Sudden Cardiac Death in Heart Failure: A 20-Year Perspective From a Mediterranean Cohort

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ABSTRACT

Background: The prediction of sudden cardiac death (SCD) in heart failure (HF) remains an unmet need. The aim of our study was to assess the prevalence of SCD over 20 years in outpatients with HF managed in a Mediterranean multidisciplinary HF Clinic, and to compare the proportion of SCD (SCD/all-cause death) to the expected proportional occurrence based on the validated Seattle Proportional Risk Model (SPRM) score.

Methods and Results: This prospective observational registry study included 2772 outpatients with HF admitted between August 2001 and May 2021. Patients were included when the cause of death was known and SPRM score was available. Over the 20-year study period, 1351 patients (48.7%) died during a median follow-up period of 3.8 years (interquartile range 1.6−7.6). Among these patients, the proportion of SCD out of the total of deaths was 13.6%, whereas the predicted by SPRM was 39.6%. This lower proportion of SCD was observed independently of left ventricular ejection fraction, ischemic etiology, and the presence of an implantable cardiac defibrillator.

Conclusions: In a Mediterranean cohort of outpatients with HF, the proportion of SCD was lower than expected based on the SPRM score. Future studies should investigate to what extend epidemiological and guideline-directed medical therapy patterns influence SCD. (*J Cardiac Fail 2023;29:236−245*)

Key Words: Sudden cardiac death, risk model, Mediterranean basin.

Lay Summary

We assessed the prevalence of SCD in a Mediterranean HF cohort managed in a multidisciplinary HF clinic over 20 years and compared the observed proportion of SCD to the expected proportional occurrence based on the SPRM score.

The proportion of SCD was significantly lower than expected by the SPRM score, independently of the degree of predicted risk, ischemic etiology, the period of admission, and the presence of an implanted ICD.

The regional habits of the Mediterranean Basin may have had an impact on the lower rate of SCD.

Introduction

The prevalence of sudden cardiac death (SCD) has declined in recent times,[1] but the prediction of sudden death in heart failure (HF) remains an unmet need. Current guidelines propose an algorithm

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Manuscript received July 15, 2022; revised manuscript received November 22, 2022; revised manuscript accepted November 28, 2022.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2022.11.016

based on the left ventricular ejection fraction (LVEF), ischemic etiology, and New York Heart Association functional class to identify high-risk patients who may benefit from primary prevention with an implantable cardiac defibrillator (ICD).[2] However, this approach is inaccurate; the guidelines were based on results from randomized clinical trials conducted almost 2 decades ago, on a background of medical therapy that is no longer considered contemporary.[3,4]

The risk of SCD has decreased with the sequential introduction of new HF medications. Each component of contemporary guideline-directed medical therapy for HF with reduced ejection fraction (HFrEF) seems to decrease the risk of the 2 major modes of death in patients with HFrEF: HF progression and SCD.[5–8]

The role of primary preventative ICDs in patients with nonischemic cardiomyopathy was previously called into question in the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial, which showed that ICDs could decreased SCDs, but not all-cause mortality, when patients were randomly assigned to an ICD. A subgroup analysis suggested that ICDs offered a survival benefit in patients less than 59 years of age, but not in older patients.[9]

Furthermore, in the subgroup of patients with nonischemic cardiomyopathy, angiotensin receptor-neprilysin inhibitor (ARNI) seemed to have a greater effect on reducing ventricular arrhythmias.[10] Accordingly, the benefit of an ICD for primary prevention remains unknown for patients with HFrEF treated with guideline-directed medical therapy; however, the benefit is most likely smaller than the observed in pivotal ICD trials.

As a result of therapeutic advances, the proportions of different modes of death in HF have shifted over the last 2 decades, with less SCD and more noncardiovascular deaths, mainly cancer.[11] In this setting, interest has grown in the development of more precise tools for selecting candidates that might benefit from an ICD in primary prevention.[12-15] Among these tools, the Seattle Proportional Risk Model (SPRM) is a validated prediction model that incorporates readily obtainable clinical variables for predicting the proportional risk of sudden death (sudden death and all-cause mortality) in patients with systolic HF.

This is a novel methodology in sudden death research through its emphasis on patients with the greatest proportion of mortality owing to sudden death rather than with the greatest absolute risk of sudden death.

The SPRM was applied to patient-level data from 2 observational ICD cohorts (National Cardiovascular Data Registry ICD Registry and Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) and 2 randomized controlled trials (Sudden Cardiac Death in Heart Failure Trial and DANISH).[16–19] Those studies showed that patients with a higher predicted risk of SCD derived greater benefit from a primary prevention ICD than those with a lower predicted risk. The SPRM risk model was validated in a Japanese HF registry.[20]

The present study aims to assess the prevalence of SCD over 20 years in a Mediterranean HF cohort managed in a multidisciplinary HF clinic and to compare the observed proportion of SCD with the expected proportional occurrence, predicted with the validated SPRM.

Methods

Study Population and Outcomes

We recruited all consecutive ambulatory patients with HF admitted to a structured multidisciplinary HF clinic at the Hospital Universitari Germans Trial i Pujol (Badalona, Spain) between August 2001 and May 2021. During the baseline visit, patients provided written consent for the use of their clinical data for research purposes. Demographic, clinical, echocardiographic, and analytical data were recorded in a specific database (REGI-UNIC).

Over the 20-year study period, the criterion for referral and corresponding catchment areas, which included approximately 200,000 inhabitants as a primary hospital of reference and approximately 850,000 inhabitants for tertiary care in the northern Barcelona metro area, remained stable. The criterion for referral to the HF clinic was HF with at least 1 hospitalization and/or depressed systolic function.[21] All patients were followed with regular follow-up visits at the HF clinic, according to their clinical needs, and all were treated according to a unified protocol. Follow-up visits included a minimum of one visit with a nurse every 3 months and 1 visit with a physician (cardiologist, internist, or family physician) every 6 months. In addition, some follow-ups included optional visits with specialists in geriatrics, psychiatry, and cardiac rehabilitation.

SCD was defined as any unexpected death, either witnessed or not, occurring within 1 hour from symptom onset in a previously stable patient, with no recognizable cause. The other modes of death were classified as HF progression (HF worsening or treatment-resistant HF, in the absence of another cause), acute myocardial infarction (directly related in time with acute myocardial infarction, whether attributable to mechanical, hemodynamic, or arrhythmic complications; the definition of acute myocardial infarction was the accepted by international guidelines at every time through the study

period), stroke, postprocedural (postdiagnostic or post-therapeutic), other cardiovascular conditions (eg, rupture of an aneurysm, peripheral ischemia, or aortic dissection), or noncardiovascular conditions. Fatal events were identified from patient health records (including hospital wards, emergency rooms, and general practitioners) or by contacting relatives. Data were verified by accessing data from the Catalan and Spanish Health Systems and the Spanish Death Registry databases. Adjudication of events was performed by staff of the HF clinic, and an ad hoc committee of 3 to 4 members chaired by J.L., which resolved all discrepancies. Patients with unknown causes of death were excluded from the main analysis. Sensitivity analyses were performed (1) excluding patients with an LVEF of 40% or greater, (2) including patients with unknown mode of death as if they had suffered a SCD, and (3) considering appropriate ICD shocks as SCD events (data available in 413 of the 427 patients with an ICD implanted).

During baseline visits, all patients provided written consent for the use of their clinical data for research purposes. The study was performed in compliance with the laws that protect personal data, in accordance with the international guidelines on clinical investigations from the World Medical Association's Declaration of Helsinki. The local ethics committee approved the study.

We used the SPRM to estimate the proportional risk of SCD. The score was calculated to predict the proportional risk of SCD for each patient, based on the variables measured at the first visit to the HF clinic. When data were missing for any variable included in the model, the patient was excluded from the main analysis, although a sensitivity analysis was performed including these patients with missing values using multiple imputations.

The SPRM includes 10 clinical variables and found that the proportion of SCDs was greater among patients that were young, male, and had a low EF, a better New York Heart Association functional class, a higher body mass index, and used digoxin. Conversely, diabetes mellitus, hypertension or hypotension, renal dysfunction, and hyponatremia decrease the relative likelihood of an SCD. In our study all risk estimations were performed by 1 author of the original score (W.C.L.).

Statistical Analyses

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are expressed as the mean ± standard deviation for normal distributions and the median and interquartile range for non-normal distribution. Normal distributions were assessed with normal quantile−quantile plots. Comparisons between groups were performed with the chi-squared test, for categorical variables, and the Student *t* test or Mann−Whitney *U* test, for continuous variables. Cumulative incidence curves for all-cause death, SCD, and other specific causes of death (progressive or refractory HF, other cardiovascular causes, and noncardiovascular causes) were plotted using Cox regression analyses; for specific causes of death Fine and Gray competing risk method was used taking into account other causes of death. The performance (discrimination and calibration) of the SPRM was assessed with the area under the curve (AUC) and the Hosmer−Lemeshow test. Statistical analyses were performed with SPSS 24 (SPSS Inc., Chicago, IL) and STATA V.13.0 (College Station, TX). A 2-sided *P* value of less than .05 was considered significant.

Results

From August 2001 to May 2021, 2975 patients with HF were admitted to the HF clinic. Of these, 203 patients were excluded, 105 owing to missing data for at least one variable that contributed to the SPRM score and 98 owing to death from unknown causes (Supplementary Fig. 1). Of the remaining 2772 patients, 1351 (48.7%) died during follow-up (median 3.8 years, interquartile range 1.6−7.6 years, range 0.2−20.0 years). From the 2772 patients with SPRM assessed, only 3 patients were lost to follow-up. Those patients were not included then in the 1351 patients analyzed in the present study. Baseline demographics, clinical characteristics, and treatments of the included patients are shown in Table 1. Supplementary Figure 2 shows enrollment numbers overtime.

Table 2 shows the differences between dead patients from SCD and those who died from other causes (either cardiovascular or noncardiovascular). Fig. 1 depicts the cumulative incidence curves for all-cause deaths and specific causes of death. The actual incidences during follow-up were 48.7% for all-cause death, 6.6% for SCD, 21.5% for death related to HF or other cardiovascular causes, and 20.6% for noncardiovascular death. Supplementary Table 1 depicts the proportion of specific causes of death among the 1351 dead patients.

The observed proportion of SCD was 13.6% among the 1351 patients that died, while the predicted by SPRM was 39.6% (**Graphical Abstract**). The SPRM predicted an annual SCD mortality rate of 3.0%, but the observed rate was 1.2%. Fig. 2 compares the percentages of predicted and observed SCDs by quintiles of SPRM risk. The observed proportion of SCD was lower than predicted in every quintile of SPRM-predicted risk.

Table 1. Baseline Demographic and Clinical Characteristics and Treatments During Follow-up

	Total Cohort ($N = 2772$)	Survivors ($n = 1421$)	Nonsurvivors ($n = 1351$)	Absolute Difference [95% CI]	*P* Value*
Age, years	66.9 ± 12.9	62.4 ± 13.4	71.7 ± 10.3	−9.3 [−10.2 to −8.4]	<.001
Male sex	1957 (70.6)	1009 (71.0)	948 (70.2)	0.8 [−2.5 to 4.2]	.629
White	2739 (98.8)	1393 (98.0)	1346 (99.6)	−1.6 [−2.3 to −0.8]	<.001
Etiology					
Ischemic heart disease	1260 (45.5)	501 (35.3)	759 (56.2)	−20.9 [−24.6 to −17.3]	<.001
Dilated cardiomyopathy	480 (17.3)	354 (24.9)	126 (9.3)	15.6 [12.9 to 18.3]	<.001
Hypertensive	232 (8.4)	90 (6.3)	142 (10.5)	−4.2 [−6.2 to −2.1]	<.001
Alcohol derived	119 (4.3)	74 (5.2)	45 (3.3)	1.9 [0.4 to 3.4]	.015
Drug induced	77 (2.8)	42 (3.0)	35 (2.6)	0.4 [−0.9 to 1.6]	.559
Valvular	253 (9.1)	102 (7.2)	151 (11.2)	−4.0 [−6.1 to −1.8]	<.001
Hypertrophic cardiomyopathy	115 (4.1)	105 (7.4)	10 (0.7)	6.6 [5.2 to 8.1]	<.001
Other	236 (8.5)	153 (10.8)	83 (6.1)	4.6 [2.6 to 6.7]	<.001
HF duration, months	7 (2−47)	5 (1−33)	12 (2−54)	−9.5 [−13.9 to −5.0] medians diff. −7	<.001
LVEF, %	36.4 ± 14.7	37.2 ± 14.5	35.6 ± 14.9	1.6 [0.5 to 2.7]	.004
LVEF ≤40%	1976 (71.3)	979 (68.9)	997 (73.8)	−4.9 [−8.3 to −1.5]	.004
NYHA functional class III−IV	723 (26.1)	197 (13.9)	526 (38.9)	−25.1 [−28.2 to −21.9]	<.001
Diabetes	1166 (42.1)	498 (35.0)	668 (49.4)	−14.4 [−18.0 to −10.8]	<.001
Hypertension	1778 (64.1)	857 (60.3)	921 (68.2)	−7.9 [−11.4 to −4.3]	<.001
COPD	458 (16.5)	165 (11.6)	293 (21.7)	−10.1 [−12.8 to −7.3]	<.001
Anemia†	1210 (43.7)	442 (31.1)	768 (56.8)	−25.7 [−29.3 to −22.2]	<.001
Renal insufficiency‡	1215 (43.8)	472 (33.2)	743 (55.0)	−21.8 [−25.4 to −18.2]	<.001
Current smoker	468 (16.9)	313 (22.0)	155 (11.5)	10.5 [7.8 to 13.3]	<.001
Atrial fibrillation/flutter	633 (22.8)	287 (20.2)	346 (25.6)	−5.4 [8.5 to 2.3]	.001
LBBB	335 (12.1)	159 (11.2)	176 (13.0)	−1.8 [−4.3 to 0.5]	.138
Heart rate	70 (60 − 80)	67 (60 − 78)	72 (63 − 80)	−3.5 [−4.6 to −2.5] medians diff. −5	<.001
Blood pressure	127.0 ± 22.0	126.3 ± 20.8	127.6 ± 23.2	−1.3 [−2.9 to 0.4]	.125
BMI, kg/m^2	27.0 (24.2−30.3)	27.1 (24.5−30.5)	26.8 (23.8−30.1)	0.6 [0.2 to 1.0] medians diff. 0.3	.007
Sodium, mmol/L	138.0 ± 3.5	137.9 ± 3.1	138.1 ± 3.7	−0.2 [−0.4 to 1.3]	.177
Creatinine	1.08 (0.86−1.47)	1.01 (0.81−1.30)	1.19 (0.92−1.64)	−0.28 [−0.36 to −0.20] medians diff. −0.18	<.001
NTproBNP, ng/L§	1670 (701−3920)	1168 (490−2800)	2763 (1300−6053)	−747 [−9548 to 8054] medians diff. −1595	<.001
Treatments (follow-up), n (%)					
ACEI or ARB	2243 (80.9)	1144 (80.5)	1099 (81.3)	−0.8 [−3.7 to 2.1]	.574
Beta-blocker	2470 (89.1)	1326 (93.3)	1144 (84.7)	8.6 [6.3 to 11.0]	<.001
ARNI	544 (19.6)	483 (34.0)	61 (4.5)	29.5 [26.8 to 32.2]	<.001
MRA	1892 (68.3)	1043 (73.4)	849 (62.8)	10.6 [7.1 to 14.0]	<.001
Loop diuretic	2463 (88.9)	1176 (82.8)	1287 (95.3)	−12.5 [−14.8 to −10.2]	<.001
Digoxin	973 (35.1)	382 (26.9)	591 (43.7)	−16.9 [−20.4 to −13.4]	<.001
Ivabradine	610 (22.0)	408 (28.7)	202 (15.0)	13.7 [10.7 to 16.8]	<.001
CRT-P	125 (5.5)	68 (4.8)	57 (4.2)	0.6 [−1.0 to 2.1]	.473
CRT-D	193 (7.0)	128 (9.0)	65 (4.8)	4.2 [2.3 to 6.1]	<.001
ICD	234 (8.4)	148 (10.4)	86 (6.4)	4.0 [2.0 to 6.1]	<.001

Data are mean ± standard deviation, median (interquartile range), or number (%).

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor and neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular renal filtration (CKD-EPI equation); HF, heart failure; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block. LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Based on Cox regression analyses.

†According to World Health Organization criteria (<13 g/dL in men and <12 g/dL in women).

‡Estimated glomerular filtration rage of <60 mL/min/1.73 m^2.

§Available for 2159 patients.

The observed proportion of SCD was lower than predicted, irrespective of the LVEF (Fig. 3 and Supplementary Fig. 3); the proportion of SCD was 15.6%, 9.6%, and 7.1% for HF with a reduced, mildly reduced, and preserved EF, with an annual rate of 1.4%, 0.7% and 0.9%, respectively. Selecting patients with an LVEF of 35% or less (the cut-off used in international guidelines for ICD implantation), the annual rate of SCD was 1.5%. The proportion of SCD was lower irrespective of whether an ICD was present, either on admission or during follow-up (Fig. 4).

The baseline SPRM-predicted risk of SCD showed a significant decrease across time periods of baseline examination ($P = .005$) (Supplementary Fig. 4A). In all time periods, the observed proportion of SCD was lower than the predicted proportion by SPRM. The observed SCD proportion was also lower than that predicted when patients were divided into quintiles of HF duration, defined as the time

Table 2. Differences Between Patients Who Died Suddenly and those Dying from Other Causes

	Nonsudden Death ($n = 1167$)	Sudden Death ($n = 184$)	Absolute Difference [95% CI]	*P* Value*
Age, years	72.3 ± 10.0	68.0 ± 11.3	4.3 [2.7 to 5.9]	<.001
Male	800 (68.6)	148 (80.4)	−11.9 [−18.2 to −5.6]	.001
White	1164 (99.7)	182 (98.9)	0.8 [−0.7 to 2.4]	.085
Etiology				
Ischemic heart disease	629 (53.9)	130 (70.7)	−16.8 [−24.0 to −9.7]	<.001
Dilated CM	104 (8.9)	22 (12.0)	−3.0 [−8.0 to 1.9]	.187
Hypertensive	131 (11.2)	11 (6.0)	5.2 [1.3 to 9.1]	.031
Alcohol derived	38 (3.3)	7 (3.8)	−0.5 [−3.4 to 2.3]	.700
Drug induced	35 (3.0)	0	3.0 [2.0 to 3.9]	.017
Valvular	140 (12.0)	11 (6.0)	6.0 [2.1 to 9.9]	.008
Hypertrophic CM	10 (0.9)	0	0.9 [0.3 to 1.3]	.208
Other	80 (6.9)	3 (1.6)	5.3 [3.0 to 7.7]	.006
HF duration, months	12 (2−55)	14.5 (2−51)	0.21 [−9.3 to 9.8] medians diff. −2.5	.583
LVEF, %	36.2 ± 15.2	32.0 ± 11.8	4.3 [1.9 to 6.6]	<.001
LVEF ≤40%	840 (71.9)	156 (84.8)	−12.8 [−18.5 to −7.0]	<.001
NYHA functional class III−IV	461 (39.5)	64 (34.8)	4.7 [−2.7 to 12.2]	.222
Diabetes	573 (49.1)	95 (51.6)	−2.5 [−10.2 to 5.2]	.523
Hypertension	806 (69.1)	115 (62.5)	6.6 [−0.9 to 14.0]	.076
COPD	257 (22.0)	36 (19.6)	2.4 [−3.7 to 8.7]	.452
Anemia†	669 (57.3)	98 (53.3)	4.0 [−3.7 to 11.8]	.300
Renal insufficiency‡	663 (56.8)	80 (43.5)	13.3 [5.6 to 21.0]	.001
Current smoker	119 (10.2)	36 (19.6)	−9.4 [−15.4 to −3.4]	<.001
Atrial fibrillation/flutter	319 (27.3)	28 (15.2)	12.1 [6.3 to 17.9]	.001
LBBB	151 (12.9)	24 (13.0)	−0.1 [−5.3 to 5.1]	.969
Heart rate	73.1 ± 14.4	71.2 ± 13.6	1.9 [−0.3 to 4.11]	.096
Blood pressure	127.9 ± 23.3	125.5 ± 22.6	2.4 [−1.2 to 6.1]	.185
BMI, kg/m^2	27.2 (23.7−29.9)	28.1 (24.5−30.8)	−0.9 [−1.7 to −0.13] medians diff. −0.9	.022
Sodium, mmol/L	138.1 ± 3.7	137.9 ± 3.9	0.17 [−0.4 to 0.76]	.568
Creatinine	1.20 (0.93−1.65)	1.56 (0.89−1.58)	−0.06 [−0.24 to 0.10] medians diff. −0.36	.209
NTproBNP, ng/L§	2808 (1299−6108)	2414 (1320−5060)	1098 [−8506 to 10703] medians diff. 394	.553
SPRM (%)	38.9 ± 14.6	44.0 ± 16.1	−5.2 [−7.5 to −2.9]	<.001
Treatments (baseline)				
ACEI or ARB	781 (66.9)	137 (74.5)	−7.5 [−14.3 to −0.7]	.042
Beta-blocker	764 (65.5)	127 (69.0)	−3.6 [−10.8 to 3.7]	.344
ARNI	3 (0.3)	1 (0.5)	−0.2 [−1.3 to 0.8]	.506
MRA	399 (34.2)	63 (34.2)	−0.0 [−7.4 to 7.3]	.990
Loop diuretic	984 (84.3)	146 (79.3)	4.9 [−1.2 to 11.2]	.090
Digoxin	294 (25.2)	40 (21.7)	3.4 [−3.0 to 9.9]	.313
Ivabradine	53 (4.5)	9 (4.9)	−3.5 [−3.6 to 3.0]	.833
CRT-P	19 (1.6)	1 (0.5)	1.0 [−0.2 to 2.4]	.258
CRT-D	12 (1.0)	6 (3.3)	−2.2 [−4.9 to 0.4]	.014
ICD	57 (4.9)	7 (3.8)	1.1 [−1.9 to 4.1]	.522
Treatments (follow-up)				
ACEI or ARB	943 (80.8)	156 (84.8)	−4.0 [−9.6 to 1.6]	.198
Beta-blocker	984 (84.3)	159 (86.4)	−2.1 [−7.4 to 3.3]	.482
ARNI	46 (3.9)	15 (8.2)	−4.2 [−8.3 to −0.1]	.011
MRA	733 (62.8)	116 (63.0)	−0.2 [−7.7 to 7.2]	.952
Loop diuretic	1117 (95.7)	170 (92.4)	3.3 [−0.7 to 7.3]	.049
Digoxin	520 (44.6)	71 (38.6)	6.0 [−1.6 to 13.5]	.129
Ivabradine	170 (14.6)	32 (17.4)	−2.8 [−9.7 to 3.0]	.318
CRT-P	49 (4.2)	8 (4.3)	−0.1 [−3.3 to 3.0]	.926
CRT-D	56 (4.8)	9 (4.9)	−0.1 [−3.4 to 3.2]	.956
ICD	74 (6.3)	12 (6.5)	−0.2 [−4.0 to 3.7]	.926

Data in mean ± standard deviation, median (interquartile range) or n (%).
CM, cardiomyopathy; SPRM, Seattle Proportional Risk Model. Other abbreviations as in Table 1.
*Based on the Student *t* test, Mann−Whitney *U* test, or χ^2 test.
†According to World Health Organization criteria (<13 g/dL in men and <12 g/dL in women).
‡An estimated glomerular filtration rate of <60 mL/min/1.73 m^2.
§Available in 843 patients.

between the onset of symptoms until death (Supplementary Fig. 4B).

Although the predicted risk of SCD was similar between patients with ischemic and nonischemic etiologies, the observed prevalence of SCD was significantly lower among patients with nonischemic etiologies (17.1% vs 9.1%, $P < .001$), overall and within every quintile of predicted risk (Fig. 5).

A total of 95 patients of the 413 with ICDs had at least 1 appropriate ICD shock, and 6 of them experienced SCD afterward. When appropriate shocks were classified as SCD, the proportion of SCD

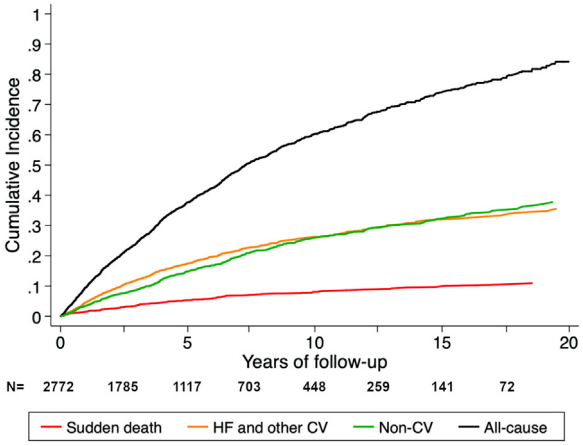

Fig. 1. Cumulative incidences of death and the different causes of death. Deaths were stratified by all-cause death (black), sudden death (red), deaths owing to progressive or refractory heart failure (HF) and other cardiovascular (CV)conditions (orange), and noncardiovascular deaths (green).

increased to 19.5% (Supplementary Fig. 5), but the predicted proportion of SCD increased to 40.1%. Taking into account the actual monitoring follow-up of the implanted ICDs (censoring follow-up at the moment of the appropriate shock), the rate of patients receiving an appropriate ICD shock was 5.5 per 100 patient-years.

When considering the 98 patients dying of unknown causes as having SCD, the proportion of SCD would have been 19.5% vs the 39.8% predicted by the SPRM (Supplementary Fig. 6). Furthermore, considering both ICD appropriate shocks and deaths from unknown cause as if they had been SCD, the proportion of SCD would have increased to 24.7% (Supplementary Fig. 7) vs a 40.3% predicted.

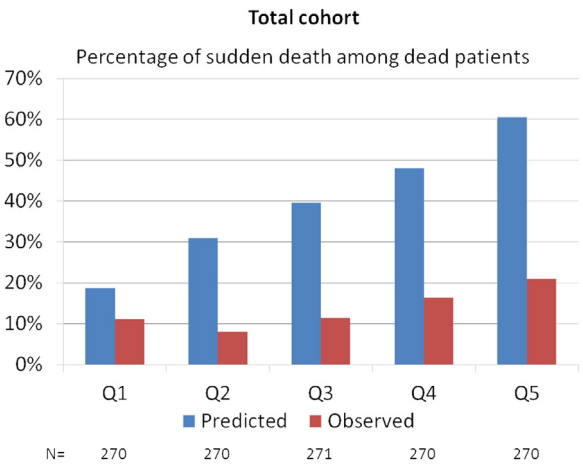

Fig. 2. Predicted proportional risk of sudden cardiac death (SCD) and observed proportion of SCD. Patients were divided into quintiles of Seattle Proportional Risk Model–predicted risk.

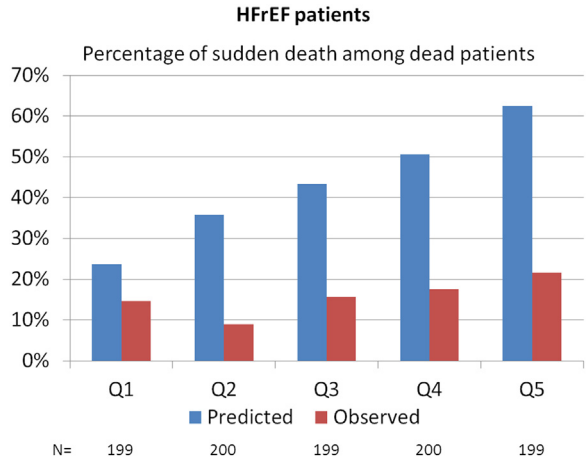

Fig. 3. Predicted proportional risk of sudden cardiac death (SCD) and observed proportion of SCD in patients with heart failure with reduced ejection fraction (HFrEF) divided into quintiles of Seattle Proportional Risk Model (SPRM)-predicted risk.

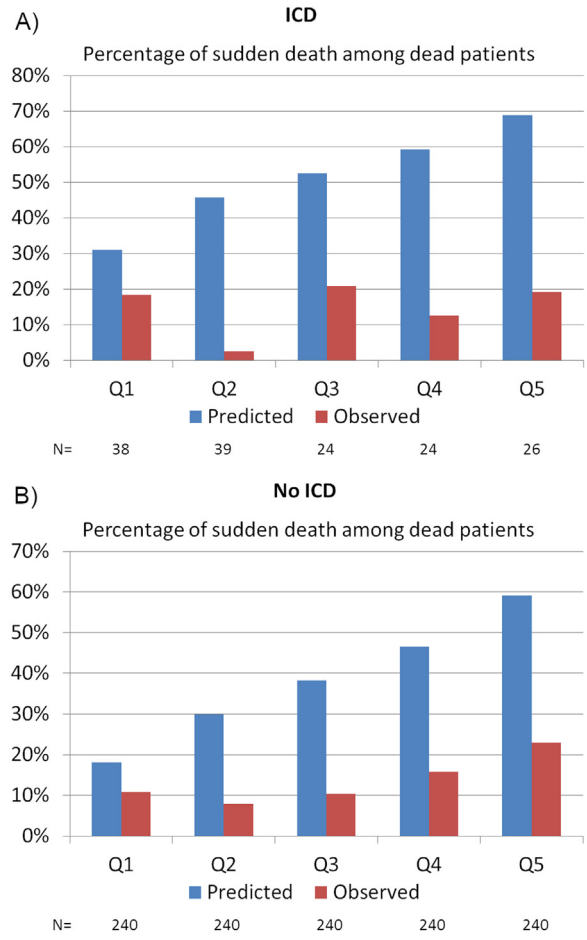

Fig. 4. Predicted proportional risk of sudden cardiac death (SCD) and observed proportion of SCD, based on the presence of an implantable cardioverter-defibrillator (ICD). Patients were divided into quintiles of Seattle Proportional Risk Model–predicted risk. (**A**) ICD carriers. (**B**) Patients without ICDs.

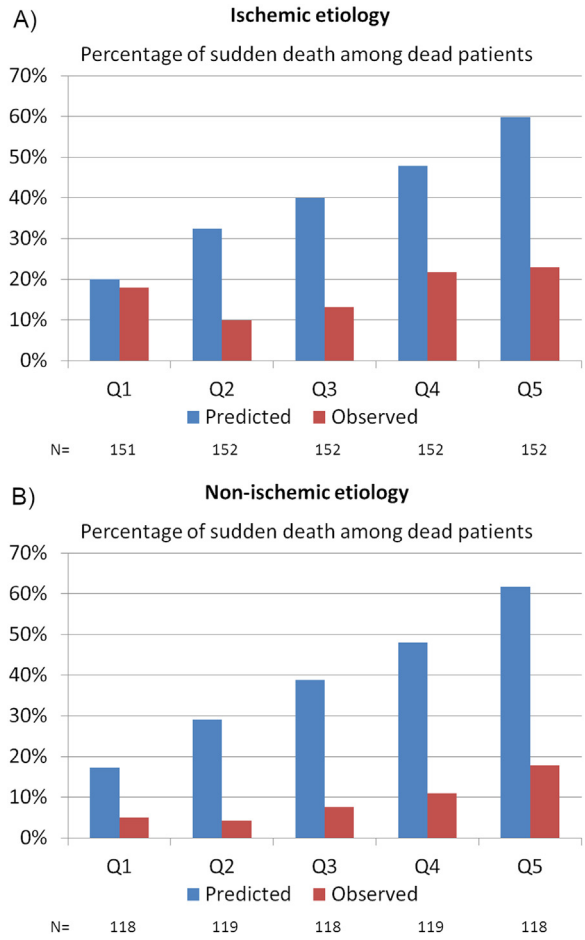

Fig. 5. Predicted proportional risk of sudden cardiac death (SCD) and observed proportion of SCD according to heart failure etiology. Patients were divided into quintiles of Seattle Proportional Risk Model–predicted risk. **(A)** Patients with ischemic etiology. **(B)** Patients with nonischemic etiology.

Finally, when including the 33 dead patients of the 105 patients with missing variables in the SPRM, the results remained unchanged (13.8% proportion of SCD vs 39.5% predicted by SPRM).

Globally, the performance of the SPRM for the mode of death in our cohort was suboptimal. AUC was 0.60 (0.55–0.65) and the Hosmer–Lemeshow test showed a *P* value of less than 0.001. However, the obtained AUC was higher than that using guideline criterion for ICD implantation (AUC 0.54 for New York Heart Association II or III and an EF of ≤35%).

Discussion

To our knowledge, this study is the first to compare the proportion of SPRM-predicted SCDs with the proportion of observed SCDs in a contemporary Mediterranean HF ambulatory cohort managed in a structured and multidisciplinary HF clinic.

The main finding of this study is that the SCD prevalence over 20 years in a Mediterranean cohort of outpatients with HF was significantly lower than that expected based on the SPRM. The predicted proportional risk of sudden death (sudden death/all-cause mortality) was 39.6%, whereas the observed was 13.6%. These results were independent of the degree of predicted risk, ischemic etiology, the period of admission, or the presence of an ICD. The observed annual SCD rate was lower than in most registries and trials with annual rates of 1.5% for an EF of 35% or less and 0.9% for an EF of more than 35%, and 1.4%, 0.7%, and 0.9% for HF with a reduced, mildly reduced, and preserved EF, respectively.

Our data may be interpreted from different perspectives. First, the SPRM may overestimate the risk of SCD in a population such as our Mediterranean cohort. In point of fact, there are differences between the SCD group of the derivation cohort of the SPRM and the SCD group of the present study, which may explain the suboptimal performance of the SPRM model in our cohort. For instance, our patients with SCD were older (69 years vs 65 years), had more ischemic etiology (70.7% vs 64.6%) and higher LVEF (30% vs 25%), the presence of New York Heart Association functional class III–IV was much lower (34.8% vs 60.4%) and treatment use was very different with a more contemporary management in our cohort.

However, the observed proportion of SCD (SCD/all-cause death) in our cohort was also much lower than the observed in most registries and trials, ranging from 28.7% in the Randomized Aldactone Evaluation Study to 58.3% in Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure[1] (eg, 32.3% in Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca–Heart Failure (GISSI-HF),[22] 36.5% in Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF),[23] 39% and 34% in Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF] and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF] trials[7,8]). For this reason, we think that the characteristics of our cohort might also play a role in this lower than expected proportional risk of SCD, rather than only an overestimation by the SPRM.

Beta-blockers, mineralocorticoid receptor antagonists (MRAs) and ARNIs have significantly decreased the incidence of SCD by 31%, 29%, and 20% respectively.[5–7] Although in the SPRM derivation cohort only 47% and 5.8% of the patients were

prescribed beta-blockers and MRA and none were prescribed an ARNI, in our cohort, after treatment optimization 86.9% of the HFrEF patients were receiving an angiotensin-converting enzyme inhibitor, ARB, or ARNI, 93.4% beta-blockers, and 74.8% MRAs. Furthermore, these treatments were strictly uptitrated to the maximal tolerated dose. Accordingly, mortality owing to noncardiovascular disease has steadily increased: in our cohort 42% of deaths were noncardiovascular. However, guideline-directed medical therapy decreases both sudden death and all-cause mortality by a similar amount in most clinical trials. Thus, guideline-directed medical therapy decreases the rate of SCD and all-cause mortality, but did not alter significantly the proportion of SCD in the SPRM derivation cohort. In EMPHASIS-HF, eplerenone decreased SCD by 23% and all-cause mortality by 22%. The proportion of SCD was 35.1% with eplerenone and 35.7% with placebo. In PARADIGM-HF, ARNI decreased SCD by 20% and all-cause mortality by 16%. The proportion of SCD was 35.2% with ARNI and 37.2% with a placebo.

Following this line, a waiting period of 3 months has been generally accepted in patients with newly diagnosed HFrEF before reassessing the LVEF and considering ICD therapy, but it seems reasonable to consider a longer waiting period of therapeutic optimization to SCD risk reduction, wherein an initial strategy of escalated pharmacotherapy may be reasonable before the implantation of an ICD. This approach may be particularly appropriate in patients with nonischemic cardiomyopathy, who have a lower proportion of SCD and in whom a greater SCD risk reduction has been observed with ARNI.[10] The DANISH trial in patients with nonischemic cardiomyopathy and a LVEF of 35% or less reaffirms the uncertainty of ICD benefit in certain cohorts, especially those with high uptake of guideline-directed medical therapy or who face greater competing risks of mortality.[9,19]

The epidemiological characteristics of our cohort may have also altered the risk of SCD, for example, differences in dietary and lifestyle patterns, ethnicity, and clinical management. In this line, the Mediterranean diet prominently features nuts and fish, which are high in omega−3 fatty acids, purported to be responsible for a protective, inverse association between this diet and the risk of SCD.[24,25.] Indeed, in our Mediterranean cohort we found that blood levels of the vegetal omega-3 fatty acid alpha-linolenic acid, representative of the dietary intake of such constituent, were related to cardiovascular death in patients with HF,[26] and in patients with acute myocardial infarction we also observed that elevated blood levels of alpha-linolenic acid were related to lower incidence of ventricular fibrillation.[27] In the GISSI-HF trial,[22] despite being performed in a Mediterranean country, the proportional risk of SCD was 32.2%, which reflects that other factors such as the percentage of guideline-directed medical therapy (eg, 62% and 40% receiving beta-blockers and MRAs in GISSI-HF trial vs 93% and 75% in our cohort) and the multidisciplinary management have also contributed to the lower observed proportion of SCD in our cohort.

The available literature has also indicated that race and ethnicity are significantly associated with the SCD burden, with higher prevalence in African American compared with Caucasian populations.[28]

Regarding the genetics of SCD, in addition to specific pathogenic variants associated with SCD risk, variations in single nucleotide polymorphisms might play a role in regional differences in the prevalence of SCD.[29]

Finally, the mode of death in this vulnerable, comorbid population might be affected by the availability of structured HF clinics with close, long-term follow-ups that allow a synergistic collaboration between specialists.

Future Directions

Further research is needed to improve our understanding of the outcomes of primary prevention ICDs in contemporary cohorts of outpatients with HF. Studies are needed to refine patient selection for ICD therapy, based on the real risk of SCD vs non-SCD death. Regional differences in the proportional risk of SCD might be due to differences in dietary and lifestyle patterns, ethnicity, protocols designed to achieve maximal doses of guideline-directed medical therapy, and the type of follow-up, among others.

Limitations

This study has some limitations. First, our sample comprised mainly patients with HFrEF treated at a multidisciplinary HF unit in a tertiary hospital, and most were referred from the cardiology department. This selection resulted in a cohort of relatively young men with HF, mostly with an ischemic etiology. Moreover, the almost exclusively Caucasian population limited the generalization of our findings. Second, patients with an unknown cause of death were not included in the study. However, these deaths comprised a relatively small proportion (7.3% of deaths), which was unlikely to have a significant influence on the results. Furthermore, this patient group showed no clinically significant differences from the studied cohort, and in a sensitivity analysis, when these patients were included in the SCD group, the main results of the study remained unchanged.

Conclusions

The proportion of SCD over 20 years in a Mediterranean outpatient cohort with HF managed in a multidisciplinary HF clinic was significantly lower than that predicted with the SPRM, independent of the degree of predicted risk, ischemic etiology, the period of admission, and the presence of an implanted ICD. Differences in the SCD group of the derivation cohort of the SPRM and this multidisciplinary managed HF cohort may have had an impact on the lower observed rate of SCD than predicted.

Declaration of Competing Interest

A.B.-G. received speaker fees from Novartis. J.N. received speaker fees from Novartis, Vifor Pharma, Boehringer Ingelheim, Astra Zeneca, Rovi, and Novonordisk. P.C. and E. S. received speaker fees from Novartis. A.B.-G. and J.L. report a relationship with Critical Diagnostics. W.L. is in the steering committee for Respircardia and Cardiac Dimensions, clinical event committees for Abbott, EBR Systems, Beckman Coulter (NTproBNP), and Siemens (NTproBNP). He has a grant support from Medtronic and is a consultant to Medtronic and Impulse Dynamics. University of Washington holds the copyright to the SPRM.

Acknowledgments

The authors thank the nurses in the heart failure unit for data collection and for their invaluable work in the unit.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.11.016.

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