Incidence and risk factors for pacemaker implantation in light-chain and transthyretin cardiac amyloidosis

Aldostefano Porcari[1]*, Maddalena Rossi[1], Francesco Cappelli[2,3], Marco Canepa[4], Beatrice Musumeci[5], Alberto Cipriani[6], Giacomo Tini[5], Giulia Barbati[7], Guerino Giuseppe Varrà[1], Cristina Morelli[3], Carlo Fumagalli[3], Mattia Zampieri[3], Alessia Argirò[3], Pier Filippo Vianello[4], Eugenio Sessarego[4], Domitilla Russo[5], Giulio Sinigiani[6], Laura De Michieli[6], Gianluca Di Bella[8], Camillo Autore[5], Federico Perfetto[3], Claudio Rapezzi[9,10], Gianfranco Sinagra[1†], and Marco Merlo[1*†]

[1]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; [2]Tuscan Regional Amyloidosis Centre, Careggi University Hospital, Florence, Italy; [3]Cardiomyopathy Unit, Careggi University Hospital, University of Florence, Florence, Italy; [4]Cardiovascular Unit, Department of Internal Medicine, University of Genova, Ospedale Policlinico San Martino IRCCS, Genoa, Italy; [5]Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy; [6]Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; [7]Biostatistics Unit, Department of Medical Sciences, University of Trieste, Trieste, Italy; [8]Department of Cardiology, University of Messina, Messina, Italy; [9]Cardiothoracic Department, University of Ferrara, Ferrara, Italy; and [10]Maria Cecilia Hospital, GVM Care & Research, Ravenna, Italy

Received 10 January 2022; revised 1 May 2022; accepted 2 May 2022; online publish-ahead-of-print 16 May 2022

Aims The incidence and risk factors of pacemaker (PM) implantation in patients with cardiac amyloidosis (CA) are largely unexplored. We sought to characterize the trends in the incidence of permanent PM and to identify baseline predictors of future PM implantation in light-chain (AL) and transthyretin (ATTR) CA.

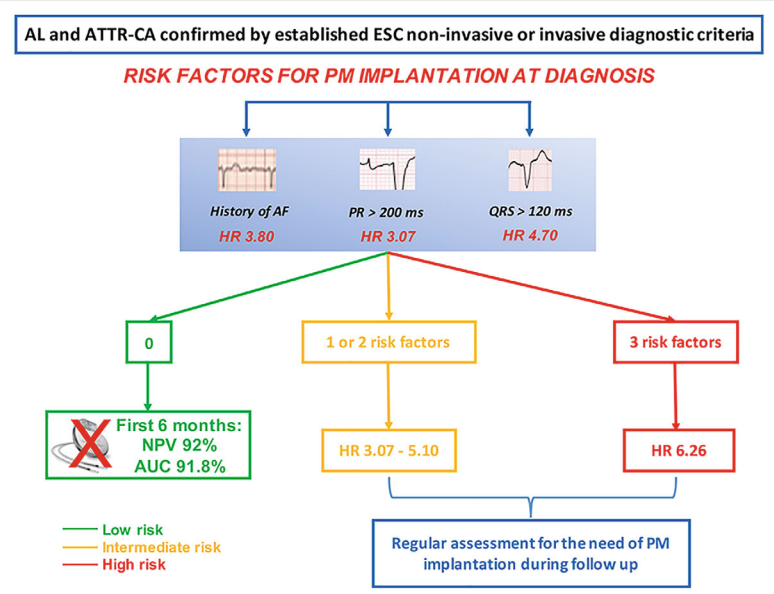
Methods and results Consecutive patients with AL and ATTR-CA diagnosed at participating centres (2017–2020) were included. Clinical data recorded within ±1 month from diagnosis were collected from electronic medical records. The primary study outcome was the need for clinically-indicated PM implantation. Patients with PM ($n = 41$) and/or permanent defibrillator in situ ($n = 13$) at CA diagnosis were excluded. The study population consisted of 405 patients: 29.4% AL, 14.6% variant ATTR and 56% wild-type ATTR; 82.5% were male, median age 76 years. During a median follow-up of 33 months (interquartile range 21–46), 36 (8.9%) patients experienced the primary outcome: 10 AL-CA, 2 variant ATTR-CA and 24 wild-type ATTR-CA ($p = 0.08$ at time-to-event analysis). At multivariable analysis, history of atrial fibrillation (hazard ratio [HR] 3.80, $p = 0.002$), PR interval (HR 1.013, $p = 0.002$) and QRS >120 ms (HR 4.7, $p = 0.001$) on baseline electrocardiogram were independently associated with PM implantation. The absence of these three factors had a negative predictive value of 92% with an area under the curve of 91.8% at 6 months.

Conclusion In a large cohort of AL and ATTR-CA patients, 8.9% received a PM within 3 years after diagnosis. History of atrial fibrillation, PR >200 ms and QRS >120 ms predicted future PM implantation.

*Corresponding author. Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Via P. Valdoni 7, 34100 Trieste, Italy. Email: aldostefanoporcari@gmail.com and marco.merlo79@gmail.com

†These authors contributed equally as last authors.

Graphical Abstract



Proposal of a flowchart to estimate the risk of pacemaker (PM) implantation in patients with light-chain (AL) and transthyretin (ATTR) cardiac amyloidosis (CA). AF, atrial fibrillation; AUC, area under the curve; ESC, European Society of Cardiology; HR hazard ratio; NPV, negative predictive value.

Keywords Light-chain cardiac amyloidosis • Transthyretin cardiac amyloidosis • Conduction system disease • Pacemaker implantation • Prognostic stratification

Introduction

Cardiac amyloidosis (CA) is an emerging cause of heart failure (HF) and mortality.[1] This condition results most frequently from age-related failure of homoeostatic mechanisms in wild-type transthyretin (ATTRwt) amyloidosis, destabilizing mutations in variant ATTR (ATTRv) amyloidosis or an haematological disorder in immunoglobulin light-chain (AL) amyloidosis.[2] Although patients often seek medical attention for the development of signs and symptoms of HF,[3,4] arrhythmias and conduction system diseases are common in CA, namely atrial fibrillation (AF), sinus node dysfunction and atrioventricular (AV) blocks.[5,6] Data regarding the incidence and prevalence of pacemaker (PM) implantation in CA are extremely scarce and focused only on ATTR-CA.[7] To the best of our knowledge, a single study on ATTR-CA reported that 10% of patients already had a PM in situ at the time of CA diagnosis and 11% underwent PM implantation during follow-up.[7] Although patients with ATTRwt-CA might be at increased risk of conduction system disorders, no study compared the rates of PM implantation in ATTR and AL-CA, investigated the clinical phenotypes at higher risk and identified tools to characterize the risk of future PM implantation in the individual patient with CA. Therefore, we designed this study to characterize the trends in the incidence of PM implantation and to identify baseline parameters able to predict the future need for PM implantation in a large cohort of well-characterized patients with AL and ATTR-CA.

Methods

This is a multicentre, retrospective, observational study performed in six Italian referral centres for cardiac amyloidosis: Trieste (Cattinara Hospital), Florence (Careggi Hospital), Genoa (San Martino Hospital), Padua (Padua University Hospital), Rome (Sant'Andrea Hospital) and Messina (Messina University Hospital). Trieste acted as coordinating centre of the study. The local Regional Institutional Review Board approved the study (identifier 43_2009), and the participating centres obtained local institutional review board approvals for the collection of anonymous data. The study was conducted according to the Declaration of Helsinki and informed consent was obtained under the institutional review board policies of the hospital administrations.

Study design and study population

Consecutive patients with AL and ATTR-CA diagnosed or referred at participating centres between 1 January 2017 and 31 December 2020 were included in the analysis. The end of follow-up was set at 31 October 2021. The diagnosis of AL and ATTR-CA was confirmed by

tissue biopsy or through established non-invasive criteria, according to the latest recommendations from the European Society of Cardiology.[8] In detail, ATTR-CA was diagnosed in presence of a Perugini grade 2 or 3 myocardial uptake at nuclear scintigraphy and absence of monoclonal protein at urine and serum tests. In patients with Perugini grade 1 myocardial uptake, the diagnosis of ATTR-CA was confirmed by endomyocardial biopsy (EMB).[8] DNA sequencing was performed in all patients diagnosed with ATTR-CA to identify mutations in the *TTR* gene.[8] Patients' baseline was set at the time of CA diagnosis at participating centres. Clinical data recorded within ±1 month from baseline were collected from electronic medical records, including all the following: (i) clinical examination, (ii) electrocardiogram (ECG), (iii) echocardiography, and (iv) blood tests. History of AF was confirmed by review of previous clinical reports documenting episodes of the arrhythmia. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min. For the purpose of estimating the incidence of PM implantation during follow-up, patients with a cardiac device in situ at the time of CA diagnosis were excluded from the analysis and those who received a permanent cardiac device without indications for pacing were censored at the time of implantation at time-to-event analysis.

Electrocardiography

Twelve-lead ECG was performed using standard equipment and retrospectively reviewed for heart rate, rhythm, QRS voltage, depolarization and repolarization abnormalities. The intervals on the surface ECG were measured by operators specifically for this analysis. Electrocardiographic parameters (in particular, left bundle branch block [LBBB], right bundle branch block [RBBB], left anterior fascicular block [LAFB] and bifascicular block [BFB]) were measured and recorded according to standard definitions.[9] In detail, first-degree AV block was defined as presence of PR interval >200 ms. Low voltages were defined as a QRS amplitude ≤0.5 mV in all limb leads or ≤1 mV in all precordial leads.

Echocardiography

Echocardiographic images stored on the electronic databases of the participating hospitals were systematically reviewed offline for this analysis. All echocardiographic parameters were measured according to standard international definitions.[10] Right ventricular systolic dysfunction was defined as presence of tricuspid annular plane systolic excursion (TAPSE) <17 mm and/or fractional area contraction <35%.[10]

Nuclear medicine

Cardiac scintigraphy was performed with different bone tracers (99mTc-DPD, 99mTc-HMDP and 99mTc-PYP) according to centres' local practice. A semi-quantitative score for cardiac uptake was obtained based on results of planar images as previously described by Perugini.[11]

Outcomes

The primary outcome of the study was PM implantation. Clinical indications for device implantation were (i) paroxysmal or permanent AV block (second-degree, 2:1 infranodal, advanced or third-degree type), (ii) syncope with sinus node dysfunction, (iii) AF with symptomatic low heart rate, (iv) syncope with documented asystolic pause/s >3 s, and (v) syncope with BFB. All-cause death was also recorded for competing risk analysis. Reversible causes of conduction system disease were systematically ruled out, including those drug-related, before implantation in all patients receiving a PM during follow-up. The follow-up protocol of the study included scheduled visits at participating centres at regular time intervals of 3 and 6 months in AL-CA and ATTR-CA, respectively, or earlier in case of clinical need; and contacting the treating physician or the general practitioner to obtain clinical data. These events were collected at scheduled follow-up evaluations, from electronic health record system, and, if needed, through telephone contacts with patients' general practitioners and/or relatives. When a PM was implanted outside the participating centres, clinical indication to device implantation was obtained by contacting the centre that performed the procedure.

Statistical analysis

Descriptive statistics between the study groups were calculated. Continuous variables were expressed as median with interquartile range (IQR, 25th–75th percentile) as data were not normally distributed according to the results of Kolmogorov–Smirnov test; categorical variables were expressed as absolute numbers and percentages. Differences between groups were evaluated using Mann–Whitney U test for continuous variables, while Chi-square or Fisher's exact test were used for dichotomous variables. The Kaplan–Meier method was used to estimate survival free from the study endpoint, and the log-rank test was used to compare the curves. Taking into account possible competing risk of all-cause death, cumulative incidence curves were also estimated and compared using the appropriate methods.[12] Univariable and multivariable Cox regression analyses were used to determine independent predictors of future PM implantation. Each variable was tested at univariable Cox analysis for the event PM implantation and whether significant ($p < 0.05$) was run into a multivariable Cox analysis. A total of 36 events occurred, 10 variables resulted significantly related to the prespecified event, thus several multivariable analyses were run with no more than four covariates. A p-value <0.05 was considered as statistically significant. All statistical analyses were performed using IBM SPSS Statistics 24.0 package (New York, NY, USA) statistical software version 20 and R (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/), packages 'cmprsk' and 'crrSC'.

Inter-centre variability analysis

There was good reliability between the centres in the assessment of echocardiographic parameters (online supplementary *Table S1*).

Results

Study population

The initial cohort consisted of 459 patients: 27.7% (n = 127) AL, 14.4% (n = 66) ATTRv and 58% (n = 266) ATTRwt. The most frequent TTR mutations in the ATTRv-CA cohort were Glu89Gln (n = 19, 29%), Ile68Leu (n = 12, 18%) and Val30Met (n = 7, 10%). At baseline evaluation, 41 patients (8.9%, 8 AL-CA, 3 ATTRv-CA and 30 ATTRwt-CA; p = 0.02) had a definitive PM and 13 (2.8%) had a permanent implantable cardioverter-defibrillator (ICD) in situ at the time of CA diagnosis, for a total prevalence of 11.8%. These patients were excluded from the study population, which consisted of 405 CA patients. Baseline characteristics of the study cohort are summarized in *Table 1*: 82.5% males, median age

Table 1 **Baseline characteristic of the study population according to pacemaker implantation during follow-up**

	Available (*n*)	Study population (*n* = 405)	No PM implantation (*n* = 369)	PM implantation (*n* = 36)	*p*-value
Age, years	405	76 (68–81)	73 (72–74)	75 (72–78)	0.575
Male sex	405	334 (82.5%)	302 (81.8%)	32 (88.9%)	0.289
BMI, kg/m^2	405	24.8 (23–30)	25 (25–26)	25 (24.26)	0.432
AL-CA	405	119 (29.4%)	109 (29.5%)	10 (27.8%)	0.220[a]
ATTRv-CA	405	59 (14.6%)	57 (15.4%)	2 (5.6%)	
ATTRwt-CA	405	227 (56%)	203 (55%)	24 (66.7%)	
NAC stage	213	2 (1–2)	2 (1–2)	2 (1–2)	0.670
Mayo stage	79	3 (2–3)	2 (2–3)	3 (2.5–4)	0.113
eGFR <60 ml/min	351	162 (46.2%)	91 (30%)	13 (36%)	0.270
NYHA class ≥III	405	100 (24.7%)	93 (25.2%)	7 (19.4%)	0.444
Previous syncope	381	17 (4.5%)	14 (4.1%)	3 (8.3%)	0.210
History of AF	405	170 (42%)	147 (39.8%)	23 (63.9%)	0.005
Electrocardiogram					
Rhythm at baseline	405				0.238
SR, %		303 (75%)	279 (75.6%)	24 (66.7%)	
AF, %		102 (25%)	90 (24.4%)	12 (33.3%)	
Heart rate, bpm	405	73 (55–82)	75 (74–76)	72 (67–76)	0.195
Dilated atria	266	128 (48.1%)	121 (48.6%)	7 (41.2%)	0.554
P-wave, ms	266	110 (80–120)	102 (99–104)	97 (86–107)	0.471
PR interval, ms	297	185 (160–219)	189 (184–194)	221 (195–246)	**0.011**
First-degree AV block	303	116 (38.3%)	101 (36.3%)	15 (62.5%)	**0.011**
AQRS, degree	370	−30 (−63–30)	−13 (−20–6)	−30 (−54–5)	**0.028**
QRS interval, ms	397	100 (87–120)	105 (102–108)	123 (113–134)	**<0.001**
QRS >120 ms	397	89 (22.4%)	72 (19.9%)	17 (48.6%)	**<0.001**
LBBB	405	39 (9.6%)	32 (8.7%)	7 (19.4%)	**0.037**
RBBB	405	71 (17.5%)	60 (16.3%)	11 (30.6%)	**0.031**
LAFB	405	144 (35.6%)	130 (35.2%)	14 (38.9%)	0.662
QRS/IVS ratio	405	6.5 (5.2–8.1)	6.4 (5.2–8.0)	6.7 (5.8–6.5)	0.355
Low QRS voltages					
Overall	405	159 (39.3%)	145 (39.3%)	14 (38.9%)	0.962
Precordial	156	9 (5.8%)	8 (5.6%)	1 (7.1%)	0.817
Peripheral	159	157 (99%)	143 (98.6%)	14 (100%)	0.658
Negative T-waves	405	92 (22.7%)	82 (22.2%)	10 (27.8%)	0.448
Pseudonecrosis	405	204 (50.4%)	188 (50.9%)	16 (44.4%)	0.456
Echocardiography					
IVS, mm	405	17 (15–19)	17 (16–17)	18 (17–19)	0.245
LVEF, %	405	55 (50–61)	55 (54–56)	52 (49–56)	**0.026**
LVEF <50%	405	94 (23.2%)	81 (22%)	13 (36.1%)	0.055
E/E'	344	16.5 (11–21)	17 (16–18)	20 (15–24)	0.412
LA diameter, mm	385	45 (40–49)	45 (44–46)	48 (45–51)	0.169
RFP	381	140 (36.7%)	131 (37.9%)	9 (25.7%)	0.155
TAPSE, mm	356	19 (15–22)	19 (18–19)	18 (17–19)	0.466
RV dysfunction	356	125 (35.1%)	114 (35.1%)	11 (35.5%)	0.964
sPAP, mmHg	342	35 (27–44)	36 (35–38)	35 (32–38)	0.696

AF, atrial fibrillation; AL, light-chain amyloidosis; ATTRv, variant transthyretin amyloidosis; AV, atrioventricular; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; CA, cardiac amyloidosis; BFB, bifascicular block; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IVS, interventricular septum; LA, left atrial; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; PM, pacemaker; RBBB, right bundle branch block; RFP, restrictive filling pattern; RV, right ventricular; SR, sinus rhythm; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

[a]Comparison between AL versus ATTR-CA.

76 years (IQR 68–81), 25% with New York Heart Association class III–IV, 42% had history of AF. At baseline evaluation, 303 (75%) patients were in sinus rhythm and 102 (25%) in AF. On 12-lead ECG, median P wave, PR interval and QRS durations were 110 ms (IQR 80–120), 185 ms (IQR 160–219) and 100 ms (IQR 87–120), respectively. Among those in sinus rhythm, first-degree AV block was found in 116 (38.3%). A wide (>120 ms) QRS complex was observed in 89 (22.4%) patients, of whom 39 (9.6%) had LBBB and 71 (17.5%) had RBBB. LAFB was present in 144 (35.6%) patients. On echocardiography, median interventricular septum (IVS) thickness was 17 mm (IQR 15–19), median left ventricular ejection fraction was 55% (IQR 50–61), median TAPSE 19 mm (IQR 15–22) and 37% of patients had a restrictive filling pattern.

Prognostic implications of surface ECG for pacemaker implantation

During a median follow-up of 33 months (IQR 21–46), 36 (8.9%) out of 405 patients experienced the primary outcome of the study: 10 among patients with AL-CA (8.4%, 2.9 events/100 patients/year), 2 among patients with ATTRv-CA (3.4%, 1 event/100 patients/year) and 24 among patients with ATTRwt-CA (10.6%, 4.2 events/100 patients/year). The overall median time to PM implantation was 18 months (13.5, 40 and 18 months in AL, ATTRv and ATTRwt-CA, respectively). Time-to-event analysis showed a similar incidence of PM implantation in patients with AL and ATTR-CA ($p = 0.65$) (online supplementary *Figure S1*). In 18 patients with Perugini grade 1 cardiac uptake on scintigraphy, the diagnosis of CA was confirmed by EMB (4 AL-CA, 3 vATTR-CA and 11 wtATTR-CA). There was no PM implantation in this group. Indications for PM implantation were similar in patients with AL and ATTR-CA (online supplementary *Tables S2* and *S3*).

Univariable analyses and the derived multivariable model with the highest χ^2 value are shown in *Table 2*. A history of AF emerged as independently associated with PM implantation (hazard ratio [HR] 3.80, $p = 0.002$), together with a longer PR interval (HR 1.013, $p = 0.002$) and a QRS >120 ms (HR 4.7, $p = 0.001$) at baseline ECG (*Figures 1* and *2*). These findings were further confirmed in a competing risk analysis for all-cause mortality (online supplementary *Figure S2*). A full list of parameters tested at multivariable analysis is shown in online supplementary *Table S4*. The risk of future PM implantation increased along with the number of the parameters identified in the main multivariable model (online supplementary *Figure S3*). Finally, the presence of either longer PR interval or history of AF in combination with BFB (RBBB + LAFB) and the contemporary presence of any two risk factors conferred an increased risk for PM implantation (HR 3.38 and 5.1, respectively), but the highest risk was found in presence of the three parameters (i.e. history of AF, PR interval >200 ms and QRS >120 ms) emerged at multivariable model (*Figure 3* and online supplementary *Figure S4*), both in AL and ATTR-CA (online supplementary *Table S5*). In the individual patient, the variable combination of history of AF, PR >200 ms, QRS >120 ms or BFB yielded a risk of PM implantation at 3 years ranging from 2.80 to 6.26 times. Patients with these risk factors had baseline characteristics in keeping with a more severe degree of cardiac amyloid infiltration (online supplementary *Table S6*). The absence of all these three risk factors had a negative predictive value for future PM implantation of 92% (88%–94%) with an area under the curve (AUC) of 91.8%. In the subgroup of patients without history of AF, the development of *de novo* AF during follow-up conferred an increased risk of PM implantation (HR 6.76, 95% confidence interval 1.85–24.72, $p = 0.004$). The need for PM implantation during follow-up was not associated with all-cause death in our cohort ($p = 0.1$).

Discussion

In the present study, more than 400 patients have been analysed from six Italian referral centres for the diagnosis and treatment of CA, being the largest analysis available in patients with AL and ATTR amyloidosis to investigate the baseline prognostic predictors of future PM implantation.

The main findings are: (i) definitive PM was present at the time of CA diagnosis in 5 (3.9%), 6 (9.1%) and 30 (11.3%) patients with AL, ATTRv and ATTRwt-CA, respectively; (ii) during a median follow-up of 33 months (21–46), 8.9% patients with CA required clinically-indicated permanent PM implantation; (iii) at extensive multivariable analyses, history of AF, longer PR interval and QRS >120 ms on baseline ECG were independently associated with subsequent PM implantation; and (iv) the presence of these three risk factors conferred the highest risk of PM implantation during follow-up.

As far as we know, this is the first study with a focus on prevalence and incidence of PM implantation in a large, well-characterized cohort of AL and ATTR-CA patients identifying clinical and instrumental parameters at presentation independently associated with PM implantation during follow-up. Data regarding prevalence and incidence of PM implantation in CA are scarce and available only on ATTR-CA.[7] The value of our analysis relies on the possibility (i) to confirm previous observations on the role of QRS >120 ms for the prediction of PM implantation; (ii) to further extend its validity also for patients with AL-CA; and (iii) to demonstrate for the first time that a history of AF, PR interval and QRS duration on baseline ECG are independently associated with subsequent PM implantation in both AL and ATTR-CA. Our results have not been shown before and deserve attention, potentially having major implications for clinical practice. Remarkably, in this analysis, CA patients with history of AF, longer PR interval and QRS duration on baseline ECG were at higher risk of future PM implantation and might deserve closer, dedicated cardiological follow-up. Moreover, patients with longer PR interval or history of AF deserve special surveillance in presence of a BFB (RBBB + LAFB) or LBBB (*Figure 3* and online supplementary *Figure S4*). These data add an important piece of information to the understanding of clinical phenotypes at higher risk of future conduction system disease that might benefit from long-term monitoring and provide tools for prediction of PM implantation in the individual patient with CA (*Graphical Abstract*). If confirmed in future dedicated studies, the combination of three simple parameters might be a novel, useful clinical tool to estimate the need for clinically-indicated PM implantation with high accuracy in the short term.

Table 2 Univariable and multivariable most accurate Cox models

	Available (*n*)	Univariable[a]		Multivariable[b]	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, years	405	1.030 (0.995–1.07)	0.092		
Male sex	405	0.477 (0.167–1.36)	0.167		
BMI, kg/m^2	405	0.986 (0.898–1.083)	0.767		
AL vs. ATTR-CA	405	1.17 (0.561–2.45)	0.674		
NAC score	213	0.978 (0.562–1.704)	0.938		
Mayo score	79	2.80 (0.914–8.445)	0.072		
eGFR <60 ml/min	351	1.008 (0.994–1.023)	0.259		
NYHA class ≥III	405	1.008 (0.596–1.704)	0.976		
Previous syncope	381	2.75 (0.834–9.064)	0.096		
History of AF	405	2.96 (1.5–5.86)	**0.002**	**3.80 (1.64–8.8)**	**0.002**
SR vs. AF at baseline	405	0.582 (0.290–1.167)	0.127		
Heart rate, bpm	405	0.985 (0.958–1.013)	0.284		
Heart rate <60 bpm	405	1.31 (0.50–3.37)	0.578		
Dilated atria	266	0.777 (0.295–2.05)	0.610		
P-wave, ms	266	0.989 (0.967–1.012)	0.356		
PR interval, ms	297	1.014 (1.007–1.022)	**0.004**	**1.013 (1.005–1.02)**	**0.002**
First-degree AV block	303	3.07 (1.33–7.07)	**0.008**		
AQRS, degree	370	0.995 (0.990–1.001)	0.133		
QRS interval, ms	397	1.021 (1.011–1.031)	**<0.001**		
QRS >120 ms	397	3.97 (2.04–7.74)	**<0.001**	**4.70 (1.90–11.7)**	**0.001**
LBBB	405	2.26 (0.989–5.16)	0.054	0.35 (0.07–1.63)	0.18
RBBB	405	2.37 (1.61–4.83)	**0.018**		
LAFB	405	1.17 (0.601–2.30)	0.636		
Low QRS voltages	405	0.995 (0.509–1.95)	0.988		
QRS/IVS ratio	405	0.993 (0.867–1.138)	0.925		
Negative T-waves	405	1.194 (0.575–2.48)	0.635		
Pseudonecrosis	405	0.814 (0.422–1.57)	0.541		
IVS, mm	405	1.086 (0.995–1.85)	0.064		
LVEF, %	405	0.979 (0.951–1.008)	0.153		
LVEF <50%	405	2.1 (1.06–4.15)	**0.033**		
E/E'	344	1.037 (1.001–1.074)	**0.045**		
LA diameter, mm	385	1.043 (1.003–1.086)	**0.037**		
RFP	381	0.695 (0.324–1.49)	0.349		
TAPSE, mm	356	0.975 (0.904–1.050)	0.502		
RV dysfunction	356	1.053 (0.517–2.142)	0.887		
sPAP, mmHg	342	0.999 (0.969–1.029)	0.927		

AF, atrial fibrillation; AL, light chain amyloidosis; ATTRv, variant transthyretin amyloidosis; AV, atrioventricular; ATTRwt, wild-type transthyretin amyloidosis; CA, cardiac amyloidosis; BFB, bifascicular block; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IVS, interventricular septum; LA, left atrial; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NAC, National Amyloidosis Centre; NYHA, New York Heart Association; PM, pacemaker; RBBB, right bundle branch block; RFP, restrictive filling pattern; RV, right ventricular; SR, sinus rhythm; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

[a]Each variable was tested at univariable Cox analysis for the main endpoint of the study.

[b]The multivariable with the highest χ^2 value (37.4) is shown. The independent prognostic value of history of AF, PR interval and QRS ≥120 ms was confirmed in an extensive multivariable analysis taking into account covariates which resulted significantly ($p < 0.05$) related to the main endpoint of the study at univariable analysis.

Prevalence and incidence of pacemaker implantation in cardiac amyloidosis

In this analysis, we report that the prevalence at baseline and the incidence during follow-up of PM implantation is high in AL and ATTR-CA patients, accounting for 8.9% of patients with a PM in situ at the time of diagnosis and 8.9% of patients requiring device implantation in the 3 years following the diagnosis (*Figure 1*). Rapezzi *et al.*[13] were the first to characterize the cardiological profile of CA patients at presentation and reported the presence of permanent PM in 3% of AL-CA, 13% of ATTRwt-CA and 3% of ATTRv-CA at the time of diagnosis. Although arrhythmias and conduction system disease are common in CA, baseline parameters able to predict the need for future device implantation represent a largely unexplored field. To the best of our knowledge, only a single study investigated the prevalence and incidence of high-grade AV block requiring PM implantation in a cohort of ATTR-CA.[7] Of note, in line with our results, the authors reported similar findings

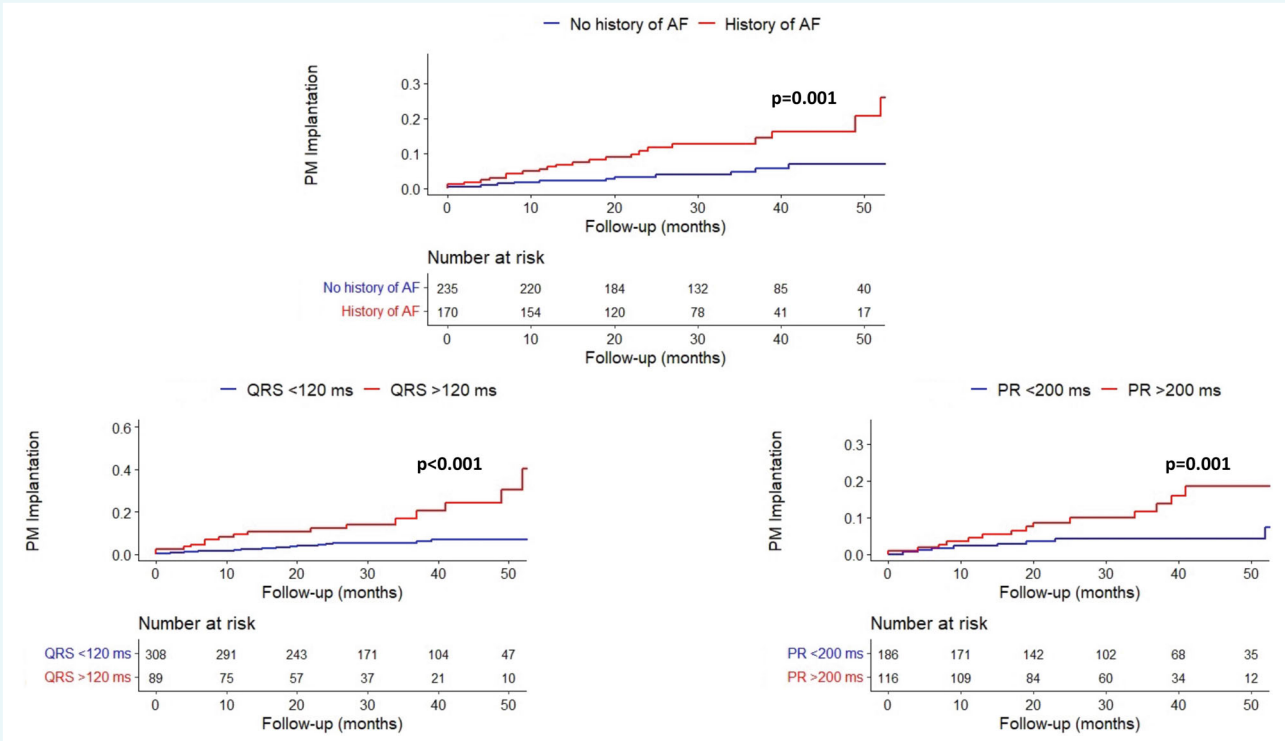


Figure 1 Cumulative incidence curves for pacemaker (PM) implantation in patients with and without history of atrial fibrillation (AF) (*upper panel*), PR interval >200 ms and QRS duration >120 ms (*lower panels*).

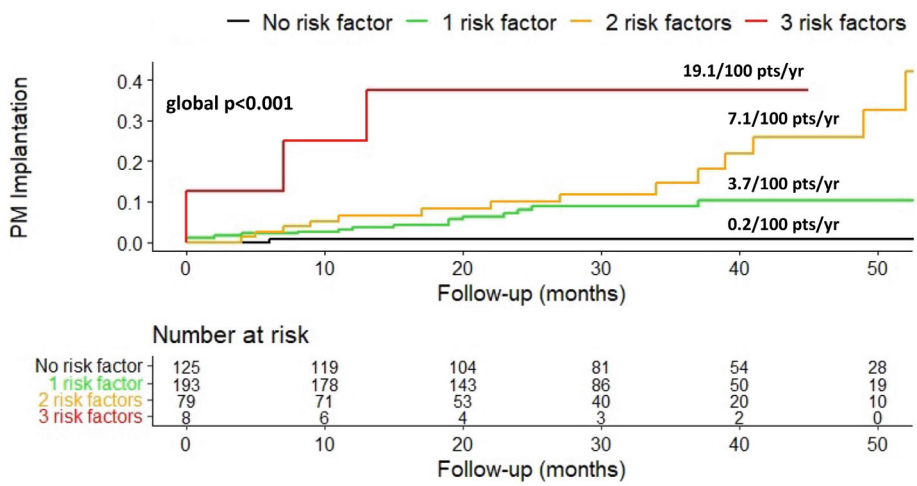


Figure 2 Incidence rate of pacemaker (PM) implantation according to (1) history of atrial fibrillation, (2) PR interval >200 ms, and (3) QRS >120 ms at baseline. Cumulative incidence is measured as number of events/100 patients/year. The rate of PM implantation is shown on the y-axis as a percentage.

with 9.5% of patients receiving PM implantation before the diagnosis and 11% of patients developing clinical indications to device implantation during follow-up.[5,7] Therefore, our findings confirm previous observations and further extend the validity of the results also for patients with AL-CA. In the present analysis, the need for clinically-indicated PM implantation during follow-up was similar in different stages of disease and among AL and ATTR-CA. Although ATTR-CA is expected to be associated with a higher incidence of PM implantation, this result might be explained by (i) the increased number of ATTR-CA patients recognized in earlier disease stages

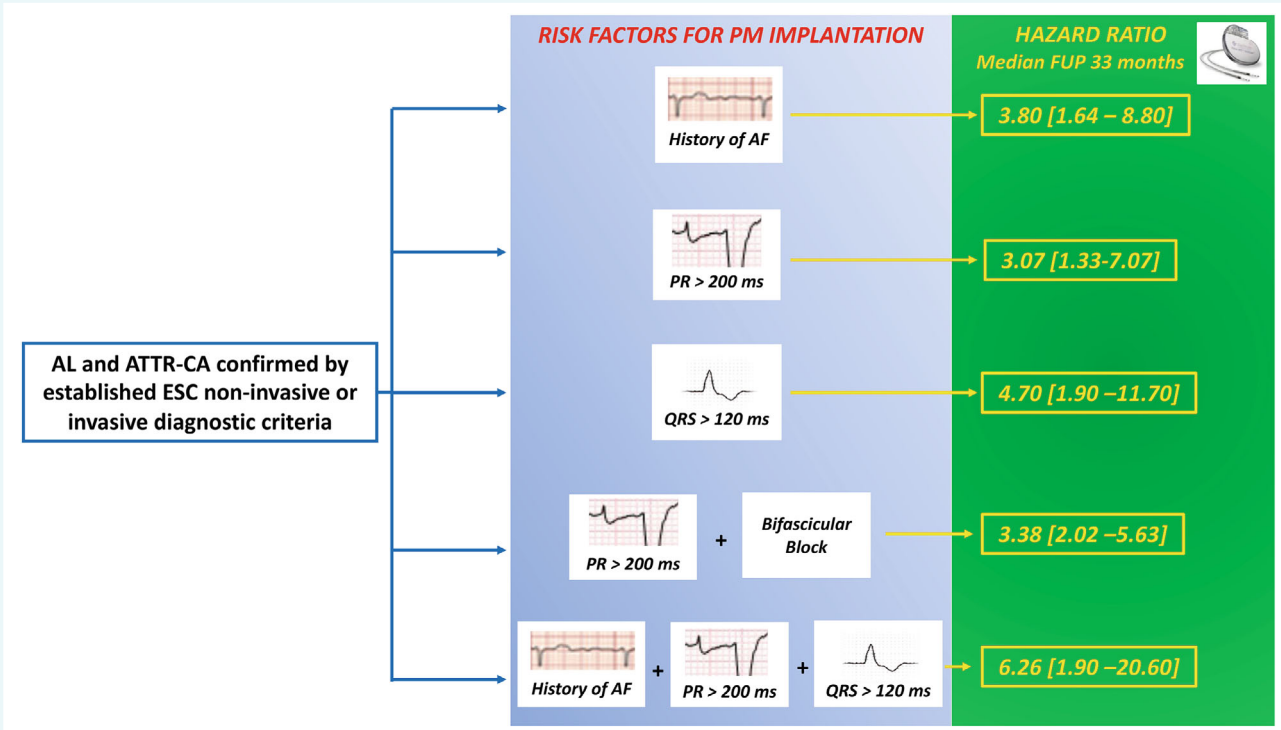


Figure 3 Risk factors for pacemaker (PM) implantation in light-chain (AL) and transthyretin (ATTR) cardiac amyloidosi (CA). AF, atrial fibrillation; ESC, European Society of Cardiology; FUP, follow-up.

compared to the past; (ii) the toxic effect exerted by immunoglobulin light chains on conduction system and the myocardium in AL-CA patients; and (iii) the common detection of bradyarrhythmias and complete AV block in patients with severe AL-CA implanted with cardiac rhythm recorders.[14] When considering the prevalence and incidence of PM implantation in the population initially screened for this study (n = 459), patients with ATTRwt-CA appeared to have the highest need for PM (online supplementary *Figure S5*). Nevertheless, whether PM implantation was clinically indicated in patients already carrying this cardiac device at baseline could not be determined and was outside the scope of the present analysis. Prospective studies on larger cohorts will be needed in this field. Finally, amyloid deposition in the heart is heterogeneous and, perhaps, factors other than the aetiology are more relevant for the risk of PM implantation such as those identified on multivariable analysis: PR interval, history of AF and QRS >120 ms. Therefore, the ability of those parameters to predict future PM implantation in the short term might aid in the accurate identification of candidates, beyond the specific CA aetiology. Dedicated staging systems[15] should be used specifically for global prognostic stratification in AL and ATTR-CA.

Baseline predictors of pacemaker implantation in cardiac amyloidosis

To the best of our knowledge, this is the first study demonstrating that a history of AF, PR interval and QRS duration on baseline ECG are independently associated with subsequent PM implantation (*Figure 1*). A number of pathophysiological and clinical reasons can explain our findings. First, AF is the most common arrhythmia in CA and results from direct atrial deposition of insoluble misfolded precursor proteins and the increase in filling pressures due to non-compliant ventricles. Although the prognostic impact of AF in CA is still under investigation, AF is considered a marker of more advanced cardiac amyloid infiltration and its prevalence increases with advancing ATTR-CA stage.[6] Second, prolongation of the PR interval confers an increased risks of AF, PM implantation, and all-cause mortality in the general population.[16] In CA, the increase in PR and QRS interval duration reflects amyloid deposition in the atria and ventricles, which disrupts tissue structure and the transmission of electrical impulses along conduction fibres.[17,18] In advanced disease stages, atrial myocyte bundles are progressively isolated with significant intra-atrial conduction delay and prolongation of P-wave duration on surface ECG.[19] Of note, in the present analysis, P-wave duration was not associated with PM implantation, thus suggesting that the prognostic value of the PR interval resided in the ability to reflect the AV rather than the intra-atrial conduction delay. Third, LBBB and RBBB leading to a wide QRS interval are known to be associated with the development of high-grade AV block leading to PM implantation.[16,20,21] In our cohort, at multivariable analysis, a QRS interval >120 ms portended a higher risk of the primary outcome, but LBBB and RBBB did not. These findings might support the hypothesis that the prognostic impact of wide QRS interval is independent from

the specific pattern of intraventricular conduction disease evident on baseline ECG. Similar results were found in a previous study on 369 ATTR-CA patients followed over 28 months where a wide QRS interval (>120 ms) on baseline ECG was the only parameter associated with the subsequent development of high-grade AV block.[7] In addition, we found that the incidence rate of PM implantation in patients with wide QRS was much higher than that of patients with LBBB or BFB (*Figure 3* and online supplementary *Figure S4*), that are known to be at risk of progression to complete AV block and/or syncope during follow-up, also in absence of structural heart disease.[22,23] This finding suggests that QRS duration might be a more sensitive marker of conduction system disease than the specific pattern of intraventricular delay (i.e. LBBB, RBBB and BFB), reasonably due to the ability to reflect the burden of amyloid deposition in the heart along with the impairment of intraventricular fascicles. Finally, the presence of a wide QRS with history of AF and longer PR interval conferred the highest risk of PM implantation in the CA setting (online supplementary *Figure S3*). These parameters emerged indeed as possible tools to estimate the risk of future PM implantation in the individual patient with CA, both in AL and ATTR amyloidosis (*Figure 3* and online supplementary *Table S5*). Notably, the presence of these risk factors was higher in CA patients with echocardiographic parameters in keeping with a more advanced cardiac infiltration, pointing at a relationship between amyloid burden and conduction system impairment (online supplementary *Table S6*). Therefore, our results strongly suggest to assess carefully medical history and baseline ECG for the presence of these risk factors and to monitor patients for the development of risk factors of PM implantation during follow-up as the risk conferred by CA is dynamic over time. The translation of these findings into clinical practice requires confirmation in further studies. The use of long-term monitoring devices in future dedicated studies on patients with CA will allow more accurate identification of candidates for PM implantation.[24] In the modern era, CA is increasingly recognized as a relatively prevalent condition.[18] Recent advances in diagnosis and treatment are going to translate into longer life expectancy of patients and more challenging clinical scenarios[25] such as the need to identify subjects at higher risk for conduction system abnormalities and PM implantation. Further research is required to determine whether initiation of specific treatments can reduce the need for cardiac device implantation and increase the survival free from PM implantation.[26]

Limitations

The study was retrospective and conducted among referral centres for the diagnosis and management of AL and ATTR-CA in Italy. Although the study protocol was designed to minimize the risk of missing patients with indications for PM implantation, we cannot completely exclude this event. The heterogeneity of TTR mutations did not allow to perform subgroup analyses in specific cohorts on ATTRv-CA patients. Data regarding the presence of hypertension and patients' medications were not available due to the retrospective nature of the study. Serum levels of troponin and natriuretic peptides were not analysed due to inter- and intra-centre differences in assay sensitivity and biomarkers in use over time. The presence and potential prognostic value of cardiac magnetic resonance parameters for prediction of PM implantation could not be explored in this analysis. Finally, CA stage could not be measured in the whole study cohort because of missing data due to the retrospective nature of the analysis. Further studies (possibly using artificial intelligence methods) are required to investigate if other clinical/laboratory parameters (including cardiac magnetic resonance parameters) can provide incremental value over the findings of the present analysis for the prediction of PM implantation in CA.

Conclusion

In a large cohort of well-characterized patients with AL and ATTR-CA, the incidence of PM implantation was high accounting for 8.9% of patients in the 3 years following the diagnosis. History of AF, PR interval and QRS >120 ms on baseline ECG independently predicted the future need for PM implantation in both AL and ATTR-CA, while disease aetiology did not. While CA patients with these features might need close monitoring during follow-up for the development of conduction system disease requiring PM implantation, the absence of all risk factors accurately identified patients without need for PM implantation in the first 6 months after diagnosis.

Supplementary Information

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

Acknowledgements

We would like to thank all the nuclear medicine doctors, haematologists, neurologists, pathologists and nephrologists of the participating centres for providing their essential contribution in multidisciplinary teams for the care of patients with amyloidosis. We would like to thank Fondazione CRTrieste, Fondazione CariGO, Fincantieri, and all the healthcare professionals for the continuous support to the clinical management of patients affected by cardiomyopathies, followed in the Heart Failure Outpatient Clinic of Trieste, and their families. Finally, a special thank is for the cardiac nurses of outpatient clinics involved in the study, for their daily, professional management of patients and their relatives.

Conflict of interest: none declared.

References

1. Gilstrap LG, Dominici F, Wang Y, Wang Y, El-Sady MS, Singh A, et al. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations among fee-for-service Medicare beneficiaries in the United States. *Circ Heart Fail*. 2019;**12**: e005407.
2. Porcari A, Merlo M, Rapezzi C, Sinagra G. Transthyretin amyloid cardiomyopathy: an uncharted territory awaiting discovery. *Eur J Intern Med*. 2020;**82**:7–15.
3. Merlo M, Porcari A, Pagura L, Cameli M, Vergaro G, Musumeci B, et al. A national survey on prevalence of possible echocardiographic red flags of amyloid cardiomyopathy in consecutive patients undergoing routine echocardiography: study design and patients characterization – the first insight from the AC-TIVE study. *Eur J Prev Cardiol*. 2022;**29**:e173–7.

4. Merlo M, Pagura L, Porcari A, Cameli M, Vergaro G, Musumeci B, et al. Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from phase 2 of AC-TIVE study, an Italian nationwide survey. *Eur J Heart Fail*. 2022. https://doi.org/10.1002/ejhf.2504.
5. Hartnett J, Jaber WA, Maurer M, Sperry B, Hanna M, Collier P, et al. Electrophysiological manifestations of cardiac amyloidosis. *JACC CardioOncol*. 2021;**3**:506–515.
6. Donnellan E, Wazni OM, Hanna M, Elshazly MB, Puri R, Saliba W, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. *JACC Clin Electrophysiol*. 2020;**6**:1118–27.
7. Donnellan E, Wazni OM, Saliba WI, Hanna M, Kanj M, Patel DR, et al. Prevalence, incidence, and impact on mortality of conduction system disease in transthyretin cardiac amyloidosis. *Am J Cardiol*. 2020;**128**:140–6.
8. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;**42**:1554–68.
9. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram. *Circulation*. 2007;**115**:1306–24.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;**16**:233–71.
11. Perugini E, Guidalotti PL, Salvi F, Cooke RMT, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99m Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol*. 2005;**46**:1076–84.
12. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;**16**:1141–54.
13. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses. *Circulation*. 2009;**120**:1203–12.
14. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HL, Fontana M, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur Heart J*. 2015;**36**:1098–105.
15. Pregenzer-Wenzler A, Abraham J, Barrell K, Kovacsovics T, Nativi-Nicolau J. Utility of biomarkers in cardiac amyloidosis. *JACC Heart Fail*. 2020;**8**:701–11.
16. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA*. 2009;**301**:2571–7.
17. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;**73**:2872–91.
18. Porcari A, Bussani R, Merlo M, Varrà GG, Pagura L, Rozze D, et al. Incidence and characterization of concealed cardiac amyloidosis among unselected elderly patients undergoing post-mortem examination. *Front Cardiovasc Med*. 2021;**8**:1680.
19. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R, et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm*. 2016;**13**:383–90.
20. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. *Eur Heart J*. 2013;**34**:138–46.
21. Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. The primary prevention study in Göteborg, Sweden. *Eur Heart J*. 2005;**26**:2300–6.
22. Rivera-López R, Cabrera-Ramos M, Jordán-Martinez L, Jimenez-Jaimez J, Macias-Ruiz R, Aguilar-Alonso E, et al. Syncope and bifascicular block in the absence of structural heart disease. *Sci Rep*. 2020;**10**:8139.
23. Santini M, Castro A, Giada F, Ricci R, Inama G, Gaggioli G, et al. Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin. *Circ Arrhythm Electrophysiol*. 2013;**6**:101–7.
24. Rehorn MR, Loungani RS, Black-Maier E, Coniglio AC, Karra R, Pokorney SD, et al. Cardiac implantable electronic devices: a window into the evolution of conduction disease in cardiac amyloidosis. *JACC Clin Electrophysiol*. 2020;**6**:1144–54.
25. Porcari A, Pagura L, Longo F, Sfriso E, Barbati G, Murena L, et al. Prognostic significance of unexplained left ventricular hypertrophy in patients undergoing carpal tunnel surgery. *ESC Heart Fail*. 2022;**9**:751–60.
26. Zhang KW, Stockerl-Goldstein KE, Lenihan DJ. Emerging therapeutics for the treatment of light chain and transthyretin amyloidosis. *JACC Basic Transl Sci*. 2019;**4**:438–48.