference between involved and uninvolved free light chains

stroke volume. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may cause symptomatic hypotension and can exacerbate a concomitant renal insufficiency. Non-dihydropyridine calcium channel blockers may bind to amyloid fibrils, causing heart block and shock (60, 61). Digoxin has been implicated in dysrhythmia and sudden death (62), but it has been more recently shown to possibly be safe in low doses and with careful monitoring (63). Amiodarone and dofetilide are the preferred antiarrhythmic agents in patients with AL-CA, given their efficacy with minimal negative inotropic effect.

Bioavailable loop diuretics such as torsemide and bumetanide are preferred because of the frequency of gut edema secondary to right-sided heart failure that impairs gastrointestinal absorption. Supportive care for patients with advanced disease and progressive hypotension includes compression stockings and midodrine.

Arrhythmia Management

Patients with atrial fibrillation should receive anticoagulants regardless of their $CHADS_2$-VASc risk score because of increased risk of intracardiac thrombosis (23, 25, 64). AL-CA also confers increased risk of systemic thromboembolism. Even patients who are in sinus rhythm but have low atrial Doppler velocities on mitral inflow pattern indicative of left atrial standstill are at high risk of intracardiac thrombosis. No trials compared warfarin to non–vitamin K antagonist oral anticoagulants (NOACs), but we have found NOACs to be safe and effective. Given the diffuse nature of amyloid infiltration in the atria and the high rate of recurrent arrhythmias, a decision to ablate should be individualized according to patient preference and severity of symptoms (65).

Conduction disease is more common in ATTR-CA, partially due to the older age of affected subjects, than in AL-CA. In one series, up to 30% of patients required permanent pacing (14). This may provide symptomatic relief, but there is no evidence that pacemakers reduce mortality. Rather, the need for a pacemaker is a marker of advanced disease associated with a poorer prognosis (5). In patients with low output states, increasing the basal pacing rate may improve cardiac output, and resynchronization therapy may also be beneficial. Since the immediate cause of death is usually profound bradycardia or pulseless electrical activity (66), intracardiac defibrillator placement also has not been proven to improve survival. Thus, the risks of intracardiac defibrillator placement, including worsening tricuspid regurgitation, may outweigh the benefits.

Increased wall thickness and small chamber size usually preclude use of left ventricular assist devices (67). However, although rarely possible due to numerous comorbidities, orthotopic heart transplant (OHT) has been performed for patients with ATTR-CA and AL-CA (68) without significant extracardiac amyloid involvement. In AL-CA, chemotherapy and autologous stem cell transplant are often performed after OHT to control the underlying plasma cell dyscrasia, though stem cell transplant is not required in the context of multiple effective plasma cell therapies (69). In several small studies, five-year survival after OHT for AL-CA and ATTR-CA ranged from 20% to 80% and from 60% to 100%, respectively, with improving survival reported in recent United Network for Organ Sharing analysis (69).

Management of Transthyretin Cardiac Amyloidosis

Improved understanding of the pathophysiology of ATTR-CA and the advent of several promising treatments have ushered in a new and exciting era that renders early diagnosis of paramount importance. Therapeutics under investigation target different points in the pathogenesis of ATTR-CA (**Figure 5**). ATTR silencers prevent synthesis of transthyretin, and stabilizers prevent dissociation of transthyretin tetramers into monomers, the rate-limiting step in amyloidogenesis. Notably, although these therapies prevent further progression of disease, their ability to reverse

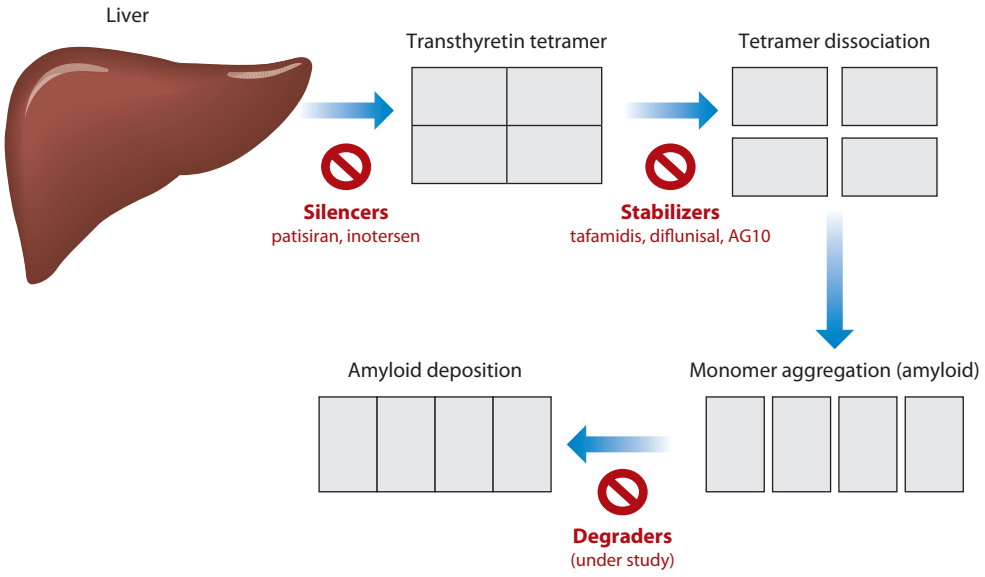


Figure 5

Mechanisms of therapeutic agents for transthyretin cardiac amyloidosis. Silencers, such as patisiran and inotersen, inhibit liver production of transthyretin. Stabilizers, such as tafamidis, diflunisal, and AG10, stabilize transthyretin tetramers to prevent dissociation and aggregation into amyloid fibrils. Degraders, which are of theoretical benefit and under investigation, would degrade amyloid fibrils and possibly extract already deposited amyloid from infiltrated organs.

the phenotype is not well established, hence the importance of early diagnosis. Monoclonal antibodies aimed at a particular epitope of ATTR, sometimes termed degraders or extractors, can theoretically reverse disease by activating macrophage-mediated clearance of already-deposited amyloid fibrils. Such agents have either failed in phase III trials or are in early-phase trials with as yet unclear efficacy.

Tafamidis, a once-daily oral drug, was first approved in Europe in 2011 for treatment of familial amyloid polyneuropathy (FAP). It has now demonstrably reduced all-cause mortality, cardiovascular-related hospitalizations, and decline in functional capacity and quality of life, in an international multicenter double-blinded placebo-controlled phase III trial of 441 patients with ATTR-CA (70). In 2.5 years of follow-up, relative risk reduction in mortality was 32% and absolute risk reduction was 13%; numbers needed to treat were 7.5 to prevent 1 death over 30 months and 4 to prevent 1 hospitalization over 1 year. In May 2019, tafamidis became the first therapy specifically for ATTR-CA approved by the US Food and Drug Administration (FDA).

Diflunisal is an FDA-approved nonsteroidal anti-inflammatory drug (NSAID) but is also a transthyretin stabilizer (71). Despite concern that NSAID use carries risk of gastrointestinal bleed, kidney injury, and heart failure exacerbation, an international randomized double-blind placebo-controlled study (72) found diflunisal to be well tolerated and to successfully slow progression of FAP. About half of the patients in this study also had ATTR-CA. Encouraging single-center studies suggest that diflunisal may slow ATTR-CA as well, without significant bleeding (73, 74). The dose used in ATTR amyloidosis, 250 mg twice daily, is half the FDA-approved recommended starting dose for diflunisal as an anti-inflammatory, which may explain the low rates of bleeding. Given its potential efficacy, low cost, and seemingly low bleeding

risk, diflunisal may be used in patients with ATTR-CA without concomitant renal dysfunction [eGFR > 45 ml/(min · 1.73 m^2)], refractory heart failure, or high bleeding risk.

Two silencers are newly approved by the FDA for polyneuropathy in ATTRv and may be used for patients who have ATTRv-CA with concomitant neuropathy but are not approved for patients with isolated ATTR-CA. Patisiran, administered intravenously, is a small interfering RNA (siRNA) that suppresses formation of ATTR. This is the first siRNA medication to achieve FDA approval, granted in August 2018, after a phase III randomized double-blinded placebo-controlled international multicenter study demonstrated its efficacy in improving polyneuropathy, quality of life, nutritional status, and autonomic function (75). Infusion-related reactions occurred in 20% of patients. In a subpopulation with ATTR-CA, patisiran was associated with reduced left ventricular wall thickness and increased end-diastolic volume and cardiac output after 18 months with an associated decrease in NT-proBNP as well. Inotersen, another silencer, administered subcutaneously, is an antisense oligonucleotide that also inhibits hepatic transthyretin production. This drug was also FDA approved for FAP after it demonstrably slowed progression and improved quality of life in a phase III randomized double-blinded placebo-controlled trial (76). A subgroup of patients with ATTR-CA similarly showed decreased left ventricular wall thickness. This finding was replicated in an open-label study of 22 enrolled patients with ATTR-CA (77).

Management of Immunoglobulin Light Chain Cardiac Amyloidosis

Patients with AL-CA require a multidisciplinary team, including an experienced hematologist, for management. Autologous stem cell transplant and anti–plasma cell therapy similar to that used for multiple myeloma are treatments for AL amyloidosis. High-dose melphalan with autologous stem cell transplant is restricted to patients who can tolerate it (78), with a median overall survival of over 10 years (79). Anti–plasma cell agents include proteasome inhibitors (bortezomib or caflizomib), immunomodulatory drugs (lenalidomide and pomalidomide), and monoclonal antibodies against plasma cell surface antigens (daratumumab). Response to treatment is graded as complete (CR), very good partial (VGPR), partial (PR), or none (NR) (80). CR is defined as a negative SPEP/UPEP with IFE with a normal serum kappa/lambda free light chain ratio. VGPR is defined as FLC-diff <4 mg/dl, PR as an FLC-diff decrease ≥50%, and NR as anything less than PR. Given the biologic link between light chain toxicity and NT-proBNP, an NT-proBNP response generally follows lowering of the light chains, with a cardiac response defined as a decrease in NT-proBNP >30% and 300 pg/ml (80, 81).

FUTURE RESEARCH

The last decade has significantly advanced diagnosis, prognosis, and management of both ATTR-CA and AL-CA, but we are at the end of the beginning (82). New treatments under investigation for AL-CA will expand the therapeutic options, resulting in continued improvements in quality of life and mortality. NEOD001 was unsuccessful in the phase III VITAL trial (83), but other antibodies, such as 11–1F4 (84), and the combination of subcutaneous daratumumab as first-line therapy with CyBorD chemotherapy (85), are under active investigation.

ATTR-CA can be diagnosed noninvasively, with resulting increasing recognition among providers, and can be treated with ATTR stabilizers. Future research will focus on investigating the role and best method of implementing screening programs for ATTR-CA in patients with heart failure and atrial fibrillation. The Screening for Cardiac Amyloidosis Using Nuclear Imaging for Minority Populations (SCAN-MP), a multicenter study funded by the National Heart, Lung, and Blood Institute, will actively ascertain the prevalence and nature of CA in elderly black and Hispanic patients with heart failure (86). The orthopedic findings that occur years before

diagnosis of ATTR-CA, and their potential role in early identification of ATTR-CA, also remain under active investigation. As more therapies gain FDA approval, future research must also investigate whether one therapy is superior to another and if combination therapy has any role.

CONCLUSIONS

CA, and ATTRwt-CA in particular, is an important etiology of HFpEF. Since treatments are most effective when started early, prompt and accurate diagnosis is critical. Fortunately, ATTR-CA can now be diagnosed noninvasively without a biopsy. Increased clinician awareness of CA, recognition of its various presentation patterns, and knowledge of the diagnostic algorithm are expected to lead to quicker diagnosis and early treatment of patients.

SUMMARY POINTS

1. ATTRwt-CA is significantly more prevalent than previously thought.
2. ATTR-CA can be diagnosed noninvasively with nuclear scintigraphy in the absence of monoclonal proteins, but AL-CA still requires a biopsy.
3. Recommended serologic testing includes SPEP/UPEP with IFE as well as analysis of kappa and lambda free light chains, NT-proBNP, troponin-T, and eGFR to evaluate the patient for AL amyloidosis and stage the patient with CA.
4. Newly available FDA-approved and emerging treatments aimed at either stabilizing ATTR or silencing ATTR production have shown efficacy in transthyretin amyloid polyneuropathy. Studies have shown tafamidis to be effective for ATTR-CA.

DISCLOSURE STATEMENT

Dr. Maurer receives consulting income from Pfizer, GSK, Eidos, Prothena, Akcea, and Alnylam, and his institution received clinical trial funding from Pfizer, Prothena, Eidos, and Alnylam.

ACKNOWLEDGMENTS

Dr. Maurer acknowledges the continued generosity of David and Landon Storrs toward the work of the Clinical Cardiovascular Research Laboratory for the Elderly on Transthyretin Amyloidosis. Dr. Maurer is supported by a K24 award from NIA (AG036778-08) and by NIH grants (R01HL139671-01 and R21AG058348). Dr. Maurer has received grant support from Pfizer, Eidos, and Alnylam and has served on advisory boards for Pfizer, Alnylam, Eidos, Akcea, Ionis, and Prothena.

LITERATURE CITED

1. Benson MD, Buxbaum JN, Eisenberg DS, et al. 2019. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid* 25:215–19
2. Kumar SK, Gertz MA, Lacy MQ, et al. 2011. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin. Proc.* 86:12–18
3. Witteles R. 2016. Cardiac amyloidosis. Am. Coll. Cardiol. Expert Anal. **https://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardiac-amyloidosis**
4. Lousada I, Comenzo RL, Landau H, et al. 2015. Light chain amyloidosis: patient experience survey from the Amyloidosis Research Consortium. *Adv. Ther.* 32:920–28

5. Pinney JH, Whelan CJ, Petrie A, et al. 2013. Senile systemic amyloidosis: clinical features at presentation and outcome. *J. Am. Heart Assoc.* 2:e000098
6. Grogan M, Scott CG, Kyle RA, et al. 2016. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J. Am. Coll. Cardiol.* 68:1014–20
7. Cornwell GG 3rd, Murdoch WL, Kyle RA, et al. 1983. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. *Am. J. Med.* 75:618–23
8. Tanskanen M, Peuralinna T, Polvikoski T, et al. 2008. 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.* 40:232–39
9. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. 2015. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur. Heart J.* 36:2585–94
10. Castano A, Narotsky DL, Hamid N, et al. 2017. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur. Heart J.* 38:2879–87
11. Morner S, Hellman U, Suhr OB, et al. 2005. Amyloid heart disease mimicking hypertrophic cardiomyopathy. *J. Intern. Med.* 258:225–30
12. Mohamed-Salem L, Santos-Mateo JJ, Sanchez-Serna J, et al. 2018. Prevalence of wild type ATTR assessed as myocardial uptake in bone scan in the elderly population. *Int. J. Cardiol.* 270:192–96
13. Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. 2015. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid* 22:171–74
14. Maurer MS, Hanna M, Grogan M, et al. 2016. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J. Am. Coll. Cardiol.* 68:161–72
15. Reilly MM, Staunton H, Harding AE. 1995. Familial amyloid polyneuropathy (TTR ala 60) in North West Ireland: a clinical, genetic, and epidemiological study. *J. Neurol. Neurosurg. Psychiatry* 59:45–49
16. Falk RH, Alexander KM, Liao R, Dorbala S. 2016. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J. Am. Coll. Cardiol.* 68:1323–41
17. Kyle RA, Larson DR, Kurtin PJ, et al. 2019. Incidence of AL amyloidosis in Olmsted County, Minnesota, 1990 through 2015. *Mayo Clin. Proc.* 94:465–71
18. Falk RH, Skinner M. 2000. The systemic amyloidoses: an overview. *Adv. Intern. Med.* 45:107–37
19. Donnelly JP, Hanna M. 2017. Cardiac amyloidosis: an update on diagnosis and treatment. *Cleveland Clin. J. Med.* 84(12 Suppl. 3):12–26
20. Shi J, Guan J, Jiang B, et al. 2010. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38alpha MAPK pathway. *PNAS* 107:4188–93
21. Brenner DA, Jain M, Pimentel DR, et al. 2004. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ. Res.* 94:1008–10
22. Gertz MA, Comenzo R, Falk RH, et al. 2005. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. *Am. J. Hematol.* 79:319–28
23. Feng D, Syed IS, Martinez M, et al. 2009. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 119:2490–97
24. Longhi S, Quarta CC, Milandri A, et al. 2015. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. *Amyloid* 22:147–55
25. Martinez-Naharro A, Gonzalez-Lopez E, Corovic A, et al. 2019. High prevalence of intracardiac thrombi in cardiac amyloidosis. *J. Am. Coll. Cardiol.* 73:1733–34
26. Bokhari S, Morgenstern R, Weinberg R, et al. 2018. Standardization of ^{99m}Technetium pyrophosphate imaging methodology to diagnose TTR cardiac amyloidosis. *J. Nucl. Cardiol.* 25:181–90
27. Bokhari S, Castano A, Pozniakoff T, et al. 2013. ^{99m}Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circ. Cardiovasc. Imag.* 6:195–201
28. Treglia G, Glaudemans A, Bertagna F, et al. 2018. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. *Eur. J. Nucl. Med. Mol. Imag.* 45:1945–55

29. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. 2017. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur. Heart J.* 38:1905–8
30. Katzmann JA, Abraham RS, Dispenzieri A, et al. 2005. Diagnostic performance of quantitative kappa and lambda free light chain assays in clinical practice. *Clin. Chem.* 51:878–81
31. Gillmore JD, Maurer MS, Falk RH, et al. 2016. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 133:2404–12
32. Phull P, Sanchorawala V, Connors LH, et al. 2018. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). *Amyloid* 25:62–67
33. Coelho T, Maurer MS, Suhr OB. 2013. THAOS—the Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr. Med. Res. Opin.* 29:63–76
34. Ihse E, Rapezzi C, Merlini G, et al. 2013. Amyloid fibrils containing fragmented ATTR may be the standard fibril composition in ATTR amyloidosis. *Amyloid* 20:142–50
35. Rapezzi C, Lorenzini M, Longhi S, et al. 2015. Cardiac amyloidosis: the great pretender. *Heart Fail. Rev.* 20:117–24
36. Nakagawa M, Sekijima Y, Yazaki M, et al. 2016. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid* 23:58–63
37. Westermark P, Westermark GT, Suhr OB, Berg S. 2014. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. *Upsala J. Med. Sci.* 119:223–28
38. Rubin J, Alvarez J, Teruya S, et al. 2017. Hip and knee arthroplasty are common among patients with transthyretin cardiac amyloidosis, occurring years before cardiac amyloid diagnosis: Can we identify affected patients earlier? *Amyloid* 24:226–30
39. Geller HI, Singh A, Alexander KM, et al. 2017. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. *JAMA* 318:962–63
40. Jacobson DR, Pastore RD, Yaghoubian R, et al. 1997. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N. Engl. J. Med.* 336:466–73
41. Ranlov I, Alves IL, Ranlov PJ, et al. 1992. A Danish kindred with familial amyloid cardiomyopathy revisited: identification of a mutant transthyretin-methionine111 variant in serum from patients and carriers. *Am. J. Med.* 93:3–8
42. Almeida MR, Hesse A, Steinmetz A, et al. 1991. Transthyretin Leu 68 in a form of cardiac amyloidosis. *Basic Res. Cardiol.* 86:567–71
43. Sattianayagam PT, Hahn AF, Whelan CJ, et al. 2012. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur. Heart J.* 33:1120–27
44. Rapezzi C, Quarta CC, Obici L, et al. 2013. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *Eur. Heart J.* 34:520–28
45. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. 2014. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. *Am. J. Cardiol.* 114:1089–93
46. Quarta CP, Longhi S, Berardini A, et al. 2012. A simple voltage/mass index improved diagnsois of cardiac amyloidosis; an electrocardiographic and echocardiographic study of 570 patients with left ventricular hypertrophy. *J. Am. Coll. Cardiol.* 59:E1586
47. Liu D, Hu K, Stork S, et al. 2014. Predictive value of assessing diastolic strain rate on survival in cardiac amyloidosis patients with preserved ejection fraction. *PLOS ONE* 9:e115910
48. Barros-Gomes S, Williams B, Nhola LF, et al. 2017. Prognosis of light chain amyloidosis with preserved LVEF: added value of 2D speckle-tracking echocardiography to the current prognostic staging system. *JACC Cardiovasc. Imag.* 10:398–407
49. Hu K, Liu D, Herrmann S, et al. 2013. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. *Eur. Heart J. Cardiovasc. Imag.* 14:205–12
50. Matthews SD, Rubin J, Cohen LP, Maurer MS. 2018. Myocardial contraction fraction: a volumetric measure of myocardial shortening analogous to strain. *J. Am. Coll. Cardiol.* 71:255–56
51. Tendler A, Helmke S, Teruya S, et al. 2015. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. *Amyloid* 22:61–66

52. Rubin J, Steidley DE, Carlsson M, et al. 2018. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J. Cardiac Fail.* 24:504–11
53. Palladini G, Campana C, Klersy C, et al. 2003. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation* 107:2440–45
54. Palladini G, Russo P, Nuvolone M, et al. 2007. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood* 110:787–88
55. Dispenzieri A, Gertz MA, Kyle RA, et al. 2004. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J. Clin. Oncol.* 22:3751–57
56. Kumar S, Dispenzieri A, Lacy MQ, et al. 2012. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J. Clin. Oncol.* 30:989–95
57. Lilleness B, Ruberg FL, Mussinelli R, et al. 2019. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. *Blood* 133:215–23
58. Gillmore JD, Damy T, Fontana M, et al. 2018. A new staging system for cardiac transthyretin amyloidosis. *Eur. Heart J.* 39:2799–806
59. Ruberg FL, Maurer MS, Judge DP, et al. 2012. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am. Heart J.* 164:222–28
60. Gertz MA, Falk RH, Skinner M, et al. 1985. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *Am. J. Cardiol.* 55:1645
61. Pollak A, Falk RH. 1993. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 104:618–20
62. Cassidy JT. 1961. Cardiac amyloidosis. Two cases with digitalis sensitivity. *Ann. Intern. Med.* 55:989–94
63. Muchtar E, Gertz MA, Kumar SK, et al. 2018. Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? *Amyloid* 25:86–92
64. Feng D, Edwards WD, Oh JK, et al. 2007. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation* 116:2420–26
65. Barbhaiya CR, Kumar S, Baldinger SH, et al. 2016. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm* 13:383–90
66. Sayed RH, Rogers D, Khan F, et al. 2015. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur. Heart J.* 36:1098–105
67. Swiecicki PL, Edwards BS, Kushwaha SS, et al. 2013. Left ventricular device implantation for advanced cardiac amyloidosis. *J. Heart Lung Transplant.* 32:563–68
68. Davis MK, Kale P, Liedtke M, et al. 2015. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. *Am. J. Transplant.* 15:650–58
69. Davis MK, Lee PH, Witteles RM. 2015. Changing outcomes after heart transplantation in patients with amyloid cardiomyopathy. *J. Heart Lung Transplant.* 34:658–66
70. Maurer MS, Schwartz JH, Gundapaneni B, et al. 2018. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N. Engl. J. Med.* 379:1007–16
71. Adamski-Werner SL, Palaninathan SK, Sacchettini JC, Kelly JW. 2004. Diflunisal analogues stabilize the native state of transthyretin. Potent inhibition of amyloidogenesis. *J. Med. Chem.* 47:355–74
72. Berk JL, Suhr OB, Obici L, et al. 2013. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA* 310:2658–67
73. Ikram A, Donnelly JP, Sperry BW, et al. 2018. Diflunisal tolerability in transthyretin cardiac amyloidosis: a single center's experience. *Amyloid* 25:197–202
74. Sekijima Y, Tojo K, Morita H, et al. 2015. Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis. *Amyloid* 22:79–83
75. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. 2018. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N. Engl. J. Med.* 379:11–21
76. Benson MD, Waddington-Cruz M, Berk JL, et al. 2018. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N. Engl. J. Med.* 379:22–31

77. Benson MD, Dasgupta NR, Rissing SM, et al. 2017. Safety and efficacy of a TTR specific antisense oligonucleotide in patients with transthyretin amyloid cardiomyopathy. *Amyloid* 24:219–25
78. Comenzo RL, Vosburgh E, Falk RH, et al. 1998. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood* 91:3662–70
79. Sanchorawala V, Sun F, Quillen K, et al. 2015. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. *Blood* 126:2345–47
80. Dispenzieri A, Buadi F, Kumar SK, et al. 2015. Treatment of immunoglobulin light chain amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus statement. *Mayo Clin. Proc.* 90:1054–81
81. Merlini G, Lousada I, Ando Y, et al. 2016. Rationale, application and clinical qualification for NT-proBNP as a surrogate end point in pivotal clinical trials in patients with AL amyloidosis. *Leukemia* 30:1979–86
82. Falk RH. 2019. Tafamidis for transthyretin amyloid cardiomyopathy: the solution or just the beginning of the end? *Eur. Heart J.* 40:1009–12
83. Liedtke M, Merlini G, Landau H, et al. 2016. The VITAL amyloidosis study: a randomized, double-blind, placebo-controlled, global, phase 3 study of NEOD001 in patients with AL amyloidosis and cardiac dysfunction. *Blood* 128:5690
84. ClinicalTrials.gov. NCT02245867. Study of chimeric fibril-reactive monoclonal antibody 11–1f4 in patients with AL amyloidosis. **https://clinicaltrials.gov/ct2/show/NCT02245867**
85. ClinicalTrials.gov. NCT03201965. 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. **https://clinicaltrials.gov/ct2/show/NCT03201965**
86. ClinicalTrials.gov. NCT03812172. Screening for cardiac amyloidosis using nuclear imaging for minority populations (SCAN-MP). **https://clinicaltrials.gov/ct2/show/NCT03812172**