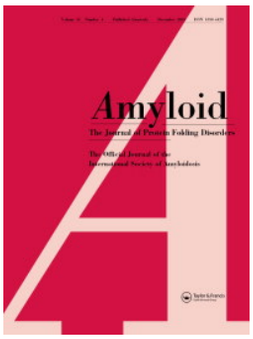

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RESEARCH ARTICLE

Incidence and predictors of sudden death in patients with cardiac amyloidosis

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ABSTRACT

Introduction: Although sudden death (SD) is a recognized complication of cardiac amyloidosis, there is scarce data about its incidence, mechanisms, and predictors. The aim of this study was to describe incidence of SD and to analyze possible risk factors.

Methods: Consecutive patients with ATTR or AL cardiac amyloidosis evaluated at two European centers were identified. SD was defined as unexpected death in clinically stable patients. Cox proportional hazard regression was performed to assess risk factors in univariate analysis. Those statistically significant were then assessed through age-adjusted multivariate analysis.

Results: Analysis included 784 patients, 569 with ATTR amyloidosis (mean age 74.1 ± 12.1 years) and 215 with AL amyloidosis (mean age 64.5 ± 10.8 years). After a median follow-up of 1.9 years, SD rate at 2 years was 1.8% in ATTR. Previous pacemaker implantation (PPM) was associated with increased risk after age-adjusted analysis (HR 4.97; 95%CI: 1.39–17.7; $p = 0.01$). SD rate in AL amyloidosis patients at 2 years was 8.0% after a median follow-up of 1.2 years. Betablockers and NYHA III-IV were independently associated with an increased risk after age-adjusted multivariate analysis (HR 7.06 95%CI (2.31–21.5) $p = 0.001$) and (HR 4.56 95%CI (1.51–13.8) $p = 0.007$) respectively.

Conclusions: SD is more frequent in AL than in ATTR cardiac amyloidosis. SD is associated with different risk factors in both entities.

Abbreviations and Acronyms: AL-CA: LIGHT-CHAIN CARDIAC AMYLOIDOSIS; ATTR-CA: TRANSTHYRETIN CARDIAC AMYLOIDOSIS; CA: CARDIAC AMYLOIDOSIS; SD: SUDDEN DEATH (SD); VA: VENTRICULAR ARRHYTHMIAS; PEA: PULSELESS ELECTRICAL ACTIVITY; ICD: IMPLANTABLE CARDIOVERTER DEFIBRILLATOR; PPM: PREVIOUS PACEMAKER IMPLANTATION

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Introduction

Cardiac amyloidosis (CA) is a group of diseases caused by extracellular deposition of amyloid fibrils in the myocardium [1]. Transthyretin amyloidosis (ATTR) and light-chain amyloidosis (AL) constitute the most common types of cardiac amyloidosis accounting for >95% of cases currently [1].

Sudden death (SD) is a recognized complication of both ATTR-CA and AL-CA although recent publications have described very different incidence rate of SD in both disorders with a relatively low incidence in ATTR-CA (0–1.6%) and a substantially higher in AL-CA (6.1–7.5%) [2,3]. Underlying mechanisms of SD in CA are varied (ventricular arrhythmias [VA] vs pulseless electrical activity [PEA] or bradyarrhythmia) and the role of implantable cardioverter defibrillators (ICD) is currently not established with most available data not supporting its use in primary prevention [4,5].

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Advances in noninvasive imaging techniques have led to an exponential growth of the number of patients with CA (particularly with ATTR-CA) seen in clinical practice, and the availability of new treatments has been accompanied by improved survival [1,6]. In this context, there is an urgent need to untangle SD in CA to provide better care for these patients.

The aim of this study was to describe incidence of SD and to analyze risk factors associated with this complication in a large cohort of patients with ATTR-CA and AL-CA.

Methods

Consecutive patients with ATTR-CA or AL-CA evaluated at Sant'Orsola Hospital (Bologna, Italy) 1986–2020 and Hospital Universitario Puerta de Hierro (Madrid, Spain) between 2008–2020 were identified for this study from prospective databases. The study complies with the Declaration of Helsinki and was approved by the institution's ethics committee. Inclusion criteria comprised age ≥18 years and a definitive diagnosis based on current guidelines [1]. Patients who did not return after initial visit and whose clinical status could not be confirmed after contacting their relatives and referring doctors were excluded.

Baseline characteristics including demographics, medical history, medical treatment, devices, ECG parameters and echocardiographic data were retrospectively retrieved by local chart review. Follow-up was performed at both participating centers. Mortality after first evaluation was registered with special focus on the cause and circumstances of death. SD was defined as unexpected death within 1 h after onset of symptoms or, if unwitnessed, death within 24 h from the last time the patient was observed alive.

Statistical analysis was performed with Student's t-test and Wilcoxon rank-sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Kaplan–Meier curves were used to describe SD incidence censored to other causes of death, heart transplantation or date of last follow-up. Cox proportional hazard regression or log-rank tests were performed to assess risk factors in univariate analysis. Variables that were associated with SD in univariate analysis were then assessed through age-adjusted multivariate analysis. Age was retained in the model irrespective of statistical association in our cohort due to its previously described association with overall mortality and SD [7]. An *ad hoc* analysis of NAC stage as a predictor of SD in patients with ATTR was performed for a subgroup of patients with available information to calculate NAC stage. STATA software version 15.1 (StataCorp, College Station, TX) was used. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Analysis included 784 patients, 569 (73%) with ATTR-CA and 215 (27%) with AL-CA. Among patients with ATTR, 155 (27.2%) were hereditary forms. The most frequent variants found in our cohort were p.(Ile88Leu) ($N=49$; 31.6%), p.(Val50Met) ($N=26$;16.8%) and p(Glu109Gln) ($N=23$; 14.8%). Table 1 shows baseline characteristics of both groups. In summary, ATTR-CA patients were older (mean age 74.1 ± 12.1 vs 64.5 ± 10.8 years; $p<0.001$), more frequently male (82.4% vs 60.9%; $p<0.001$) and had more ICDs implanted (2.1% vs 0%; $p=0.04$). After a median follow-up of 1.7 years (IQR: 0.7-3.6), 26 patients (3.3%) (15 [7.0%] with AL and 11 [1.9%] with ATTR-CA) suffered a SD. Patients with AL-CA had higher risk of SD than patients with ATTR-CA (HR 4.19; 95%CI: 1.92-9.13; $p<0.001$).

Among patients with ATTR-CA, median follow-up was 1.9 years (IQR: 0.9–3.7) with a median time from initial evaluation to SD of 1.7 years (IQR: 0.7–3.6). Event rate at 2 years was 1.8% (0.72 events/100 person-years). PEA was the first rhythm in 4 cases (36%) while no information was available in the remaining cases. In nine cases, (2%) SD occurred while resting or sleeping and no cases were

Table 1. Baseline characteristics.

	ATTR-CA (569)	AL-CA (215)	*P*-value
Age (years)	74.1 (12.1)	64.5 (10.8)	<0.001
Male sex	469 (82.4%)	132 (60.9%)	<0.001
ATTRv	155 (27.2%)	–	–
Comorbidities			
Atrial fibrillation	281 (50.0%)	32 (15.5%)	<0.001
Stroke	42 (7.5%)	20 (9.8%)	0.32
CKD	11 (1.9%)	19 (8.8%)	<0.001
Polyneuropathy	154 (30.0%)	42 (21.5%)	0.02
Previous syncope	54 (9.7%)	22 (10.7%)	0.67
Baseline NYHA			<0.001
NYHA I-I	455 (80.0%)	128 (59.5%)	
NYHA III-IV	114 (20.0%)	87 (40.5%)	
Devices			
Pacemaker	69 (12.1%)	11 (5.1%)	0.004
ICD	12 (2.1%)	0 (0%)	0.04
ECG			
PR (ms)	200.7 (44.4)	181.3 (37.1)	<0.001
Low voltages	129 (27.9%)	115 (55.8%)	<0.001
AVB			0.05
Normal	208 (57.1)	126 (68.5%)	
1st degree AVB	151 (41.5%)	56 (30.4%)	
2nd degree AVB	3 (0.8%)	1 (0.5%)	
Complete AVB	2 (0.6%)	1 (0.5%)	
Ventricular conduction abnormalities			<0.001
Absence	258 (46.5%)	132 (65.0%)	
LBBB	53 (9.6%)	3 (1.5%)	
RBBB	76 (13.7%)	16 (7.9%)	
Incomplete BBB	103 (18.6%)	45 (22.2%)	
Paced	48 (8.7%)	6 (3.0%)	
RBBB + LAB	17 (3.1%)	1 (0.5%)	
Echocardiography			
SWT (mm)	17.8 (3.3)	16.5 (2.9)	<0.001
LVEF (%)	55.3 (12.1)	55.9 (12.8)	0.38
LA diameter (mm)	46.3 (6.9)	44.2 (6.8)	<0.001
Pharmacological treatment at baseline evaluation			
Betablockers	224 (41.0%)	51 (25.1%)	<0.001
Calcium antagonist	28 (5.1%)	5 (2.5%)	0.16
Digoxin	13 (2.4%)	2 (1%)	0.38
Amiodarone	22 (4.0%)	9 (4.4%)	0.80

Abbreviations: AL-CA: Light-chain cardiac amyloidosis; ATTR-CA: Transthyretin cardiac amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; AVB: Atrioventricular block; BBB: Bundle branch block; CKD: Chronic kidney disease; ECG: Electrocardiogram; ICD: Implantable cardioverter defibrillator; LAB: Left anterior block; LA: Left atrium; LBBB: Left bundle branch block; LVEF: Left ventricular ejection fraction; RBBB: Right bundle branch block; SWT: Septal wall thickness.

reported during physical activity. Table 2 shows univariate analysis of potential risk factors for SD in ATTR-CA. Previous pacemaker implantation (PPM) was the only factor that was associated with increased risk for SD and remained significant after age-adjusted analysis (HR 4.97; 95%CI: 1.39–17.7; $p = 0.01$). A subanalysis of 357 patients with NAC stage information (62.7%) did not show differences among groups (Log-rank $p = 0.34$) Supplementary material). Figure 1 shows KM curves according to PPM presence. Among patients with ICD ($N = 12$, 2.1%) no SD were reported, and no patients had an appropriate discharge. Only one patient had a sustained ventricular tachycardia episode that did not respond to antitachycardia pacing but was self-terminated.

Table 2. Univariate and multivariate analysis of risk factors for SD in ATTR-CA.

	HR	95%CI	P value
Univariate analysis			
Age	1.04	0.99-1.11	0.13
Male sex	1.01	0.22-4.67	0.99
ATTRv	1.12	0.32-3.92	0.86
AF	1.25	0.37-4.19	0.72
CVA	1.57	0.20-12.4	0.67
Previous syncope	1.08	0.14-8.51	0.94
NYHA III-IV	1.49	0.32-6.99	0.62
Pacemaker	5.81	1.65-20.5	**0.006**
ICD	–	–	0.67
PR ≥ 200 ms	4.76	0.48-47.0	0.18
QRS ≥ 120 ms	1.75	0.47-6.55	0.41
Low voltage ECG	0.35	0.04-2.87	0.33
IVS (mm)	0.97	0.81-1.17	0.77
LVEF (%)	1.01	0.96-1.07	0.65
Betablockers	1.58	0.45-5.50	0.47
Calcium antagonist	–	–	0.46
Digoxin	–	–	0.62
Amiodarone	–	–	0.51
Multivariate analysis			
Age	1.04	0.98-1.11	0.20
Pacemaker	4.97	1.39-17.7	**0.01**

Abbreviations: ATTR-CA: Transthyretin cardiac amyloidosis; ATTRv: Hereditary transthyretin amyloidosis; CVA: Cardiovascular accident; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; IVS: Interventricular septum; LVEF: Left ventricular ejection fraction; SD: Sudden death.

Among patients with AL-CA, median follow-up was 1.2 years (IQR: 0.4-3.3) with a median time to event of 0.2 years (IQR: 0.1-0.5). Event rate at 2 years was 8.0% (2.93 events/100 person-years). PEA was the first rhythm in 8 cases (53.3%) while no information was available in the remaining cases. Again, SD occurred while resting or sleeping in the majority of individuals (12, 80%) and there were not SD during physical activity. Table 3 shows univariate analysis of potential risk factors for SD in AL-CA. Treatment with betablockers and advanced NYHA (III-IV) were the only factors associated with an increased risk of SD and remained significant after age-adjusted multivariate analysis with a seven-fold risk of SD in patients receiving betablockers (HR 7.06 95%CI (2.31-21.5) $p = 0.001$) and a four-fold risk for patients in NYHA III-IV (HR 4.56 95%CI (1.51-13.8) $p = 0.007$). Figure 2 and Figure 3 show KM curve according to betablockers and NYHA in AL CA.

Discussion

To our knowledge, this is largest cohort of patients with CA describing SD incidence and risk factors reported to date. Our results show that patients with AL-CA present significantly higher risk of SD compared with patients with ATTR-CA and highlight that risk factors associated with SD vary between CA types suggesting that underlying mechanisms may be different between these two entities.

Overall SD event rate in patients with ATTR-CA was relatively low providing a general reassuring message for clinicians following these patients. Surprisingly, the only identified risk factor in this subgroup was previous PPM

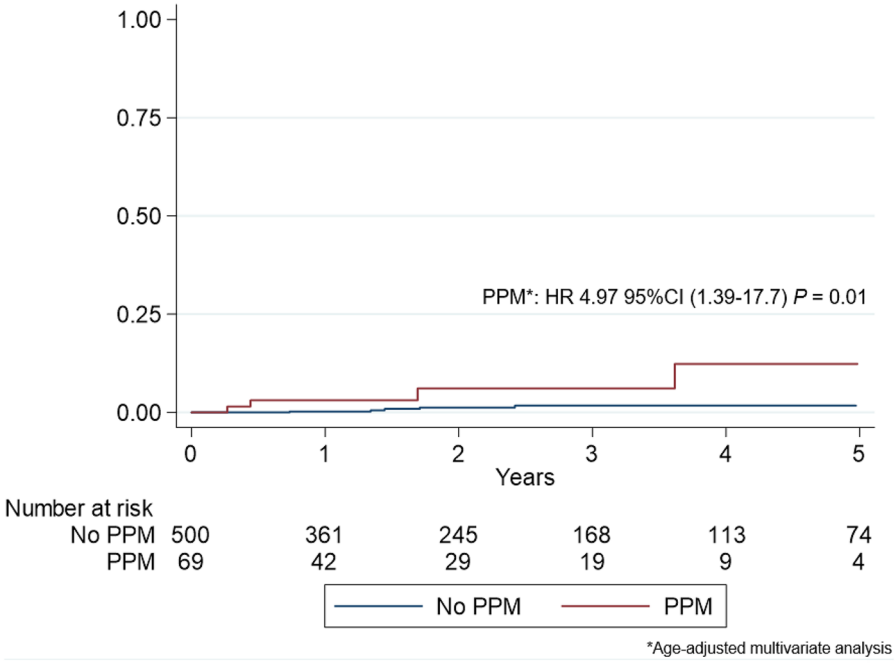

Figure 1. Kaplan–Meier curves for identified risk factors of sudden death (SD) in ATTR cardiac amyloidosis. SD in ATTR according to previous pacemaker implantation. HR: Hazard ratio. PPM: Previous pacemaker.

implantation, Despite the underlying mechanism of SD could not be retrieved in most cases, a possible explanation could be related to the mechanism of SD in ATTR-CA as VA, PEA and non-cardiac causes would not be prevented by pacemakers and advanced conduction disturbances might be simply a marker of a more advanced stage of the disease. This explanation might be further supported by a previous work published by Pinney et al. in which PPM was associated with higher mortality in a cohort of patients with ATTR [8].

Table 3. Univariate and multivariate analysis of risk factors for SD in AL-CA.

	Univariate analysis		
	HR	95%CI	*P* value
Age	0.99	0.95–1.04	0.83
Male sex	0.89	0.32–2.50	0.82
AF	1.13	0.25–5.07	0.87
CVA	2.55	0.71–9.16	0.15
Previous syncope	1.54	0.34–6.88	0.57
NYHA III-IV	3.90	1.33–11.5	**0.01**
Pacemaker	1.66	0.22–12.7	0.62
PR ≥ 200 ms	0.22	0.03–1.72	0.15
QRS ≥ 120 ms	1.30	0.29–5.88	0.73
Low voltage ECG	1.29	0.46–3.63	0.63
IVS (mm)	1.03	0.87–1.21	0.73
LVEF (%)	0.97	0.93–1.01	0.10
Betablockers	5.28	1.77–15.8	**0.003**
Calcium antagonist	–	–	0.54
Amiodarone	–	–	0.40
Multivariate analysis			
Age	0.97	0.92–1.02	0.25
Betablockers	7.06	2.31–21.5	0.001
NYHA III-IV	4.56	1.51–13.8	0.007

Abbreviations: AL-CA: Light-chain cardiac amyloidosis; CVA: Cardiovascular accident; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; IVS: Interventricular septum; LVEF: Left ventricular ejection fraction; SD: Sudden death.

In contrast, patients with AL-CA showed a significant risk of SD during follow-up and particularly during the initial 6 months after baseline evaluation when most events clustered. The fact that treatment with betablockers was one of the predictors of SD suggests that conduction disturbances or low heart rate could be involved in the pathophysiology of SD in these patients. These results are in line with a previous work by Sayed et al. that identified extreme bradycardia as the most frequent trigger of SD in a cohort of 20 patients with AL-CA and implantable loop recorders [9]. Our results suggest that betablockers should be avoided unless strictly necessary for heart rate control in line with previous studies showing a deleterious effect in patients with CA [10,11]. Additionally, advanced NYHA was associated with an increased risk of SD which suggests that patients with more advanced stages of the disease might be at greater risk and might benefit from closer rhythm follow-up.

Some limitations should be considered when interpreting our results. Firstly, sample size might be underpowered to assess risk factors for a rare event such as SD. Moreover, the small number of events limits the robustness of a multivariate analysis. Additionally, information was collected retrospectively leading to a significant proportion of missing data for serum biomarkers to establish disease stage, and in some cases, remotely from the incident event, which might lead to errors in identifying the cause of death. Moreover, despite our best efforts to elucidate the circumstances of SD in all patients, these remained unknown in a significant proportion of cases including those with previous pacemakers where interrogation was not available, although the fact that PEA was the most frequent documented rhythm suggest that it might play a role as the underlying mechanism in some cases.

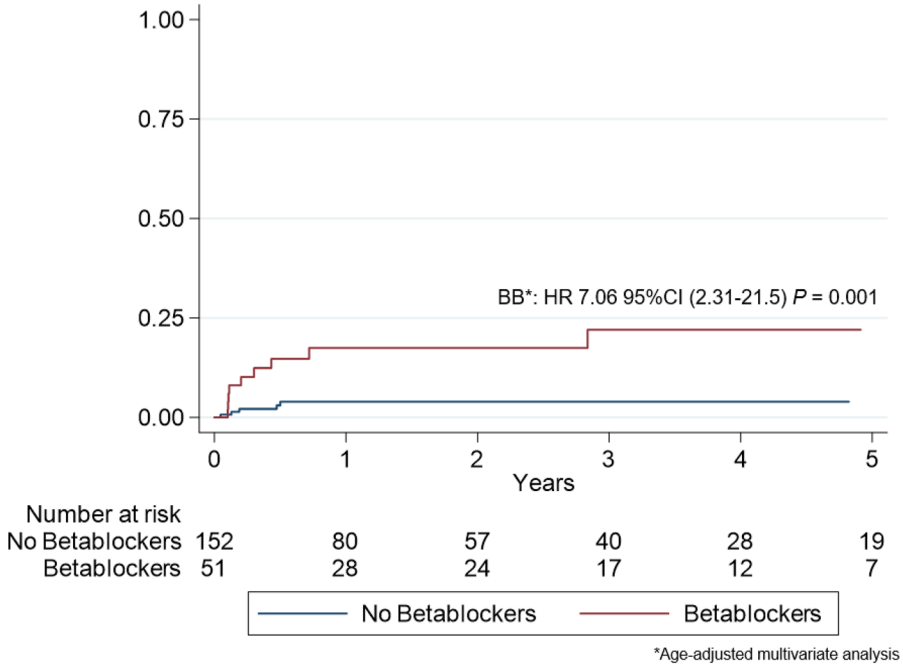

Figure 2. Kaplan–Meier curves for betablocker prescription and sudden death (SD) in AL cardiac amyloidosis. SD in AL according to betablocker prescription. HR: Hazard ratio.

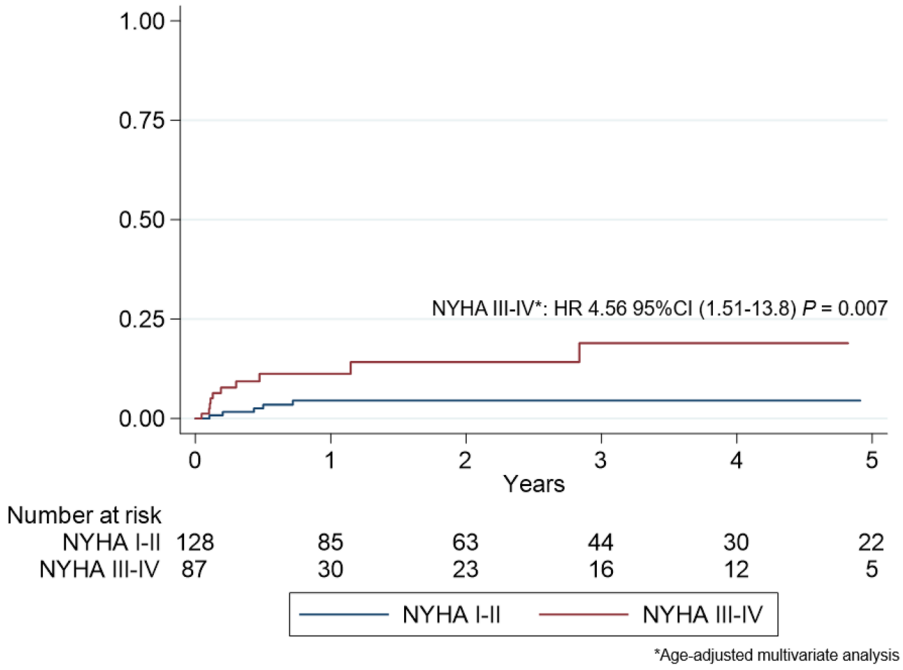

Figure 3. Kaplan–Meier curves for advanced NYHA (III-IV) and sudden death (SD) in AL cardiac amyloidosis. SD in AL according to NYHA III-IV. HR: Hazard ratio.

Conclusions

SD is significantly more frequent in AL-CA than in ATTR-CA. SD in AL-CA usually occur during the first months of follow-up and treatment with betablockers and NYHA III-IV were independently associated with increased risk of SD. In patients with ATTR-CA, SD is rare and is associated with previous PPM implantation

Disclosure statement

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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