Syncope in Primary Prevention Implantable Cardioverter Defibrillator Patients

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ABSTRACT: **Background:** Syncope is a common clinical condition spanning from benign to life-threatening diseases. There is sparse information on the outcomes of syncopal patients who received an implantable cardiac defibrillator (ICD) for primary prevention of sudden cardiac death (SCD).

Objectives: To assess the outcomes and prognosis of patients who underwent implantable cardiac defibrillator (ICD) implantation for primary prevention of SCD and compare them to patients who presented with or without prior syncope.

Methods: We compared the medical records of 75 patients who underwent ICD implantation for primary prevention of SCD and history of syncope to those of a similar group of 80 patients without prior syncope. We assessed the episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), shock, anti-tachycardia pacing (ATP) and mortality in each group during follow-up.

Results: Mean follow-up was 893 days (810–976, 95%CI) (no difference between groups). There was no significant difference in gender or age. Patients with prior syncope had a higher ejection fraction rate (35.5 ± 12.6 vs. 31.4 ± 8.76, $P = 0.02$), experienced more episodes of VT (21.3% vs. 3.8%, $P = 0.001$) and VF (8% vs. 0%, $P = 0.01$), and received more electric shocks (18.7% vs. 3.8%, $P = 0.004$) and ATP (17.3% vs. 6.2%, $P = 0.031$). There were no differences in inappropriate shocks (6.7% vs. 5%, $P = 0.74$), cardiovascular mortality (cumulative 5 year estimate 29.9% vs. 32.2%, $P = 0.97$) and any death (cumulative 5 year estimate 38.1% vs. 48.9%, $P = 0.18$).

Conclusions: Patients presenting with syncope before ICD implantation seemed to have more episodes of VT/VF and shock or ATP. No differences in mortality were observed

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KEY WORDS: syncope, sudden death, implantable cardiac defibrillator (ICD), ventricular fibrillation (VF), ventricular tachycardia (VT)

Syncope is a common and elusive diagnosis, accounting for approximately 3% of emergency room visits and 1% to 6% of hospital admissions [1,2]. Accordingly, its prognosis varies widely, with 1 year mortality rates ranging from 0% in the case of vasovagal events up to 30% in the presence of heart disease. Patients who are candidates for primary prevention of sudden cardiac death (SCD) with an implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy device (CRT-D) frequently present with or have a history of previous syncope. The association between syncope and ventricular arrhythmias is not always clear and the cause of syncope may remain undiagnosed [3-9].

There is limited information regarding the outcome of patients implanted with an ICD or CRT-D for a primary prevention indication where syncope occurred prior to the implantation. The aim of this study was to assess the outcome and prognosis of patients implanted with an ICD or CRT-D for a primary prevention indication, comparing patients who had a syncopal history before the implantation to a similar group of patients without syncopal episodes.

PATIENTS AND METHODS

We conducted a retrospective evaluation of 155 consecutive patients who underwent ICD or CRT-D implantation at our institution for primary prevention of SCD during the period May 2009 to June 2012. We compared 75 patients with a history of prior syncope (up to 6 months before the implantation) to a non-matched control group of 80 patients without prior syncope. The mean follow-up after the ICD implantation was 893 days (range 810–976, 95% confidence interval).

We assessed the number of ventricular tachycardias (VT), ventricular fibrillations (VF), and shock and anti-tachycardia pacing (ATP) treatments, as well as cardiovascular and total deaths in each group during follow-up. Syncope was defined as a sudden loss of consciousness with inability to maintain postural tone, not related to anesthesia or seizure disorder, and spontaneous recovery reported by the patient or an observer. This excludes cardiac arrest, which requires resuscitation [3]. The ICDs were programmed in a similar way.

Statistical analyses were performed using IBM SPSS v.20 (IBM Corporation, USA). All tests were two-tailed, and $P < 0.05$ was considered significant. Baseline parameters and outcome measures in both groups were compared using the Students *t*-test for continuous variables and the Pearson chi-square test for categorical variables. Survival analysis was performed using the Kaplan-Meier procedure with log-rank testing for statistical significance. Cumulative survival was derived from life table analysis.

Table 1. Patients' baseline characteristics

	Syncope (n=75)	No syncope (n=80)	*P* value
Age, years	65.0 ± 13.4	68.9 ± 11.7	0.058
Men, %	77.3	86.3	0.210
Hypertension, %	60	67.5	0.403
Diabetes mellitus, %	36	47.5	0.193
Dyslipidemia, %	61.3	68.8	0.4
Renal failure, %	14.7	2.5	0.008
AF, %	14.7	33.8	0.008
Ischemic CM, % (n)	40 (30)	67.7 (54)	0.001
Non-ischemic CM, % (n)	40 (30)	22.5 (18)	0.024
HCM, % (n)	18.7 (14)	7.5 (6)	0.054
EF, %	35.5 ± 12.6	31.4 ± 8.76	0.02
ACEI/ARB, %	66.7	78.8	0.105
Beta-blockers, %	72	92	0.01
Spironolactone, %	26.7	41.3	0.06
Amiodarone, %	24	16.3	0.2
Class 1 AAD, %	9.3	1.3	0.03

AF = atrial fibrillation, CM = cardiomyopathy, HCM = hypertrophic cardiomyopathy, EF = ejection fraction, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, AAD = anti-arrhythmic drugs

RESULTS

Patient's baseline characteristics are presented in Table 1. Patients with prior syncope had a higher incidence of non-ischemic cardiomyopathy (CM): 40% (n=30) vs. 22.5% (n=18), *P* = 0.02; and a lower incidence of ischemic CM: 40% (n=30) vs. 67.7% (n=54), *P* = 0.001.

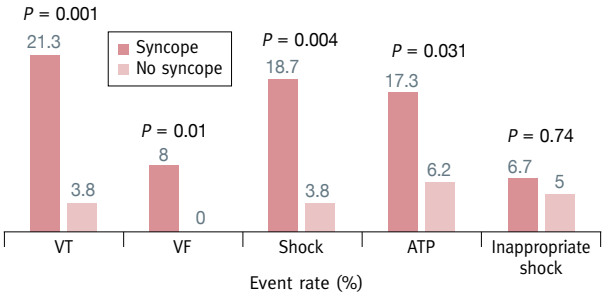
Patients with prior syncope had a higher ejection fraction rate (35.5 ± 12.6 vs. 31.4 ± 8.76, *P* = 0.02), a higher rate of renal failure (14.7% vs. 2.5%, *P* = 0.008) and less atrial fibrillation than patients without syncope (14.7% vs. 33.8%, *P* = 0.008)

Patients with prior syncope had a higher incidence of class 1 anti-arrhythmic drug intake (9.3% vs. 1.3%, *P* = 0.03) and a lower incidence of beta-blocker intake (72% vs. 92%, *P* = 0.01). No differences were observed in age (65.0 ± 13.4 vs. 68.9 ± 11.7, *P* = 0.058) or gender (77.3% vs. 86.3%, *P* = 0.2).

Patients with syncope had more episodes of VT (21.3% vs. 3.8%, *P* = 0.001) and VF (8% vs. 0%, *P* = 0.01) and received more electric shocks (18.7% vs. 3.8%, *P* = 0.004) and ATP treatments (17.3% vs. 6.2%, *P* = 0.031). There were no differences with regard to inappropriate shocks (6.7% vs. 5%, *P* = 0.74) [Figure 1]. There were no differences in cardiovascular mortality (cumulative 5 year estimate 29.9% vs. 32.2%, *P* = 0.97) and total mortality (cumulative 5 year estimate 38.1% vs. 48.9%, *P* = 0.18) during the follow-up [Figure 2].

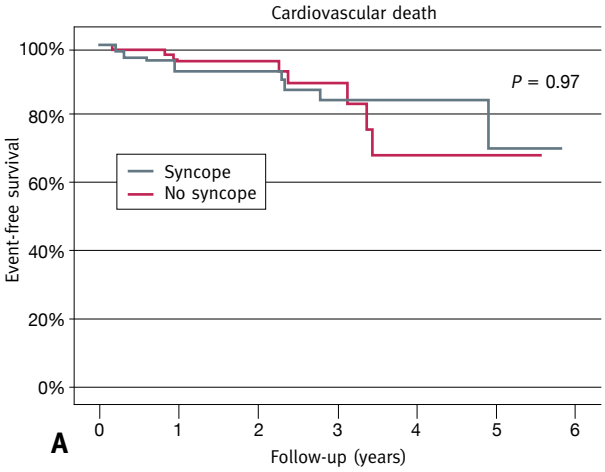
Re-analysis of our data excluding patients with hypertrophic cardiomyopathy (HCM) revealed 61 patients with a prior syn-

Figure 1. Events in patients with and without previous syncope



VT = ventricular tachycardia, VF = ventricular fibrillation, ATP = anti-tachycardia pacing

Figure 2. Kaplan-Meyer curve: **[A]** Cardiovascular mortality and **[B]** Total mortality during follow-up



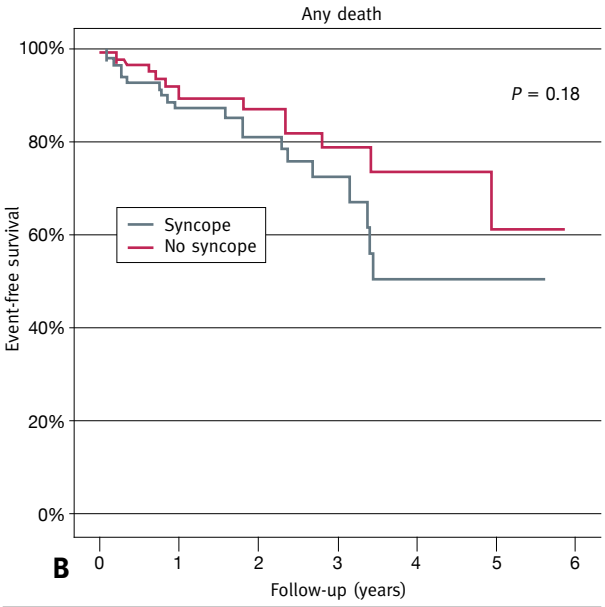


Table 2. Baseline characteristics of patients without hypertrophic cardiomyopathy

	Syncope (n=61)	No syncope (n=74)	*P* value
Age, years	67.0 ± 11.3	69.9 ± 12.6	0.06
Men, %	78.7	86.5	0.1
Hypertension, %	73	65.6	0.2
Diabetes mellitus, %	39.3	48.6	0.18
Dyslipidemia, %	65.6	71.6	0.2
Renal failure, %	14.8	2.7	0.01
AF, %	11.5	35.1	0.001
Ischemic CM, % (n)	58.8 (30)	78.3 (54)	0.01
Non-ischemic CM, % (n)	41.2 (21)	21.7 (15)	0.01
EF,%	32 ± 13.8	29.4 ± 6.3	0.09
ACEI/ARB, %	77	83.8	0.7
Beta-blockers, %	77	93.2	0.07
Spironolactone, %	32.8	44.6	0.11
Amiodarone, %	27.9	16.2	0.07
Class 1 AAD, %	8.2	0	0.017

AF = atrial fibrillation, CM = cardiomyopathy, HCM = hypertrophic cardiomyopathy, EF = ejection fraction, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, AAD = anti-arrhythmic drugs

cope and 71 patients without. Baseline characteristics are shown in Table 2. In this analysis, patients with prior syncope had a higher incidence of non-ischemic CM: 41.2% (n=21) vs. 21.7% (n=15), $P = 0.01$; and a lower incidence of ischemic CM: 58.8% (n=30) vs. 78.3% (n=54), $P = 0.01$.

There were no differences in ejection fraction rate (32 ± 13.8 vs. 29.4 ± 6.3, $P = 0.09$), but patients with prior syncope had a higher incidence of renal failure (14.8% vs. 2.7%, $P = 0.01$) and less atrial fibrillation than patients without syncope (11.5% vs. 35.1%, $P = 0.001$). Patients with prior syncope had a higher incidence of class 1 anti-arrhythmic drug intake (8.2% vs. 0%, $P = 0.017$). No differences were observed in age (67.0 ± 11.3 vs. 69.9 ± 12.6, $P = 0.06$) or gender (78.7% vs. 86.5%, $P = 0.1$).

Patients with syncope had more episodes of VT (23% vs. 4.1%, $P = 0.004$) and VF (7.2% vs. 0%, $P = 0.04$) and received more electric shocks (19.7% vs. 4.1%, $P = 0.008$). There were no differences in the rate of inappropriate shocks (6.5% vs. 5.5%, $P = 0.5$) or of ATP therapy (19.7% vs. 6.8%, $P = 0.142$). No differences in cardiovascular and total mortality (cumulative 5 year estimate, $P = 0.22$ and $P = 0.9$ respectively) were observed during follow-up.

DISCUSSION

Traditionally, implantation of ICD and CRT-D for prevention of SCD is divided into primary and secondary indications and there are clear guidelines for these indications [10]. Syncope in patients with left ventricular dysfunction may indicate an arrhythmic event and, therefore, a worse prognosis. Nevertheless, the cause of syncope is usually difficult to establish and raises the possibility that in any particular patient device implantation may represent a primary or secondary prevention indication.

According to current guidelines, ICD is indicated in syncopal patients who developed sustained VT or VF on electrophysiology study (EPS) (class I indication), in patients with non-ischemic CM and significant left ventricular dysfunction (class IIa indication), or in patients with advanced structural heart disease and negative syncopal evaluation (class IIb indication) [10-15].

There are an increasing number of patients with a clear-cut indication for primary ICD implantation who present with or developed syncope prior to the implantation. In these cases ICD is implanted without extensive invasive diagnostic tests such as EPS.

Only the Canadian Implantable Defibrillator Study (CIDS) [14], a secondary prevention trial, included patients with unmonitored syncope and subsequent documentation of either spontaneous VT (> 10 seconds) or sustained (> 30 seconds) monomorphic VT induced by EPS. In this subgroup of patients no differences were observed between patients treated with amiodarone and those who received an ICD.

In our study population patients implanted with an ICD for a primary prevention of SCD indication and a history of syncope had a significant higher incidence of VT, VF, appropriate shock therapy and ATP therapy compared to similar patients without previous syncope, suggesting that syncope in this population is usually related to ventricular arrhythmia or is a marker for future development of ventricular arrhythmia. Interestingly, despite a higher incidence of episodes of VT/VF and shocks or ATP no differences in mortality were observed.

The limitations of our study include the retrospective evaluation of patient outcomes, small sample size, and the non-matched population.

In conclusion, our study suggests that in patients who fulfill the indications for ICD implantation for primary prevention of SCD, the presence of syncope indicates an increased risk of future development of ventricular arrhythmia.

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