HHS Public Access

Author manuscript

*Curr Heart Fail Rep*. Author manuscript; available in PMC 2023 October 01.

Published in final edited form as:

*Curr Heart Fail Rep*. 2022 October ; 19(5): 356–363. doi:10.1007/s11897-022-00570-1.

# Update on Disease-Specific Biomarkers in Transthyretin Cardiac Amyloidosis

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## Abstract

**Purpose of Review—**Transthyretin cardiac amyloidosis (ATTR-CM) is an infiltrative cardiomyopathy and an increasingly recognized cause of morbidity and mortality. There remains substantial delay between initial symptoms and diagnosis. With the recent emergence of various targeted therapies proven to reduce morbidity and mortality, there is an imperative to diagnose subclinical disease. Biomarkers may be well-suited for this role.

**Recent Findings—**Conventional markers of heart failure, such as natriuretic peptides and cardiac troponins, and estimated glomerular filtration rate are associated with risk in ATTR-CM. Circulating transthyretin (TTR) levels parallel TTR kinetic stability, correlate with disease severity, and may serve as indirect markers of ATTR-CM disease activity and response to targeted treatment. There is also growing evidence for the correlation of TTR to retinol-binding protein 4, a biomarker which independently associates with this disease. The rate-limiting step for ATTR pathogenesis is dissociation of the TTR homotetramer, which may be quantified using subunit exchange to allow for early risk assessment, prognostication, and assessment of treatment response. The protein species that result from the dissociation and misfolding of TTR are known as nonnative transthyretin (NNTTR). NNTTR is quantifiable via peptide probes and is a specific biomarker whose reduction is positively correlated with improvement in neuropathic ATTR amyloidosis. Neurofilament light chain (NfL) is released into the blood after axonal damage and correlates with neuropathic ATTR amyloidosis, but its clinical use in ATTR-CM is uncertain.

**Summary—**Conventional markers of heart failure, transthyretin, retinol-binding protein 4, transthyretin kinetic stability, non-native transthyretin, peptide probes, and neurofilament light

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chain have potential as biomarkers to enable early, subclinical diagnosis in patients with transthyretin cardiac amyloidosis.

**Keywords**

Transthyretin amyloidosis; Biomarkers; Retinol binding protein; Nonnative transthyretin; Peptide probes; Neurofilament light chain

## Introduction

Transthyretin cardiac amyloidosis (ATTR-CM) is an infiltrative cardiomyopathy caused by the deposition of misfolded transthyretin (TTR) amyloid fibrils. TTR is the second most abundant protein in the serum, found in its wild-type form as a homotetramer. Instability in this homotetramer may arise in individuals with both wild-type (ATTRwt) and hereditary (ATTRv) forms of TTR. Variants in the *TTR* gene that destabilize the tetramer predispose to disease. However, patients with ATTRwt may also have kinetically stable TTR and multifactorial causes for low circulating TTR levels [1].

In disease state, deposition of TTR amyloid occurs throughout the body, with symptoms arising from deposition in neurologic and cardiac tissues. Infiltration into cardiac tissues manifests as heart failure, conduction system disease, and arrythmias [2]. Cardiac symptoms are often preceded by neurologic symptoms including carpal tunnel syndrome, spinal stenosis, and neuropathy [3]. These manifestations impact patient quality of life and increase health resource utilization [4, 5].

After symptoms have started, there remains a significant delay to diagnosis from symptoms onset. For instance, the French Daily Impact of Amyloidosis Study from 2022 included 333 patients with ATTR-CM and found that median delay from presentation to confirmed diagnosis was 27.4 months [6]. Furthermore, patients utilize health care resources frequently in the period just before diagnosis. Data from 1034 patients with ATTR-CM at the UK National Amyloidosis Center between 2000 and 2017 suggest that patients used hospital services a median of 17 times during the 3 years before diagnosis [4].

The previously poor prognosis of ATTR-CM has improved with the emergence of two pharmacologic treatment strategies. These novel treatments target the production of amyloidogenic TTR via two mechanisms: (1) silencing hepatic translation (small interfering RNAs, e.g., patisiran) and (2) TTR kinetic stabilization (e.g., tafamidis). Tafamidis has been shown to reduce hospitalization and all-cause mortality in patients with ATTR-CM [7••]. The treatments offer greater benefits when administered at early stages of the disease [8, 9].

The advent of these beneficial treatments creates an imperative for earlier detection of disease, prognostication, and response to treatment. Herein, we describe a selection of biomarkers that have been studied in ATT-CM and discuss the potential for their clinical utility.

## Conventional Heart Failure Biomarkers in ATTR-CM

In patients with ATTR-CM, natriuretic peptides and cardiac troponins are commonly elevated, and estimated glomerular filtration rate (eGFR) is commonly decreased [10]. The prohormone of B-type natriuretic peptide (proBNP) is released by cardiomyocytes under hemodynamic stress and is cleaved into two fragments: B-type natriuretic peptide and amino terminal-proBNP (NT-proBNP) [11]. Elevated natriuretic peptides are the sine qua non biomarkers that define risk in conventional heart failure [12]. Although likely reflective of abnormal intracardiac hemodynamics in cardiac amyloidosis, elevated natriuretic peptides may also serve as surrogates for the degree of myocardial amyloid infiltration [13].

Similar to natriuretic peptides, cardiac troponins are frequently elevated in cardiac amyloidosis and indicate the presence of cardiac injury [14, 15]. Troponins are often disproportionately elevated in ATTR-CM as compared to other etiologies of cardiomyopathy [15]. One study sought to evaluate the diagnostic utility of high-sensitivity cardiac troponin T (hs-cTnT) levels in discriminating cardiac amyloidosis from patients with cardiac hypertrophy caused by other etiologies [15]. Serum hs-cTnT levels were measured in 96 patients with cardiac amyloidosis (40 ATTRwt, 33 ATTRv, and 23 light chain) and 91 controls with cardiomyopathy and biopsy-confirmed absence of amyloidosis [15]. Median hs-cTnT levels were higher in every ATTR-CM subgroup as compared to normal controls, with the highest median level in light chain group (0.073 ng/mL), then the ATTRwt group (0.048 ng/mL), then the ATTRv group (0.032 ng/mL) [15]. Using receiver operating characteristic analysis, the best hs-cTnT cutoff values for detecting ATTR-CM were 0.0315 ng/mL (AUC: 0.820, sensitivity: 0.83, and specificity: 0.76) for ATTRwt, and 0.0286 ng/mL (AUC: 0.686, sensitivity: 0.58, and specificity: 0.68) for ATTRv [15]. These troponin cutoff values lack the test characteristics for definitive diagnosis and may be clinically confounded by factors such as renal clearance [16].

Since both natriuretic peptides and cardiac troponins are disproportionately elevated in patients with cardiac amyloidosis, it is not surprising that these two biomarkers are routinely incorporated into ATTR-CM risk scores.

One staging system derived from 360 patients with antemortem diagnosis of ATTRwt at the Mayo Clinic combines troponin and NT-proBNP (Table 1) [17]. This staging system was created using biomarker cutoffs of 0.05 ng/mL for Troponin T and 3000 pg/mL for NT-proBNP [17]. Stage I is defined as both biomarkers measuring below cutoff, Stage II as one of two biomarkers above either cutoff, and Stage III as both biomarkers above the cutoff [17]. The median survival for each stage at 4 years was 57%, 42%, and 18% for Stage I, Stage II, and Stage III, respectively [17]. While the lack of uniformity across troponin assays between health care systems has diminished the generalizability of this staging system, the strata remain informative for stratifying a patient's prognosis [18].

Gillmore et al. sought to refine the staging system by incorporating the estimated glomerular filtration rate (eGFR) [19]. This staging system derived from 869 patients with ATTR-CM at the UK National Amyloidosis Centre combines NT-proBNP and eGFR (Table 1). Stage 1 was defined as NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 mL/min, Stage II as meeting only

one (but not both) of these cutoffs, and Stage III as NT-proBNP > 3000 ng/L and eGFR < 45 mL/min [19]. The median survival for each stage was 69 months, 47 months, and 24 months for Stages I, II, and III, respectively [19].

Levels of NT-proBNP and cardiac troponin may be impacted by targeted treatment for ATTR-CM. For example, data from the Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy trial (ATTR-ACT) demonstrated a greater increase in NT-proBNP over 30 months for patients assigned to placebo compared with patients who were assigned to tafamidis [7••]. Among an unselected cohort of 72 patients with baseline and follow-up measurements of troponin following treatment with tafamidis, there was a non-significant increase in troponin from a baseline of 61.2 ± 3.8 to 66.9 ± 5.1 ($p = 0.057$) [20•]. However, there was no control group in this study, and this limitation identifies an unmet need to define changes in troponin levels during treatment with tafamidis.

In summary, NT-proBNP, troponin, and eGFR are non-specific surrogates for disease severity and progression that may be useful in ATTR-CM. Recent consensus by the European Society of Cardiology has adopted NT-proBNP and troponin into their criteria for disease progression in patients with ATTR-CM [21]. The ease of use and availability of these biomarkers makes them a reasonable choice for a universal measure of staging and progression.

## Transthyretin

TTR, also known as prealbumin, is a homotetrameric protein synthesized in the liver and choroid plexus that circulates in blood. Its primary function is to transport thyroxine and retinol through interactions with RBP4 [1]. ATTR pathogenesis occurs when the TTR tetramer destabilizes and dissociates into monomers. These amyloidogenic monomers misfold and subsequently aggregate to form amyloid fibrils which then deposit into tissues [22]. ATTR-CM occurs when TTR-based amyloid aggregates infiltrate myocardium. Destabilizing mutations in the TTR protein decrease the kinetic stability of the TTR tetramer which promotes amyloidogenesis. Thus, circulating TTR levels parallel TTR kinetic stability and may serve as indirect markers of ATTR-CM disease activity and response to targeted treatment.

The TTR assay quantifies TTR/prealbumin based on immunoturbidimetric assay via antibody recognition [23]. Normal serum TTR range is 18 to 45 mg/dL and can be affected by nutritional status, renal impairment, liver dysfunction, corticosteroid therapy, and chronic inflammatory states [23–26]. There are no current guidelines for the interpretation of TTR levels in the setting of these comorbidities.

Biochemically, patients with ATTRwt may have kinetically stable TTR, yet plasma TTR can be lower in these individuals, and lower circulating TTR is associated with shorter survival [1]. In this context, the precise etiology of lower circulating TTR may be less ATTR-specific and multifactorial. At present, there is no widely accepted staging system that utilizes TTR values. Serum levels of TTR in healthy adults range from 18 to 45 mg/dL and are dependent on age, race, nutritional status, and net state of inflammation [27]. Among 116 patients with

biopsy-proven ATTRwt, survival times were compared using a baseline TTR cutoff of ≥ 18 mg/dL versus < 18 mg/dL; the median survival was 4.1 years in the former group and 2.8 in the latter group [1]. Thus, these data suggest that lower TTR is associated with a more adverse prognosis in ATTRwt [1].

Data from population-based studies suggest that lower TTR is associated with higher risk of incident heart failure and may identify carriers of pathogenic *TTR* alleles. Greve et al. analyzed two similar population-based studies of the Danish population, the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS), comprising 16,967 individuals in total [28]. This analysis sought to evaluate the association of low plasma TTR with risk of incident heart failure. These investigators observed that a plasma TTR concentration at or below each cohort's $5^{th}$ percentile was associated with a ~ 40–60% greater relative risk of incident heart failure (hazard ratios: 1.6 in CGPS, 1.4 in CCHS)—possibly a link with ATTR-CM [28]. In these cohorts, carriers of destabilizing *TTR* variants had lower circulating TTR levels in comparison with wild-type, non-carriers. On the other hand, carriers of *TTR* variants that stabilize TTR had higher serum TTR levels and a had lower incidence of heart failure. For example, patients with the T119M TTR-stabilizing mutation had a 16.5% higher baseline concentration of TTR compared with wild-type, non-carriers [28]. The latter observation is similar to data presented by Hornstrup et al. which demonstrated that, in comparison with non-carriers ($N$ = 1615), TTR levels were ~ 17% higher in T119M *TTR* mutation carriers ($N$ = 35,183 μg/mL vs. 157 μg/mL, $p$ = 0.007) [29].

Circulating TTR levels may also distinguish carriers of destabilizing (i.e., amyloidogenic) or stabilizing *TTR* alleles from non-carriers. In one study of 47 Swedish carriers of the V30M *TTR* variant and 16 non-carrier controls from the same geographic area in northern Sweden, TTR levels were lower in V30M allele carriers compared with age-and sex-matched controls (16.8 vs. 22.0 mg/dL, $p$ = 0.005) [30]. Furthermore, lower circulating TTR does not appear to be genotype specific. Rather, it is related to the presence of structural stability conferred by the specific allele. For example, TTR levels were measured and compared in 828 Caucasian and 826 African-American individuals [31]. TTR levels were not associated with age, race, or sex [31]. Rather, it was more closely associated with genotype. There were 12 African-American V122I *TTR* carriers identified, and, in comparison with the other 814 African-American non-carriers, circulating TTR levels were lower than non-carriers (17.1 vs 22.9 mg/dL) [31].

Circulating TTR levels also vary for individuals receiving treatment for ATTR-CM or polyneuropathy and vary based on the method by which TTR amyloidogenesis is inhibited. The APOLLO Phase 3 trial was an 18-month-long randomized, double-blind, placebo-controlled trial among 225 patients treated with patisiran, an siRNA, versus controls [32••]. In the treatment arm, median reduction in the serum TTR level during the 18 months was 81% (range, – 38 to 95) and was similar across age, sex, or genotype [32••]. These observations are consistent with the effect of patisiran which halts the translation of TTR protein, thus leading to lower circulating TTR levels.

An alternative therapy is TTR stabilization with treatments like tafamidis or acoramidis. These drugs bind to the thyroxine binding sites in the TTR protein and prevent TTR tetramer dissociation—the rate-limiting step in amyloidogenesis. Gamino et al. evaluated 31 patients with ATTR-CM (25 ATTRwt and 6 ATTRv) treated with tafamidis, obtaining serum TTR before and after administrations of tafamidis for at least 1.7 months (52 days) [33•]. Prior to therapy, TTR levels were 20.6 ± 5.6 mg/dL and similar among ATTRwt and ATTRv patients [33•]. Post-treatment, TTR levels increased by a median of 40% ($p < 0.0001$) in the ATTRwt patients and a median of 37% ($p = 0.046$) in the ATTRv patients [33•]. In a similar study of 72 patients with ATTR-CM (67 ATTRwt and 5 ATTRv) who had TTR levels measured at tafamidis initiation and after 21 weeks, mean TTR level increased by 34.5% ($p < 0.0001$), representing an absolute increase in TTR levels from 21.8 mg ± 0.7 mg/dL to 29.3 ± 0.86 mg/dL [20•]. A novel TTR stabilizer, acoramidis (previously known as AG10), was studied in a Phase 2 clinical trial, and its efficacy was assessed by measuring circulating TTR levels in response to treatment. In this study (49 patients: 38 ATTRwt, 11 ATTRv), there was a 7% decrease in serum TTR in the untreated group, compared to a 36% increase in those treated in the lower dose group and a 51% increase in the higher dose group (both $p < 0.0001$ compared to placebo) by 28 days [34]. In aggregate, these observations suggest TTR levels may be surrogates of ATTR-CM therapeutic efficacy, but whether they are directly related to incremental clinical benefit is unknown.

## Retinol-Binding Protein 4 (RBP4)

Retinol-binding protein 4 (RBP4) transports retinol, or vitamin A, in the blood. RBP4 is synthesized in the liver and adipose tissue, excreted in the urine, and functions to stabilize the TTR tetramer [35, 36]. Amyloidogenic mutations of TTR stimulate RBP4 detachment, causing greater urinary excretion of RPB4 and consequently lower serum concentrations [35]. In addition, lower serum RBP4 concentrations may in turn destabilize TTR, but the direct implication on TTR amyloidogenesis is unclear [35, 37]. In patients with transthyretin amyloid polyneuropathy, TTR is highly correlated with circulating RBP4 ($r^2 = 0.89$, $p < 10^{-15}$) [38].

In addition, RPB4 may also have association with disease penetrance and symptom age at onset. Santos et al. analyzed 318 patients with V30M ATTR in Portugal via genotype analysis of several single-nucleotide polymorphisms (SNPs) of various genes, including those of *RBP4* [37]. In their analysis, 4 SNP variants of *RPB4* had statistically significant impact on age of ATTR onset: 2 SNPs were associated with later onset of disease (increasing age of onset by 10 and 19 years), while 2 other SNPs were associated with earlier age of onset (by 9 and 28 years) [37].

Arvanitis et al. have to evaluate the utility of RPB4 as a biomarker of risk in ATTR-CM [39, 40]. Their initial study compared 47 patients with heart failure found to have genetically normal TTR (nonamyloid controls) versus 27 patients with biopsy-confirmed ATTR-CM due to V122I *TTR* variant [39]. After controlling for demographic differences and confounding, serum RBP4 levels were lower in ATTR-CM patients compared with controls (31.7 vs 49.4 μg/mL, $p < 0.001$) [39]. In a second study by the same authors, 25 patients with biopsy-confirmed ATTR-CM due to the V122I *TTR* variant were compared with 50

non-amyloid heart failure patients, and patients with ATTR-CM had lower circulating RBP4 than controls [40]. Similar to circulating TTR, RPB4 may be a marker of ATTR-CM disease. However, whether this is incremental to TTR needs further study.

## Measurement of TTR Kinetic Stability

The rate-limiting step for ATTR pathogenesis is dissociation of the TTR tetramer [41]. Both wild-type and mutated TTR have a range of thermodynamic and kinetic stability [42, 43]. Thus, methods to measure kinetic stability may serve as a proxy for prediction of clinical disease or prognosis. Previously, the best available methods for assessing TTR kinetic stability were TTR immunoblotting or denaturation followed by immunoturbidity, methods that are limited by their assessment of stability in nonnative conditions and rigorous quantification of electrophoresis gels [44–46]. More recently, Rappley et al. proposed a reproducible approach for quantifying TTR tetramer kinetic stability directly in plasma via subunit exchange assay in buffer [46]. This novel approach allows for assessment under physiologic conditions and eliminates cumbersome difficulties of previous methods [46]. Measurement of subunit exchange in response to drug treatment is quantifiable and gives insight into relative drug potency [47]. Nelson et al. compared subunit exchange of ATTRwt plasma samples at set concentrations of TTR-stabilizing drugs (tafamidis, acoramidis, diflunisal, and tolcapone) [47]. Daily doses of tafamidis and acoramidis reduced the rate of wild-type TTR tetramer dissociation by ≥ 96% at mean peak plasma concentrations of ≈28 μM and ≈11 μM, respectively [47]. In sum, these studies suggest that subunit exchange quantification may allow for early risk assessment, prognostication, and assessment of treatment response. Whether this highly specialized test is scalable to the extent that it would influence clinical care is unknown.

## Nonnative Transthyretin and Peptide Probes

The protein species that result from the dissociation of the transthyretin tetramer into monomers, which subsequently misfold and aggregate, form a spectrum of aggregate structures including oligomers and amyloid fibrils; these species are collectively referred to as nonnative transthyretin (NNTTR) [43]. A recent study sought to investigate NNTTR's potential as a biomarker for both diagnostic and prognostic utility among V30M *TTR* carriers and wild-type *TTR* non-carriers. Plasma NNTTR was quantified using a newly developed sandwich ELISA. This novel assay repeatedly heated and cooled engineered monomeric TTR to induce NNTTR, which were then used to configure specific antibodies. The assay detected significant plasma levels of NNTTR in most pre-symptomatic V30M *TTR* carriers [43]. Notably, NNTTR was not detected in age-matched control plasma, as well as in other patients with polyneuropathy. Echoing prior observations, NNTTR levels were substantially reduced after initiation of tafamidis [43].

Direct detection methods for NNTTR are not without limitations. The highly dynamic and interconverting nature of amyloidogenic NNTTR species limits biophysical characterization of their structures [48]. Novel studies are underway that employ computational methods that track the dynamics of single molecules over time to better assess the early dynamics that result in nonnative monomeric conformations [48]. Molecular investigations suggest that

assembly of monomers, with nonnative interface along their β-strands, may enhance stability of misfolded amyloidogenic proteins [49].

Alternatively, NNTTR may be measured indirectly via the use of peptide probes [50]. Schonhoft et al. hypothesized that native TTR is more densely packed than NNTTR and developed peptide probes that integrated into the misfolded structures at defect sites not found in the native TTR [50]. These peptide probes thus allow for quantification of NNTTR irrespective of TTR genotype. In 32 ATTR patients (15 ATTRwt, 6 V122I, 4 T60A, 7 other), peptide probes identified increased NNTTR in patients with a primary neuropathy phenotype, but not in primary cardiomyopathy phenotypes [50]. Among 15 Portuguese V30M *TTR* patients with ATTR polyneuropathy, peptide probes were used to detect NNTTR at baseline and after therapy with tafamidis. After 12 months of treatment, there was a 180% decrease in NNTTR [50].

NNTTR is therefore quantifiable both directly and indirectly via peptide probes and is a specific biomarker whose reduction is positively correlated with improvement in neuropathic ATTR amyloidosis. TTR-stabilizing drugs decrease NNTTR, though larger prospective studies are needed to determine its clinical utility.

## Neurofilament Light Chain

Neurofilament is an intrinsic determinant of axonal caliber and conduction velocity in neurons [51]. One of the three major neurofilament components, neurofilament light chain (NfL) is released into the blood after axonal damage [52]. Elevated NfL has been associated with multiple neurogen-erative diseases [53, 54]. More recently, investigations have evaluated the association between cardiac amyloidosis and NfL. One single center analysis of 17 patients with ATTRv versus healthy controls found that mean values of NfL were significantly higher in the ATTRv cases (88.8 pg/mL vs. 18 pg/mL; $p < 0.0001$) [55]. In another study, Kapoor et al. compared NfL in 73 patients with pathogenic *TTR* mutations versus 16 healthy controls, with neuropathy impairment score (NIS) score measured in patients with symptomatic neuropathy [56]. There was a statistically significant, positive correlation between NIS and NfL ($rs(30 = 0.65$; $p < 0.0001$) [56].

A secondary analysis using plasma samples from the APOLLO trial found that NfL levels of healthy controls were fourfold lower than in patients with ATTRv amyloidosis with polyneuropathy [57]. NfL levels at 18 months increased with placebo (99.5 pg/mL vs 63.2 pg/mL, effect 36.3 pg/mL [16.5–56.1]) and decreased with patisiran treatment (48.8 pg/mL vs 72.1 pg/mL, effect − 23.3 pg/mL [− 33.4 to – 13.1]) from baseline. At 18 months, improvement in modified Neuropathy Impairment Score + 7 score after patisiran treatment significantly correlated with reduced NfL ($R = 0.43$ [0.29–0.55]) [57].

In sum, these observations support the positive correlation between neurofilament light chain and ATTR amyloidosis, making it a promising biomarker to detect polyneuropathy, facilitate an earlier ATTR diagnosis, and monitor disease progression. However, whether NfL has any utility in cardiac ATTR-CM is unknown.

## Serum Free Light Chains

When considering a diagnosis of cardiac amyloidosis, light-chain amyloidosis (AL) and ATTR are the two most common amyloid types. Serum free light chain (sFLC) tests can aid in distinguishing these two types of amyloidosis. Human antibodies are composed of two heavy chains and two light chains; in humans, these light chains are kappa and lambda. sFLC tests measure the amount of kappa, lambda, and their relative ratio. An abnormal kappa-to-lambda ratio may indicate the presence of AL. Because AL is more aggressive than ATTR, ruling in or ruling out AL amyloidosis is crucial. As such, sFLC are essential for the initial workup of amyloidosis. Furthermore, a normal kappa-to-lambda ratio is a key component to ruling out AL [58]. Normal sFLC levels have a negative predictive value of 89% for AL amyloid, so a negative sFLC may allow for a nonbiopsy (radionuclide scintigraphy only) diagnosis of ATTR-CM [59, 60]. On the other hand, abnormal sFLC levels cannot reliably distinguish between AL versus ATTR-CM and may indicate the presence of AL. Thus, a tissue biopsy is indicated to confirm diagnosis [58].

Biopsy is needed when sFLC levels are abnormal because confounding factors may lead to elevated sFLC and/or an abnormal kappa:lambda ratio in ATTR-CM. For example, there is a high prevalence of coexistent monoclonal gammopathy of undetermined significance (MGUS) in patients with ATTR-CM [61]. In a retrospective analysis of 226 patients with biopsy-proven ATTR-CM (155 ATTRwt, 71 ATTRv), 39% of those with ATTRwt and 49% of those with ATTRv had a concomitant MGUS [61]. Additionally, sFLC are excreted by the kidneys and can be elevated in patients with ATTR-CM and chronic kidney disease (CKD) [62].

## Conclusion

ATTR-CM is an increasingly recognized cause of morbidity and mortality, and there remains substantial delay between initial symptoms and diagnosis. With the recent emergence of targeted therapies, now proven to reduce morbidity and mortality, there is an imperative to narrow the gap between subclinical disease and time to diagnosis and intervention. There is a need for biomarkers that are effective surrogates for diagnosis, prognosis, and response to treatment. Although conventional heart failure biomarkers like natriuretic peptides and cardiac troponin are associated with risk, they are not specific to ATTR-CM. Alternatively, scientific evidence for the utility of ATTR-specific biomarkers such as TTR, RBP4, TTR kinetic stability, or NNTTR is growing. Yet, numerous questions about their clinical utility remain.

## Conflict of Interest

Justin Grodin received research funding from the Texas Health Resources Clinical Scholarship and the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R01HL160892 and receives consulting income from Pfizer and Eidos Therapeutics. Caleb Hood declares no conflict of interest. Nicholas Hendren declares no conflict of interest. Rose Pedretti declares no conflict of interest. Lorena Saelices declares no conflict of interest. Lori Roth has done consulting work with Eidos Therapeutics.

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• Of importance

•• Of major importance


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**Table 1**

Prognostic staging systems for ATTR-CM

| | Mayo staging system (17) | UK staging system (19) |
|---|---|---|
| Population | ATTRwt-CM | ATTRwt-CM and ATTRv-CM |
| Parameters | Troponin T≤ 0.05 ng/mL<br>NT-proBNP ≤ 3000 pg/mL | NT-proBNP ≤ 3000 pg/mL<br>eGFR ≥ 45 mL/min |
| Median survival in months from diagnosis | | |
| Stage 1: Both parameters normal | 66 | 69.2 |
| Stage 2: 1 parameter abnormal | 40 | 46.7 |
| Stage 3: Both parameters abnormal | 20 | 24.1 |

ATTR-CM transthyretin amyloid cardiomyopathy, ATTRv-CM variant transthyretin amyloid cardiomyopathy, ATTRwt-CM wild-type transthyretin amyloid cardiomyopathy, eGFR estimated glomerular filtration rate, NT-proBNP N-terminal pro-B-type natriuretic peptide