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ORIGINAL RESEARCH

Survival Following Implantable Cardioverter-Defibrillator Implantation in Patients With Amyloid Cardiomyopathy

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BACKGROUND: Outcomes data in patients with cardiac amyloidosis after implantable cardioverter-defibrillator (ICD) implantation are limited. We compared outcomes of patients with ICDs implanted for cardiac amyloidosis versus nonischemic cardiomyopathies (NICMs) and evaluated factors associated with mortality among patients with cardiac amyloidosis.

METHODS AND RESULTS: Using National Cardiovascular Data Registry's ICD Registry data between April 1, 2010 and December 31, 2015, we created a 1:5 propensity-matched cohort of patients implanted with ICDs with cardiac amyloidosis and NICM. We compared mortality between those with cardiac amyloidosis and matched patients with NICM using Kaplan-Meier survival curves and Cox proportional hazards models. We also evaluated risk factors associated with 1-year mortality in patients with cardiac amyloidosis using multivariable Cox proportional hazards regression models. Among 472 patients with cardiac amyloidosis and 2360 patients with propensity-matched NICMs, 1-year mortality was significantly higher in patients with cardiac amyloidosis compared with patients with NICMs (26.9% versus 11.3%, $P<0.001$). After adjustment for covariates, cardiac amyloidosis was associated with a significantly higher risk of all-cause mortality (hazard ratio [HR], 1.80; 95% CI, 1.56–2.08). In a multivariable analysis of patients with cardiac amyloidosis, several factors were significantly associated with mortality: syncope (HR, 1.78; 95% CI, 1.22–2.59), ventricular tachycardia (HR, 1.65; 95% CI, 1.15–2.38), cerebrovascular disease (HR, 2.03; 95% CI, 1.28–3.23), diabetes mellitus (HR, 1.55; 95% CI, 1.05–2.27), creatinine = 1.6 to 2.5 g/dL (HR, 1.99; 95% CI, 1.32–3.02), and creatinine >2.5 (HR, 4.34; 95% CI, 2.72–6.93).

CONCLUSIONS: Mortality after ICD implantation is significantly higher in patients with cardiac amyloidosis than in patients with propensity-matched NICMs. Factors associated with death among patients with cardiac amyloidosis include prior syncope, ventricular tachycardia, cerebrovascular disease, diabetes mellitus, and impaired renal function.

Key Words: amyloid ■ cardiomyopathy ■ nonischemic cardiomyopathy ■ implantable cardioverter-defibrillator ■ mortality

Amyloidosis, an infiltrative multisystem disease, is complicated by cardiac involvement in 50% to 60% of patients and can result in progressive heart failure, arrhythmias, and conduction abnormalities.[1] Immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (aTTR) account for the vast majority of cardiac amyloidosis cases, with the remaining 5% caused by rare forms such as heavy chain and apolipoprotein amyloid.[2] Amyloidosis fibril deposition is the common pathophysiologic mechanism; however, the natural history of these diseases is significantly different with AL being more rapidly progressive and fatal. Electromechanical dissociation is thought to be the most common cause of sudden cardiac death in patients with cardiac amyloidosis, but ventricular arrhythmias are also common.[3,4] Implantable

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CLINICAL PERSPECTIVE

What Is New?

- Patients with cardiac amyloidosis who have an implantable cardioverter-defibrillator implanted have a 26.9% 1-year mortality rate, which is significantly higher than patients with propensity-matched nonischemic cardiomyopathy.
- Impaired renal function, syncope, ventricular tachycardia, cerebrovascular disease, and diabetes mellitus are risk factors for death after implantable cardioverter-defibrillator implantation in patients with cardiac amyloidosis.

What Are the Clinical Implications?

- Patients with cardiac amyloidosis who have implantable cardioverter-defibrillators implanted are at a high risk of mortality; thus, careful patient selection and shared decision-making surrounding implantable cardioverter-defibrillator implantation are important.

Nonstandard Abbreviations and Acronyms

AL	light-chain amyloidosis
aTTR	transthyretin amyloidosis
DM	diabetes mellitus
HR	hazard ratio
ICD	implantable cardioverterdefibrillator
IQR	interquartile range
NICM	nonischemic cardiomyopathy
RR	relative risk

cardioverter-defibrillators (ICDs) are safe and effective in treating sudden cardiac death caused by fatal arrhythmias in cardiomyopathy; however, data regarding the use of ICDs in patients with cardiac amyloidosis are limited. Previous single-center and multicenter retrospective studies evaluating mortality in patients with cardiac amyloidosis receiving ICDs have been small, methodologically limited, and inconclusive regarding the outcomes.[5–8] Current guidelines suggest individualized decision-making regarding ICD implantation in patients with cardiac amyloidosis based on limited evidence and unclear benefit in this population.[9] Furthermore, current guidelines recommend against ICDs in patients with less than 1- year expected survival,[9] but predictors of survival in patients with cardiac amyloidosis and ICDs are poorly understood.

In this study, we evaluated the risk of mortality after ICD implantation in patients with cardiac amyloidosis compared with patients with other nonischemic cardiomyopathies (NICMs). We also investigated factors associated with 1-year mortality exclusively among patients with cardiac amyloidosis. This information may offer patients with cardiac amyloidosis and healthcare providers vital information regarding risk and prognosis after ICD implantation.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. The Yale University Human Investigation Committee approved the present analysis with a waiver of informed consent.

Data Sources

The National Cardiovascular Data Registry's ICD Registry was established in 2005 by the American College of Cardiology and the Heart Rhythm Society as a centralized registry for patients receiving ICD implantations. The goal of the registry was to improve safety, treatment, and patterns of care for patients receiving an ICD.[10] The registry met the Centers for Medicare and Medicaid Services data collection requirements, and in early 2006 they mandated that all Medicare patients receiving primary prevention ICDs be included in the registry, although this requirement was recently terminated in February 2018. Though hospitals were mandated to report only on Medicare beneficiaries receiving ICDs for primary prevention between 2006 and 2018, 90% of participating hospitals reported on other patient populations as well, such as those receiving ICDs for secondary prevention and those insured by other payers.[10] The ICD Registry data collection methods have previously been described and validated.[11–13] After initial training of the centers, data are subjected to random audits, with 10% of the centers randomly audited every year.[11]

Vital status was obtained using the National Death Index (https://www.cdc.gov/nchs/ndi/index.htm). The National Death Index is a centralized database of death record information that is maintained by the Centers for Disease Control and Prevention's National Center for Health Statistics. The National Death Index is available for a per-case fee to epidemiologists and other health and medical investigators. Records are obtained from state and local-government vital records offices; they contain identifiable information including names, social security numbers, demographic data, and date and cause of death. The accuracy of the National Death Index has been described previously.[14–16]

Study Population

All patients in the ICD Registry from April 1, 2010 through December 31, 2015 were included in the study (Figure 1). Patients with cardiac amyloidosis were

identified, and then a propensity-matched cohort of patients with other patients with NICMs enrolled in the registry during the same period was created as a comparator group. Patients with NICMs were chosen as a comparator group to provide a large cohort of patients and a frame of reference for comparison with which the cardiology community is familiar. Diagnoses of cardiac amyloidosis and NICMs were established using site-reported data from version 2.1 of the ICD Registry data collection form. According to the data dictionary, cardiac amyloidosis is defined as patients with a structural abnormality of the heart other than nonischemic dilated cardiomyopathy, ischemic heart disease, valvular heart disease, prior heart transplant, and a diagnosis of cardiac amyloidosis. The specific type of amyloid cardiomyopathy is not collected in the ICD Registry. A patient with a NICM is defined as one who has a history of nonischemic dilated cardiomyopathy documented by heart failure and reduced systolic function (ejection fraction <40%). Patients with other infiltrative

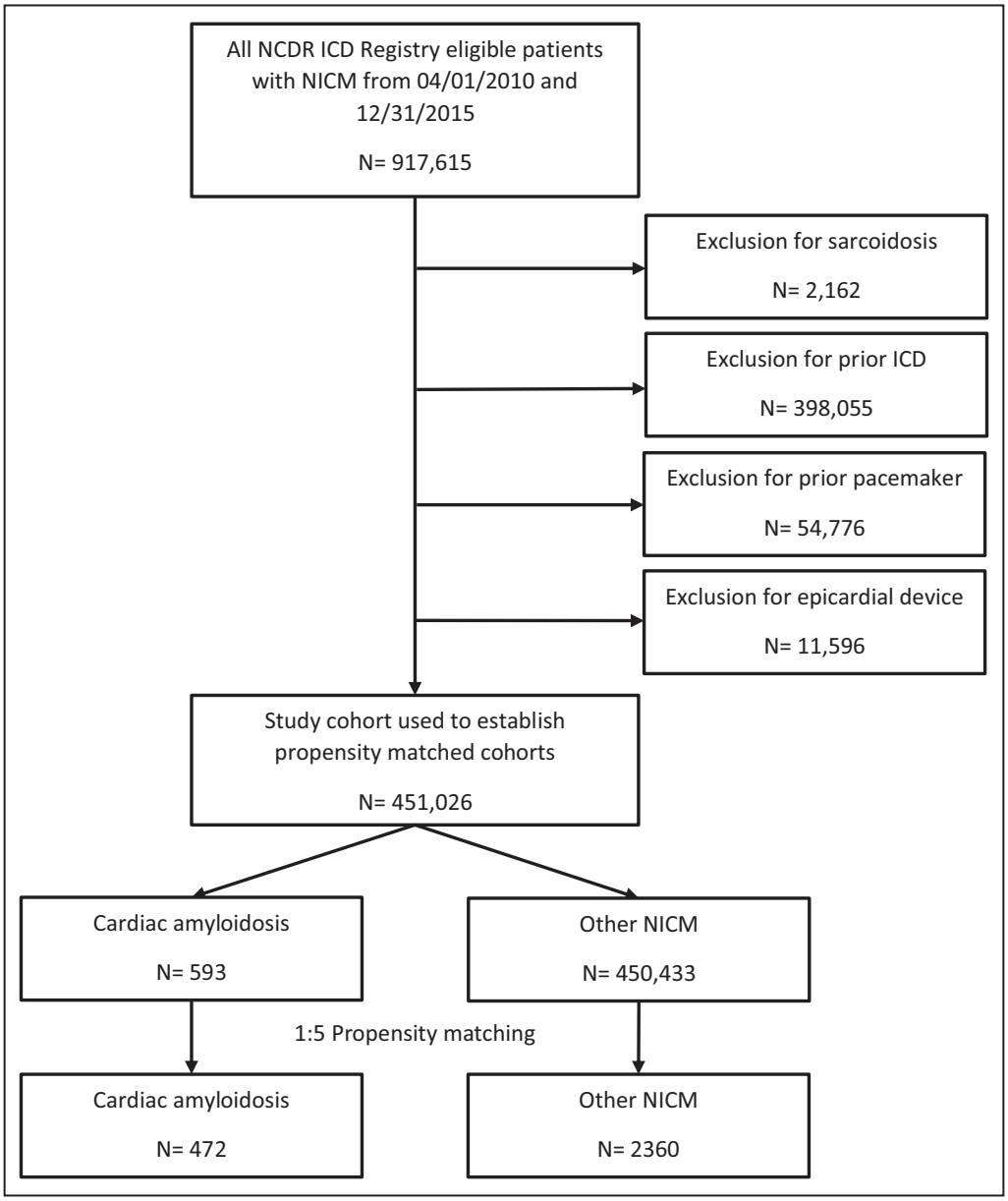

Figure 1. Study population selection flow diagram.
All patients in the NCDR ICD Registry with a diagnosis of cardiac amyloid or nonischemic cardiomyopathy who had ICDs (with or without CRT), implanted from April 1, 2010 through December 31, 2015, were included in the study. Patients with sarcoidosis, prior ICDs, prior pacemakers, or epicardial devices were excluded. A 1:5 propensity-matched cohort of patients with cardiac amyloidosis and NICMs was created. CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NCDR, National Cardiovascular Data Registry; and NICM, nonischemic cardiomyopathy

cardiomyopathies, such as cardiac sarcoidosis, were excluded from the study. Patients with a previous ICD or pacemaker and patients with epicardial lead placement were excluded.

Propensity Score Matching and Outcomes

Patients were matched on sex, age (±1 year), and propensity score using a nearest-neighbor matching technique[17,18] with 1 amyloid cardiomyopathy and up to 5 patients with NICMs. The propensity score was calculated using the logistic regression model with patients with cardiac amyloidosis as the dependent variable. The following variables were included in the model: congestive heart failure, New York Heart Association class, syncope, family history of sudden death, ventricular tachycardia, cerebrovascular disease, diabetes mellitus (DM), dialysis, chronic lung disease, hypertension, left ventricular ejection fraction (grouped by ≤30%, 30%–40%, >40%), creatinine, and ICD indication (primary or secondary prevention). A greedy matching technique was employed to match patients using the logit of the propensity-score matching with a caliper width of 0.001 difference of the logit of the propensity score. The success of matching was assessed by calculating the standardized difference in the unmatched and matched cohort; a standardized difference of <10% has been proposed as a reasonable level balance between baseline covariates.[19] The primary outcome was all-cause death.

Statistical Analysis

Baseline characteristics between patients with cardiac amyloidosis and patients with NICMs were compared using the chi-square test for categorical variables and the *T* test for continuous variables. McNemar's test was used for paired proportions or paired *t* tests for continuous variables in the matched cohort. Median and interquartile range (IQR) or number and percent with associated *P* values and standardized difference are reported. For the primary outcome of all-cause mortality, the Kaplan-Meier method was used to calculate the event-free survival rates, and differences were compared using the stratified log-rank test to account for the matched nature of our sample.[20,21] Event-free rates were compared using a Cox-proportional hazards regression model with a robust variance estimator.[21] Subgroup analysis was performed for the following groups: age (<60 years of age, ≥60 years of age), sex, history of syncope, left ventricular function (<30%, 30%–40%, >40%), inducible ventricular arrhythmia at electrophysiology study, pacing indication (combined second- and third-degree heart block), abnormal intraventricular conduction, and indication (primary versus secondary). These subgroups represent important demographic and patient characteristics that are indications for ICD implantation in infiltrative cardiomyopathies in recent guidelines.[22,23] To select variables significantly associated with death among patients with cardiac amyloidosis and patients with NICMs, multivariable Cox-proportional hazards regression models censored at 2 years with the stepwise method were used. A separate multivariable Cox-proportional hazards regression model using only patients with cardiac amyloidosis and censored at 1 year from date of ICD implantation was done to evaluate patient factors associated with mortality. Medications were excluded from this analysis. Variables were selected for the models if they had a *P* value <0.05. The statistical analyses were completed using SAS version 9.4 (SAS, Cary, NC).

RESULTS

Baseline Patient Population and Propensity Matched Cohort

Between April 1, 2010 and December 31, 2015, there were 917 615 patients in the ICD Registry. After excluding patients with a prior ICD (n=398 055) or pacemaker (n=54 776), patients with an epicardial system (n=11 596), and patients with sarcoidosis (n=2162), 451 026 patients were available for analysis (Figure 1). The baseline characteristics of the entire cohort prior to propensity matching are shown in Table S1. Of these patients, 593 had cardiac amyloidosis and 450 433 had another form of NICM. After establishing a 1:5 propensity-score-matched cohort, 472 patients with cardiac amyloidosis were successfully matched with 2360 patients with NICMs (Figure 1). The average age of the patients in the overall cohort was 68 years; 22.7% of patients were female. The most common indication for ICD implantation was primary prevention (76.1%), and 26.3% of patients received a cardiac resynchronization therapy defibrillator device. The baseline characteristics of the propensity-matched cohort are displayed in Table 1. Patients with cardiac amyloidosis were overall very similar to those with NICMs in the propensity-matched cohort. However, patients with cardiac amyloidosis were more likely to have a history of prior ventricular tachycardia and third-degree heart block.

Mortality for Patients With Amyloid Cardiomyopathy Compared With NICMs

The 1-year mortality rate of patients with cardiac amyloidosis was 26.9%, which was significantly higher than the propensity-matched patients with NICMs

Table 1. Baseline Characteristics of the Propensity-Matched Cohort Overall and Among Those With Cardiac Amyloidosis Compared With Nonischemic Cardiomyopathy After ICD Implantation

Description	Total n (%)	Amyloidosis n (%)	NICM n (%)	*P* Value
All	2832 (100)	472 (100)	2360 (100)	
Demographics				
Age, mean (SD), y	68.2 (11.8)	68.2 (11.8)	68.2 (11.8)	0.98
Sex female	642 (22.7)	107 (22.7)	535 (22.7)	1.00
Race				0.67
White (non-Hispanic)	1853 (65.4)	299 (63.3)	1554 (65.8)	
Black (non-Hispanic)	816 (28.8)	146 (30.9)	670 (28.4)	
Hispanic	110 (3.9)	17 (3.6)	93 (3.9)	
Other	53 (1.87)	10 (2.1)	43 (1.8)	
Clinical history				
Heart failure	2388 (84.3)	392 (83.1)	1996 (84.6)	0.41
NYHA Class				0.30
Class I	370 (13.1)	69 (14.6)	301 (12.8)	
Class II	989 (34.9)	159 (33.7)	830 (35.2)	
Class III	1327 (46.9)	219 (46.4)	1108 (46.9)	
Class IV	131 (4.6)	25 (5.3)	106 (4.5)	
Syncope	681 (24.1)	116 (24.6)	565 (23.9)	0.79
Family history of sudden death	102 (3.6)	17 (3.6)	85 (3.6)	0.74
Atrial fibrillation/flutter	1299 (45.9)	221 (46.8)	1078 (45.7)	0.67
VT	1101 (38.9)	224 (47.5)	877 (37.2)	<0.001
VT type				0.24
Nonsustained VT	628 (57.0)	143 (63.8)	485 (55.3)	
Sustained monomorphic VT	289 (26.3)	49 (21.9)	240 (27.4)	
Sustained polymorphic VT	74 (6.7)	10 (4.5)	64 (7.3)	
Sustained monomorphic and polymorphic VT	33 (3.0)	7 (3.1)	26 (3.0)	
Unknown	77 (7.0)	15 (6.7)	62 (7.0)	
Cerebrovascular disease	316 (11.2)	50 (10.6)	266 (11.3)	0.77
Lung disease	429 (15.2)	67 (14.2)	362 (15.3)	0.36
Diabetes mellitus	643 (22.7)	112 (23.7)	531 (22.5)	0.47
Sleep apnea	361 (12.8)	57 (12.1)	304 (12.9)	0.82
Dialysis	132 (4.7)	19 (4.0)	113 (4.8)	0.38
Hypertension	1922 (67.9)	325 (68.9)	1597 (67.7)	0.37
Patient life expectancy of ≥1 y				0.70
No	69 (2.4)	10 (2.1)	59 (2.5)	
Yes	1176 (41.5)	204 (43.2)	972 (41.2)	
Not documented	1552 (54.8)	254 (53.8)	1298 (55.0)	
Diagnostic studies				
Left ventricular ejection fraction				0.75
≤30	1413 (49.9)	236 (50.0)	1177 (49.9)	
>30–40	630 (22.3)	99 (21.0)	531 (22.5)	
>40	699 (24.7)	119 (25.2)	580 (24.6)	
QRS duration				0.84
≤140	2115 (74.7)	353 (74.8)	1762 (74.7)	
>140	677 (23.9)	111 (23.5)	566 (24.0)	
Creatinine, mean (SD)	1.57 (1.7)	1.63 (1.4)	1.56 (1.7)	0.38
Inducible ventricular arrhythmia on EP study	310 (11.0)	28 (5.9)	282 (11.9)	0.00

(*Continued*)

Table 1. Continued

Description	Total n (%)	Amyloidosis n (%)	NICM n (%)	*P* Value
Abnormal intraventricular conduction	1357 (47.9)	244 (51.7)	1113 (47.2)	0.19
Cardiac rhythm paced	44 (1.6)	7 (1.5)	37 (1.6)	0.89
Cardiac rhythm third-degree heart block	53 (1.9)	20 (4.2)	33 (1.4)	0.00
Brain natriuretic peptide, mean (SD)	1111 (1468)	1244 (1617)	1072 (1421)	0.24
Medications				
ACE inhibitor	979 (34.6)	165 (35.0)	814 (34.5)	0.85
Angiotensin receptor blocker	457 (16.1)	77 (16.3)	380 (16.1)	0.91
Aspirin	1544 (54.5)	252 (53.4)	1292 (54.7)	0.59
Beta-blocker	1996 (70.5)	339 (71.8)	1657 (70.2)	0.48
Statin	1379 (48.7)	223 (47.2)	1156 (49.0)	0.49
Nonstatin lipid medication	105 (3.7)	19 (4.0)	86 (3.6)	0.69
Clopidogrel	260 (9.2)	39 (8.3)	221 (9.4)	0.45
Ticlopidine	9 (0.3)	3 (0.6)	6 (0.3)	0.18
Prasugrel	9 (0.3)	1 (0.2)	8 (0.3)	0.65
Antiarrhythmic agent	546 (19.3)	90 (19.1)	456 (19.3)	0.73
Diltiazem	37 (1.3)	7 (1.5)	30 (1.3)	0.71
Verapamil	14 (0.5)	2 (0.4)	12 (0.5)	0.81
Other calcium channel blocker	128 (4.5)	24 (5.1)	104 (4.4)	0.52
Digoxin	166 (5.9)	29 (6.1)	137 (5.8)	0.77
Diuretic	2073 (73.2)	341 (72.2)	1732 (73.4)	0.61
Hydralazine	146 (5.2)	26 (5.5)	120 (5.1)	0.70
Long-acting nitroglycerin	148 (5.2)	28 (5.9)	120 (5.1)	0.45
Warfarin	973 (34.4)	169 (35.8)	804 (34.1)	0.47
Procedural factors				
ICD indication				0.69
Primary prevention	2156 (76.1)	356 (75.4)	1800 (76.3)	
Secondary prevention	676 (23.9)	116 (24.6)	560 (23.7)	
Device type				0.95
Single chamber	722 (25.5)	124 (26.3)	598 (25.3)	
Dual chamber	1355 (47.9)	224 (47.5)	1131 (47.9)	
CRT-D	746 (26.3)	123 (26.1)	623 (26.4)	

ACE indicates angiotensin converting enzyme; CRT-D, cardiac resynchronization therapy defibrillator; EP, electrophysiology; ICD, implantable cardioverter-defibrillator; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; and VT, ventricular tachycardia.

at 11.3% ($P<0.001$). The difference in survival began immediately after implant and continued to progressively widen over time (Figure 2). The median follow-up for patients with amyloid cardiomyopathy was 42 months (IQR, 25–62 months) and 46 months (IQR, 27–64 months) for patients with NICMs. The median time from ICD implantation to death was 12 months (IQR, 4–26 months) for patients with amyloidosis and 19 months (IQR, 5–35 months) for those with NICMs.

After adjusting for factors significantly associated with death in multivariate analysis, cardiac amyloidosis was associated with a significantly increased risk of death compared with NICMs (hazard ratio [HR], 1.80; 95% CI, 1.56–2.08; Table 2). This finding was consistent in nearly all subgroups evaluated including age (<60 years of age, ≥60 years of age); sex; syncope; left ventricular ejection fraction (≤30%, 30%–40%, >40%), inducible ventricular arrhythmia at electrophysiology study, abnormal intraventricular conduction, and ICD indication (primary versus secondary prevention). The only subgroup tested in which amyloid cardiomyopathy was not associated with increased mortality was the presence of advanced (2nd or 3rd degree) heart block (relative risk [RR], 2.32; 95% CI, 0.66–8.16).

Univariate and Multivariable Predictors of Mortality Among Patients With Cardiac Amyloidosis

Among patients with cardiac amyloidosis and an ICD, several variables were associated with an increased risk of mortality within 1 year after ICD implantation

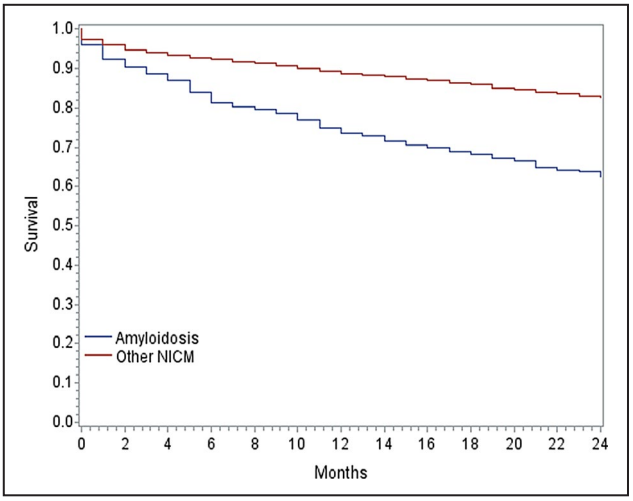

Figure 2. Probability of survival.
Kaplan-Meier curves for survival following implantable cardioverter-defibrillator implantation stratified by type of cardiomyopathy. Survival in patients with cardiac amyloidosis was significantly lower than the propensity-matched cohort of patients with NICMs. NICM indicates nonischemic cardiomyopathy.

in univariate analysis including heart failure duration <3 months (HR, 1.68; 95% CI 1.03–2.76), syncope (HR, 1.84, 95% CI, 1.28–2.65), ventricular tachycardia (HR, 1.66; 95% CI, 1.17–2.36), cerebrovascular disease (HR, 1.98; 95% CI, 1.25–3.14), dialysis (HR, 3.37; 95% CI, 1.86–6.12), creatinine = 1.5 to 2.5 g/dL (HR, 2.01; 95% CI, 1.33–3.03), creatinine >2.5 (HR, 3.60; 95% CI, 2.27–5.70), and secondary prevention ICD indication (HR, 1.96; 95% CI, 1.36–2.81) (Table S2). In multivariable analysis, the following risk factors remained significantly associated with mortality: syncope (HR, 1.78; 95% CI, 1.22–2.59), ventricular tachycardia (HR, 1.65; 95% CI, 1.15–2.38), cerebrovascular disease (HR, 2.03; 95% CI, 1.28–3.23), DM (HR, 1.55; 95% CI, 1.05–2.27), creatinine = 1.6 to 2.5 g/dL (HR, 1.99; 95% CI, 1.32–3.02), and creatinine >2.5 g/dL (HR, 4.34; 95% CI, 2.72–6.93) (Table 3). Definitions for variables significant in multivariable analysis are provided in Table S3.

DISCUSSION

This study of 472 patients with cardiac amyloidosis and ICDs is the largest study of this population to date and found 2 key findings. First, cardiac amyloidosis was associated with a mortality rate of 26.9% at 1 year after ICD implantation compared with 11.3% among a propensity-matched cohort of patients with other NICMs. After adjustment for covariates, cardiac amyloidosis was associated with a significantly higher risk of all-cause mortality compared with NICMs (HR, 1.80; 95% CI, 1.56–2.08), and these findings were consistent in essentially all subgroups we evaluated. Second, we identified 6 variables independently associated with 1-year mortality in patients with cardiac amyloidosis who underwent ICD implantation: syncope (HR, 1.78; 95% CI, 1.22–2.59), ventricular tachycardia (HR, 1.65; 95% CI, 1.15–2.38), cerebrovascular disease (HR, 2.03; 95% CI, 1.28–3.23), DM (HR, 1.55; 95% CI, 1.05–2.27), creatinine = 1.6 to 2.5 g/dL (HR, 1.99; 95% CI, 1.32–3.02), and creatinine >2.5 (HR, 4.34; 95% CI, 2.72–6.93).

Our finding that 26.9% of patients with amyloid cardiomyopathy die within 1 year of ICD implantation is fairly consistent with previous studies that were smaller and less definitive.[5,6] The largest prior study to date in this population included 53 patients with cardiac amyloidosis and an ICD implanted at the Mayo Clinic, and 60% of these patients died over a mean 1.9±1.8 years of follow-up.[7] In another study of 45 patients with cardiac amyloidosis, 26.7% died over 1.4±1.2 years of follow-up.[8] Although we cannot account for the competing risk of death from progression of underlying disease, our study confirms the high mortality of patients with cardiac amyloidosis despite ICD implantation in a much larger cohort treated at multiple centers around the United States, making our results broadly generalizable.

We also found that patients with cardiac amyloidosis were at a significantly increased risk of mortality compared with propensity-matched patients with patients with NICMs. In subgroup analysis, we found that the risk of death was significantly higher in all subgroups tested except for advanced heart block. We suspect that patients who present with heart block and thus require a pacing device may receive an ICD earlier in their disease course; this likely represents a length time bias rather than an actual difference. It is possible that some patients within the NICM cohort had undiagnosed cardiac amyloidosis; recent studies have shown a prevalence of aTTR in 13% of patients with heart failure with preserved ejection fraction[24] and 16% among patients with patients with severe aortic stenosis.[25] This may result in an underestimation of the true difference in survival. Overall, these findings highlight the progressive nature of the disease and further confirm that the natural history of patients with cardiac amyloidosis differs substantially from other NICMs despite ICD implantation.

The 2 primary types of cardiac amyloidosis, AL and aTTR, have markedly different prognoses. AL has traditionally been associated with survival of less than 1 year; however, advances in the treatment of AL[26] and new therapies targeted at aTTR[27,28] may change the landscape for these patients. The NCDR ICD Registry does not collect data on the type of amyloid cardiomyopathy; however, age can be used as a proxy for the type of amyloid cardiomyopathy as most patients with AL will be captured in the <60 years-of-age group and aTTT in the ≥60 years-of-age group.[29–32] Age was

Table 2. Relative Risk of Death for Patients With Cardiac Amyloidosis Compared With Nonischemic Cardiomyopathy and an ICD Through 2 Years of Follow-Up Overall and in Subgroups

Description	Unadjusted			Adjusted		
	Relative Risk	95% CI	*P* Value	Relative Risk	95% CI	*P* Value
Overall	1.85	1.61–2.13	<0.001	1.80	1.56–2.08	<0.001
Age, y						
Age<60	2.54	1.78–3.62	<0.001	2.67	1.85 –3.86	<0.001
Age≥60	1.74	1.49–2.03	<0.001	1.71	1.46–2.01	<0.001
Sex						
Male	1.85	1.58–2.17	<0.001	1.84	1.56–2.16	<0.001
Female	1.85	1.35–2.52	<0.001	1.67	1.21–2.31	0.002
Syncope						
No	1.72	1.46–2.02	<0.001	1.73	1.47–2.04	<0.001
Yes	2.34	1.77–3.09	<0.001	2.00	1.48–2.70	<0.001
Left ventricular ejection fraction (%)						
Unknown	2.14	0.93–4.92	0.08	2.20	0.84–5.78	0.11
≤30	1.73	1.42–2.11	<0.001	1.67	1.37–2.04	<0.001
>30–40	1.91	1.42–2.57	<0.001	1.74	1.27–2.38	0.001
>40	2.07	1.54–2.78	<0.001	1.95	1.43–2.65	<0.001
Abnormal intraventricular conduction						
No	2.24	1.84–2.73	<0.001	2.19	1.79–2.68	<0.001
Yes	1.52	1.24–1.87	<0.001	1.51	1.23–1.86	<0.001
Second- or third-degree heart block						
No	1.85	1.60–2.14	<0.001	1.81	1.56–2.09	<0.001
Yes	1.49	0.71–3.13	0.29	2.32	0.66–8.16	0.192
ICD indication						
Primary prevention	1.69	1.44–2.00	<0.001	1.70	1.44–2.01	<0.001
Secondary prevention	2.39	1.82–3.15	<0.001	2.16	1.63–2.87	<0.001

ICD indicates implantable cardioverter-defibrillator.

not predictive of mortality in the multivariable analysis; however, patients <60 years of age had a relative risk of 2.7 and patients ≥60 years of age had a relative risk of 1.7 compared with patients with NICMs in subgroup analysis, suggesting that the risk of death in younger patients with AL may be higher despite ICD implantation.

We identified a number of risk factors for mortality in patients with amyloid cardiomyopathy and ICDs, which have been poorly assessed in prior studies because of their limited size and patient data. Syncope and ventricular tachycardia are well-established risk factors for mortality in patients with cardiovascular disease. Although previous studies have identified ventricular arrhythmias[3,33] as a risk factor for mortality in patients with cardiac amyloidosis, the 2 studies on patients with cardiac amyloidosis with ICDs discussed above found that ventricular arrhythmias were not associated with differences in survival.[7,8] In our study of a much larger cohort, ventricular tachycardia was associated with increased mortality despite ICD presence. It is likely that ventricular tachycardia is a manifestation of progressive infiltration and scar burden and represents progression towards end-stage disease.

We also found that patients with impaired renal function were at significantly increased risk of mortality, and that there was a dose-response relationship between kidney disease and worse prognosis. Importantly, among patients with creatinine >2.5 the risk of death was more than 4-fold higher compared with those without kidney dysfunction (HR, 4.34; 95% CI, 2.72–6.93). Over 50% of patients with AL have renal involvement and many patients progress to dialysis.[34–36] In an earlier study of 145 patients with AL, those with renal AL had significantly better outcomes compared with patients without renal involvement; however, patients without renal AL had a disproportionally higher prevalence of cardiac amyloidosis, which likely accounted for the unexpected outcomes.[34] When patients with renal AL were compared with patients without concomitant renal and cardiac AL, survival was not significantly different.[34] Although renal impairment is not a hallmark of aTTR, renal function, using estimated glomerular filtration

Table 3. Patient Risk Factors Significantly Associated With 1-Year Survival in Multivariable Analysis Among Those With Cardiac Amyloidosis

Parameter	Hazard Ratio	95% CI	*P* Value
Syncope	1.78	1.22–2.59	0.003
Ventricular tachycardia	1.65	1.15–2.38	0.01
Prior cerebrovascular disease	2.03	1.28–3.23	0.003
Diabetes mellitus	1.55	1.05–2.27	0.03
Creatinine = 1.6–2.5 g/dL	1.99	1.32–3.02	0.001
Creatinine >2.5 g/dL	4.34	2.72–6.93	<0.001

rate, has been identified as an independent prognostic factor in cardiac aTTR and has been incorporated into a new staging system.[37] We cannot discern the type of amyloidosis or the etiology of the kidney disease, but we clearly demonstrate that the combination of cardiac amyloidosis and kidney dysfunction portends a markedly worse prognosis compared with those with normal renal function.

We also identified DM as a risk factor significantly associated with increased mortality among those with cardiac amyloidosis receiving an ICD. To our knowledge, DM has not previously been associated with mortality in patients with cardiac amyloidosis; our data suggest that DM should be taken into account when considering an ICD and patients with DM should be followed closely.

In summary, our findings suggest that patients with a history of syncope, ventricular tachycardia, DM, cerebrovascular disease, or renal dysfunction may be at particularly high risk for death within 1 year of ICD implantation. Despite ICD implantation, mortality remains relatively high in patients with cardiac amyloidosis. These findings underscore the importance of careful patient selection for ICD implantation, shared decision-making with these patients, and close follow-up after implantation.

Limitations

There are several limitations to this study. First, as a retrospective observational study, we were not able to account for all potential confounding factors, and our sample size was limited for subgroup analyses. However, the ICD Registry collects a large number of data elements, including patient characteristics, which were utilized in our analysis to limit the chances of significant residual confounding, and this data source was complete relative to prior studies of this topic. Second, the diagnosis of cardiac amyloidosis or other forms of cardiomyopathy was site-reported. It is possible that some patients with amyloid cardiomyopathy or other specific cardiomyopathies are included in the NICM cohort; therefore, our data may underestimate any differences between the 2 groups. Third, the ICD Registry does not collect data on the type of amyloidosis. Different types of amyloid cardiomyopathy are treated differently and carry disparate prognoses, but as discussed above, a cut-off of 60 years of age roughly correlates with the 2 most common types of amyloid cardiomyopathy, which allowed us to indirectly evaluate for differential outcomes. This study also does not have a control group of patients who did not receive an ICD or have ICD therapy data; thus, our data does not reflect the disease course or prognosis of patients with amyloid cardiomyopathy without ICDs; hence, we were not able to make direct inferences about the effectiveness of ICD implantation/therapy in prolonging survival. However, our comparison with matched patients with other NICMs allowed us to evaluate for overall prognosis despite ICD implantation. The ICD Registry is not linked to manufacturer-collected device programming and therapy data, which could provide more information on appropriate and inappropriate shocks and that could be the subject of future studies. Lastly, we did not report cause of death. Although we had vital statistics data on cause of death through the National Death Index, prior reports have suggested that this is an inaccurate method of assessing cause of death.[38]

Conclusions

In this study, we showed that, among patients with cardiac amyloidosis, mortality after ICD implantation was over 25% within 1 year, which is more than double that of propensity- matched patients with other NICMs. After controlling for other comorbidities, cardiac amyloidosis remained strongly associated with a higher risk of death compared with other NICMs. Risk factors for death at 1 year among those with cardiac amyloidosis and an ICD included syncope, ventricular tachycardia, cerebrovascular disease, DM, and impaired renal function. These data offer important information for physicians and patients when deciding whether to place an ICD in those with cardiac amyloidosis and a clearer sense of prognosis in the years after implantation.

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Supplementary Materials

Tables S1–S3

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Supplemental Material

Table S1. **Baseline characteristics stratified by type of cardiomyopathy for entire non-propensity matched cohort.**

Description	Total n (%)	Amyloidosis n (%)	NICM n (%)	p-value
All	451026	593	450433	
Demographics				
Age, mean (SD), years	65 (13.4)	68 (11.6)	65 (13.4)	<0.001
Sex female	129665 (28.7)	127 (21.4)	129538 (28.8)	<0.001
Race				<0.001
White (non-Hispanic)	338217 (75.0)	377 (63.6)	337840 (75.0)	
Black (non-Hispanic)	72839 (16.1)	186 (31.4)	72653 (16.1)	
Hispanic	28375 (6.3)	19 (3.2)	28356 (6.3)	
Other	11595 (2.6)	11 (1.9)	11584 (2.6)	
Clinical history				
Heart failure	364299 (80.8)	500 (84.3)	363799 (80.8)	0.08
NYHA class				0.001
Class I	64320 (14.3)	78 (13.2)	64242 (14.3)	
Class II	164261 (36.4)	204 (34.4)	164057 (36.4)	
Class III	207963 (46.1)	278 (46.9)	207685 (46.1)	
Class IV	12623 (2.8)	33 (5.6)	12590 (2.8)	
Syncope	75418 (16.7)	155 (26.1)	75263 (16.7)	<0.001
Family history of sudden death	16617 (3.7)	25 (4.2)	16592 (3.7)	0.71
Atrial fibrillation/flutter	132002 (29.3)	281 (47.4)	131721 (29.2)	<0.001

Ventricular tachycardia (VT)	135002 (29.9)	298 (50.3)	134704 (29.9)	<0.001
Ventricular tachycardia type				<0.001
Non-sustained VT	69603 (51.6)	199 (66.8)	69404 (51.5)	
Sustained monomorphic VT	36777 (27.2)	61 (20.5)	36716 (27.3)	
Sustained polymorphic VT	9007 (6.7)	11 (3.7)	8996 (6.7)	
Sustained monomorphic and polymorphic VT	6024(4.5)	9 (3.0)	6015 (4.5)	
Unknown	13418 (9.9)	18 (6.0)	13400 (9.9)	
Cerebrovascular disease	65347 (14.5)	58 (9.8)	65289 (14.5)	<0.001
Lung disease	95653 (21.2)	77 (13.0)	95576 (21.2)	<0.001
Diabetes mellitus	174893 (38.8)	116 (19.6)	174777 (38.8)	<0.001
Sleep Apnea	60186 (13.3)	80 (13.5)	60106 (13.3)	0.04
Current dialysis	14339 (3.2)	24 (4.0)	14315 (3.2)	0.11
Hypertension	360190 (79.9)	360 (60.7)	359830 (79.9)	<0.001
Patient life expectancy of ≥ 1 year				<0.001
No	10850 (2.4)	15 (2.5)	10835 (2.4)	
Yes	165575 (36.7)	249 (42.0)	165326 (36.7)	
Not documented	272660 (60.5)	320 (54.0)	272340 (60.5)	
Diagnostic studies				
LVEF				<0.001
≤30	322976 (71.6)	246 (41.5)	322730 (71.6)	
>30 to 40	72044 (16.0)	122 (20.6)	71922 (16.0)	

>40	49668 (11.0)	205 (34.6)	49463 (11.0)	
QRS duration (non-VT paced complex)				0.23
≤140	324745 (72.0)	445 (75.0)	324300 (72.0)	
>140	119686 (26.5)	139 (23.4)	119547 (26.5)	
Creatinine, mean (SD)	1 (1.2)	2 (1.4)	1 (1.2)	<0.001
Inducible ventricular arrhythmia on EP study	310 (11.0)	28 (5.9)	282 (12.0)	0.0003
Abnormal intraventricular conduction	1357 (47.9)	244 (51.7)	1113 (47.2)	0.19
Cardiac rhythm paced	44 (1.6)	7 (1.5)	37 (1.6)	0.89
Cardiac rhythm third degree heart block	53 (1.9)	20 (4.2)	33 (1.4)	<0.0001
Brain natriuretic peptide, mean (SD)	1111 (1468)	1244 (1617)	1072 (1421)	0.24
Medications				
ACE inhibitor	269415 (59.7)	172 (29.0)	269243 (59.8)	<0.001
Angiotensin receptor blocker	79842 (17.7)	82 (13.8)	79760 (17.7)	0.01
Aspirin	320489 (71.1)	294 (49.6)	320195 (71.1)	<0.001
Beta blocker	404455 (89.7)	369 (62.2)	404086 (89.7)	<0.001
Statin	300452 (66.6)	258 (43.5)	300194 (66.6)	<0.001
Non-statin lipid medication	38127 (8.5)	22 (3.7)	38105 (8.5)	<0.001
Clopidogrel	103730 (23.0)	42 (7.1)	103688 (23.0)	<0.001

Ticlopidine	608 (0.1)	3 (0.5)	605 (0.1)	0.01
Prasugrel	9624 (2.1)	1 (0.2)	9623 (2.1)	0.001
Antiarrhythmic agents	65577 (14.5)	116 (19.6)	65461 (14.5)	0.002
Diltiazem	7422 (1.6)	7 (1.2)	7415 (1.6)	0.37
Verapamil	1895 (0.4)	2 (0.3)	1893 (0.4)	0.76
Other calcium channel blocker	31129 (6.9)	25 (4.2)	31104 (6.9)	0.01
Digoxin	63164 (14.0)	30 (5.1)	63134 (14.0)	<0.001
Diuretic	278244 (61.7)	439 (74.0)	277805 (61.7)	<0.001
Hydralazine	24570 (5.4)	27 (4.6)	24543 (5.4)	0.34
Long acting nitroglycerin	51466 (11.4)	28 (4.7)	51438 (11.4)	<0.001
Warfarin	103859 (23.0	215 (36.3)	103644 (23.0)	<0.001
Procedural factors				
ICD indication				0.01
Primary prevention	356999 (79.2	445 (75.0)	356554 (79.2)	
Secondary prevention	94027 (20.8	148 (25.0)	93879 (20.8)	
Device type				<0.001
Single chamber	139427 (30.9)	156 (26.3)	139271 (30.9)	
Dual chamber	166460 (36.9)	300 (50.6)	166160 (36.9)	
CRT-D	144185 (32.0)	135 (22.8)	144050 (32.0)	

NICM, non-ischemic cardiomyopathy; SD, standard deviation; NYHA, New York Heart Association; VT, ventricular tachycardia; ACE, angiotensin converting enzyme; EP, electrophysiology; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator

Table S2. Univariate model for one-year survival among patients with cardiac amyloidosis.

Description	Hazard ratio	95% CI	p-value
All			
Demographics			
Age	1.00	0.99-1.02	0.74
Sex female	0.90	0.59-1.38	0.64
Race			
Black (non-Hispanic)	1.15	0.80-1.67	0.45
Hispanic	0.92	0.34-2.51	0.87
Other	0.37	0.05-2.63	0.32
Clinical history			
Heart failure	1.33	0.80-2.22	0.27
Duration of heart failure	1.68	1.03-2.76	0.04
<3 months			
NYHA class			
Class I	0.88	0.48-1.59	0.67
Class III	1.28	0.86-1.90	0.93
Class IV	0.96	0.41-2.27	0.67
Syncope	1.84	1.28-2.65	0.001
Family history of sudden		0.10-1.66	0.21
death	0.41		
Atrial fibrillation/flutter	1.15	0.81-1.62	0.44
Ventricular tachycardia	1.66	1.17-2.36	0.005

Cerebrovascular disease	1.98	1.25-3.14	0.004
Lung disease	1.39	0.88-2.18	0.16
Diabetes mellitus	1.41	0.96-2.07	0.08
Sleep apnea	0.87	0.48-1.57	0.65
Dialysis	3.37	1.86-6.12	0.0001
Hypertension	1.16	0.79-1.71	0.45
Patient life expectancy of ≥1 year	0.76	0.53-1.09	0.13
Diagnostic Studies			
Left ventricular ejection fraction			
>30 to 40	0.85	0.53-1.36	0.50
>40	0.91	0.59-1.40	0.67
QRS duration >140	0.73	0.47-1.14	0.16
Creatinine 1.5-2.5 mg/dL	2.01	1.33-3.03	0.0009
Creatinine >2.5 mg/dL	3.60	2.27-5.70	<0.0001
Inducible ventricular arrhythmia on EP study	0.48	0.18-1.31	0.15
Abnormal intraventricular conduction	0.88	0.62-1.24	0.47
Paced rhythm	1.74	0.55-5.46	0.34
Second degree heart block	0.61	0.09-4.38	0.63
Third degree heart block	0.93	0.38-2.26	0.86

Brain natriuretic peptide	1.00	1.00-1.00	0.12
Procedural factors			
ICD indication			
Secondary prevention	1.96	1.36-2.81	0.0003
Device type			
Single chamber	0.72	0.46-1.12	0.14
CRT-D	0.82	0.54-1.25	0.37

NYHA, New York Heart Association; ACE; angiotensin converting enzyme; EP, electrophysiology; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy defibrillator

Table S3. Definitions of Variables Significant in Multivariable Analysis.

Syncope	Sudden loss of consciousness with loss of postural tone, not related to anesthesia, with spontaneous recovery as reported by patient or observer
Ventricular tachycardia	Three or more consecutive complexes in duration emanating from the ventricles at a rate of >100 beats per minute
Cerebrovascular disease	History of stroke (loss of neurological function with abrupt onset and symptoms >24 hours) OR Transient ischemic attack (loss of neurological function with abrupt onset and symptoms <24 hours) OR Non-invasive/invasive carotid test with > 79% occlusion or previous carotid artery surgery/intervention for carotid artery stenosis
Diabetes mellitus	Physician diagnosis

	OR Fasting blood sugar greater than 126 mg/dL