ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 772–779
Published online 19 June 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12308

ORIGINAL RESEARCH ARTICLE

Features of atrial fibrillation in wild-type transthyretin cardiac amyloidosis: a systematic review and clinical experience

Yuliya Y. Mints[1], Gheorghe Doros[2], John L. Berk[1,3], Lawreen H. Connors[3,4] and Frederick L. Ruberg[3,5]*

[1]*Department of Medicine, Boston Medical Center, Boston, MA, USA;* [2]*Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA;* [3]*Amyloidosis Center, Boston University School of Medicine, Boston Medical Center, Boston, MA, USA;* [4]*Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston Medical Center, Boston, MA, USA;* [5]*Section of Cardiovascular Medicine, Department of Medicine, Boston University School of Medicine, Boston Medical Center, Boston, MA, USA*

Abstract

Aims Wild-type transthyretin (ATTRwt) cardiac amyloidosis has emerged as an important cause of heart failure in the elderly. Atrial fibrillation (AF) commonly affects older adults with heart failure and is associated with reduced survival, but its role in ATTRwt is unclear. We sought to explore the clinical impact of AF in ATTRwt.

Methods and results Patients with biopsy-proven ATTRwt cardiac amyloidosis (n = 146) were retrospectively identified, and clinical, echocardiographic, and biochemical data were collected. Patients were classified as AF or non-AF and followed for survival for a median of 41.4 ± 27.1 months. Means testing, univariable, and multivariable regression models were employed. A systematic review was performed. AF was observed in 70% (n = 102). Mean age was similar (AF, 75 ± 6 vs. non-AF, 74 ± 5 years, P = 0.22). Anticoagulant treatment of patients with AF was as follows: 78% warfarin, 17% novel anticoagulant, and 6% no anticoagulation. Amiodarone was prescribed to 24%. There were no differences in left ventricular ejection fraction (P = 0.09) or left atrial volume (P = 0.87); however, mean diastolic dysfunction grade was higher in AF (mean 2.7 ± 0.5 vs. 2.4 ± 0.5, P = 0.01). While creatinine (P = 0.52) and B-type natriuretic peptide (P = 0.48) were similar, patients with AF had lower serum transthyretin concentrations (221 ± 51 vs. 250 ± 52 μg/mL, $P < 0.01$). Survival between groups was similar (P = 0.46).

Conclusions These data provide an evidence basis for clinical management and demonstrate that AF in ATTRwt does not negatively impact survival. Further analysis of the relationship between transthyretin concentration and AF development is warranted.

Keywords Cardiac amyloidosis; Transthyretin; Atrial fibrillation

Received: 1 February 2018; Revised: 6 April 2018; Accepted: 30 April 2018
**Correspondence to: Frederick L. Ruberg, Section of Cardiovascular Medicine, Boston Medical Center, 88 E. Newton Street, Boston, MA 02118, USA. Tel: 617 638 8968; Fax: 617 638 8969. Email: frruberg@bu.edu*

Introduction

Wild-type transthyretin amyloidosis (ATTRwt) is an underappreciated cause of cardiomyopathy that results from deposition of misfolded transthyretin (TTR) protein fibrils. TTR, also commonly known as prealbumin and synthesized by the liver, is a serum transport protein for thyroxine and retinol. Amyloidosis resulting from TTR deposition (ATTR) is categorized by the genetic structure of the protein. ATTRwt (wild-type, formerly known as senile systemic amyloidosis) occurs virtually exclusively in the elderly, whereas ATTRm (mutant) can manifest earlier in life clinically as familial amyloid polyneuropathy or cardiomyopathy. Autopsy series demonstrate myocardial TTR amyloid deposition in up to 25% of elderly men,[1] and the clinical phenotype of ATTRwt has strongly been associated with heart failure in the elderly.[2,3]

Given the advanced age of ATTRwt patients, it is not at all surprising that atrial fibrillation (AF)[4] is the most commonly observed heart rhythm disturbance associated with this disease. While not directly compared, data suggest that AF

may be more common in ATTRwt (62–67%)[5,6] than other aetiologies of heart failure (13–27%).[7] Similarly, while there is a well-recognized association between AF and reduced survival among patients with heart failure,[8] this interaction has not been explored in ATTRwt. Information regarding AF duration in respect to paroxysmal vs. long standing has not been reported. Thus, there currently are limited data available regarding medical management patterns and clinical impact of AF in ATTRwt. Such guidance would be clinically important as management of AF in cardiac amyloidosis presents a challenge given that several commonly administered medications to treat AF are poorly tolerated in ATTRwt, such as calcium channel blockers[9–11] and digoxin.[12]

Therefore, we sought to define the clinical characteristics of patients with ATTRwt cardiac amyloidosis who concurrently have AF. We hypothesized that patients with AF would have different biochemical and cardiac structural/functional profiles, as well as different outcomes with respect to survival. Our second objective was to define practice patterns in management (anticoagulation strategy and rate/rhythm control approach), to determine safety outcomes and tolerance of administration. Finally, we performed a systematic search to review existing literature regarding AF in ATTRwt with respect to outcomes and management.

Methods

Study population

We conducted a retrospective cohort study of n = 146 patients with biopsy and genetically proven ATTRwt cardiac amyloidosis who were referred to the Boston University Amyloidosis Center between June 1994 and January 2014. Study procedures and initial observations were reported previously.[5] In brief, all patients had a histologic diagnosis of amyloidosis from tissue biopsy with confirmation of TTR in the amyloid deposits by immunohistochemistry, immunogold electron microscopy, or mass spectrometry. Available clinical data were collected from medical records and included medical history, physical examination, and laboratory studies of organ function. Date of death was obtained from medical records or publicly available databases. Participants provided written informed consent to participate in the study, which was approved by the Boston University Medical Campus Institutional Review Board, and conformed with the principles of the Declaration of Helsinki.

Cardiac imaging

Two-dimensional, colour flow, and spectral Doppler echocardiographic imaging was performed from standard parasternal, apical, and subcostal views. Standard American Society of Echocardiography reporting parameters for cardiac structure and function were measured, and images were post-processed for longitudinal strain using speckle tracking imaging (GE Echo PAC) as previously described. Assessment of diastolic function grade for patients in sinus rhythm was determined according European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines.[13] In the context of AF, five consecutive cardiac cycles were averaged for peak transmitral E and mitral annular tissue Doppler e′ velocities. Technetium pyrophosphate (PYP) imaging was performed in patients after 2013 according to protocol as previously described.[14]Echocardiographic features were previously described[5] and analysed in accordance with established American Society of Echocardiography guidelines.[15]

Electrocardiography and assignment of atrial fibrillation

The presence of AF was confirmed by electrocardiogram or cardiology clinic notes documenting a history of AF. If patients had a history of AF but were in sinus rhythm on baseline electrocardiogram, they were designated as paroxysmal AF. If the baseline electrocardiogram demonstrated AF, they were designated as long-standing AF. Patients with persistent and permanent AF were categorized as long-standing AF.[16] The use of antiarrhythmics and anticoagulants was assigned at the initial visit to the Amyloidosis Center. Follow-up was performed by phone with all participants in June 2016 to update any significant interval events for patients who did not receive the majority of their care at Boston University Medical Center or were lost to clinical follow-up.

Statistical analysis

All statistical analyses were conducted using SAS (version 9.3). Univariate regression methods were employed to compare baseline demographic and characteristics between patients who had AF and those who did not. Kaplan–Meier estimates were used to estimate survival distributions overall and by subgroup. Cox regression was used to compare survival across AF types and to estimate hazard ratios for survival while adjusting for age.

Literature search methods

A systematic review of the literature was carried out using the PubMed database with the search term ‘amyloidosis AND atrial fibrillation’. The search term ‘amyloidosis’ was

chosen to be most inclusive since ATTRwt was previously termed senile systemic or senile cardiac amyloidosis. Articles were reviewed and included if they mentioned AF in ATTRwt cardiac amyloidosis. Case reports were excluded, and only English language papers were retrieved. The literature search was performed on 18 October 2017, and papers were included if retrieved by that date.

Results

Patient characteristics

The patient characteristics are summarized in *Table 1*. The study population (n = 146) was composed of 142 male (97.3%) and 142 Caucasian (97.2%) patients, with an average age of 74.5 ± 6.2 years at presentation. Of the 146 total patients, there were 102 patients with AF (69.8% of the total cohort), of which 44 (43.1%) had paroxysmal AF and 58 (56.9%) had long-standing forms of AF. No significant differences were seen between the patients with AF and the remainder of the study population with regard to age, gender, body mass index, and common cardiovascular risk factors, such as hypertension. Characteristics stratified by type of AF can be found in Supporting Information, *Table S1*.

Signs and symptoms

There was an increased incidence of peripheral oedema in patients with AF compared with those without (69% vs. 40.5%, P = 0.002). However, there were no significant differences in other signs and symptoms whether self-reported (dyspnoea on exertion and orthostasis) or objective measures (jugular venous distension). Both populations had a similar distribution of patients with New York Heart Association class >1 (*Table 1*).

Serum markers

Patients with AF had lower serum TTR concentration (221 ± 51 μg/mL) compared with those without AF (250 ± 52 μg/mL, P = 0.005). Serum TTR concentrations are lower in permanent or longstanding AF as compared with paroxysmal AF or non-AF ($P < 0.001$; *Figure 2A*). Patients in both populations were found to have similar serum albumin and creatinine levels, and there were no significant differences in serum retinol binding protein, troponin I, or B-type natriuretic protein (*Table 1*).

Survival

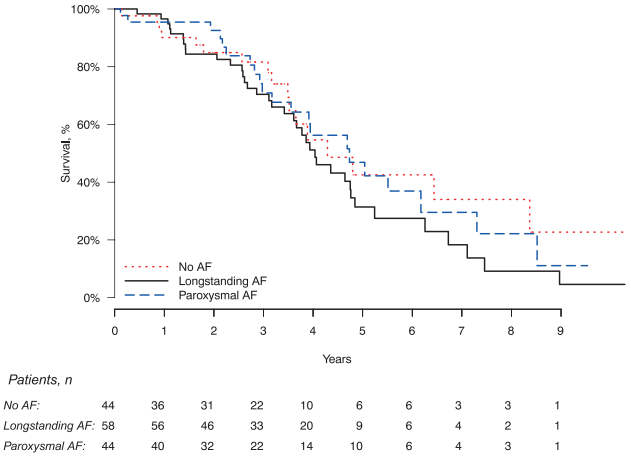
There were 39 deaths among patients with AF (38.2%) and 10 deaths among patients without AF (25%, log-rank P = 0.41) over a median observation period of 41.4 ± 27.1 months. Age-adjusted survival was similar among patients with AF and non-AF (hazard ratio 1.23, P = 0.46; *Figure 1*). There was no difference in survival when stratified by AF type, paroxysmal (hazard ratio 1.04, P = 0.89) or long standing (hazard ratio 1.37, P = 0.29). We have recently reported that a TTR concentration of <180 mg/dL was associated with reduced survival in ATTRwt.[17,18] Among patients with AF, we observed

Table 1 Baseline clinical and demographic characteristics

	All patients (n = 146)	ATTRwt with AF (n = 102)	ATTRwt without AF (n = 44)	P value
Male, n (%)	142 (97.3)	100 (98.1)	42 (95.5)	0.38
Age at diagnosis (years), mean ± SD	74.5 ± 6	74.9 ± 6	73.6 ± 6	0.22
BMI (kg/m^2), mean ± SD	28.6 ± 4.1	28.5 ± 3.9	28.7 ± 4.4	0.86
NYHA function class >1, n (%)	125 (87.4)	87 (85.3)	38 (92.7)	0.23
AF type				
Paroxysmal, n (%)	43 (29.5)	43 (42.2)	—	—
Permanent, n (%)	58 (39.7)	58 (56.9)	—	—
Serum TTR (μg/mL), mean ± SD	**231 ± 53**	**221 ± 51**	**250 ± 52**	**0.005**
Serum albumin (g/dL), mean ± SD	4.1 ± 0.3	4.1 ± 0.4	4.2 ± 0.3	0.25
Serum creatinine (mg/dL), mean ± SD	1.35 ± 0.5	1.37 ± 0.5	1.31 ± 0.4	0.52
Serum retinol binding protein (μg/mL), mean ± SD	36.2 ± 14.5	35.1 ± 13.6	38.6 ± 16.1	0.24
Troponin I (ng/mL), mean ± SD	0.20 ± 0.31	0.16 ± 0.19	0.27 ± 0.46	0.09
B-type natriuretic protein (pg/mL), mean ± SD	466.4 ± 321.9	479.3 ± 318.9	436.9 ± 330.8	0.48
Orthostatic hypotension, n (%)	13 (9.4)	11 (11.2)	2 (5)	0.42
Dyspnoea on exertion, n (%)	122 (85.3)	88 (87.1)	34 (81)	0.34
Peripheral oedema, n (%)	**87 (60)**	**70 (69)**	**17 (40.5)**	**0.002**
Elevated jugular venous pressure, n (%)	47 (32.9)	34 (33.7)	13 (31)	0.75
Systolic blood pressure (mmHg), mean ± SD		122.6 ± 15.3	127.2 ± 15.4	0.10
Diastolic blood pressure (mmHg), mean ± SD		75.5 ± 9.1	76.1 ± 7.5	0.69
Heart rate (b.p.m.), mean ± SD		71.5 ± 11.9	69.5 ± 11.8	0.35

AF, atrial fibrillation; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

Figure 1 Kaplan–Meier analysis of age-adjusted survival stratified based on presence of atrial fibrillation (AF) in wild-type transthyretin amyloidosis. There is no significant difference in survival in patients with paroxysmal AF (hazard ratio 1.04, *P* = 0.89) or permanent AF (hazard ratio 1.37, *P* = 0.29) as compared with those who do not have AF.



borderline significant survival differences with this threshold (hazard ratio 2.0, *P* = 0.059; *Figure 2B*). The primary cause of death with heart failure which was noted in 22 of 39 (56%) of desceased patients with AF, and 8 of 10 (80%) of deceased patients without AF.

Imaging findings

Echocardiographic parameters are summarized in *Table 2*. Patients in both AF and non-AF groups had similar chamber dimensions, as well as wall thickness. With respect to systolic function, left ventricular ejection fraction (47.0 ± 11% vs. 50.0 ± 12%, *P* = 0.09) and global longitudinal strain were similar (−9.4 ± 3.2% vs. −9.4 ± 3.0%, *P* = 0.98) in the AF and non-AF subgroups. Diastolic function, in contrast, was more impaired in patients with paroxysmal AF by E/A ratio (3.0 ± 1.3 vs. 2.0 ± 1.2, *P* = 0.005), manifest as Grade III diastolic dysfunction (74 vs. 43%). Interestingly, by PYP imaging, patients with AF had a lower heart to contralateral chest ratio that was just above the threshold for significance (1.83 ± 0.22 vs. 2.16 ± 0.51, *P* = 0.05).

Medical management of atrial fibrillation

Among patients with AF, 33 patients (32.3%) received an antiarrhythmic drug and the remainder (67.7%) were managed with a rate control/anticoagulation strategy. Of those managed by rhythm control, 24 were taking amiodarone and 8 were taking another class antiarrhythmic drug, including sotalol, dofetilide, and propafenone (*Table 3*). One patient was managed with both amiodarone and another antiarrhythmic drug (at different times). There was no difference in survival among patients treated with a rate control strategy vs. those treated with a rhythm control strategy (i.e. no antiarrhythmic therapy; *Figure 3*, *P* = 0.08). Digoxin was employed in six patients (5.9%). Cardioversion was performed at least once in 38.5% of AF patients. Left atrial thrombus was noted in six patients prior to the initiation of anticoagulation. There was no significant difference between pacemaker or implantable cardioverter defibrillator/cardiac

Figure 2 (A) Box and whisker plots demonstrating serum transthyretin (TTR or prealbumin) levels stratified by the presence and type of atrial fibrillation (AF) in wild-type transthyretin amyloidosis. Note that serum TTR concentrations are lower in permanent or longstanding AF vs. paroxysmal or no AF, *P* = 0.0002. (B) Survival in patients with atrial fibrillation (AF), stratified by TTR (TTR or prealbumin) concentration that is above or below 180 μg/dL in ATTR wild-type amyloidosis. Hazard ratio is 2.00 (*P* = 0.059).

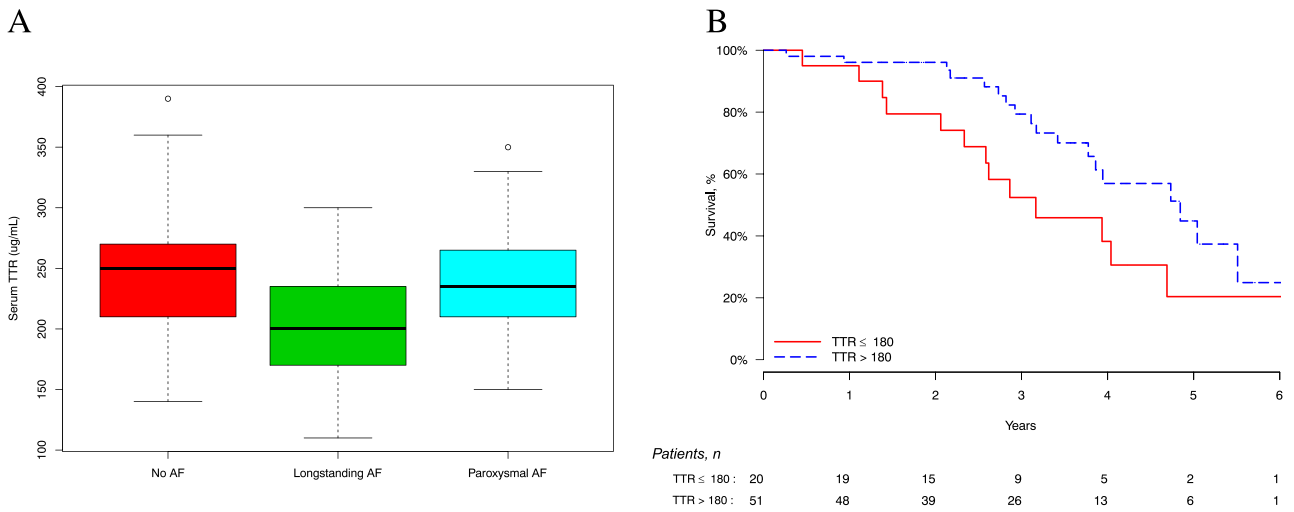


Table 2 Echocardiographic characteristics

	All patients (n = 146)	ATTRwt with AF (n = 102)	ATTRwt without AF (n = 44)	P value
LVEF (%), mean ± SD	48.0 ± 11	47.0 ± 11	50 ± 12	0.09
Left atrial volume (mL), mean ± SD	95.9 ± 26.3	95.6 ± 23.8	96.7 ± 33.1	0.87
Left atrial volume indexed to body surface area (mL/m^2), mean ± SD	**49.7 ± 13.8**	**49.4 ± 12.1**	**50.5 ± 17.8**	**0.77**
PA systolic pressure (mmHg), mean ± SD	41.8 ± 10.7	41.9 ± 9.7	41.6 ± 14.3	0.93
TDI E′ septal, mean ± SD	4.1 ± 1.5	4.1 ± 1.5	3.8 ± 1.6	0.36
TDI E′ lateral, mean ± SD	5.6 ± 1.9	5.7 ± 1.9	5.4 ± 1.8	0.46
E/E′ septal, mean ± SD	24.1 ± 12.2	24.5 ± 12.8	22.9 ± 10.7	0.59
E/A ratio, mean ± SD	**2.7 ± 1.4**	**3.0 ± 1.3**[a]	**2.0 ± 1.2**	**0.005**
Grade of diastolic dysfunction, mean ± SD	**2.7 ± 0.5**	**2.7 ± 0.5**[a]	**2.4 ± 0.5**	**0.012**
Grade II (n), %	26 (35)	14 (26)	12 (57)	
Grade III (n), %	48 (65)	39 (74)	9 (43)	
Global longitudinal strain, %	−9.4 ± 3.1	−9.4 ± 3.2	−9.4 ± 3.0	0.98
Deceleration time (ms), mean ± SD	197.9 ± 45.1	196.3 ± 46.2	202.1 ± 43.3	0.63
Pulmonary vein S (cm/s), mean ± SD	31.2 ± 9.6	30.3 ± 8.7	34.7 ± 12.4	0.23
Pulmonary vein D (cm/s), mean ± SD	65.7 ± 19.6	67.5 ± 20.6	59.5 ± 15.0	0.26

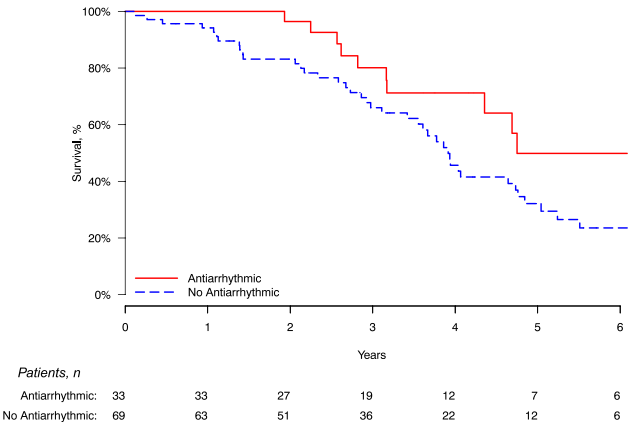
AF, atrial fibrillation; ATTRwt, wild-type transthyretin amyloidosis; LVEF, left ventricular ejection fraction; PA, pulmonary artery; SD, standard deviation; TDI, tissue Doppler imaging.
[a]Patients with paroxysmal AF only.

Table 3 Medical management of atrial fibrillation

	ATTRwt with AF (n = 102)
Anticoagulation, n (%)	94 (92.2)
Warfarin	79 (77.5)
DOAC	17 (16.7)
Antiarrhythmic use, n (%)	33 (32.3)
Amiodarone	24 (23.5)
Other antiarrhythmics	8 (7.8)
Cardioversion ≥1, n (%)	40 (39.2)
Pacemaker/ICD, n (%)	37 (36.3)

AF, atrial fibrillation; ATTRwt, wild-type transthyretin amyloidosis; DOAC, direct-acting oral anticoagulants; ICD, implantable cardioverter defibrillator.

Figure 3 Survival in patients with atrial fibrillation stratified by the use of antiarrhythmic medications. There is no significant difference in survival among those patients who were treated with a rhythm or rate control strategy (hazard ratio 1.70, P = 0.08).



resynchronization therapy use among AF patients compared with non-AF (36.3 vs. 22.7%, P = 0.12).

The majority of patients were managed with warfarin at some point in their treatment (77.5%). Direct-acting oral anticoagulants were used in 17 patients (16.7%), a trend in the more recent epoch 2006–16. However, eight patients (7.7%) did not receive any anticoagulant. Three reported complications of anticoagulation occurred: one subdural haematoma (warfarin), one patient with gastrointestinal bleed (warfarin), and one patient with haematuria (rivaroxaban).

Discussion

The study describes the clinical features, outcomes, and management strategies employed to treat AF in ATTRwt cardiac amyloidosis. To our knowledge, this study is the first to specifically characterize AF with data drawn from the largest cohort of biopsy-proven ATTRwt patients yet described. Our principal findings are that AF occurs in a majority (70%) of ATTRwt patients, patients with AF have more diastolic dysfunction than non-AF patients, and unlike other cardiomyopathies, AF does not appear to impact survival. We also describe the proportion of patients with paroxysmal vs. long-standing AF and describe the clinical features, choice of rate vs. rhythm control, and anticoagulation in this large referral centre patient population.

We performed a systematic review to inform our understanding and summarize the current literature of AF in ATTRwt. The initial search of 'amyloidosis AND atrial fibrillation' yielded 132 articles. Of these, 13 articles included

patients with ATTRwt cardiac amyloidosis and mentioned AF incidence or management. Key findings of these articles are summarized below. All of the studies, except for two,[3,19] reported an increased incidence of AF in ATTRwt patients. There was similar reported survival in those with AF as compared with those without; however, the incidence of heart failure was greater.[20] Our findings are consistent with these reports, although our cohort is significantly larger than those reported previously.

With respect to complications of AF, prior reports suggest that patients with ATTRwt were at higher risk for development of intracardiac thrombus[21,22] and stroke due to electromechanical dissociation, while anticoagulation with warfarin was effective in lowering the risk of intracardiac thrombus and thrombo-embolic events.[20,22] Data regarding medical management efficacy were limited to one study that reported that rhythm control management was attempted among a small number of patients with amiodarone or flecanide, but ultimately, a rate control strategy was chosen.[20] We noted a rhythm control strategy in 31.7, and among those in whom a rhythm control strategy was pursued, there was no significant difference in survival (hazard ratio 1.70, $P = 0.08$; *Figure 3*).

Outcomes with catheter ablation for AF, atrial flutter, and atrial tachycardia yielded conflicting results. Tan *et al*. reported symptomatic improvement at 6 months in those who underwent both atrial ablation and atrioventricular nodal ablation, with recurrence-free survival of 60% at 3 years[23]; however, Barbhaiya *et al*. found that recurrence rate was 83% at 1 year after ablation.[24] Only a small number of patients in our study were treated with catheter ablation for atrial flutter and none for AF. Given the small numbers, we were unable to draw meaningful conclusions from outcomes with this strategy.

A prior histological study found that TTR amyloid protein tends to have a predilection for deposition in the atria.[19] Since then, several studies have demonstrated an increased incidence of AF, especially in the ATTRwt form of amyloidosis (compared with ATTRm or AL).[5,20] Our findings are similar to Longhi *et al*.[20] in that AF is associated with a greater degree of heart failure but does not appear to be associated with increased mortality in a larger patient sample.

The aetiology of the association between reduced serum TTR concentration and AF is unclear. It does not appear related to renal clearance of TTR, at least as determined by creatinine clearance. While we have previously observed an association between lower TTR concentration and survival in ATTRwt, we were unable to reproduce this finding among patients with AF, although the interaction was borderline significant. One possible explanation for the reduced TTR concentration is that patients with AF have greater deposition of the TTR amyloid protein in the atria, causing myofibril disarray and promoting AF. This deposition was not evidenced upon PYP imaging, wherein we observed a lower heart : contralateral chest ratio among patients with AF. While we observed that patients had similar left atrial dimensions on echocardiography, the changes may be at the microscopic level and require histological analysis to evaluate. Increased atrial deposition may also explain the skew towards worsened diastolic function among patients with AF.

Despite the challenges that management of AF poses among patients with ATTRwt, there does not appear to be a difference in survival with AF or no AF when adjusted for age, and furthermore, no difference in survival across the subtype of AF. This observation is substantiated by the similarities we observed in clinical characteristics, biomarkers, and echocardiographic profiles between patients with AF and those without. Our data also suggest that even with the current diversity in management of AF, mortality remains unchanged. These findings can reassure patients and providers that AF can be managed as per clinical preference with no distinct advantage to any particular strategy. We would recommend, based upon our collective clinical experience, our review of the literature, and the data presented here, that asymptomatic patients in AF be treated with anticoagulation and rate control, as needed, while a rhythm control approach can be reserved for symptomatic patients.

Limitations

This was a retrospective study thus limited by recall bias. Many patients seen at our centre for a baseline evaluation did not return for follow-up (some owing to death), and thus, some interval events were solely determined by phone interview. As this was a cohort composed of referral patients to our Amyloidosis Center, and most were treated by their local physicians, patients did not undergo routine monitoring for AF, and thus, there may have been unrecognized episodes among those categorized as sinus rhythm. While we followed established guidelines from the European Association of Cardiovascular Imaging/American Society of Echocardiography regarding assessment of diastolic function in the presence of AF, our assessment of diastolic function was limited by the high proportion of patients with persistent AF (40%) at the time of echocardiography. This study was also limited by lack of trans-oesophageal echocardiographic data such as left atrial appendage velocities and the presence of appendage thrombi, which would further inform our understanding of the efficacy of anticoagulant treatment in AF. Finally our study was also limited by the relatively short mean period of follow-up (3.4 years) and limited ability to report stroke outcomes and bleeding events, as most patients received treatment off-site. However, as our study demonstrates similar mortality in AF and non-AF groups, we can conclude that

mortal stroke or bleeding events likely occurred equally between the two groups.

In summary, to our knowledge, we present here the largest description of the clinical and imaging features of AF among patients with ATTRwt cardiac amyloidosis yet reported. Our data serve to inform clinical management and can also serve as a basis from which to develop future, prospective studies regarding optimal management strategies with respect to arrhythmia control and stroke prevention.

Conflict of interest

F.L.R. acknowledges consulting relationships with Caelum BioSciences and GlaxoSmithKline and research support from Eidos Therapeutics.

Funding

NIH R01 AG031804 and the Young Family Amyloid Research Fund (L.H.C.) and NIH R21 AG R21AG050206 and Eidos Therapeutics (F.L.R.).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical and echocardiographic characteristics stratified by type of atrial fibrillation.

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