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A bio-clinical approach for prediction of sudden cardiac death in outpatients with heart failure: The ST2-SCD score

Josep Lupón [a,b,c,d,1], Germán Cediel [b,1], Pedro Moliner [a,b,1], Marta de Antonio [a,b,1], Mar Domingo [a,1], Elisabet Zamora [a,b,c,d,1], Julio Núñez [d,e,f], Beatriz González [a,1], Evelyn Santiago-Vacas [a,b,1], Javier Santesmases [a,1], Maria Isabel Troya [a,1], Crisanto Díez-Quevedo [a,1], Maria Boldó [a,1], Jaume Barallat [g,1], Antoni Bayes-Genis [a,b,c,d,*,1]

[a] Heart Failure Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
[b] Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain
[c] Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] CIBER Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain
[e] Cardiology Department, Hospital Clínico Universitario, INCLIVA, València, Spain
[f] Department of Medicine, Universitat de València, València, Spain
[g] Biochemistry and Clinical Analysis Service, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

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ABSTRACT

Background: Sudden cardiac death (SCD) is one of the main modes of death in heart failure (HF) patients and its prediction remains a real challenge. Our aim was to assess the incidence of SCD at 5 years HF contemporary managed outpatients, and to find a simple prediction model for SCD.
Methods: SCD was considered any unexpected death, witnessed or not, occurring in a previously stable patient with no evidence of worsening HF or any other cause of death. A competing risk strategy was adopted using the Fine-Gray method of Cox regressions analyses that considered other causes of death as the competing event.
Results: The derivation cohort included 744 consecutive outpatients (72% men, age 67.9 ± 12.2 years, left ventricular ejection fraction [LVEF] 36% ± 14). During follow-up, 312 deaths occurred, 40 SCDs (5.4%). Age, haemoglobin, eGFR, HF duration, high-sensitivity troponin T, NTproBNP, and ST2 were associated with SCD in univariate analyses; HF duration ($p = 0.006$), eGFR ($p < 0.001$), LVEF <45% ($p = 0.03$), and ST2 ($p = 0.006$) remained in multivariable analysis. A predictive score (ST2-SCD) including dichotomous variables (ST2 > 45, LVEF <45%, HF duration >3 years, eGFR < 55, age ≥ 60 years and male sex) provided a Harrell's C-statistic of 0.82 (0.76-0.89)), reaching 0.87 (0.80–0.95) in the validation cohort ($n = 149$).
Conclusions: In contemporary managed HF, SCD occurred in 5.4% of outpatients, accounting for 12.8% of all deaths at 5 years. Of the 3 studied biomarkers, only ST2 remained independently associated with SCD. A model containing age, sex, ST2, eGFR, LVEF, and HF duration reasonably predicted 5-years risk of SCD.

1. Introduction

Heart failure (HF) progression and sudden cardiac death (SCD) are the main modes of death in patients with HF [1]. The incidence of SCD has declined over the last two decades in patients with chronic HF and reduced left ventricular ejection fraction (LVEF), from 13.4% in RALES to 7.6% in EMPHASIS (both values at 3 years) [2]. Yet, its prediction remains difficult because of the various parameters possibly associated with it (many of which are also associated with all-cause mortality) and the difficulty in selecting the most influential parameter. In addition, it is hard to separate SCD from other causes of death, which are more frequent in chronic HF patients. Strategies are needed to better identify those who have a higher risk of SCD and who might benefit most from an implantable cardioverter-defibrillator (ICD). This will help optimize the management of patients with HF, prevent SCD, and avoid the comorbidities associated with an ICD implant in patients not at risk. Many risk models based on clinical variables have been proposed for all-cause death stratification of HF patients [3]. More recently, the addition of biomarkers have increased the accuracy of such predictions [4–7]. However, the prediction of the risk of SCD has been limited [8–13] and the use of multiple biomarkers is even less explored [14]. Simple

Abbreviations: HF, heart failure; SCD, sudden cardiac death; LVEF, left ventricular ejection fraction; ICD, implantable cardiac defibrillator; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; ST2, interleukin-1 receptor-like 1.

* Corresponding author at: Head, Heart Institute, Hospital Universitari Germans Trias i Pujol, Carretera de Canyet s/n 08916, Badalona (Barcelona), Spain. Department of Medicine, Universitat Autònoma Barcelona.
E-mail address: abayesgenis@gmail.com (A. Bayes-Genis).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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scores for predicting SCD are lacking. Thus, the objectives of our study were to assess the prevalence of SCD at 5 years in a cohort of patients managed according to international guidelines and closely followed, and to find a simple prognostic predictive model of SCD.

2. Methods

2.1. Study population, follow-up and outcomes

The derivation cohort (Barcelona cohort) included consecutive ambulatory patients managed in a multidisciplinary HF Unit in an outpatient setting from May 2006 to July 2010, irrespective of the duration of the HF syndrome [5,15]. Patients were referred to the unit by cardiology or internal medicine departments and, to a lesser extent, from the emergency or other hospital departments. The principal referral criterion was HF according to the European Society of Cardiology guidelines [16–18] irrespective of aetiology, at least one HF hospitalization, and/or reduced LVEF. Blood samples were obtained between 09:00 am and 12:00 pm and were stored at −80 °C, without previous freeze–thaw cycles.

All participants provided written informed consent, and the local ethics committee approved the study. The regular visitation schedule was reported elsewhere [5,15,19]. For the present study, all patients were followed up to five years or until the time of death. SCD at 5 years was the primary outcome. The criteria for such a diagnosis were any unexpected death, witnessed or not, of a previously stable patient with no evidence of worsening HF in the previous days, unless a cause other than cardiac was obvious. Other cardiovascular causes of death were progression of HF (worsening HF or treatment-resistant HF, in the absence of another cause); acute myocardial infarction; stroke; procedural (post-diagnostic or post-therapeutic cardiovascular procedure); or other cardiovascular causes (e.g., rupture of an aneurysm, peripheral ischemia, or aortic dissection). Non-cardiovascular deaths were also registered. Patients who died of unknown cause and those with an implanted ICD were excluded from the analysis.

An external validation cohort (Ruti cohort) included consecutive HF outpatients from January 2012 to August 2013, in which ST2 was routinely measured at the first HF unit visit. The referral criterion and the clinical management of these patients were similar to those of the derivation cohort. All patients also fulfilled the requirement of completed 5 year follow-up. Clinical characteristics of both cohorts are shown in Table 1. Although LVEF and most comorbidities were similar in both cohorts, several differences were present: patients in the validation cohort had less ischemic aetiology, shorter duration of HF, higher prevalence of diabetes and higher levels of NTproBNP. Fatal events were identified from the clinical records of patients with HF, hospital wards, the emergency room, general practitioners, or by contacting the patient's relatives.

Furthermore, data were verified from the databases of the Catalan and Spanish Health Systems. Adjudication of events was performed by the physicians and nurses of the HF Unit (JL, M de A, BG, MD). The study was performed in compliance with the law protecting personal data, in accordance with the international guidelines on clinical investigation of the World Medical Association's Declaration of Helsinki.

2.2. Statistical analysis

Categorical variables were expressed as absolute numbers (percentages). Continuous variables were expressed as the mean ± standard deviation or median (quartile Q1 to Q3) according to normal or non-normal distributions. The normal distribution was assessed with normal Q to Q plots. Differences between patients, based on the vital status at the end of the study, were assessed using the chi-squared test, student *t*-test, Mann-Whitney *U* test, Kruskal-Wallis test, and means comparisons (ANOVA) with post-hoc Scheffé analysis, as needed. Univariate and multivariate Cox regression analyses were performed with SCD as the dependent variable; multivariable analyses were performed including the significant covariates from the univariate analysis. A competing risk strategy using the Fine and Gray method was adopted, considering any other kind of death (cardiovascular or non-cardiovascular) as competing events for SCD. Cumulative incidence curves for SCD, HF related, other cardiovascular death, and non-cardiovascular death were plotted. *P*-values were obtained using the Fine-Gray method. Variables that remained significant in the regression model were transformed in a dichotomous manner more convenient for clinical use, choosing the best cut-off point according the area under the ROC curve. Age ≥ 60 years (also according the area under the ROC curve) and male sex were forcedly added into the predictive model. Harrell's C-statistic was calculated for the resulting score obtained based on the presence or absence of these risk factors, taking into account the competitive risk and time-to-event outcome. Internal validation was implemented using bootstrapping [20]. This non-parametric method, which estimates the sampling distributions of a predictor variable by resampling with replacements from the original sample, provides an impression of the validity of predictions in new but similar patients. For each group of 1000 bootstrap samples, the model was refitted and tested against the observed sample to derive an estimate of the predictive accuracy and bias. Harrell's C-statistic was derived for each of these 1000 samples. The bootstrap-corrected performance or "optimism" [21], was quantified by assessing the difference between Harrell's C-statistics in the original sample and in the bootstrap sample. The average optimism was derived by repeating the above steps 1000 times. The bootstrap-corrected performance of the original stepwise model is an honest estimate of internal validity [21].

In order to address the specificity of the score, Harrell's C-statistics was also calculated for other non-sudden cardiovascular death and also for all-cause death (non-sudden). Several other specific sensitivity analyses were also performed.

Table 1
Baseline demographic and clinical characteristics of the derivation (Barcelona) and validation (Ruti) cohorts.

	Barcelona cohort	Ruti cohort	p
	N = 744	N = 149	
Age, y	68.4 ± 12.4	66.4 ± 13.6	0.07
Males, n (%)	524 (70.4)	104 (69.8)	0.88
Aetiology, n (%)			0.007
Ischemic heart disease	374 (50.3)	59 (39.6)	
Dilated CM	69 (9.3)	25 (16.8)	
Hypertensive CM	77 (10.3)	21 (14.1)	
Alcohol CM	45 (6)	8 (5.4)	
Drug-induced CM*	21 (2.8)	9 (6.0)	
Valvular	88 (11.8)	20 (13.4)	
Other	70 (9.4)	7 (4.7)	
HF duration, months	26 (4–68)	6 (2–24)	<0.001
LVEF, %	37 ± 14	37 ± 14.2	0.90
LVEF < 45%, n (%)	552 (74.2)	113 (75.8)	0.67
Previous AMI, n (%)	315 (42.3)	42 (28.2)	0.001
LBBB, n (%)	97 (13)	18 (12.1)	0.75
NYHA III–IV, n (%)	211 (28.4)	33 (22.1)	0.12
Hypertension, n (%)	467 (62.8)	104 (69.8)	0.10
Diabetes mellitus, n (%)	264 (35.5)	72 (48.3)	0.003
Blood tests			
Haemoglobin, g/dL	12.9 ± 1.8	12.7 ± 1.8	0.13
Sodium, mmol/L	139.2 ± 3.5	137.7 ± 4.3	<0.001
eGFR, mL/min/ 1.73 m^2	53.5 ± 26.8	57.8 ± 28	0.08
NT-proBNP, ng/L	1362 (498–3074)	1779 (702–4163)	0.01
ST2, ng/mL	38 (30.5–50.6)	41.8 (30.6–58.5)	0.07
Treatments#, n (%)			
ACEI or ARB	680 (91.4)	123 (82.6)	0.001
Beta-blocker	671 (90.2)	132 (88.6)	0.55
MRA	431 (57.9)	94 (63.1)	0.24
Loop diuretic	663 (89.1)	134 (89.9)	0.77
Digoxin	331 (44.5)	56 (37.6)	0.12
Sacubitril/Valsartan	0	9 (6)	<0.001
Ivabradine	14 (1.9%)	44 (29.5)	<0.001
CRT-P	25 (3.4)	9 (6)	0.12

Data represent the mean ± SD, median (Q1-Q3), or n (%). *Chemotherapy agents, # During follow-up. ACEI: angiotensin converting enzyme inhibitor; AMI: acute myocardial infarction; ARB: angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; CM: cardiomyopathy; eGFR: estimated glomerular filtration rate (CKD-EPI equation); HF: heart failure; Hs-TnT: high-sensitivity troponin T; ICD: implantable cardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-brain natriuretic peptide. ST2: Interleukin-1 receptor-like 1.

Finally, external validation was performed in the Ruti cohort as mentioned above. Statistical analyses were performed with SPSS 15 (SPSS Inc., Chicago, IL, USA) and STATA V.13.0 (College Station, Texas, USA). A two-sided $p < 0.05$ was considered significant.

3. Results

After excluding 27 patients who died from unknown causes and 93 with an implanted ICD, 744 consecutive ambulatory patients treated at a multidisciplinary HF unit were consecutively included in the derivation Barcelona cohort. The demographic and clinical characteristics of these patients relative to vital status and cause of death are included in Supplementary Table 1. During follow-up, 312 deaths occurred; the causes of death were: progression of HF, 92 patients; SCD, 40; acute myocardial infarction, 17; stroke, 10; cardiovascular procedure, 7; other cardiovascular causes, 24; and non-cardiovascular causes, 122. As shown in Fig. 1, SCD accounted for the 12.8% of all deaths and occurred in the 5.4% of the total cohort. Supplementary Fig. 1 shows the annual rates of all-cause death and SCD. The variables associated with SCD in univariate analyses were age ($p = 0.005$), haemoglobin ($p = 0.004$), estimated glomerular filtration rate (eGFR) ($p < 0.001$), HF duration ($p = 0.009$), high-sensitivity troponin T (hs-TnT) ($p < 0.001$), N-terminal pro-brain natriuretic peptide (NT-proBNP) ($p = 0.002$), and interleukin-1 receptor-like 1 (ST2) ($p = 0.001$) (Table 2). In a multivariable analysis (backward stepwise) that included all these variables and other considered clinically relevant such as male sex ($p = 0.17$), NYHA

class ($p = 0.09$), LVEF <45% ($p = 0.06$), ischemic aetiology (p = 0.06), beta-blocker treatment ($p = 0.55$), and loop diuretic dose (p = 0.06), only HF duration ($p = 0.006$), eGFR ($p < 0.001$), LVEF <45% ($p = 0.03$), and ST2 (p = 0.006) remained in the model (Table 2).

A predictive model obtained with these four variables (as continuous) plus age and sex achieved a Harrell's C statistic of 0.81 (0.74–0.88) for the prediction of 5-year risk of SCD. For easier clinical practice applicability, the variables obtained in the regression model together with age and gender were incorporated in a predictive score, the ST2-SCD score, in a dichotomous manner: ST2 > 45 ng/ml, LVEF <45%, HF duration >3 years, eGFR < 55 ml/min/1.73 m^2, age ≥ 60 years and male sex. The ST2-SCD score obtained based on the presence or absence of these variables had a slightly better C-statistic (0.82 [0.76–0.89]. This method was considered clinically easier to use than scoring based on beta-coefficients and indeed have identical performance (C-statistic (0.82 [0.76–0.89]. Internal validation using 1000 bootstrapping showed an average Harrell's C-statistic of 0.81 and the bootstrap-corrected performance (optimism) was −0.001. The ST2-SCD score easily stratified the probability of suffering SCD, ranging from a 0% risk in the lowest-scoring group of patients (0–1 risk factors) to 26.7% in the highest-scoring group (6 risk factors) (Fig. 2).

Several sensitivity analyses were also performed: a) prediction of 5-years death from other non-sudden cardiovascular causes: C-statistic 0.70 (0.66–0.74); b) prediction of 5-years death from non-SCD of any cause: C-statistic 0.71 (0.68–0.74); c) subgroup analyses relative to LVEF: C-statistics 0.82 (0.75–0.89) and 0.81 (0.71–0.91) for patients with LVEF < 45% and ≥45%, respectively; d) model without age and sex: C-statistic 0.79 (0.72–0.86); e) subgroup analyses according to guidelines indication of ICD (NYHA II-III and LVEF < 35%): C-statistic 0.79 (0.70–0.89) and 0.87 (0.80–0.93) for patients with and without ICD indication respectively; f) including patients with ICD: C-statistic 0.78 (0.71–0.86).

Finally, external validation was conducted in the Ruti cohort. Out of 185 patients, six were excluded due to death of unknown causes and 30 due to an implanted ICD. Of the remaining 149 patients, six died from SCD and 58 from other causes. The ST2-SCD score for the validation cohort, using the six risk factors mentioned above, had a Harrell's C statistic of 0.87 (0.80–0.95). In a sensitivity analysis including patients with ICD, the obtained C statistic was 0.89 (0.83–0.95). Supplementary Table 2 shows baseline demographic and clinical characteristics of the derivation (Barcelona cohort) and validation (Ruti cohort) cohorts when patients with and ICD were included for the sensitivity analyses. Supplementary Table 3 shows multivariable analysis (backward stepwise) when patients with and ICD were included.

Table 2
Cox regression analysis for risk of SCD at 5 years; other causes of death were considered competing risks.

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.05	1.01–1.08	0.005	–	–	–
Male sex	1.71	0.79–3.70	0.17	–	–	–
Ischemic aetiology	1.86	0.97–3.56	0.06	–	–	–
Previous AMI	1.68	0.90–3.14	0.10			
LBBB	1.20	0.50–2.88	0.60			
NYHA III-IV	1.72	0.91–3.24	0.09	–	–	–
HF duration*	1.62	1.13–2.32	0.009	1.64	1.15–2.33	0.006
LVEF < 45%	2.48	0.97–6.33	0.06	2.88	1.12–7.42	0.03
ACEI-ARB	1.14	0.35–3.78	0.83			
Diabetes mellitus	1.10	0.58–2.09	0.77			
Beta-blocker treatment	0.75	0.29–1.92	0.55	–	–	–
Loop diuretic dose	1.60	0.98–2.65	0.06	–	–	–
MRA	1.08	0.57–2.03	0.81			
CRT	2.38	0.75–7.56	0.14			
Haemoglobin	0.81	0.71–0.94	0.004	–	–	–
Sodium	0.98	0.89–1.07	0.60			
eGFR	0.97	0.96–0.99	<0.001	0.98	0.97–0.99	<0.001
NT-proBNP*	1.53	1.17–1.99	0.002	–	–	–
ST2*	1.46	1.16–1.83	0.001	1.39	1.10–1.76	0.006
Hs-TnT*	1.62	1.27–2.08	<0.001	–	–	–

* The variable has been log-transformed for its utilization due to highly skewed distribution and 1 standard deviation used for HR calculation. ACEI: angiotensin converting enzyme inhibitor; AMI: acute myocardial infarction; ARB: angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; eGFR: estimated glomerular filtration rate (CKD-EPI equation); HF: heart failure; Hs-TnT: high-sensitivity troponin T; ICD: implantable cardiac defibrillator; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; NT-proBNP: N-terminal pro-brain natriuretic peptide. ST2: Interleukin-1 receptor-like 1.

4. Discussion

There are two main results for this study. At 5 years, SCD occurred in only 5% of outpatients with HF treated with contemporary treatments. This is in concordance with what has been observed during the last decade in clinical trials of patients with HF and reduced LVEF [2]. However, it is still important to identify those patients with low and high risks of SCD to improve their management, especially the decision to implant an ICD that might eventually prevent SCD but is associated with unwanted comorbidities. In this context, the second main result of this study is the development of a simple and easy-to-use score for estimating the probability of suffering SCD in the next 5 years –the ST2-SCD score. This score includes only six dichotomous variables: age, sex, LVEF, eGFR, HF duration, and ST2. The Harrell's C-statistic obtained with such score was

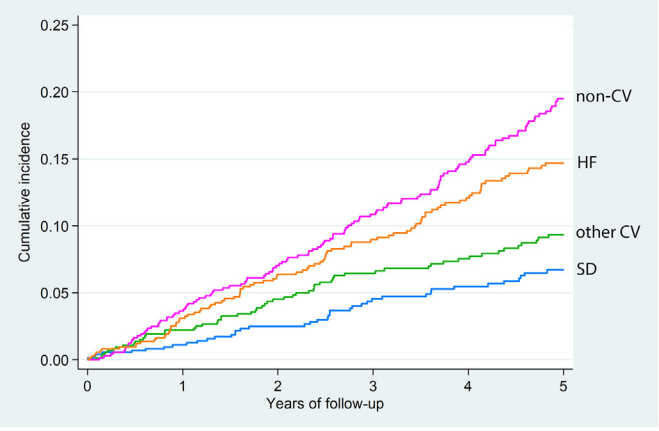

Fig. 1. Title: Cumulative incidence curves according to the mode of death. Caption: SCD occurred significantly less frequently than the other cardiovascular and non-cardiovascular causes of death.

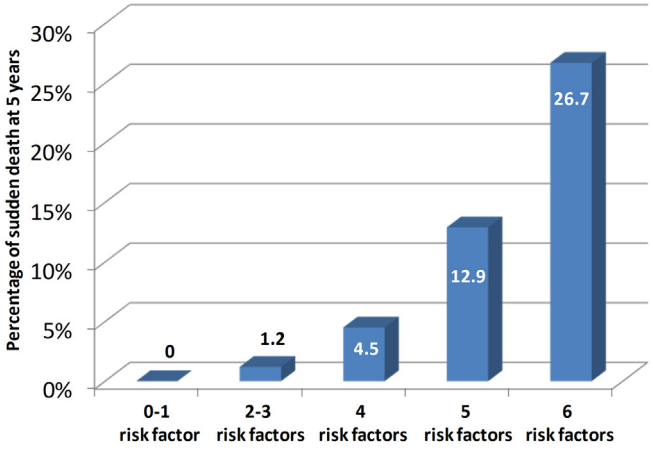

Fig. 2. Title: Probability of suffering SCD based on the ST2-SCD score. Caption: The probability of SCD progressively increased from 0% in the lowest-scoring group (0–1 risk factor) to 26.7% in the highest-scoring group (6 risk factors).

0.82, indicating a more than reasonable predictive capacity, when considering that competitive risk and the time-to-event outcome were included in its calculation. More importantly, the score allows the discrimination of a subgroup of patients with a very low risk of SCD at 5 years when no risk factor or one risk factor was present based on the established cut-off points (0%) and a very high risk (26.7%) when all six risk factors were present.

Predicting all-cause death has been studied more extensively [3–8] with better results than for SCD. This is likely because the proper diagnosis of SCD is more difficult than for all-cause death and the definitions of SCD in trials may not always be identical [2]. Competitive risk statistical tools should be used, but are not always [8,9,10,13], which can lead to inaccurate comparisons of the different models. Finally, as occurred with all-cause death prediction models, evaluations with the C-statistic may differ depending on whether the time-to-event outcome is taken into account [22], as it should be when assessing survival prediction models.

The obtained C-statistic was better to that obtained with a bio-clinical model in the HF-ACTION trial (0.75) where creatinine, body mass index, sex, dosage of loop diuretic agent, LVEF, Canadian Cardiovascular Society angina classification, resting electrocardiogram ventricular conduction abnormality, NT-proBNP, Galectin-3, and ST2 were included. It should be emphasized that in this work the authors also used competing risk strategies, as we did, and that the number of patients ($N = 813$) and episodes of SCD ($N = 42$) were quite similar; all their patients had LVEF ≤35% and the median follow-up was 2.5 years. In the present study, we included patients with higher LVEF values and they were followed up to 5 years. In the HF-ACTION trial the authors did show the incremental contribution of biomarkers over the clinical model without biomarkers with improvement in the C-statistics, as we have previously demonstrated for all-cause death with the BCN-bio-HF-calculator [5,6]. In the present study we wished to find the shortest predictive model. and, for applicability, we transformed the variables in a dichotomous manner.

Ramírez et al. [10] showed that the inclusion of electrocardiogram markers (T-wave index of average alternans, T-peak-to-end restitution, and T-wave morphology restitution) improved the area under the curve for SCD prediction over a clinical model (male gender, NYHA class III, LVEF≤35%) from 0.66 to 0.77. These ECG markers are not usually used in real-life clinical practice and we did not have this information. The only ECG marker we assessed was the presence of a left bundle branch block, which was significantly associated with SCD in a previous study of patients with preserved LVEF (I-PRESERVE Trial) [11]. We did not confirm this association in our cohort, and other clinical variables independently associated with SCD, such as age, sex, history of diabetes or acute myocardial infarction, were also not associated with SCD in our study. In the multivariable analysis of Adabag et al. [11] and in other studies [23], NT-proBNP remained statistically significantly associated; in our study, it was only statistically significantly associated with SCD in the univariate analysis, not the multivariable analysis. Remarkably, the same phenomenon was observed with hs-TnT in our cohort. Of the three studied biomarkers (ST2, NTproBNP, and hs-TnT), only ST2 remained statistically associated with SCD at 5 years. ST2 has already been related to SCD in previous studies [24] and, as mentioned, improved the reclassification for risk of SCD prediction in the HF-ACTION Trial [14]. Our study, together with these two others, supports the concept that the use of biomarkers can provide better and objective information about prognosis and risk of SCD for improved management of HF patients.

Another advantage of specifically predicting the risk of SCD is that although the probability of suffering SCD also increases with the risk of all-cause death, the benefit of implanting an ICD might be different. In the study of Mozaffarian et al. [8], the Seattle HF Model was used in a categorical manner for stratifying the risk of SCD. When using the score of 0 as a reference, patients with a score of 1 had a 50% higher risk of SCD, patients with a score of 2 had a nearly 3-fold higher risk, and patients with a score of 3 or 4 had a nearly 7-fold higher risk; in addition, the 1-year area under the receiver operating curve was 0.68. However, the same group of authors found that in the SCD-HF trial the ICD implantation decreased the relative risk of SCD by 88% in the lowest-risk group based on a modified Seattle HF Model (~2.5% to 4.5% annual mortality rate) versus 24% in the highest-risk group (~19% annual mortality rate) and decreased the relative risk of total mortality by 54% in the lowest-risk group versus no benefit (2%) in the highest-risk group [25]. In that study, the C-statistic was 0.66 for predicting SCD and 0.71 for predicting all-cause death.

Remarkably, in our study the ST2-SCD score showed significantly better Harrell's C-statistics for predicting SCD than other non-sudden cardiovascular death and any other non-sudden cause of death at 5 years (0.82 [0.76–0.89] vs. 0.70 [0.66–0.74] and vs. 0.71 [0.68–0.74], respectively).

The variables or risk factors included in the score beyond ST2 should also be mentioned. LVEF is an important prognostic marker in patients with HFrEF, with a lower LVEF associated with a worse prognosis [26]. A lower LVEF has also already been associated with SCD in many trials [2,9]. Renal function is a known risk factor for all-cause death in patients with HF [27], independent of the equation used for its estimation [16,28]. However, its relationship with SCD is more controversial. The present study and others [2] found that renal dysfunction was positively associated with SCD; while, another study [13] found that a high creatinine level was associated with a disproportionally lower risk of SCD. The duration of HF as a risk factor has been less explored. Remarkably, in the analysis of Shen et al. 2 of 12 HF trials of patients with reduced LVEF, the cumulative risk of SCD during follow-up increased significantly according to the length of time between the diagnosis of HF and randomization in the nine trials with this information available.

It is noteworthy that the developed ST2-SCD score is simple and with few variables. Many variables that have previously been associated with SCD in other studies such as history of diabetes [2,11–13,29,30]; ischemic aetiology and/or history of myocardial infarction [2,12,29]; HF symtoms [2,29]; and left bundle branch block [11] did not remain in the multivariable backward stepwise model when using competing risks in our analysis. Other complex electrocardiographic or electrophysiological examinations, measures of autonomic function, or cardiac imaging tools, namely cardiac magnetic resonance or I-123 metaiodobenzylguanidine scintigraphy [31,32], have been reported of values for SCD prediction, but are not readily available in most clinical practices.

Remarkably, in sensitivity analyses the score showed a comparable performance when patients with an implanted ICD at baseline or receiving an ICD during follow-up were included in the study.

Finally, the aim of developing this score was never to advice beyond Guidelines recommendations for implanting an ICD or being used instead such recommendations, but to help physicians in clinical situations of uncertainty.

5. Limitations

Our population was a general HF population treated at a HF unit in a tertiary hospital. Most patients were white and referred from the cardiology department and, thus, relatively young men with HF of ischemic aetiology and reduced LVEF. As such, the risk prediction might be more accurate in these patients. The sample size of the studied cohort and the limited number of SCD episodes is an acknowledged limitation. Although similar to other pivotal studies [10,12,24], our reported SCD episodes are smaller than other studies [11,13]. The external validation was performed in a limited size cohort and few events. However, differences in several demographics and clinical and treatment characteristics reinforce the reliability of the validation. In addition, no external validation was performed in most previous models assessing SCD [9–14]. Overfitting the multivariable model is unlikely and reduced by using backward stepwise model, which at the end yielded 4 independent variables in the model (1 for every 10 events). We cannot discard

that the relatively low number of implanted ICD in our cohort may have influence on patient selection and the reported data. However, many patients significantly improve LVEF during the first year of treatment in our HF Clinic [33,34], and these patients have a low incidence of SCD [33]. The ST2-SCD score is based on ambulatory patients with chronic HF and may not be applicable to an inpatient acutely decompensated HF population. The score is based on routinely assessed clinical variables and one biomarker. The use of other more complex tools, as mentioned above, might eventually improve the accuracy of the risk of SCD prediction.

6. Conclusions

In a contemporary HF cohort managed according to a structured HF clinic, SCD only accounted only for 12.8% of all deaths at 5 years, affecting only 5.4% of the cohort. Of the studied biomarkers (ST2, NTproBNP, and high-sensitivity troponin T), only ST2 remained independently associated with SCD. A simple model derived from competing risk analysis and containing age, sex, ST2, eGFR, LVEF, and HF duration predicted the risk of SCD at 5 years with a Harrell's C-statistic of 0.82.

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Declaration of Competing Interest

Dr. A. Bayes-Genis has received lecture honoraria from Roche Diagnostics and Critical Diagnostics and Dr. J. Lupón from Roche Diagnostics. Dr. A. Bayes-Genis and Dr. J. Lupón report relationships with Critical Diagnostics. The rest of the authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.046.

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