Prevalence, Incidence, and Impact on Mortality of Conduction System Disease in Transthyretin Cardiac Amyloidosis

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Transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly recognized infiltrative cardiomyopathy in which conduction system disease is common. The aim of our study was to define the incidence and prevalence of high-grade atrioventricular (AV) block requiring pacemaker implantation in our quaternary referral center. This was a single-center retrospective cohort study of 369 consecutive patients with ATTR-CA who underwent 12-lead electrocardiogram at the time of ATTR-CA diagnosis. During a mean follow-up of 28 months, serial ECGs and the electronic medical record were examined for the development of high-grade AV block and pacemaker implantation. Wild-type ATTR-CA (wtATTR-CA) was diagnosed in 261 patients and 108 had hereditary ATTR-CA (hATTR-CA). A total of 35 (9.5%) had high-grade AV block requiring pacemaker implantation at the time of diagnosis of ATTR-CA. The most common conduction abnormalities evident on the baseline ECG were a wide QRS complex, present in 51% with wtATTR-CA and 48% with hATTR-CA (p = 0.62), followed by first-degree AV block, which was present in 49% with wtATTR-CA and 43% with hATTR-CA (p = 0.31). During follow-up, high-grade AV block developed in 10% of those with hATTR-CA and 12% of patients with wtATTR-CA (p = 0.64). On multivariable models, high-grade AV block was not significantly associated with increased mortality. More advanced ATTR-CA stage and a history of obstructive coronary artery disease were associated with increased mortality on multivariable models. In conclusion, the incidence and prevalence of high-grade AV block is high in patients with ATTR-CA. Patients with ATTR-CA require close monitoring during follow-up for the development of conduction system disease. **© 2020 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2020;128:140−146)**

Transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly recognized infiltrative cardiomyopathy caused by the extracellular deposition of insoluble misfolded precursor proteins.[1,2] In general, ATTR-CA is classified by the sequence of the *TTR* gene, either as wild-type ATTR-CA (wtATTR-CA) in which no mutation is identified, and hereditary ATTR-CA (hATTR-CA) when a mutation is present.[1] Conduction system disease is common in ATTR-CA, with atrial fibrillation (AF) representing the most commonly encountered rhythm disturbance.[3] A substantial number of patients with ATTR-CA develop a requirement for permanent pacemaker (PPM) implantation during their disease course as amyloid fibrils infiltrate the conduction system.[2] This is problematic as the dyssynchrony caused by inter- and intraventricular conduction delay as a result of right ventricular pacing within a small, restricted ventricle has marked deleterious impacts on cardiac structure and function and may increase mortality.[4] At present, the incidence and prevalence of high-grade atrioventricular (AV) block in ATTR-CA is not well established. Furthermore, the extent to which AV block impacts survival in ATTR-CA has not previously been studied. In this study we aimed to assess the prevalence of conduction abnormalities on 12-lead surface electrocardiogram (ECG) at the time of diagnosis of ATTR-CA and the incidence of sinus node dysfunction and high-grade AV block during follow-up. The aims of our study were to determine the incidence and prevalence of conduction system disease in patients with ATTR-CA; to investigate differences in the incidence and prevalence of conduction system disease across the different ATTR-CA subtypes; and to examine the extent to which conduction system disease impacts outcomes in patients with ATTR-CA.

Methods

This was a retrospective cohort study of 369 consecutive patients diagnosed with ATTR-CA at our institution between January 2004 and January 2019. The diagnosis of ATTR-CA was established either from tissue biopsy with confirmation of TTR in the amyloid deposits by immunogold electron microscopy, immunohistiochemistry or mass spectrometry, or through previously established nonbiopsy criteria.[5] Diagnosis using nonbiopsy criteria required that all of the following were met: heart failure with an echocardiogram or cardiac magnetic resonance imaging consistent

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with or suggestive of amyloidosis, grade 2 or 3 cardiac uptake on a radionuclide scan, and absence of a detectable monoclonal protein on serum or urine immunofixation electrophoresis, or serum free light chain assay.[5] DNA sequencing was performed in all patients to assess for the presence of a mutation in the TTR gene. Patients were assigned to stage 1-3 based on the UK National Amyloidosis Staging System.[6] In this scoring system, stage 1 is defined as N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤3000 ng/L and estimated glomerular filtration rate (eGFR) ≥45 ml/min and stage 3 is defined as NT-proBNP> 3000 ng/L and eGFR <45 ml/min whereas all other patients are assigned to Stage 2.

Data were collected from individual analysis of electronic medical records after obtaining approval from our Institutional Review Board. Date of diagnosis of ATTR-CA was determined. Laboratory data, including NT-proBNP, troponin T, and eGFR were recorded. New York Heart Association (NYHA) functional class was recorded.

Only patients who underwent 12-lead ECG at the time of diagnosis with ATTR-CA were included in our study. Electrocardiographic parameters were measured and recorded according to standard definitions.[7] During follow-up, serial ECG tracings were examined for the development of conduction disease. Similarly, the electronic medical record was reviewed for the implantation of cardiac devices during follow-up.

All patients underwent a comprehensive echocardiographic assessment using commercially available instruments (Philips Medical Systems, NA, Bothell, WA; General Electric Medical Systems, Milwaukee, WI; and Siemens Medical Solutions USA, Inc, Malvern, PA). Echocardiographic parameters were assessed according to standard guidelines.[8]

All statistical analysis was performed using SPSS statistical software version 25 (IBM Corporation, Armonk, New York). A 2-sided p-value <0.05 was considered statistically significant. Differences in baseline clinical, electrocardiographic, and echocardiographic characteristics were compared between patients with hATTR-CA and wtATTR-CA, and also between patients with the Val122Ile mutation and with the Thr60Ala mutation. Continuous variables are expressed as mean ± standard deviation (SD). Categorical data are presented as n (percentages). Differences between the 2 groups were compared using analysis of variance for continuous variables. The chi-square test was used for categorical variables. Cumulative event rates as a function over time were obtained using the Kaplan-Meier method and event curves of different outcomes were compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were developed to determine independent predictors of high-grade AV block and mortality. Hazard ratios (HRs) and their 95% confidence intervals (CIs) are reported from the proportional hazards models.

Results

Baseline characteristics of the study cohort are shown in Table 1. The mean age of the entire study cohort was 76 ± 10 and the study population was predominantly male (82%). The majority of patients had wtATTR-CA (71%). Age was significantly higher in patients with wtATTR-CA compared to hATTR-CA (78 ± 9 vs 73 ± 10, p <0.001) and more patients with wtATTR-CA had a history of obstructive coronary artery disease. Left ventricular ejection fraction was lower in patients with hATTR-CA (44% ± 16% vs 48% ± 14%, p = 0.03).

The average heart rate at the time of diagnosis was 76 ± 16 beats per minute. Across the entire study cohort, 263 (71%) patients were in normal sinus rhythm on their initial ECG, whereas 101 (27%) were in AF, 35 (9.5%) were paced, and 5 (1%) were in a junctional rhythm. Left axis deviation was present in 98 (27%) and 32 (9%) had right axis deviation. The mean PR interval, QRS duration, and QTc duration were 208 ± 61, 124 ± 34, and 486 ± 49 ms, respectively. Of those who were in normal sinus rhythm, first-degree AV block was present in 123 (47%). A wide QRS complex was observed in 185 (50%), of whom 49 (13%) had left bundle branch block and 67 (18%) had right bundle branch block. Left anterior fascicular block was noted in 20 (5%) patients and left posterior fascicular block was present in 1 (0.3%), while bi- and trifascicular block were observed in 4 (1.1%) and 2 (0.5%) patients, respectively. Significantly more patients with hATTR-CA were in normal sinus rhythm at the time of diagnosis (87% vs 65%, p <0.001), and a higher proportion of those with wtATTR-CA were in AF at diagnosis (33% vs 13%, p <0.001). Average duration of the QRS complex was also longer in wtATTR-CA (127 ± 35 vs 118 ± 3531 ms, p = 0.02). The most common gene mutation identified in our cohort was Val122Ile, which was present in 75 (69%), followed by Thr60Ala, present in 12 (11%). Baseline ECG characteristics and prevalence of conduction disease for these groups are shown in Table 2.

At the time of ATTR-CA diagnosis, 35 (9.5%) patients had pacemakers in situ for high-grade AV block, 27 (10%) with wtATTR-CA and 8 (7%) with hATTR-CA (Figure 1, p = 0.38). During a mean follow-up of 28 months, sinus node dysfunction occurred in 24 (7%) of the study population, whereas 42 (11%) developed high-grade AV block. Sinus node dysfunction occurred in 9 (8%) patients with hATTR-CA and 15 (6%) with wtATTR-CA (p=0.36). Similarly, high-grade AV block developed in 11 (10%) patients with hATTR-CA and 31 (12%) with wtATTR-CA (Figure 2, p = 0.64). Significantly more patients with the Thr60Ala mutation had high-grade AV block at the time of ATTR-CA diagnosis (Figure 1, p = 0.002). However, the incidence of high-grade AV block was similar in both groups (Figure 2, p = 0.15).

The incidence of high-grade AV block and sinus node dysfunction did not differ significantly according to ATTR-CA stage. High-grade AV block occurred in 9% with Stage 1, 13% with Stage 2, and 12% with Stage 3 disease (p = 0.59). Similarly, sinus node dysfunction developed in 2% of those with Stage 1, 9% with Stage 2, and 7% with Stage 3 ATTR-CA (p = 0.12). Only a QRS duration ≥120 ms on baseline ECG was significantly associated with the subsequent development of high-grade AV block on multivariable analyses (HR 4.71, 95% CI 1.97 to 11.26, p <0.001), while normal sinus rhythm (HR 0.39, 95% CI 0.21 to 0.73, p = 0.003) and a QRS duration <100 ms (HR 0.17,

Table 1
Baseline characteristics of patients with wild-type (wtATTR-CA) and hereditary (hATTR-CA) transthyretin cardiac amyloidosis

Variable	wtATTR-CA (n = 261)	hATTR-CA (n = 108)	p-Value
Age (years)	78±9	73±10	<0.001
Men	223 (85%)	80 (74%)	0.01
Diabetes mellitus	40 (15%)	26 (24%)	0.05
Obstructive CAD	83 (32%)	23 (21%)	0.04
Beta Blocker	98 (37.5%)	31 (29%)	0.11
Digoxin	17 (6.5%)	7 (6.5%)	0.99
ACEi/ ARB	49 (19%)	24 (22%)	0.45
Aldosterone antagonist	64 (24.5%)	24 (22%)	0.64
NYHA functional class	2.6±0.66	2.5±0.73	0.11
ATTR-CA Stage	2.1±0.8	2.2±0.8	0.79
NT-proBNP (pg/ml)	7355±9492	8949±12957	0.21
eGFR (ml/min/1.73m^2)	45±15	43±15	0.49
Left atrial volume index (ml/m^2)	47±16	44±13	0.18
Left ventricular end-diastolic diameter (cm)	4.3±0.8	4.2±0.7	0.56
Left ventricular end-systolic diameter (cm)	3.2±0.8	3.2±0.8	0.98
Interventricular septal thickness (cm)	1.8±0.4	1.8±0.5	0.13
Posterior LV wall thickness (cm)	1.6±0.4	1.7±0.4	0.07
LV mass index (g/m^2)	155±47	156±55	0.96
Ejection fraction (%)	48±14	44±16	0.03
Heart rate (bpm)	75±17	78±15	0.17
Sinus rhythm	169 (65%)	94 (87%)	<0.001
Atrial fibrillation	87 (33%)	14 (13%)	<0.001
Junctional rhythm	5 (2%)	0	0.15
PR interval (ms)	212±65	201±50	0.14
QRS duration (ms)	127±35	118±31	0.02
QTc duration (ms)	488±51	478±42	0.11
1st degree AV block	83 (49%)	40 (43%)	0.31
Wide QRS complex	133 (51%)	52 (48%)	0.62
Left bundle branch block	39 (15%)	10 (9%)	0.18
Right bundle branch block	48 (18%)	19 (18%)	0.86
Interventricular conduction delay	34 (13%)	23 (21%)	0.05
Bifascicular block	3 (1%)	1 (1%)	0.85
Trifascicular block	1 (0.4%)	1 (0.9%)	0.52
High-grade AV block	27 (10%)	8 (7%)	0.38

CAD = coronary artery disease; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NYHA = New York Heart Association; eGFR = estimated glomerular filtration rate; LV = left ventricle.

95% CI 0.06 to 0.49, p = 0.001) were associated with a reduced risk of high-grade AV block (Table 3).

Death occurred in 230 (62%) patients during follow-up, 166 (64%) with wtATTR-CA and 64 (59%) hATTR-CA (p=0.42). Among patients who developed high-grade AV block, death occurred in 35 (83%), compared to 15 (62.5%) of those with sinus node dysfunction, and 180 (29%) with neither (Figure 3, log-rank 6.03, p=0.014).

On Cox proportional hazards analyses, advanced ATTR-CA stage (HR 3.32, 95% CI 2.28 to 4.83, p <0.001), and a history of obstructive coronary artery disease (HR 1.82, 95% CI 1.09 to 3.03, p = 0.02) were associated with increased mortality, while high-grade AV block was not (Table 4, HR 1.8, 95% CI 0.83 to 3.88, p = 0.14).

Discussion

Transthyretin cardiac amyloidosis represents an increasingly recognized infiltrative cardiomyopathy in which extracellular deposition of insoluble precursor proteins can result in progressive conduction system disease. Data regarding the incidence and prevalence of conduction system disease in this patient population is currently lacking. In this study, we found that: (1) high-grade AV block was present at the time of diagnosis of ATTR-CA in 9.5% of our study cohort; (2) during a mean follow-up of 28 months, 11% required permanent pacemaker implantation for the development of high-grade AV block and a further 7% went on to develop sinus node dysfunction; (3) the development of sinus node dysfunction and high-grade AV block were not independently associated with increased mortality on multivariable models adjusting for ATTR-CA stage, or a history of obstructive coronary artery disease; and (3) rates of high-grade AV block did not differ significantly among patients with wild-type and hereditary ATTR-CA.

Baseline electrocardiographic characteristics across the 3 major types of cardiac amyloid (AL, hATTR-CA, and wtATTR-CA) were previously studied by Rapezzi et al. Among 15 patients with wtATTR-CA, pacemakers were present at the time of diagnosis in 13%, compared with 3% of those with hATTR-CA.[2]

Electrocardiographic features traditionally associated with the development of high-grade AV block include prolonged AV interval, right and left bundle branch block.[9–12]

Table 2
Baseline electrocardiographic characteristics and the prevalence of sinus node dysfunction and high-grade AV block among patients carrying the Val122Ile gene mutation compared to the Thr60Ala mutation

Variable	Val122Ile (n = 75)	Thr60Ala (n = 12)	p-Value
Age (years)	76±9	67±10	0.003
Men	55 (73%)	9 (75%)	0.9
Obstructive CAD	12 (16%)	2 (17%)	0.97
Diabetes mellitus	22 (29%)	1 (8%)	0.17
Beta blocker	23 (31%)	2 (17%)	0.32
Digoxin	7 (7%)	1 (8%)	0.83
ACEi/ ARB	16 (21%)	3 (25%)	0.72
Aldosterone antagonist	20 (27%)	0	0.04
NYHA functional class	2.5±0.8	2.3±0.6	0.3
ATTR-CA stage	2.2±0.7	1.5±0.5	0.001
NT-proBNP (pg/ml)	9737±12093	1607±1216	0.04
eGFR (mL/min/1.73m^2)	41±15	53±8	0.008
Left Atrial Volume Index (ml/m^2)	46±14	41±15	0.39
Left ventricular end-diastolic diameter (cm)	4.2±0.7	4.5±0.7	0.22
Left ventricular end-systolic diameter (cm)	3.2±0.8	3.2±0.6	0.75
Interventricular septal thickness (cm)	1.8±0.5	1.8±0.5	0.96
Posterior LV wall thickness (cm)	1.7±0.4	1.6±0.4	0.42
LV mass index (g/m^2)	158±58	138±74	0.48
Ejection fraction (%)	42±16	58±11	0.002
Interventricular septal thickness (cm)	10 (13%)	1 (8%)	0.63
PR interval (ms)	201±51	202±55	0.97
QRS duration (ms)	113±26	126±41	0.14
QTc duration (ms)	476±39	486±49	0.44
1st degree AV block	26 (35%)	4 (33%)	0.82
Wide QRS complex	32 (43%)	6 (50%)	0.63
Left bundle branch block	6 (8%)	0	0.31
Right bundle branch block	15 (20%)	2 (17%)	0.79
Interventricular conduction delay	15 (20%)	3 (25%)	0.69
Sinus node dysfunction	4 (5%)	2 (17%)	0.15
High-grade AV block	2 (3%)	3 (25%)	0.002

CAD = coronary artery disease; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NYHA = New York Heart Association; eGFR = estimated glomerular filtration rate; LV = left ventricle.

Of interest, in our study only a wide QRS on baseline ECG was associated with the subsequent development of high-grade AV block. This likely indicated that AV block in ATTR-CA likely represents the result of ongoing conduction system infiltration of insoluble fibrils rather than progression of lower grades of conduction disease evident on the baseline ECG. If this is the case, therapies that limit disease progression may offer promise in reducing the need to pacemakers in this population.

Although the development of high-grade AV block was not independently associated with increased mortality on multivariable models in the present study, the inter- and intraventricular dyssynchrony produced by right ventricular (RV) pacing has important hemodynamic implications which may be even more pronounced in patients with ATTR-CA. It is well-established that a high RV pacing burden is associated with increased rates of congestive heart failure and chamber dilation.[13] A RV pacing burden ≥40%

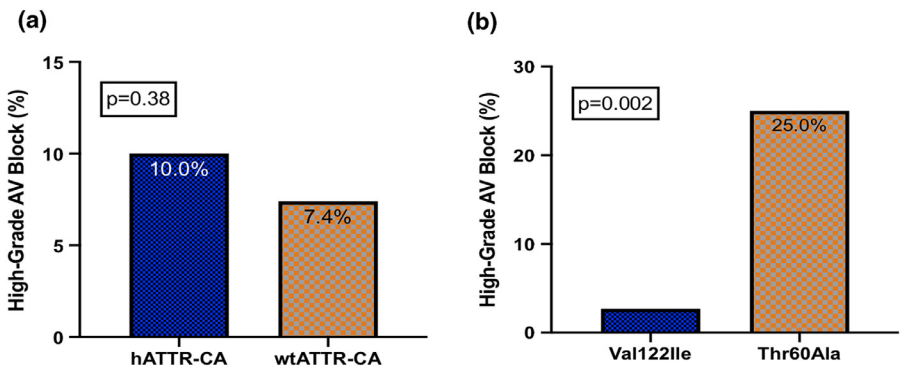

Figure 1. Prevalence of high-grade atrioventricular block at the time of diagnosis (a) in hereditary and wild-type transthyretin cardiac amyloidosis; and (b) among those with the Val122Ile and Thr60Ala mutation.

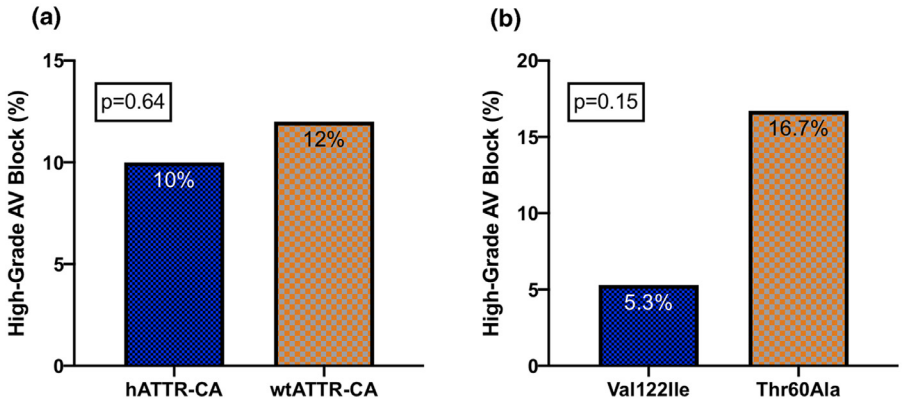

Figure 2. Incidence of high-grade atrioventricular block during follow-up (a) in patients with hereditary and wild-type transthyretin cardiac amyloidosis; and (b) in patients with the Val122Ile and Thr60Ala mutation.

Table 3
Univariable and multivariable Cox regression analyses for the development of high-grade AV block

	Univariable		Multivariable	
Variable	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	0.99 (0.96-1.03)	0.61		
ATTR-CA stage	1.18 (0.79-1.77)	0.41		
eGFR	1.01 (0.99-1.04)	0.26		
Obstructive CAD	1.58 (0.82-3.03)	0.17		
Digoxin use	0.28 (0.04-2.02)	0.21		
Beta blocker use	1.26 (0.68-2.34)	0.46		
hATTR-CA	0.81 (0.41-1.61)	0.55		
Diabetes mellitus	1.18 (0.58-2.4)	0.65		
Normal sinus rhythm	0.34 (0.19-0.63)	0.001	0.39 (0.21-0.73)	0.003
Atrial fibrillation	2.27 (0.89-5.8)	0.09	1.97 (0.77-5.05)	0.16
PR interval ≥200 msec	0.73 (0.28-1.9)	0.52		
QRS duration ≥120 ms	5.2 (2.2-12.37)	<0.001	4.71 (1.97-11.26)	<0.001
QRS duration <100 msec	0.15 (0.055-0.43)	<0.001	0.17 (0.06-0.49)	0.001
Ejection fraction	0.99 (0.97-1.01)	0.3		
LV mass index	1.0006 (0.997-1.02)	0.2		

CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; LV = left ventricle.

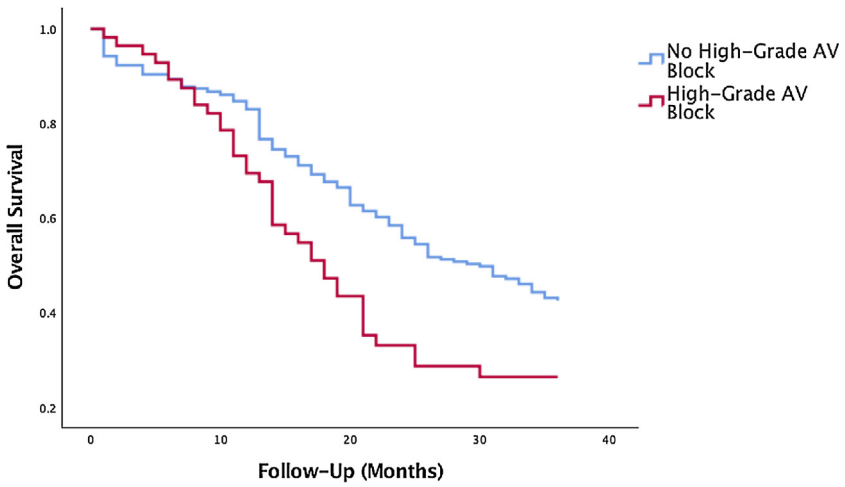

Figure 3. Kaplan-Meier curve for all-cause mortality in patients with high-grade atrioventricular (AV) block compared with those without high-grade AV block. Log-rank 6.03, p = 0.014.

has been shown to represent an important threshold, above which the risk of pacing-induced cardiomyopathy and heart failure hospitalization are elevated.[14,15] Given the preponderance of first-degree AV block and high-grade AV block in ATTR-CA, it is not always possible to avoid a high RV pacing burden. We previously studied this question in 78 patients with ATTR-CA with cardiac devices, and found worsening LVEF in 86% of those who were RV paced

Table 4
Univariable and multivariable Cox regression analyses for all-cause mortality

	Univariable		Multivariable	
Variable	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	1.02 (1.005-1.04)	0.01	1.03 (0.997-1.06)	0.08
ATTR-CA stage	1.93 (1.6-2.34)	<0.001	3.32 (2.28-4.83)	<0.001
Obstructive CAD	1.66 (1.25-2.2)	<0.001	1.82 (1.09-3.03)	0.02
Digoxin use	0.97 (0.6-1.57)	0.89		
Beta blocker use	0.94 (0.72-1.24)	0.66		
hATTR-CA	0.93 (0.7-1.24)	0.62		
Diabetes mellitus	0.7 (0.5-0.99)	0.05	0.7 (0.4-1.24)	0.22
Normal sinus rhythm	0.73 (0.56-0.96)	0.02	2.03 (0.26-16.08)	0.5
Atrial fibrillation	1.35 (1.03-1.78)	0.03	1.5 (0.19-12.07)	0.7
PR interval ≥200 ms	0.99 (0.72-1.4)	0.99		
QRS duration ≥120 ms	0.98 (0.76-1.28)	0.91		
QRS duration <100 ms	1.08 (0.83-1.4)	0.58		
Ejection draction	0.988 (0.98-0.997)	0.008	0.98 (0.96-1)	0.05
LV mass index	1.004 (1-1.008)	0.06	0.998 (0.992-1.003)	0.46
High-grade AV block	1.57 (1.08-2.26)	0.017	1.8 (0.83-3.88)	0.14
Sick sinus syndrome	0.57 (0.34-0.97)	0.037	0.998 (0.46-2.18)	0.99

CAD = coronary artery disease; LV = left ventricle.

≥40% of the time, compared with 26% of those who were RV paced <40%(p <0.0001, 6). A higher RV pacing % was also associated with worsening NYHA functional class and severity of mitral regurgitation.[4]

Our study has limitations. Firstly, the retrospective nature of the study and its single-center setting limit its generalizability. Furthermore, ATTR-CA is a heterogeneous disease with numerous genotypes. The mutations that were most commonly observed in our cohort apply to our institution and may not reflect the most common genotypes encountered elsewhere. Our study spanned an era during which recognition of ATTR-CA was rapidly expanding. Hence, many patients had advanced disease at the time of diagnosis, as evidenced by the subnormal mean LVEF on baseline echocardiogram.

In conclusion, the incidence and prevalence of high-grade AV block is high in patients with ATTR-CA. Patients with ATTR-CA require close monitoring during follow-up for the development of conduction system disease.

Author Contributions

EoinDonnellan: Conceptualization, Methodology, Writing − Original draft preparation, Writing − Reviewing and Editing; **OussamaWazni:** Conceptualization, Methodology; **WalidSaliba:** Methodology, Writing − Original draft preparation; **Mazen Hanna:** Conceptualization; **Mohamed Kanj**: Supervision; **Divyang Patel:** Software; **Bryan Wilner**: Writing − Original draft preparation; **ArshneelKochar**: Writing − Original draft preparation; **WaelJaber:** Supervision,Conceptualization, Methodology, Writing − Original draft preparation, Writing − Reviewing and Editing

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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