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Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System

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ABSTRACT

BACKGROUND Wild-type transthyretin cardiac amyloidosis (ATTRwt) is increasingly recognized as an important cause of heart failure.

OBJECTIVES The purpose of this study was to determine the natural history of ATTRwt and the predictors of survival.

METHODS We retrospectively reviewed patients diagnosed with ATTRwt at the Mayo Clinic through 2013 and recorded clinical data and survival data. Factors affecting overall survival (OS) were identified, and a prognostic staging system was developed.

RESULTS The median age of the 360 patients diagnosed before death was 75 years (range: 47 to 94 years), and 91% were male. Presenting signs and symptoms included dyspnea or heart failure in 67% and atrial arrhythmias in 62%. Median OS from diagnosis was 3.6 years and did not change over time. Multivariate predictors of mortality included age, ejection fraction, pericardial effusion, N-terminal pro–B-type natriuretic peptide, and troponin T. A staging system was developed that used thresholds of troponin T (0.05 ng/ml) and N-terminal pro–B-type natriuretic peptide (3,000 pg/ml). The respective 4-year OS estimates were 57%, 42%, and 18% for stage I (both values below cutoff), stage II (one above), and stage III (both above), respectively. Stage III patients were at an increased risk of mortality after adjustment for age and sex compared with stage I patients (hazard ratio: 3.6; $p < 0.001$).

CONCLUSIONS The natural history of ATTRwt is poor. We report a novel cardiac biomarker staging system that enables risk stratification in an era of emerging treatment strategies. (J Am Coll Cardiol 2016;68:1014–20)

The first report of age-related deposition of amyloid in the heart and use of the term *senile amyloid* is attributed to Soyka in 1876 (1). Subsequent autopsy studies reported a wide variation in the prevalence of amyloid in the hearts of elderly people, ranging from 2% to 80% depending on the techniques used for diagnosis and the cohort studied (2–5). Cardiac amyloid deposition was believed to be of dubious clinical significance, and it was often considered an incidental finding unlikely to cause cardiac dysfunction (6). Until the 1980s, all reported cases of senile cardiac amyloid were diagnosed after death (7). As late as 1988, our coauthors, Drs. Kyle and Gertz, sought to determine "whether senile cardiac amyloidosis is responsible for clinically-important

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disease and whether it can be recognized in the living patient" (7).

Early reports of cardiac amyloid in the elderly described the atria as the most common site, often with minor deposits (4). When biochemical techniques became available to determine the composition of amyloid fibrils, it became clear that there were 2 distinct forms of amyloid in the senescent heart (8). Isolated atrial amyloid was found to be derived from atrial natriuretic factor. The diffuse form of amyloid involving the ventricular myocardium (also found in the atria, valves, and cardiac vessels) was found to be related to pre-albumin and was termed *senile cardiac amyloid* (8). Eventually it was recognized that the deposits in senile cardiac amyloid were derived from transthyretin (TTR) (9). Although initially thought to be localized to the heart, it was recognized that wild-type TTR amyloid could be found in extracardiac tissue, which prompted use of the term *senile systemic amyloidosis* (10). The term *ATTRwt* (wild-type TTR cardiac amyloidosis) is now preferred to indicate that deposits in age-related cardiac amyloid are composed of nonmutated (wild-type) TTR, in contrast to familial cardiac amyloid caused by TTR mutation (ATTRm).

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In recent years, ATTRwt, once thought to be an incidental pathological finding, has been increasingly recognized as an important cause of heart failure and cardiac arrhythmias, especially in men over the age of 60 years (11–14). Recent studies have demonstrated an increasing rate of diagnosis of cardiac amyloid caused by ATTRwt compared with immunoglobulin light chain (AL) (13–15). Several reports have suggested that ATTRwt could be an important cause of heart failure with preserved ejection fraction (HFpEF) (16). A recent study found that 13% of patients over the age of 60 years with HFpEF and left ventricular wall thickness of 12 mm or more had a positive DPD (^{99}mTc-3,3-disphosphono-1,2-propanodicarboxylic acid scintigraphy) scan, a finding highly suggestive of ATTRwt (17). Given the burden of heart failure in society and the economic implications for health-care delivery, recognition of ATTRwt will likely continue to be of increasing importance. As emerging therapies are currently being studied in multiple clinical trials, the diagnosis of ATTRwt will no longer be purely academic. The purpose of this study was to determine the natural history and predictors of survival in a large series of patients with ATTRwt.

METHODS

A retrospective review of all patients with a diagnosis of ATTRwt seen at Mayo Clinic, Rochester, Minnesota, from 1965 through 2013 was performed with our institutional amyloid database. The Mayo Clinic Institutional Review Board approved the study. Clinical and laboratory findings, including demographics, symptoms, echocardiography, electrocardiography, presence or absence of atrial arrhythmias at diagnosis, laboratory studies, genotyping, and survival, were assessed. Vital status was determined with use of the clinical record, Social Security Death Index, Accurint, and yearly letters sent to patients. The database was closed to follow-up vital status as of April 30, 2015.

PATIENTS. Patients were included if they had the following: 1) tissue confirmation of amyloid from cardiac biopsy or autopsy, or a positive biopsy of an extracardiac site in the presence of typical echocardiographic and clinical features; and 2) a tissue diagnosis of ATTR in the absence of a TTR mutation or a family history consistent with hereditary ATTR. Typing was performed by immunohistochemistry or laser microdissection mass spectrometry, according to the era of diagnosis. Genotyping to exclude TTR mutation was performed in 190 (53%) of the 360 patients diagnosed before death. Patients without tissue confirmation of amyloid deposition, either by endomyocardial biopsy or extracardiac tissue biopsy, were excluded. Patients with typical clinical and imaging findings, including those with technetium pyrophosphate scintigraphy consistent with ATTR, were excluded if tissue confirmation of amyloid was not available.

BIOMARKERS. The troponin T assay was performed with sensitive second-generation assays (Roche Diagnostics, Indianapolis, Indiana). Levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured with an electrochemiluminescence sandwich immunoassay on an Elecsys System 2010 (Roche Diagnostics).

STATISTICAL METHODS. Baseline characteristics of subjects were characterized by number and percentage or median and interquartile range (IQR) for continuous variables. Characteristics were compared between patients diagnosed before and after death by use of Pearson chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light-chain amyloidosis

ATTRm = familial (mutant) transthyretin amyloidosis

ATTRwt = wild-type transthyretin amyloidosis

CI = confidence interval

HFpEF = heart failure with preserved ejection fraction

HR = hazard ratio

IQR = interquartile range

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OS = overall survival

TTR = transthyretin

The mortality endpoint was defined using time to death for deceased subjects and time to last known follow-up for those last known to be alive. Subjects who were diagnosed after death were excluded from survival analyses given the post-mortem timing of diagnosis. Kaplan-Meier methods were used to plot survival by time, and the log-rank test was used to test for differences between groups. Expected survival was computed with use of age- and sex-matched rates from the U.S. white population and was compared with a 1-sample log-rank test.

Cox proportional hazards regression was used to test for association of baseline variables with mortality. Results of these models are summarized as hazard ratio (HR) and 95% confidence interval (CI). To examine the sensitivity of cutpoints to individual data points, a 4-fold cross-validation approach was used. Subjects were randomly divided into 4 groups, and 1 group was systematically omitted from analyses. The approach of Contal and O'Quigley (18) was used to find the optimal cutpoints for NT-proBNP and troponin T within each subset. Because similar cutpoints were found across all subsets, a representative cutpoint was chosen and is reported for the whole group. Survival c-statistics were calculated to measure the discriminatory ability of the models. A "leave 1 out" cross-validation approach was used to calculate cross-validated c-statistics and assess stability of parameter estimates. Two-sided tests were used for all analyses, and $p \leq 0.05$ was considered significant. SAS version 9.4 (Cary, North Carolina) was used for all analyses.

RESULTS

Fifty-four patients were diagnosed with ATTRwt post-mortem, including all patients diagnosed before 1980 (data not shown). Patients diagnosed post-mortem were older (median [range]: 87.0 [69 to 99] years vs. 75.5 [47 to 94] years; $p \leq 0.001$) and more likely to be female (31% vs. 9%; $p \leq 0.001$) than those diagnosed before death. The demographics and baseline characteristics of the 360 patients diagnosed with ATTRwt before death are outlined in Table 1. The majority (93%) of patients with an antemortem diagnosis were Caucasian males over the age of 70 years. The youngest patient was diagnosed at age 47 years and underwent heart transplantation at 48 years of age; there was no evidence of TTR mutation by mass spectrometry of either the endomyocardial biopsy tissue or the explanted heart or by DNA sequencing. Four patients were diagnosed in the sixth decade of life and 61 in the seventh decade. Mass spectrometry tissue typing was performed in 158 (44%). At the time of diagnosis, clinical symptoms of dyspnea were reported in 67% of patients and edema in 53%, and a diagnosis of heart failure was recorded in 67%, atrial fibrillation/flutter in 62%, and carpal tunnel syndrome in 39%.

TABLE 1 Baseline Characteristics of Patients With Antemortem Diagnosis of ATTRwt (N = 360)

	n or n (%)	Median (Q1, Q3)
Age, yrs		75.5 (71.0, 81.0)
<60	5 (1.3)	
61–70	61 (17)	
71–80	177 (49)	
80–90	114 (32)	
> 90	3 (1)	
Male	327 (91)	
Decade of diagnosis		
1980–1989	12 (3)	
1990–1999	63 (18)	
2000–2009	137 (38)	
2010–2013	148 (41)	
Systolic blood pressure, mm Hg	324	120.0 (104.0, 130.0)
Diastolic blood pressure, mm Hg	324	70.0 (60.0, 78.0)
Serum creatinine, mg/dl	333	1.3 (1.1, 1.6)
Troponin T, ng/ml	195	0.04 (0.02, 0.08)
>0.05 ng/ml	69 (35)	
NT-proBNP, pg/ml	191	2838.0 (1697.0, 6062.0)
>3,000 pg/ml	93 (49)	
BNP, pg/ml	86	457.0 (272.0, 850.0)
Serum albumin, g/dl	238	3.4 (3.1, 3.7)
Uric acid, g/dl	223	7.5 (6.0, 9.1)
Biopsy site, positive for amyloid		
Endomyocardial biopsy	260 (72)	
Bone marrow biopsy	61 (17)	
Fat aspirate	47 (13)	
Carpal ligament biopsy	9 (3)	
Small intestine biopsy	11 (3)	
Rectal biopsy	4 (1)	
ECG rhythm	347	
Atrial fibrillation/flutter	215 (62)	
Sinus/atrial paced rhythm	132 (38)	

ATTRwt = wild-type transthyretin cardiac amyloidosis; BNP = B-type natriuretic acid; ECG = electrocardiogram; NT-proBNP = N-terminal pro–B-type natriuretic acid; Q1, Q3 = first and third quartiles.

Echocardiographic data of patients diagnosed before death are shown in Table 2. As expected, patients had markedly elevated left ventricular mass index (median: 160 g/m^2; IQR: 132 to 195 g/m^2) with restrictive filling (median E/A ratio: 2.0 [IQR: 1.0 to 3.0]; median mitral deceleration time: 174 ms [IQR: 148 to 195 ms]), and 56% had a documented pericardial effusion. Left ventricular ejection fraction (LVEF) at diagnosis was <50% in 151 patients (45%) and <40% in 93 (27.9%).

Patients aged 70 years or older at diagnosis had higher troponin T (median: 0.04 [IQR: 0.02 to 0.09] ng/ml) than those age <70 years (0.02 [IQR: 0.01 to

0.04] ng/ml; $p < 0.001$), had higher uric acid (7.7 [IQR: 6.1 to 9.1] g/dl vs. 6.5 [IQR: 5.4 to 8.4] g/dl; $p = 0.010$) and lower left atrial volume (47.0 [IQR: 41.0 to 56.0] ml/m^2 vs. 53.0 [IQR: 47.5 to 63.5] ml/m^2; $p = 0.010$), and less commonly had endomyocardial biopsy performed (205 [70%] vs. 55 [83%]; $p = 0.026$).

Ninety-seven percent of patients not known to be deceased had follow-up within 3 years before database censorship, and 70% had follow-up within 2 years. At a median follow-up of 2.6 years, 240 patients had died. The overall median survival was 3.6 years and was similar throughout the time period of the study (Figure 1). Troponin T was measured in 195 patients within 3 months of diagnosis and NT-proBNP in 191, and both were measured in 154 patients. Given the predictive power offered by cardiac biomarkers among patients with AL amyloidosis, we explored thresholds of troponin T and NT-proBNP that would be prognostic in ATTRwt. To establish optimal cutpoints, cross-validation was used in combination with the method of Contal and O'Quigley. Across the 4 cross-validation sets, this method resulted in similar cutpoints for troponin T, and a cutpoint of 0.05 μg/l was found to be associated with death, with an age- and sex-adjusted HR of 2.34 (95% CI: 1.46 to 3.76; $p < 0.001$) (Central Illustration). For NT-proBNP, similar cutpoints were also found across the cross-validation sets, and a cutpoint of 3,000 ng/l was found to be associated with death, with an age- and sex-adjusted HR of 2.2 (95% CI: 1.36 to 3.60) (Central Illustration). A staging system was then created that used cardiac biomarker cutoffs of 0.05 ng/ml for troponin T and 3,000 pg/ml for NT-proBNP, with stage I defined as both values being below the cutoff, stage II as 1 value being above, and stage III as both values being above, as shown in the Central Illustration. The respective 4-year OS rates were 57%, 42%, and 18% ($p < 0.001$). Stage III patients demonstrated a median survival of 20 months (HR vs. stage I: 3.6; 95% CI: 2.02 to 6.42; $p < 0.001$).

Other univariate predictors of survival included age, ejection fraction, mitral deceleration time, estimated right atrial and pulmonary artery systolic pressures, cardiac index, stroke volume index, serum uric acid, and the presence of a pericardial effusion. The septal and posterior wall thicknesses, left ventricular mass index, relative wall thickness, left ventricular systolic and diastolic dimensions, left atrial volume index, and blood pressures were not predictive of survival. In a multivariate analysis, age (HR: 1.07; 95% CI: 1.03 to 1.12), ejection fraction <50% (HR: 1.76; 95% CI: 1.07 to 2.88), NT-proBNP >3,000 pg/ml (HR: 1.57; 95% CI: 0.93 to 2.63), and troponin T ≥0.05 ng/ml (HR: 2.27; 95% CI: 1.36 to 3.77) remained predictive of survival. In an alternate multivariate analysis that included stage, the estimates were similar for age (HR: 1.08; 95% CI: 1.04 to 1.12) and ejection fraction <50% (HR: 1.85; 95% CI: 1.12 to 3.06), whereas stage III subjects were found to be at a 3.4-times higher risk than stage I subjects (HR: 3.41; 95% CI: 1.89 to 6.16), and stage II subjects were not significantly different compared with stage I (HR: 1.24; 95% CI: 0.66 to 2.33).

TABLE 2 Echocardiographic Findings (Within 6 Months of Diagnosis)

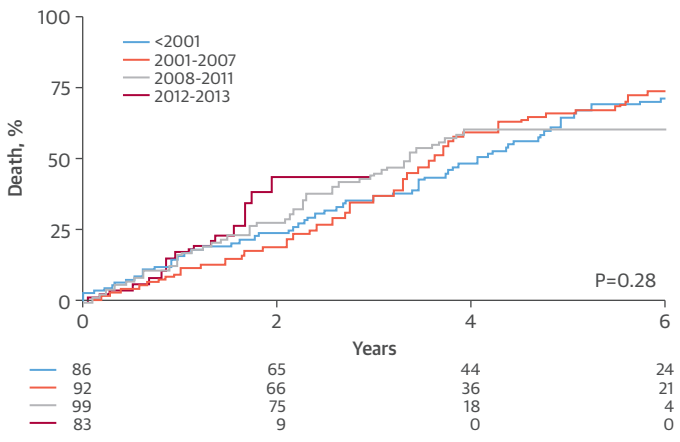
	Observations (n)	Median (Q1, Q3)	Normal
LV end-diastolic diameter, mm	223	46.0 (43.0, 51.0)	42–57
LV septal wall thickness, mm	318	17.0 (15.0, 20.0)	6–11
LV posterior wall thickness, mm	221	15.0 (13.0, 18.0)	6–11
Relative wall thickness, mm	218	0.7 (0.6, 0.8)	0.24–0.42
Ejection fraction, %	333	51.0 (38.0, 61.8)	>55
LV mass index, g/m^2	282	160.0 (132.0, 195.0)	60–115
Stroke volume index, cc/m^2	180	37.0 (30.0, 44.0)	32–54
Cardiac index, L/min/m^2	198	2.5 (2.1, 2.9)	2.6–4.2
Mitral deceleration time, ms	269	174.0 (148.0, 195.0)	171–229
Mitral E/A ratio	126	2.0 (1.0, 3.0)	0.6–1.3
LA volume index, cc/m^2	166	48.0 (42.0, 57.0)	16–31
Estimated pulmonary artery systolic pressure, mm Hg	217	43.0 (34.0, 50.0)	<35
Pericardial effusion, n (%)	321	181 (56%)	

Normal values are general range for men age >60 years.
LA = left atrial; LV = left ventricular; other abbreviations as in Table 1.

DISCUSSION

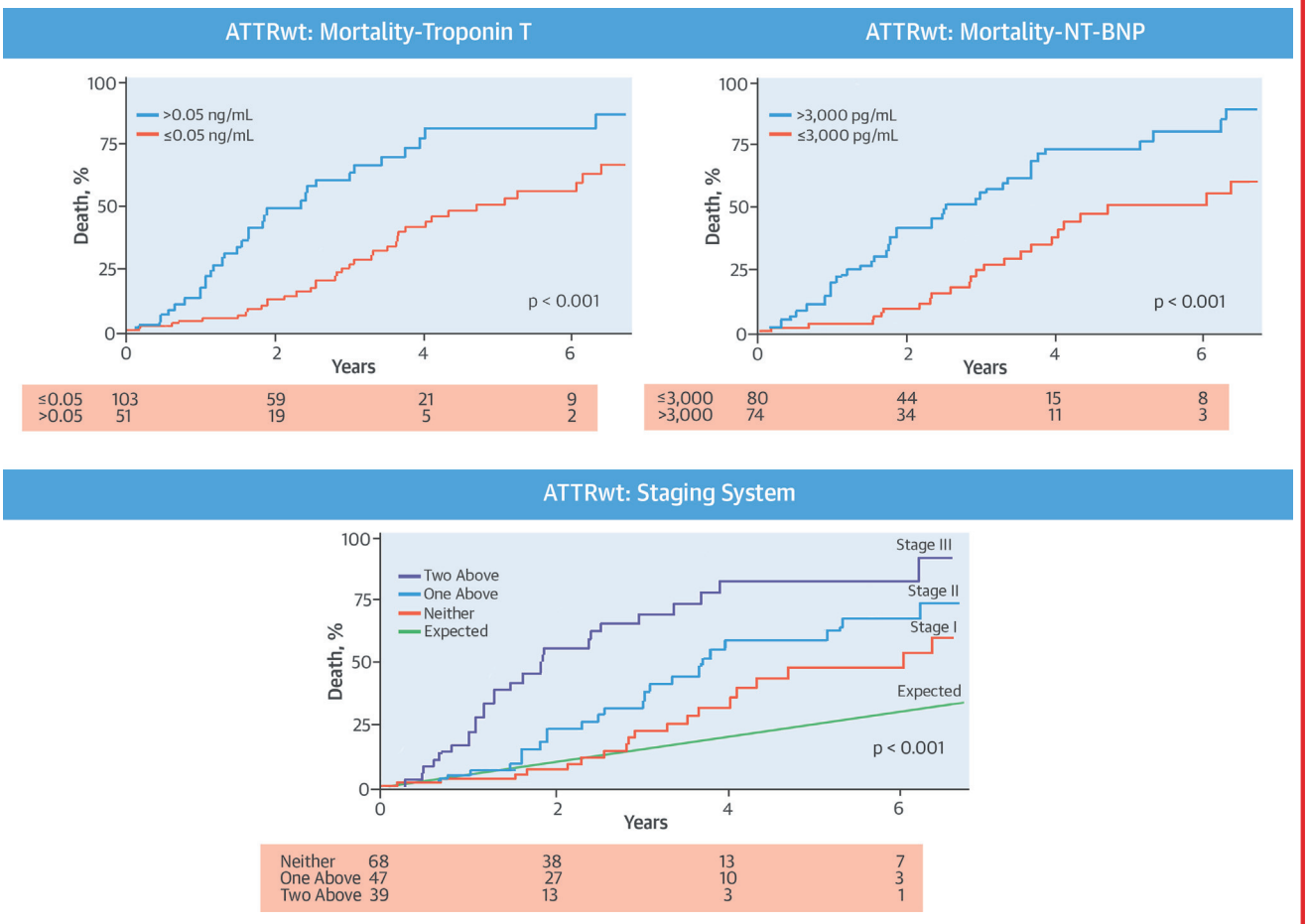
ATTRwt has been increasingly recognized as an important and often undiagnosed cause of heart failure in the elderly (12). Our study, which is

FIGURE 1 Mortality According to Year of Diagnosis



Numbers below the plot represent number of subjects at risk at each time point.

CENTRAL ILLUSTRATION **Natural History of ATTRwt: Mortality by Soluble Cardiac Biomarkers**



Grogan, M. et al. J Am Coll Cardiol. 2016;68(10):1014-20.

(Top left) Death rates based on troponin T cutpoint of 0.05 ng/ml. Numbers below the plot represent number of subjects at risk at each time point. The age- and sex-adjusted hazard ratio (HR) was 2.34 (95% confidence interval [CI]: 1.46 to 3.76) with a c-statistic of 0.72 (95% CI: 0.66 to 0.78). Cross-validated c-statistic was 0.71 (95% CI: 0.65 to 0.78). **(Top right)** Death rates based on N-terminal pro-B-type natriuretic peptide (NT-proBNP) cutpoint of 3,000 pg/ml. Numbers below the plot represent number of subjects at risk at each time point. The age- and sex-adjusted HR was 2.22 (95% CI: 1.36 to 3.60) with a c-statistic of 0.72 (95% CI: 0.65 to 0.78). Cross validated c-statistic was 0.71 (95% CI: 0.65 to 0.78). **(Bottom)** Death rates based on staging system, overlaid with expected survival based on age and sex. Numbers below the plot represent numbers of subjects at risk at each time point. The age- and sex-adjusted HR was 1.42 (95% CI: 0.79 to 2.57) for 1 above and 3.60 (95% CI: 2.02 to 6.42) for 2 above, with a c-statistic of 0.74 (95% CI: 0.68 to 0.80). Cross-validated c-statistic was 0.73 (95% CI: 0.67 to 0.79). ATTRwt = wild-type transthyretin cardiac amyloidosis.

the largest series reported to date, consists of a well-characterized cohort of patients with ATTRwt, diagnosed by endomyocardial biopsy in more than 70%. There are 3 novel findings of this report. First, we found a wider age range of affected individuals than previously reported. Second, significantly more female patients were diagnosed after death than before death, which suggests that ATTRwt might be more common in women than previously recognized. Third, we describe a simple cardiac biomarker staging system to risk stratify patients.

Although most of the recent literature has referred to ATTRwt disease of elderly males, even early reports of "senile" cardiac amyloidosis included patients as young as 57 years (19). The median age of 75.5 years in our series is very similar to recent reports (13,14); however, our youngest patient was 47 years old at diagnosis, which challenges the concept that this is a disease exclusively of the elderly. Although age at diagnosis did not change significantly during the time period of this study, the age at diagnosis could decrease in the future with increased

awareness and expanding diagnostic techniques, such as nuclear scintigraphy. Similar to other centers (13,14), we have experienced a dramatic increase in ATTRwt patients, with 41% of our patients being diagnosed in the last 3 years of the study.

In our series, only 9% of patients diagnosed with ATTRwt before death were women, consistent with the male preponderance noted in multiple recent series (11,13,14); however, 31% of patients diagnosed post-mortem in our study were women, similar to the sex prevalence reported in previous autopsy series. One of the largest autopsy series was that of Hodkinson and Pomerance (4), who found amyloid deposits in almost 50% of an unselected autopsy series of people over the age of 60 years, with a prevalence of 56% in women compared with 37.5% in men. However, women more commonly had atrial amyloid, likely isolated atrial amyloid caused by atrial natriuretic factor deposition, rather than ATTR. Although tissue typing was not available, it is noteworthy that 29% of the women in that series had ventricular amyloid deposits. A recent series of HFpEF patients over the age of 60 years with left ventricular wall thicknesses >12 mm demonstrated a positive DPD scan consistent with a presumptive diagnosis of ATTRwt in 13%, without a sex difference (17). Our results also suggest that ATTRwt might be more common in women than has been recognized previously.

These data support the notion that ATTRwt is underdiagnosed. A potential clue to consider the diagnosis could be nonvalvular atrial fibrillation. Nearly two-thirds of patients had atrial arrhythmias at the time of diagnosis, a statistic that is striking and similar to recent reports (13,14). Routine long-term electrocardiographic monitoring was not performed, and thus, the true incidence of atrial fibrillation was likely higher. Another important finding is that although cardiac amyloid, including ATTRwt, is generally considered to be a condition of preserved ejection fraction, both our data and those of Connors et al. (14) demonstrate that the range of LVEF at presentation among patients with ATTRwt is wide. Of note, almost one-half of our patients had LVEF of <50% at diagnosis, which emphasizes the point that LVEF might be reduced in ATTRwt, although left ventricular chamber size is typically normal.

As clinicians become more attuned to the diagnosis of ATTR, presumably the diagnosis will be made earlier, and the anticipated overall survival rates will improve because of lead-time bias from the current median of 3.6 years. Identifying factors that differentiate patients' risk is therefore imperative. On the basis of the utility of troponin and NT-proBNP to predict outcomes in AL amyloidosis (20), we developed a staging system for patients with ATTRwt, which demarcates 3 populations of patients with different OS. Patients with stage III disease (troponin T >0.05 ng/mg and NT-proBNP >3,000 pg/ml) had a median survival of only 20 months in contrast to a median OS of 66 and 40 months for patients with stage I and II disease, respectively. Although we could not demonstrate a statistically significant difference between stages I and II, we speculate that this is because of the sample size. Although a number of other risk factors have been identified by us and by others (14) (age, uric acid, relative wall thickness, ejection fraction, and the presence of a pericardial effusion), we believe that this simple biomarker system will be as helpful for guiding ATTRwt patients as the comparable biomarker systems have been for patients with AL (21–23). The appeal of a biomarker staging system includes widespread availability and the lack of reliance on expensive cardiac imaging tests. This novel staging system should help guide clinical decision making and clinical trial enrollment and interpretation.

STUDY LIMITATIONS. Limitations of our study include the retrospective nature, incomplete data for some variables, and lack of New York Heart Association functional classification. Details regarding a history of hypertension were not available; however, the median systolic and diastolic blood pressures at diagnosis were not elevated. Not all patients had genotyping, largely because of unavailability in earlier decades. Similarly, mass spectrometry was not performed in all patients, and earlier techniques of tissue typing were less reliable. A subset of patients with both cardiac biomarkers available within 3 months of diagnosis was used for development of the staging system.

CONCLUSIONS

ATTRwt, once thought to be an incidental finding of little clinical significance, is increasingly recognized as an important cause of heart failure and atrial arrhythmias. Our study demonstrates that ATTRwt is associated with a poor prognosis and challenges the assumption that this is a disorder limited to elderly males. A simple cardiac biomarker staging system provides important prognostic information and allows for risk stratification in an era of rapidly emerging therapeutic strategies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with heart failure caused by wild-type transthyretin cardiac amyloidosis, elevated blood levels of troponin and NT-proBNP are associated with a poor prognosis.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the treatment implications of various biomarker profiles in patients with heart failure caused by wild-type transthyretin cardiac amyloidosis.

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KEY WORDS amyloidosis, senile systemic amyloidosis, transthyretin, wild-type