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Syncope and risk of sudden cardiac arrest in coronary artery disease

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ABSTRACT

Background: Syncope has been associated with increased risk of sudden cardiac arrest (SCA) in specific patient populations, such as hypertrophic cardiomyopathy, heart failure, and long QT syndrome, but data are lacking on the risk of SCA associated with syncope among patients with coronary artery disease (CAD), the most common cause of SCA. We investigated this association among CAD patients in the community.
Methods: All cases of SCA due to CAD were prospectively identified in Portland, Oregon (population approximately 1 million) as part of the Oregon Sudden Unexpected Death Study 2002–2015, and compared to geographical controls. Detailed clinical information including history of syncope and cardiac investigations was obtained from medical records.
Results: 2119 SCA cases (68.4 ± 13.8 years, 66.9% male) and 746 controls (66.7 ± 11.7 years, 67.0% male) were included in the analysis. 143 (6.8%) of cases had documented syncope prior to the SCA. SCA cases with syncope were >5 years older and had more comorbidities than other SCA cases. After adjusting for clinical factors and left ventricular ejection fraction (LVEF), syncope was associated with increased risk of SCA (OR 2.8; 95%CI 1.68–4.85). When analysis was restricted to subjects with LVEF ≥50%, the risk of SCA associated with syncope remained significantly elevated (adjusted OR 3.1; 95%CI 1.68–5.79).
Conclusions: Syncope was associated with increased risk of SCA in CAD patients even with preserved LV function. These findings suggest a role for this clinical marker among patients with CAD and normal LVEF, a large subgroup without any current means of SCA risk stratification.

1. Introduction

Syncope is a common medical problem, with a reported incidence of 6.2 per 1000 person-years in the general population [1], accounting for about 1% of all emergency department visits [2]. Syncope can be the manifestation of a multitude of clinical conditions ranging from relatively benign to life-threatening. With a standardized diagnostic approach, the underlying etiology can be determined in the majority of patients [3]. However, clinical management of syncope can pose major challenges, with particular concern among both providers and patients regarding risk of future adverse clinical events, including sudden cardiac arrest (SCA).

The prognosis of syncope varies widely depending on the underlying etiology [2,4]. Previous studies have demonstrated that patients with cardiac etiologies for syncope have higher mortality rates compared to patients with non-cardiac or unknown causes of syncope [1,5,6]. In the presence of heart failure with reduced left ventricular (LV) function, hypertrophic cardiomyopathy, or a primary electrical disease such as long QT or Brugada syndrome, syncope predicts increased risk of SCA [7–11]. However, there is a significant lack of data regarding risk of SCA associated with syncope in the broader population of patients with coronary artery disease (CAD), which is the most common underlying cause of SCA [12].

In a large, ongoing community-based study of SCA in the US Northwest, we evaluated the association between syncope and SCA among CAD patients, with the ability to incorporate clinical factors and cardiac investigations performed prior to the SCA event. Additionally, we

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sought to determine whether assessment of LV function is helpful in distinguishing syncope patients at high risk of SCA.

2. Methods

2.1. Study population

The Oregon Sudden Unexpected Death Study (Oregon SUDS) is an ongoing, population-based study that prospectively ascertains cases of out of hospital cardiac arrest in the Portland, Oregon metropolitan region (catchment area of approximately one million). Analysis is conducted using a case-control design. The methods of the study have been previously described in detail [13,14]. Briefly, subjects with an out-of-hospital cardiac arrest were prospectively identified through three main sources: the emergency medical response system (EMS), local hospital emergency rooms, and the county's medical examiner's office. All existing documents, including the EMS report, patient's complete lifetime medical records, death certificate and autopsy report, if available, were obtained for each case.

Based on this comprehensive information, in-house adjudication was performed by three physicians in order to determine whether the case fulfilled pre-specified criteria for SCA and CAD. Control subjects were concomitantly enrolled from the same geographical region and were required to have documented CAD. They were recruited from clinics of participating health systems, from individuals receiving coronary angiography, from patients transported by EMS for symptoms suggestive of coronary ischemia, and from members of a local health maintenance organization. Medical records for each potential control were reviewed in the same manner as the cases.

Subjects for the present analysis were enrolled from February 1st 2002 to January 31st 2015, and were at least 18 years of age. Medical records were reviewed for baseline demographic data and clinical history. A cardiologist analyzed archived 12-lead electrocardiograms (ECGs) performed prior and unrelated to the SCA event, if available, for the presence of conduction disturbances, and resting heart rate, QRS duration and QTc-interval (corrected according to the Bazett's formula) were measured. Heart rate and QRS duration were obtained from automated ECG reports. QT-interval was measured manually from the beginning of the QRS complex to the end of the T wave in lead V_5 defined by the tangent of the downslope of the T wave using a digital onscreen software program (DataInf Measure; DataInf GmbH; Tübingen, Germany). Information on LV ejection fraction (LVEF) was collected from archived imaging reports available in the medical records. LV mass index, adjusted for body surface area, was calculated for subjects with necessary echocardiographic parameters available using the linear formula as recommended by the American Society of Echocardiography [15]. Subjects with severe aortic stenosis or hypertrophic cardiomyopathy were excluded from the echocardiographic analysis. All included cases had their echocardiography performed prior and unrelated to cardiac arrest (for 66% of cases, assessment of LV function was performed within two years of arrest), and if multiple echocardiograms were available, the one closest to SCA was included in the analysis. The majority of controls (81%) had echocardiograms available that were performed within 2 years of ascertainment.

2.2. Definitions

SCA was defined as a sudden, unexpected pulseless condition of likely cardiac origin; unwitnessed cases were required to have been seen in a normal state of health within 24 h of death [12]. Using pre-specified criteria, cases with chronic terminal illnesses, end-stage heart failure or with non-cardiac etiology for cardiac arrest, such as trauma, drug overdose, cerebrovascular accident or pulmonary embolism, were excluded during the adjudication process. Both survivors and non-survivors of cardiac arrest were included as cases. For the present study, SCA cases were required to have significant established CAD; or, if they were ≥50 years but with no documented CAD, were presumed to have CAD (in published autopsy studies the proportion of subjects with CAD in this group has been >90%) [16]. Recruited controls had an established CAD as well, but were required not to have a history of cardiac arrest or sustained ventricular arrhythmias, thereby enabling the identification of risk factors specific to SCA as opposed to CAD.

Established CAD was defined as having ≥50% stenosis in a major coronary artery, or a history of myocardial infarction or coronary revascularization. Hypertension was identified from clinical history or use of antihypertensive medication; diabetes mellitus was defined as documentation of diabetes in the medical records or by the use of insulin or other hypoglycemic agent; chronic renal insufficiency as clinical history of chronic kidney disease in the medical records or ongoing dialysis; and pulmonary disease as history of asthma or chronic obstructive pulmonary disease (COPD), or medical therapy for these conditions.

Information on syncope was systematically collected from the medical records of the patients. According to guidelines, syncope is defined as transient loss of consciousness supposedly due to transient global cerebral hypoperfusion that is characterized by rapid onset, short duration and spontaneous complete recovery [2]. Unconsciousness due to other factors such as epileptic seizures, intoxication, or metabolic disorders such as hypoglycemia was not classified as syncope, nor was pre-syncope that did not lead to complete loss of consciousness.

This study was approved by the Institutional Review Boards of Cedars-Sinai Medical Center, Oregon Health and Science University and all participating hospitals and health systems.

2.3. Statistical analysis

Independent-samples *t*-tests and Pearson's chi-square tests were used for bivariate case-control and case-case comparisons for continuous and categorical variables, respectively. A multivariable logistic regression model was used to estimate odds ratios (OR) with 95% confidence intervals (CI) for SCA risk associated with history of syncope. Adjustments to the models were made for covariates that differed between the groups. Age was added as a continuous variable and race, hypertension, diabetes, history of COPD or asthma, chronic renal insufficiency, use of beta-blockers, digoxin or antiarrhythmic medication, and LVEF (<50% vs. ≥50%) were added as categorical variables. Separate subgroup analysis according to LVEF was also conducted among subjects with information available on LV function. Two-sided statistical tests were used, and *P* values ≤0.05 were considered statistically significant.

3. Results

3.1. Characteristics of SCA cases and controls

3074 subjects (2328 SCA cases, 746 controls with CAD) aged ≥18 years had medical records available for analysis. After excluding 209 cases without evidence of significant CAD from the analysis, 2119 SCA cases remained in the final analysis. Overall, 277 cases survived to hospital discharge (16.1% of cases with resuscitation attempted). The demographic characteristics of the subjects are presented in Table 1. SCA cases were slightly older (68.4 ± 13.8 vs. 66.7 ± 11.7 years; $p = 0.003$) compared to controls, and less likely to be of white European descent (86.5% vs. 91.8%, $p < 0.001$), but no difference in sex distribution between the groups was observed (66.9% vs. 67.0% male). Cases were more often diabetics and were more likely to have chronic renal insufficiency, pulmonary disease and reduced LV function than controls. Antiarrhythmic medication and digoxin were more commonly used among cases, but beta-blocker medication was more common among controls.

3.2. Syncope and risk of SCA according to LV function

143 (6.8%) SCA cases had experienced a documented episode of syncope prior and unrelated to their cardiac arrest, compared to 35 (4.7%) controls, with an unadjusted 1.5-fold risk of SCA (OR 1.5; 95% CI 1.01–2.15; $p = 0.05$). In a multivariate model including age, race, hypertension, diabetes, chronic renal insufficiency, pulmonary disease, use of beta-blockers, digoxin and antiarrhythmic medication together with

Table 1
Demographics and clinical characteristics of subjects.

	Cases ($n = 2119$)	Controls ($n = 746$)	*P* value
Age (years)	68.4 ± 13.8	66.7 ± 11.7	0.003
Male	1417 (66.9%)	500 (67.0%)	0.94
Ethnicity			0.0004
White	1811 (86.5%)	656 (91.8%)	
Black	154 (7.4%)	25 (3.5%)	
Other	128 (6.1%)	34 (4.8%)	
Syncope	143 (6.8%)	35 (4.7%)	0.04
Hypertension	1450 (68.4%)	554 (74.3%)	0.003
Diabetes	796 (37.6%)	236 (31.6%)	0.004
Pulmonary disease	685 (32.3%)	187 (25.1%)	0.0002
Chronic renal insufficiency	453 (21.4%)	111 (14.9%)	0.0001
History of myocardial infarction	716 (33.8%)	354 (47.4%)	<0.0001
EF ≤ 35%[a]	212 (27.1%)	69 (12.0%)	<0.0001
QTc (ms)[b]	451.7 ± 38.8	427.5 ± 32.7	<0.0001
Medication[c]			
Beta-blockers	878 (46.6%)	462 (66.1%)	<0.0001
Antiarrhythmic	359 (19.0%)	67 (9.6%)	<0.0001
Digoxin	247 (13.1%)	32 (4.6%)	<0.0001

Data are presented as mean ± SD or n (%).
[a] EF information available for 783 cases and 574 controls.
[b] QTc information available for 601 cases and 563 controls.
[c] Medication information available for 1885 cases and 699 controls.

Table 2
Multivariable adjusted odds ratios (ORs) and 95% confidence intervals (CI) for SCA associated with syncope, according to left ventricular function.

	OR	95% CI	*P* value
All subjects[a]	2.8	1.68–4.85	0.0001
LVEF >35%[b]	2.9	1.59–5.01	0.0004
LVEF ≥50%[c]	3.1	1.68–5.79	0.0003

Adjusted for age, race, hypertension, diabetes, pulmonary disease, chronic renal insufficiency, beta-blockers, antiarrhythmic medication, digoxin and LVEF (LVEF for all subjects only).
[a] 755 cases, 520 controls.
[b] 551 cases, 455 controls.
[c] 407 cases, 371 controls.

LVEF, syncope remained significantly associated with SCA (Table 2). Fig. 1 presents the risk of SCA associated with syncope according to LVEF, and distribution of LVEF in these patients. When analysis was restricted to subjects with normal LVEF ≥50%, 12.1% of cases and 4.6% of controls had presented with syncope ($p < 0.001$), and after adjusting for demographic and clinical variables the SCA risk associated with a history of syncope remained significant in this group (OR 3.1; 95% CI 1.68–5.79; $p < 0.001$) (Table 2).

3.3. Comparison between cases and controls with history of syncope

In order to identify clinical factors associated with syncope that may predict future SCA, we compared SCA cases with history of syncope to controls that had experienced syncope but not cardiac arrest. SCA cases with syncope were older (73.7 ± 13.1 vs. 67.5 ± 10.2 years, $p = 0.01$) than controls, but there were no significant differences in race, sex, hypertension, diabetes, pulmonary disease or renal insufficiency. The proportion of patients with reduced LVEF ≤35% was larger among cases with syncope compared to controls with syncope, but this finding did not reach statistical significance (27.7% vs. 12.0%, $p = 0.18$). No significant difference in QRS duration was noted between the cases and controls, but QTc interval was longer (462 ± 43 ms vs. 430 ± 42 ms, $p = 0.002$) among SCA cases with history of syncope. Cases with syncope were also more likely to be on antiarrhythmic medication (28.4% vs. 5.9%, $p = 0.006$) and digoxin (17.9% vs. 2.9%, $p = 0.03$) compared to controls with syncope, but there was no difference in beta-blocker use. In a multivariable model including several demographic/clinical variables, antiarrhythmic medications and LVEF, every 20 ms increase in QTc interval among syncope patients was associated with 2.6-fold increased risk for SCA (95% CI 1.12–5.87, $p = 0.03$), compared to 1.5-fold increased risk (95% CI 1.34–1.70, $p < 0.001$) associated with 20 ms QTc prolongation among patients without history of syncope.

3.4. Characterization of SCA cases with and without history of syncope

Table 3 demonstrates the characteristics of SCA cases with and without history of syncope. Cases with syncope were older and had higher prevalence of hypertension, renal insufficiency, and history of atrial fibrillation, but there were no differences in LV function or LV mass index between the groups. The prevalence of conduction abnormalities and electrocardiographic characteristics of SCA cases with and without syncope are also presented in Table 3. No significant differences in heart rate, QRS duration, QTc interval or conduction abnormalities were observed. However, SCA cases with syncope were more likely to have class I or III antiarrhythmic medications, but no significant differences in the use of beta-blockers, digoxin, diuretics, ACE inhibitors or Ca-channel blockers were noted between the cases with and without syncope. In controls with and without history of syncope, no differences in medication use were observed (data not shown).

4. Discussion

Syncope is often a difficult clinical condition to evaluate and manage, with a large differential diagnosis ranging from benign conditions to life-threatening diseases. Data has been lacking on the association between syncope and SCA in the community. In this population-based study, we addressed the risk of SCA associated with syncope in subjects with CAD. Overall, 7% of patients who suffered SCA had sought medical attention for syncope prior to their cardiac arrest. Syncope was a significant predictor of SCA in these patients independent of several clinical confounding factors, suggesting the potential of syncope events as clinical predictors of increased SCA risk in patients with CAD. Moreover, when analysis was restricted to subjects with preserved LV function, a sub-group for which there is a critical need to established new methods of risk stratification, syncope remained associated with 3-fold risk of SCA.

The prognostic significance of syncope has varied depending on the population studied. In the Framingham Heart Study general population cohort, syncope from any cause was associated with 31% increase in mortality. Cardiac syncope was associated with a two-fold risk of mortality, while vasovagal syncope appeared to have a benign prognosis [1]. A Danish registry study comparing 37,000 first-time syncope patients without previous comorbidities to 185,000 matched controls, demonstrated only 6% increase in mortality associated with syncope, but an increased risk of cardiovascular hospitalizations, stroke and

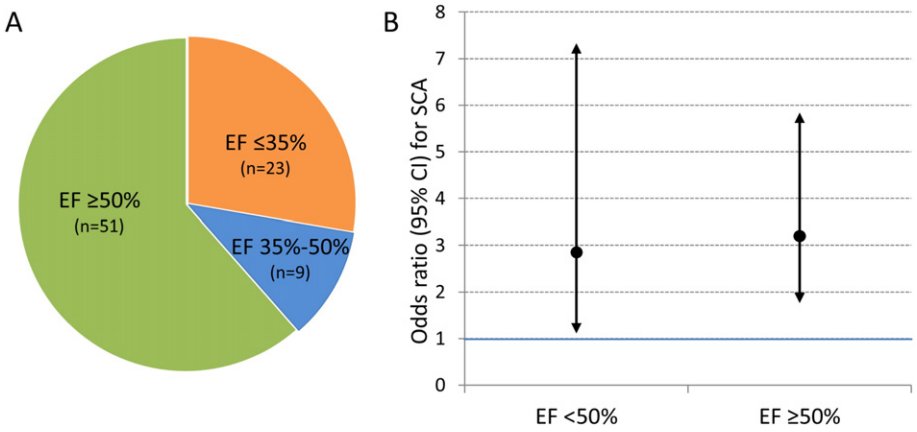

Fig. 1. Association between left ventricular ejection fraction and sudden cardiac arrest in patients with syncope. A. Distribution of left ventricular ejection fraction (EF) in syncope patients who suffered future sudden cardiac arrest (SCA). B. Adjusted risk of SCA associated with syncope in patients with reduced and normal left ventricular function.

Table 3
Clinical, echocardiographic and electrocardiographic characteristics of SCA cases with and without syncope.

	Syncope (n = 143)	No syncope (n = 1976)	P value
Age (years)	73.7 ± 13.1	68.0 ± 13.8	<0.0001
Male	91 (63.6%)	1326 (67.1%)	0.39
Ethnicity			0.62
White	120 (83.9%)	1691 (86.7%)	
Black	12 (8.4%)	142 (7.3%)	
Other	11 (7.7%)	117 (6.0%)	
Hypertension	109 (76.2%)	1341 (67.9%)	0.04
Diabetes	53 (37.1%)	743 (37.6%)	0.90
Pulmonary disease	43 (30.1%)	642 (32.5%)	0.55
Chronic renal insufficiency	41 (28.7%)	412 (20.8%)	0.03
History of atrial fibrillation	52 (36.4%)	424 (21.5%)	<0.0001
*Medication***			
Beta-blockers	72 (53.7%)	806 (46.0%)	0.08
Antiarrhythmic	38 (28.4%)	321 (18.3%)	0.004
Digoxin	24 (17.9%)	223 (12.7%)	0.09
Diuretics	72 (53.7%)	817 (46.7%)	0.11
LVEF ≤35%	23 (27.7%)	189 (27.0%)	0.90
Left ventricular hypertrophy[a]	28 (45.2%)	185 (41.8%)	0.68
Heart rate (bpm)	75.5 ± 17.1	79.1 ± 18.9	0.08
QRS (ms)	105.8 ± 31.4	103.0 ± 24.6	0.42
QTc (ms)	462.1 ± 43.1	450.7 ± 38.3	0.07
Cardiac conduction			0.83
Normal conduction	50 (54.4%)	488 (54.5%)	
Low-grade conduction abnormality[b]	12 (13.0%)	99 (11.0%)	
High-grade conduction abnormality[c]	30 (32.6%)	309 (34.5%)	

Data are presented as mean ± SD or n (%). Information available on medications for 134 syncope and 1751 non-syncope cases, on LVEF for 83 syncope and 700 non-syncope cases, on left ventricular hypertrophy for 62 syncope and 443 non-syncope cases, and on electrocardiographic data for 90 syncope and 883 non-syncope cases.

[a] Defined as echocardiographic LV mass index ≥110 g/m^2 in women and ≥134 g/m^2 in men.

[b] First-degree atrioventricular block, isolated left anterior or posterior fascicular block, or incomplete left/right bundle-branch block.

[c] Complete left/right bundle-branch block, intraventricular conduction delay (QRS ≥ 120 ms) or II- or III-degree atrioventricular block.

** Medication information available for 134 cases with syncope and 1751 no-syncope cases.

device implantation [17]. However, an earlier study comparing patients with and without syncope matched for cardiovascular disease and other important clinical variables did not identify syncope as an independent risk factor for cardiac mortality or cardiovascular events; rather, prognosis was determined by underlying cardiac comorbidities, especially heart failure [18]. Several studies conducted among emergency department patients have later suggested, that age and underlying cardiovascular diseases instead of the mechanism of syncope are related to future hospitalizations and mortality [19–21]. In the present study, we also observed that among SCA patients, those with a history of syncope were significantly older and had more comorbidities than SCA cases without syncope. However, even after adjusting for clinical factors and LV function, syncope was associated with increased risk of SCA among the CAD population.

In patients with heart failure and reduced LV systolic function, syncope has been associated with increased risk of sudden death regardless of the etiology of syncope [22]. However, to our knowledge the present study is the first to demonstrate that the association between syncope and SCA is independent of LV systolic function. In fact, we observed a three-fold increased risk of SCA also among patients with preserved LV ejection fraction. These findings may have implications for the process of improving risk stratification in patients who suffer SCA with preserved LVEF. The scientific literature has established that the majority of SCA events (at least 50%) occur among patients with preserved LVEF [23,24], yet current guidelines do not provide any means of risk stratifying this large sub-group [25,26]. Patients with coronary disease and syncope appear to be a special population in this regard and the potential role of syncope as a clinical risk marker in patients with preserved LVEF and coronary disease warrants further evaluation.

Underlying etiologies of syncope vary depending on the group of patients studied. In younger age groups, vasovagal and neurally mediated syncope are the most prevalent causes, but in older populations, cardiac causes of syncope together with orthostatic hypotension and carotid sinus hypersensitivity become more common [2]. When a cardiac disease condition or conduction abnormality is present, the suspicion for a cardiac origin of syncope has to be high, and often further diagnostic work-up, including electrophysiological study, are needed for the diagnosis and therapeutic decisions. However, this does not mean that every syncopal episode in cardiac patients is due to bradycardia or ventricular tachyarrhythmia. Even among subjects with a bundle-branch block and history of syncope who are at high risk of developing atrioventricular block, comprehensive evaluation including insertion of a loop recorder revealed non-bradycardia related mechanisms in a significant number of patients [27]. Similar observations on competing etiologies for syncope have been made in ICD trials demonstrating that not all syncopal episodes are due to poorly tolerated and self-limiting ventricular arrhythmias even in this high-risk group. For example, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) performed among heart failure patients with reduced LVEF showed that appropriate ICD shocks were more common in patients with syncope, yet the ICD did not reduce the mortality risk associated with syncope; nor did it protect against syncope recurrences compared to amiodarone or placebo [7]. While the retrospective analysis of syncope in the present study precluded precise categorization of syncopal events, it is likely that among SCA victims, non-arrhythmic and multifactorial mechanisms are important contributors to syncope. These data are in accordance with our finding that conduction abnormalities were not more prevalent in SCA cases with history of syncope compared to those without documented syncopal episodes.

Identifying individuals at high risk of future adverse events and mortality has been a focus of multiple prior studies, and several risk stratification tools have been developed in order to help in syncope risk stratification in emergency departments [28,29]. The present study does not directly answer how to distinguish high-risk individuals with syncope from those with better prognosis. However, syncope patients with subsequent cardiac arrest were older and had a markedly longer QTc interval than controls with syncope. Even after adjusting for clinical factors, medications and LVEF, QTc prolongation was strongly associated with SCA among syncope patients suggesting the potential utility of incorporating QTc interval into the risk stratification algorithms. This is in accordance with previous observations from different population samples linking QT prolongation with SCA [30,31]. Besides genetic predisposition and QT prolonging medications, acquired comorbidities including myocardial infarction and other structural heart disease can cause prolongation of the QT interval [30,31]. It is thus possible that in addition to vulnerability for ventricular arrhythmias caused by prolonged repolarization, prolonged QT interval can reflect underlying cardiac pathology or QT prolonging medication associated with adverse outcome in patients with syncope.

Strengths of the present study include the prospective ascertainment of SCA cases and the community-based approach. Since SCA is most often due to an acute or chronic manifestation of CAD, the controls recruited in Oregon SUDS were CAD patients making the observed differences between the groups likely to be specific to SCA. However, several limitations should also be considered while interpreting the results. Although SCA cases were prospectively and uniformly collected, since SCA can often be the first manifestation of cardiac disease, medical records were not uniformly available for every case leading to some potential for bias. This is especially true in the subgroup with echocardiographic data available, a subset that is more likely to have cardiovascular disease or risk factors. Another limitation is the retrospective classification of syncope. During the adjudication process, information on syncope was systematically and

meticulously collected from the medical records. However, the exact mechanism of syncope or its timing relatively to cardiac arrest could not be reliably addressed. Also, our reported occurrence of syncope is likely to underestimate prevalence, since all patients with syncope may not seek medical attention for their symptoms. Finally, it is possible that for some patients with syncope a timely medical intervention may have prevented future SCA.

5. Conclusion

These findings demonstrate that syncope is a significant risk factor for SCA among CAD patients even with preserved LV systolic function, highlighting the need for comprehensive evaluation and risk assessment of these patients. The current lack of effective SCA risk stratification in patients with preserved LVEF represents a significant and critical knowledge gap, and these findings suggest that a renewed focus on comprehensive investigation of the potential role of syncope as a clinical risk marker is warranted.

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Conflict of interest

None.

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