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CLINICAL ELECTROPHYSIOLOGY: CHANNELOPATHIES

A Primary Prevention Clinical Risk Score Model for Patients With Brugada Syndrome (BRUGADA-RISK)

Shohreh Honarbakhsh, BSc,[a] Rui Providencia, MD, PhD,[a] Jorge Garcia-Hernandez, PhD,[b] Claire A. Martin, PhD,[c] Ross J. Hunter, PhD,[a] Wei Y. Lim,[a] Claire Kirkby, MSc,[a] Adam J. Graham, BSc,[a] Ardalan Sharifzadehgan, MD, PhD,[d,e,f] Victor Waldmann, MD, MPH,[d,e,f] Eloi Marijon, MD, PhD,[d,e,f] Carmen Munoz-Esparza, MD,[g] Javier Lacunza, MD,[g] Juan Ramón Gimeno-Blanes, MD, PhD,[g] Benedicte Ankou, MD,[h] Philippe Chevalier, MD, PhD,[h] Nátalia Antonio, MD, PhD,[i] Luís Elvas, MD,[i] Silvia Castelletti, MD,[i] Lia Crotti, MD, PhD,[j] Peter Schwartz, MD, PhD,[j] Mauricio Scanavacca, MD, PhD,[k] Francisco Darrieux, MD, PhD,[k] Luciana Sacilotto, MD,[k] Johanna Mueller-Leisse, MD, MSc,[l] Christian Veltmann, MD,[l] Alessandro Vicentini, MD,[m] Andrea Demarchi, MD,[m] Nuno Cortez-Dias, MD,[n] Pedro Silverio Antonio, MD,[n] João de Sousa, MD,[n] Pedro Adragao, PhD,[o] Diogo Cavaco, MD,[o] Francisco Morosco Costa, MD,[o] Ziad Khoueiry, MD,[p] Serge Boveda, MD,[q] Mario João Sousa, MD,[q] Zeynab Jebberi, MD,[q] Patrick Heck, MA, DM,[c] Sarju Mehta, BSc,[r] Giulio Conte, MD, PhD,[s] Tardu Ozkartal, MD,[s] Angelo Auricchio, MD, PhD,[s] Martin D. Lowe, PhD, BSc,[a] Richard J. Schilling, MD,[a] David Prieto-Merino, PhD,[t] Pier D. Lambiase, PhD,[a] for the Brugada Syndrome Risk Investigators

ABSTRACT

OBJECTIVES The goal of this study was to develop a risk score model for patients with Brugada syndrome (BrS).

BACKGROUND Risk stratification in BrS is a significant challenge due to the low event rates and conflicting evidence.

METHODS A multicenter international cohort of patients with BrS and no previous cardiac arrest was used to evaluate the role of 16 proposed clinical or electrocardiogram (ECG) markers in predicting ventricular arrhythmias (VAs)/sudden cardiac death (SCD) during follow-up. Predictive markers were incorporated into a risk score model, and this model was validated by using out-of-sample cross-validation.

RESULTS A total of 1,110 patients with BrS from 16 centers in 8 countries were included (mean age 51.8 ± 13.6 years; 71.8% male). Median follow-up was 5.33 years; 114 patients had VA/SCD (10.3%) with an annual event rate of 1.5%. Of the 16 proposed risk factors, probable arrhythmia-related syncope (hazard ratio [HR]: 3.71; $p < 0.001$), spontaneous type 1 ECG (HR: 3.80; $p < 0.001$), early repolarization (HR: 3.42; $p < 0.001$), and a type 1 Brugada ECG pattern in peripheral leads (HR: 2.33; $p < 0.001$) were associated with a higher risk of VA/SCD. A risk score model incorporating these factors revealed a sensitivity of 71.2% (95% confidence interval: 61.5% to 84.6%) and a specificity of 80.2% (95% confidence interval: 75.7% to 82.3%) in predicting VA/SCD at 5 years. Calibration plots showed a mean prediction error of 1.2%. The model was effectively validated by using out-of-sample cross-validation according to country.

CONCLUSIONS This multicenter study identified 4 risk factors for VA/SCD in a primary prevention BrS population. A risk score model was generated to quantify risk of VA/SCD in BrS and inform implantable cardioverter-defibrillator prescription. (J Am Coll Cardiol EP 2021;7:210–22) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From [a]The Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom; [b]Farr Institute of Health Informatics Research, University College London, London, United Kingdom; [c]Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom; [d]Cardiology Department, European Georges Pompidou Hospital, Paris, France; [e]Paris Descartes University, Paris, France; [f]Paris Cardiovascular Research Center (INSERM U970), Paris, France; [g]Inherited Cardiac Disease Unit, University Hospital Virgen Arrixaca, Murcia, Spain; [h]Rhythmology Department, Hôpital Cardiovasculaire Louis Pradel, Claude Bernard University, Lyon, France; [i]Cardiology Department, Coimbra Hospital and University Centre, Coimbra, Portugal; [j]Laboratory of Cardiovascular

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Brugada syndrome (BrS) is an inherited cardiac channelopathy, diagnosed by coved ST-segment elevation in electrocardiogram (ECG) leads V_1 to V_3 in structurally normal hearts with a prevalence of 1 to 30 per 10,000 depending on ethnicity (1). It is associated with ventricular arrhythmias (VAs) and sudden cardiac death (SCD). Risk assessment is challenging, especially in initially asymptomatic cases (2,3). Several clinical and ECG markers have been proposed, but these are mainly derived from single-center studies with no validation in other cohorts (4–9). No study has provided a comprehensive assessment of all proposed risk factors in an international multicenter cohort.

The goal of the current study was to review the major proposed clinical and ECG markers to determine their predictive role in VA/SCD risk in patients with BrS and no prior cardiac arrest and to develop a risk score model using easily acquired clinical markers.

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METHODS

STUDY DESIGN. This analysis was a multicenter international cohort study involving a retrospective evaluation of prospectively collected registries including patients with BrS and no history of cardiac arrest. The study conforms to the principles of the Declaration of Helsinki. The authors from each participating center guarantee the integrity of their institution data and had approval from a local ethics committee/internal review board. Subjects gave informed consent in accordance with local protocol.

Baseline characteristics data were collected by using paper and electronic records. Sixteen clinical and ECG markers were tested for their predictive role of VA/SCD during follow-up (**Table 1**).

VARIABLE DEFINITIONS. Definition of BrS. BrS and a type 1 ECG pattern were defined as per guidelines (Supplemental Methods, **Figure 1A**) (10). Patients with <1 year of follow-up were excluded.

Symptoms, co-morbidities, and family history. With the consensus of 2 senior cardiologists, a syncopal episode was labeled as either probable arrhythmia-related (PAR) or unlikely arrhythmia-related syncope. A family history of SCD was defined as unexpected death at ≤45 years of age in a first-degree relative with no known history of heart disease. A history of atrial fibrillation (AF)/atrial flutter and sinus node disease (SND) was recorded (Supplemental Methods).

ECG markers. The ECG reviewing process and the definitions used for these markers are detailed in the Supplemental Methods and **Figure 1** (11–15).

Clinical investigations. Patients who underwent programmed ventricular stimulation (16) (Supplemental Methods) and had polymorphic ventricular tachycardia (VT)/ventricular fibrillation (VF) induced or a ventricular effective refractory period (VERP) <200 ms were identified. SCN5A gene mutation carriers were also identified. The use of programmed ventricular stimulation or genetic testing was conducted per the center's practice.

VA/SCD during follow-up. VA during follow-up was defined as aborted SCD by cardioversion of VT/VF or documented sustained VT (>200 beats/min) or VF either on ambulatory Holter monitor, loop recorder, and/or implantable cardioverter-defibrillator (ICD) interrogation. SCD was defined if there was a documented VA at the time of death or no other cause was identified.

STATISTICAL ANALYSIS. The descriptive statistical analysis method is outlined in the Supplemental Methods.

Statistical models. Because this was a multicenter study, the variability of each variable and the outcome of VA/SCD during follow-up were analyzed in accordance with the hospital site (Supplemental Methods). Cox proportional hazards regression

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AUC = area under the curve
BrS = Brugada syndrome
CI = confidence interval
ECG = electrocardiogram
ER = early repolarization
HC = Harrell's C
ICD = implantable cardioverter-defibrillator
NNT = number needed to treat
PAR = probable arrhythmia-related
SCD = sudden cardiac death
SND = sinus node disease
VA = ventricular arrhythmia
VERP = ventricular effective refractory period
VF = ventricular fibrillation
VT = ventricular tachycardia

Genetics, Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico, Italiano, Milan, Italy; [k]Arritmia, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; [l]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [m]Policlinico San Matteo Pavia Fondazione IRCCS, Pavia, Italy; [n]Department of Cardiology, Santa Maria University Hospital, Lisbon Academic Medical Centre and Cardiovascular Centre of the University of Lisbon, Faculty of Medicine, Lisbon, Portugal; [o]Cardiology Department, Santa Cruz Lisboa Hospital, Lisbon, Portugal; [p]Institute Saint Pierre, Perpignan, France; [q]Clinique Pasteur, Toulouse, France; [r]Addenbroke's Hospital, Cambridge, United Kingdom; [s]Cardiac Electrophysiology Unit, Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; and the [t]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.

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TABLE 1 Factors Reviewed in the Cohort to Determine if They Played a Role in the Risk Stratification of Patients With BrS

Age at diagnosis
Sex
Probable arrhythmia-related syncope
Diagnosis by family screening of SCD
Spontaneous type 1 Brugada ECG pattern
SCN5A mutation
Positive programmed ventricular stimulation
VERP <200 ms
SND
AF/atrial flutter
ER in peripheral leads
Type 1 Brugada ECG pattern in peripheral leads
aVR sign
Significant S-wave in lead I
QRS duration >120 ms in V_2
QRS fragmentation

AF = atrial fibrillation; aVR = augmented vector right; BrS = Brugada syndrome; ECG = electrocardiogram; ER = early repolarization; SCD = sudden cardiac death; SND = sinus node disease; VA = ventricular arrhythmia; VERP = ventricular effective refractory period.

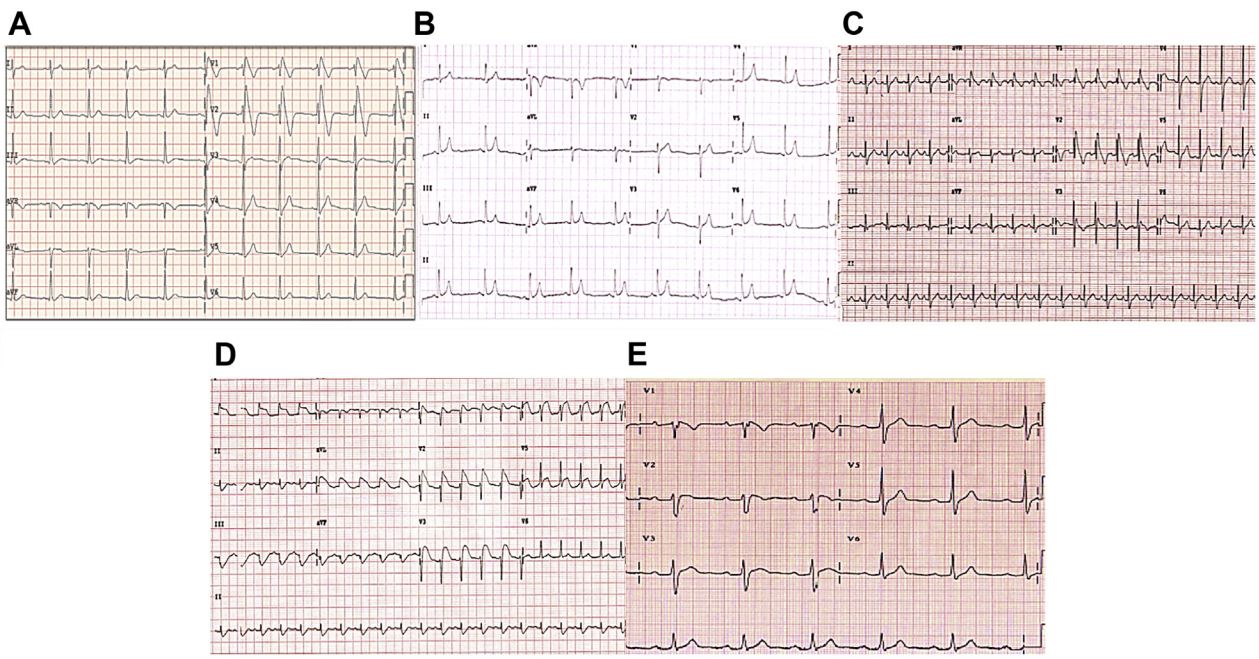
models were used to estimate the effect of the risk factor on the outcome. Interactions with sex were also assessed to determine whether separate models were required for men and women. Country was not included as a risk factor to ensure that the model was generalizable to other countries, but hospital was included as a frailty term to account for the clustered nature of the data. Schoenfeld residuals were used to check for violations of the proportional hazards assumption. Backward elimination was used as the primary method to select predictors.

Risk score derivation. From the final multivariable model, a point-based score was derived, each factor providing a number of points equal to its coefficient in the model (i.e., the log[HR]) multiplied by 10. The total score of a patient is the addition of the points from all risk factors present in that patient. The exponential of the total score divided by 10 is equal to the hazard ratio (HR) of that patient compared with the HR of a patient with no risk factors (the "reference" patient).

Estimation of risk of event. The actual risk of a patient having an event within a particular follow-up time depends on the risk of the reference patient (reference risk) (Supplemental Methods).

Internal validation of the model. Discrimination was assessed by using Harrell's C (HC) statistics. Because of the multinational nature of the data, HC statistics were estimated within each country separately. If heterogeneity measures (I^2) and tests

FIGURE 1 12 Lead Electrocardiogram Markers Assessed as Potential Risk Factors for VA/SCD



Markers on 12-lead electrocardiograms that were assessed as potential risk factors for VAs/ in patients with Brugada syndrome (BrS) during follow-up. **(A)** Type 1 spontaneous electrocardiogram pattern. **(B)** Early repolarization. **(C)** Augmented vector right sign. **(D)** Peripheral type 1 Brugada electrocardiogram pattern. **(E)** QRS fragmentation (in lead V_1). SCD = sudden cardiac death; VA = ventricular arrhythmia.

TABLE 2 Baseline Characteristics

	Whole Cohort (N = 1110)	Symptomatic (n = 204)	Asymptomatic (n = 906)	p Value
Age, yrs	51.8 ± 13.6	51.5 ± 16.1	50.9 ± 14.7	0.63
Male	790 (71.2)	144 (70.6)	646 (71.3)	0.86
Ethnicity				
White	936 (84.3)	175 (85.8)	761 (84.0)	0.59
African/Afro-Caribbean	21 (1.9)	4 (2.0)	17 (1.9)	1.00
South American	117 (10.5)	18 (8.8)	99 (10.9)	0.45
South Asian	20 (1.8)	4 (2.0)	16 (1.8)	0.77
East Asian	16 (1.4)	3 (1.5)	13 (1.4)	1.00
Other comorbidities				
Hypertension	198 (17.8)	24 (11.8)	174 (19.2)	0.01
Type 2 diabetes	92 (8.3)	10 (4.9)	82 (9.1)	0.07
Dyslipidemia	150 (13.5)	25 (12.3)	125 (13.8)	0.65
CVA	45 (4.1)	6 (2.9)	39 (4.3)	0.44
Other noncardiac disease	95 (8.6)	2 (1.0)	93 (10.3)	<0.001
Syncope	352 (32.0)	/	/	
Unlikely arrhythmia related	148 (42.0)			
Probable arrhythmia related	204 (58.0)			
Mode of diagnosis				
Suspected cardiac symptoms	410 (36.9)	155 (76.0)	255 (28.1)	<0.001
Incidental diagnosis	462 (41.6)	26 (12.7)	436 (48.1)	<0.001
Family screening of SCD	53 (4.8)	10 (4.9)	43 (4.7)	0.86
Family screening of BrS	174 (15.7)	13 (6.4)	161 (17.8)	<0.001
Unknown	11 (1.0)	0	11 (1.2)	0.23
Type 1 Brugada ECG pattern				
Spontaneous	388 (35.0)	117 (57.4)	271 (29.9)	<0.001
Provocation	722 (65.0)	87 (42.6)	635 (70.1)	<0.001
Ajmaline	462 (64.0)	57 (65.5)	405 (63.8)	0.81
Flecainide	225 (31.2)	23 (26.4)	202 (31.8)	0.34
Fever	35 (4.8)	7 (8.0)	28 (4.4)	0.33
Family history of SCD in first-degree relatives	235 (21.2)	51 (25.0)	184 (20.3)	0.15
Genetic testing	731 (65.9)	125 (61.3)	606 (66.9)	0.14
Programmed ventricular stimulation	406 (36.6)	77 (37.7)	329 (36.3)	0.75
VERP assessment	436 (39.3)	84 (41.2)	352 (38.9)	0.59
Primary prevention ICD	172 (15.5)	88 (43.1)	84 (9.3)	<0.001

Values are mean ± SD or n (%).
CVA = cerebrovascular accident; ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

suggest evidence of heterogeneity, an average across all countries was then estimated with a random effects model (Supplemental Methods). Calibration was examined comparing 5-year predicted risks (using an average reference risk across the dataset) with Kaplan-Meier estimated risks.

External validation with out-of-sample predictions. A cross-validation according to country was used for the external validation of the study risk score model by removing each country to create the risk model and then testing the model in that specific country ("out-of-sample cross-validation") (Supplemental Methods).

RESULTS

BASELINE CHARACTERISTICS. The study included 1,110 patients with BrS recruited across 16 centers in 8 countries (United Kingdom, France, Germany, Spain, Italy, Switzerland, Portugal, and Brazil) (Table 2). The number of patients contributed by each hospital varied from 3 to 262.

VA/SCD DURING FOLLOW-UP. The mean follow-up time was 5.33 ± 4.0 years. Of the 1,110 patients, 114 had a VA/SCD event (10.3%) during follow-up, with an annual event rate of 1.5% (1.2% to 1.8%). Of the 114 patients with an event, 11 patients died of SCD (9.6%). These patients were predominantly male (8 of 11), of White ethnicity (10 of 11), had a BrS diagnosis after investigation for syncope (6 of 11), and had spontaneous type 1 ECG (9 of 11). Of the 11 patients with SCD, 5 also had a history of PAR syncope, and 4 had a family history of SCD. Seven of the 11 patients had undergone programmed ventricular stimulation, and this was positive in 2 patients.

TABLE 3 Differences in Proposed Risk Factors Between Those With VA/SCD Versus Those Without VA/SCD During Follow-Up

	VA/SCD (n = 114)	No VA/SCD (n = 996)	p Value
Age at diagnosis, yrs	43.2 ± 16.0	43.7 ± 13.4	0.85
Male	86 (75.4)	704 (70.7)	0.44
Probable arrhythmia-related syncope	67 (58.8)	137 (13.8)	<0.001
Diagnosis by family screening of SCD	13 (11.4)	40 (4.1)	0.002
Spontaneous type 1 Brugada ECG pattern	89 (78.1)	299 (30.0)	<0.001
Genetic testing	74 (64.9)	657 (66.0)	0.75
SCN5A mutation	21 (28.4)	154 (23.4)	0.39
Programmed ventricular stimulation	52 (45.6)	350 (35.1)	0.04
Inducible polymorphic VT or VF	23 (44.2)	105 (30.0)	0.06
VERP assessment	55 (48.2)	359 (36.0)	0.02
VERP <200 ms	11 (20.0)	77 (21.4)	1.00
SND	3 (2.6)	25 (2.5)	1.00
AF/atrial flutter	8 (7.0)	71 (7.1)	1.00
aVR sign	25 (21.9)	134 (13.5)	0.02
Significant S-wave in lead I	33 (28.9)	261 (26.2)	0.58
QRS duration >120 ms in V_2	17 (14.9)	105 (10.5)	0.21
QRS fragmentation	12 (10.5)	88 (8.8)	0.60
Type 1 Brugada ECG pattern in peripheral leads	42 (36.8)	31 (3.1)	<0.001
ER	43 (37.7)	72 (7.2)	<0.001
Persistent	38 (88.4)	39 (54.2)	<0.001
Follow-up, yrs	6.7 ± 4.0	6.1 ± 4.0	0.11

Values are mean ± SD or n (%).
AF = atrial fibrillation; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

Of the 1,110 patients, 591 (53.2%) and 209 (18.8%) patients completed 5 and 10 years of follow-up, respectively. The following variables were significantly more common in patients with a history of VA/SCD compared with patients without VA/SCD during follow-up: 1) PAR syncope; 2) a spontaneous type 1 Brugada ECG pattern; 3) early repolarization (ER) in peripheral leads; and 4) a type 1 Brugada ECG pattern in peripheral leads (Table 3).

Of the 1,110 patients, 70 (6.3%) had a history of PAR syncope and none of the aforementioned additional risk markers. Of these patients, 8 (11.4%) had VA/SCD during follow-up, giving them an annual event rate of 1.30% (95% confidence interval [CI]: 0.60 to 2.46). In the remaining 134 (12.1%) patients with PAR syncope and the presence of 1 or more of the aforementioned markers, 59 (44.0%) patients had an event during follow-up ($p < 0.001$). The annual event rate in patients with PAR syncope which had none or a combination of the other identified risk makers was 2.1% (95% CI: 1.8 to 2.5). The annual event rate in patients with PAR syncope and none of the other risk markers was 1.0% (95% CI: 0.7 to 1.1).

Data heterogeneity between hospitals. The heterogeneity test was significant for all 16 variables tested according to hospital (Supplemental Table 1). Of the 1,110 patients, 731 (66.5%) underwent genetic testing for SCN5A mutations, 406 (36.9%) received programmed ventricular stimulation, and 436 (39.6%) underwent VERP assessment. Because all patients did not undergo these investigations, these variables were not included when creating the risk score model (Supplemental Results). They were not shown to be significant predictors of VA/SCD on univariate analysis (Table 4).

RISK SCORE MODEL. The separate Cox proportional hazards model for each variable showed that the aforementioned 4 variables had strong statistical evidence of association with VA/SCD during follow-up (Table 4). These variables were incorporated into a risk score model and were applicable across both sexes. After external validation with out-of-sample predictions, 4 of these variables showed a strong significant effect in the separate and multivariable models across all of the cross-validation samples with stable HRs (Supplemental Tables 2 and 3 and Supplemental Figure 1). The risk factor "Diagnosis by family screening of SCD" did not show an effect when the country Spain was removed from the estimation sample. Exploring the data, it was found that this factor was especially predictive for Spain, where the 9 patients who were diagnosed by using results of family screening of SCD also had the outcome. This variable was not included in the final model due to its selective nature. The results from the cross-validation by country justify the selection of the 4 risk factors discussed in the following sections.

PAR syncope. Patients with PAR syncope had a lower mean restricted survival compared with patients without PAR syncope (7.7 years [95% CI: 7.0 to 8.4] vs. 9.6 years [95% CI: 9.4 to 9.7]; $p < 0.001$) (Figure 2A). This revealed an HR of 3.71 (95% CI: 2.41 to 5.70; $p < 0.001$) for VA/SCD during follow-up. The 5-year predicted risk of event in patients with PAR syncope and none of the other study identifiable risk factors was 4.9%.

Spontaneous type 1 ECG pattern. Patients with a spontaneous type 1 ECG pattern had a lower mean restricted survival compared with patents without this pattern (8.8 years [95% CI: 8.6 to 9.1] vs. 9.8 years [95% CI: 9.7 to 9.9]; $p < 0.001$) (Figure 2B). This revealed an HR of 3.80 (95% CI: 2.31 to 6.24; $p < 0.001$). The 5-year predicted risk of event in patients with a spontaneous type 1 ECG pattern and none of the other study identifiable risk factors was 5.9%.

ER in peripheral leads. The presence of ER in peripheral leads resulted in a lower mean restricted survival compared with patents without ER in peripheral leads (7.9 years [95% CI: 7.3 to 8.4] vs. 9.6

TABLE 4 HRs From Cox Regression Models and Derived Points Per Risk Factor

	Separate Univariate Models			Multivariate Model				
	HR	95% CI	p Value	HR	95% CI	p Value	Log(HR)	Score
Age at diagnosis	1.00	0.99–1.01	0.90					
Male	0.99	0.64–1.51	0.95					
Probable arrhythmia–related syncope	5.92	4.05–8.63	<0.001	3.71	2.41–5.70	<0.001	1.15	12
Diagnosis by family screening of SCD	3.31	1.85–5.91	<0.001	4.56	2.39–8.71	<0.001		
Spontaneous type 1 Brugada ECG pattern	5.93	3.71–9.48	<0.001	3.80	2.31–6.24	<0.001	1.38	14
SCN5A mutation	1.19	0.71–1.99	0.52					
Positive programmed ventricular stimulation (induction of polymorphic VT or VF)	1.46	0.83–2.54	0.19					
VERp <200 ms	0.88	0.42–1.86	0.74					
SND	1.01	0.32–3.20	0.99					
AF/atrial flutter	0.91	0.44–1.86	0.79					
ER in peripheral leads	6.07	4.12–8.94	<0.001	3.42	2.17–5.41	<0.001	1.21	9
Type 1 Brugada ECG pattern in peripheral leads	6.86	4.69–10.04	<0.001	2.33	1.48–3.67	<0.001	0.94	12
aVR sign	1.62	1.04–2.52	0.03					
Significant S-wave in lead I	1.25	0.84–1.87	0.27					
QRS interval >120 ms in V_2	1.26	0.75–2.11	0.39					
QRS fragmentation	1.09	0.61–1.95	0.77					

CI = confidence interval; HRs = hazard ratios; other abbreviations as in Tables 1 and 3.

years [95% CI: 9.5 to 9.7]; p < 0.001) (Figure 2C). This revealed an HR of 3.42 (95% CI: 2.17 to 5.41; p < 0.001). The 5-year predicted risk of event in patients with ER in peripheral leads and none of the other study identifiable risk factors was 4.9%.

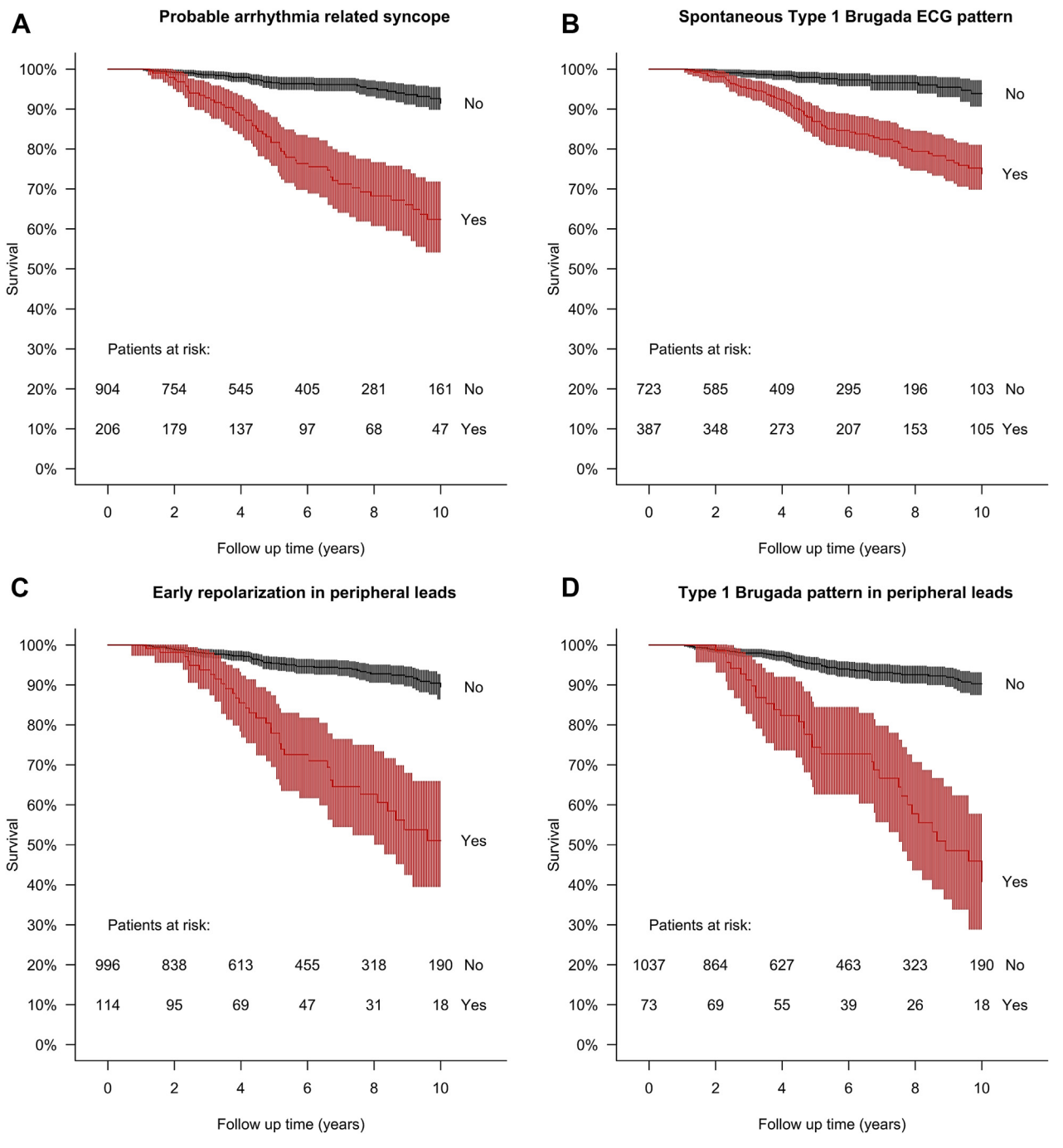
Type 1 Brugada ECG pattern in peripheral leads. Patients with a type 1 Brugada ECG pattern in peripheral leads had a lower mean restricted survival compared with patents without this pattern (7.71 years [95% CI: 7.0 to 8.4] vs. 9.6 years [95% CI: 9.4 to 9.7]; p < 0.001) (Figure 2D). This revealed an HR of 2.33 (95% CI: 1.48 to 3.67; p < 0.001). The 5-year predicted risk of event in patients with a type 1 Brugada ECG pattern in peripheral leads and none of the other study identifiable risk factors was 3.6%.

RISK SCORE. Calculator http://brugadariskscore.com. The final risk score model consisted of the 4 variables, which were binary, whereby a "yes" value increased the hazard. An automatic backward step algorithm also produced the same model. The Schoenfeld residuals analysis did not show any evidence against the proportional hazards assumptions (all p values were >0.05; for the global test; p = 0.27). Each of the 4 variables was allocated a point score based on the predictive strength of the variable, with the possibility of a maximum score of 47 points (Tables 4 and 5, Central Illustration). Using the Central Illustration and Supplemental Table 4, the total points obtained from the risk score model for a patient can be translated into the predicted risk of VA/SCD during 5 years of follow-up. Supplemental Table 5 also shows by how much the 5-year predicted risk of events would increase (in the average model) for having the risk factor of interest without any of the other identified risk factors or in the presence of different combinations of the other 3 identified risk factors. For example, a patient with a spontaneous type 1 ECG pattern has an additional increased 5-year predicted risk of 2.1% compared with a patient with a nonspontaneous type 1 ECG pattern and none of the other identified risk factors. The distribution of number of risk factors per country is presented in Supplemental Figure 2.

RISK SCORE MODEL DISCRIMINATION AND CALIBRATION. The HC statistics showed strong heterogeneity between countries (I^2 = 86%; p < 0.01) both in-sample and out-of-sample. The random effects average HC statistics across countries was 0.88 (95% CI: 0.82 to 0.95) and 0.88 (95% CI: 0.81 to 0.94) for in-sample and out-of-sample predictions, respectively (Supplemental Figures 3A and 3B).

Hosmer-Lemeshow (HM) plots according to country showed a good correlation between the predicted risk with the study model and observed risk estimated by using a Kaplan-Meier analysis for in-sample and out-of-sample predictions, particularly when calibrating the score to country (Supplemental Figures 4A and 4B, Supplemental Table 6). Calibration according to risk level also showed a good correlation between predicted and observed risk for in-sample and out-of-sample predictions (Supplemental

FIGURE 2 KM Curves Showing Survival Free of VA/SCD Events According to Presence or Absence of the 4 Identified Risk Markers



Kaplan-Meier curves showing survival free from ventricular arrhythmias/sudden cardiac death in patients with Brugada syndrome when comparing the presence and absence of the 4 risk markers identified. **(A)** With and without probable arrhythmia-related syncope; **(B)** with and without spontaneous type 1 Brugada electrocardiogram (ECG) pattern; **(C)** with and without early repolarization in peripheral leads; and **(D)** with and without a type 1 Brugada ECG pattern in peripheral leads. The curves show lower ventricular arrhythmia/sudden cardiac death survival in those with probable risk markers compared with those without. The table below each Kaplan-Meier curves shows the number at risk for each time period. KM = Kaplan-Meier; other abbreviations as in Figure 1.

Results, Supplemental Figures 5A and 5B, and Supplemental Table 7).

Recalibration regression showed a significant heterogeneity in the recalibration needs between countries (Supplemental Figures 6A and 6B), likely accounted for by the differences in average scores and survival rates between countries (Supplemental Table 8 and Supplemental Figures 3A and 3B).

Figure 3 illustrates the simulated effect of using different thresholds of 5-year VA/SCD risk to implant an ICD. This enables one to identify specific cut points at which the cost-efficacy of ICD implantation could be determined and optimal thresholds to protect the greatest number of patients appropriately. Assuming that an ICD implant will effectively treat the VA event to prevent SCD, at the threshold of 3% at 5-year risk prediction, the number needed to treat (NNT) with an ICD to save 1 life was 8 and 9 in uncalibrated and calibrated models, respectively. At the 5% and 10% threshold, this would be 7 (8 with calibrated model) and 5 patients. The risk score model incorporating the 4 identified risk factors showed a sensitivity of 71.2% (95% CI: 61.5% to 84.6%) and a specificity of 80.2% (95% CI: 75.7% to 82.3%) in predicting VA/SCD at 5 years when using the 10% cutoff threshold.

RISK SCORE MODEL IN PATIENTS WITHOUT PRIOR PAR SYNCOPE. The in-sample HC statistics of the model was 0.80 (95% CI: 0.72 to 0.88) in patients without previous PAR syncope. There was also a good correlation between the predicted and the observed risk, with a mean prediction error of 2.46% at 5 years of follow-up. The risk model showed a sensitivity of 68.2% and a specificity of 61.0% in predicting VA/SCD in patients without prior PAR syncope when using a cutoff of 5% predicted risk with calibrated models (Supplemental Figure 7).

TABLE 5 Risk Factors, Scores, and Average 5-Year Predicted Risks of VA/SCD

Type 1 Brugada ECG Pattern in Peripheral Leads	Probable Arrhythmia-Related Syncope	ER in Peripheral Leads	Spontaneous Type 1 BRS ECG Pattern	Score Points	Average Risk of VA/SCD, %
0	0	0	0	0	1.5
1	0	0	0	9	3.6
0	1	0	0	12	4.9
0	0	1	0	12	4.9
0	0	0	1	14	5.9
1	1	0	0	21	11.5
1	0	1	0	21	11.5
1	0	0	1	23	13.9
0	1	1	0	24	15.2
0	1	0	1	26	18.3
0	0	1	1	26	18.3
1	1	1	0	33	33.4
1	1	0	1	35	39.1
1	0	1	1	35	39.1
0	1	1	1	38	48.8
1	1	1	1	47	80.7

The table shows all possible risk factor combinations in the data and their associated score points. Abbreviations as in Table 1.

DISCUSSION

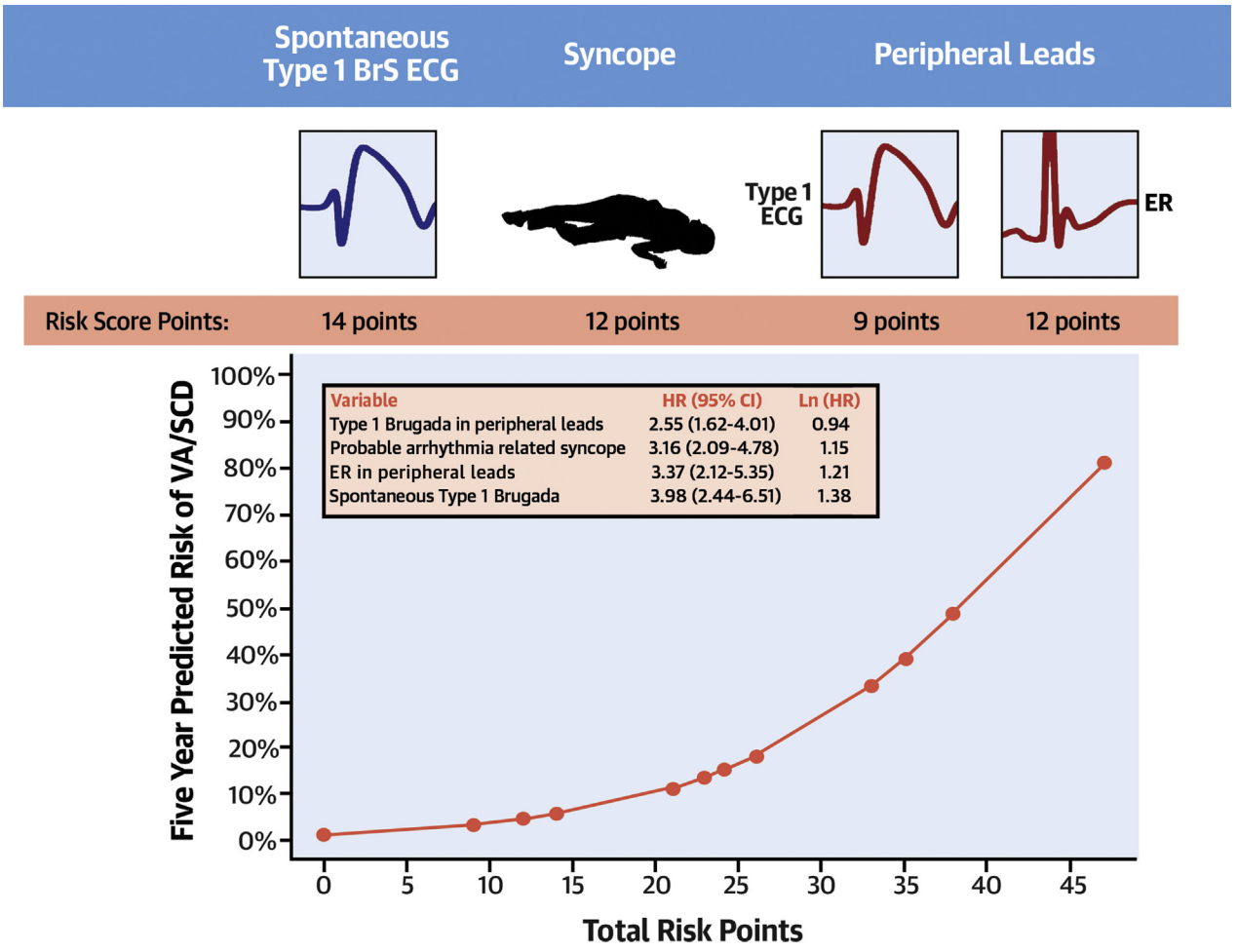
Through this multicenter international study, the role of 16 proposed risk factors for VA/SCD in BrS was evaluated in one of the largest BrS cohorts published to date. Many factors previously proposed from small single-center cohorts did not play such an important role in this primary prevention cohort, whereas other less frequently reported markers are more important predictors of VA/SCD. By incorporating these factors into a risk score model, we have developed a scoring system that has a high predictive power.

PAR syncope and a spontaneous type 1 Brugada ECG pattern remain independent predictors of VA/SCD compatible with the findings of numerous BrS studies (2,6,17–19). Interestingly, the presence of ER and a type 1 Brugada ECG pattern in peripheral leads, which has previously only been assessed in a few studies, were shown to be independent predictors of VA/SCD in this cohort (12,20–22).

This study is the first, to the best of our knowledge, that assessed all 16 proposed risk factors in a single study; others have only assessed the role of <10 proposed risk factors (2,17,18,23). We were able to assess the comparative predictive accuracy of each marker in a multicenter population in which center-specific selection biases are less likely to operate. This is a limitation of single-center studies that have only focused on a smaller number of risk factors and the effects of referral bias and disease severity in specific families may operate. Furthermore, by including patients from 15 European centers, it allows the establishment of a cohort that should better represent a general BrS population, making the findings more applicable in European subjects.

The study findings are compatible with those of Delise et al. (19), who also evaluated risk factors for VA/SCD in a primary prevention BrS cohort. Both studies have shown that syncope and spontaneous type 1 ECG were predictors of VA/SCD during follow-up on multivariate analysis and that the presence of additional risk factors resulted in a higher risk of VA/SCD. However, the remaining 3 risk factors that were identified in the current study were not evaluated by Delise et al. (19), and it therefore remains unclear whether these markers would have also been predictors of VA/SCD during follow-up in that cohort.

CENTRAL ILLUSTRATION **Brugada Risk Calculator: http://brugadariskscore.com: Risk Score Calculation and Predicted Event Rates Presented Graphically Over 5 Years**



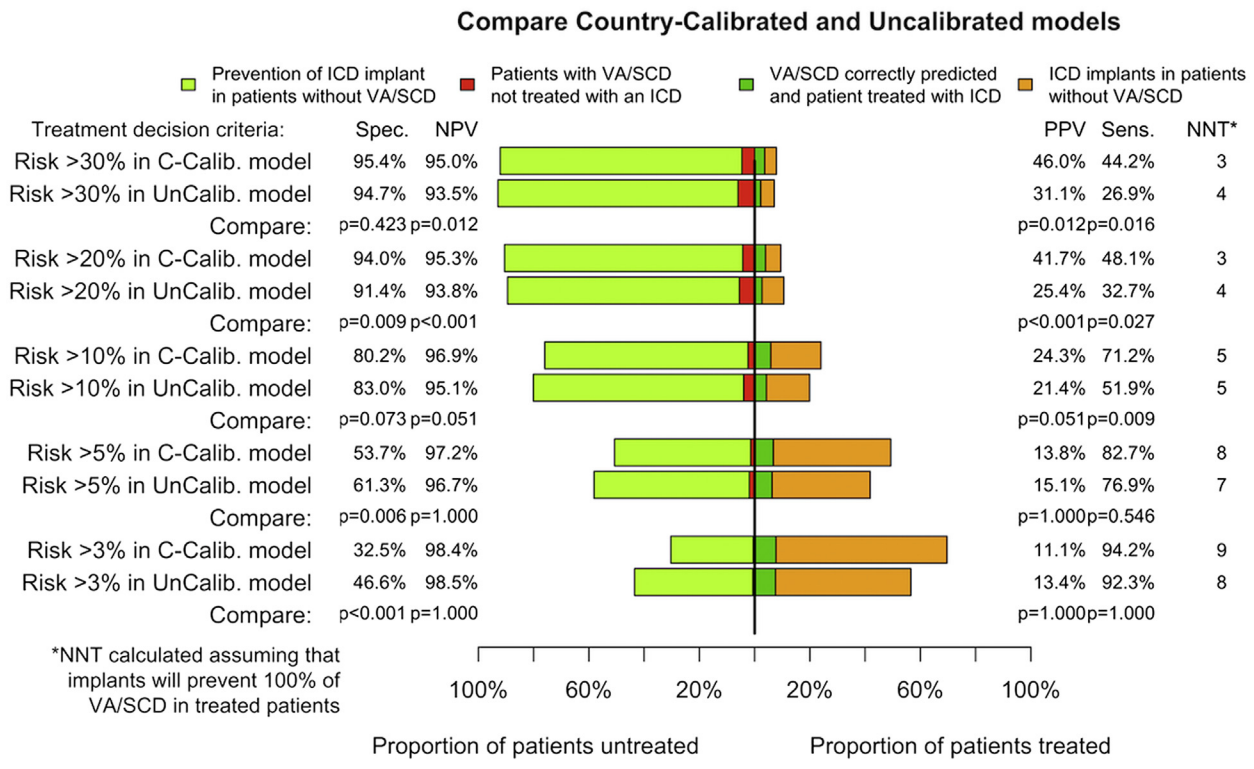
Honarbakhsh, S. et al. J Am Coll Cardiol EP. 2021;7(2):210–22.

The total number of points for a patient is added up in accordance to the variables present and represented on the x-axis. The **red curve** above it estimates the predicted risk of ventricular arrhythmias (VAs)/sudden cardiac death (SCD) for the patients in the whole cohort during a 5-year follow-up. The **dots on the curves** represent actual values that a patient can be assigned with a combination of the 4 variables. BrS = Brugada Syndrome; ECG = electrocardiogram; ER = early repolarization.

To validate this risk score model, an out-of-sample cross-validation according to country was performed. The evaluation consistently showed that the 4 risk factors included in the risk score model exhibit consistent results across all cross-validation samples. These findings thereby justify the selection of the risk factors and the coefficients of this model. When applying models developed in 1 country/setting to a different one, it is important to determine whether recalibration of the model to the new country/setting's rate of events and average score is needed. As shown with this model, the recalibration needs of a country were variable, again emphasizing the importance of model recalibration. Models are frequently applied in a new setting without recalibration partly due to the absence of data to recalibrate. As shown in this study, the risk score model can be used effectively in different countries; it is important to highlight, however, that it might perform even better if it was recalibrated to the country it was applied to using mean risk scores and 5-year mean survival.

In the current study, there was a significant difference in the prevalence of certain variables across hospitals. Further to this, the observed event rate among countries also varied. These findings

FIGURE 3 **Impact of the Risk Prediction Model on Clinical Decision-Making**



The bars represent the proportion of patients who would have received an implantable cardioverter-defibrillator (ICD) **(right of 0)** and those who would have not **(left of 0)** at specific risk thresholds. Each of the 2 proportions is further divided into patients with and without ventricular arrhythmia (VA)/sudden cardiac death (SCD) events at the end of the 5-year follow-up. Sensitivity (Sens.), Specificity (Spec.), positive predictive values (PPVs), and negative predictive values (NPVs) are also presented for the model when applied at the different risk levels. The figure also shows the differences in these parameters whether the risk score model is used calibrated (C-Calib) or uncalibrated (UnCalib).

emphasize that there are differences in the BrS cohorts among hospitals and countries. Therefore, when establishing a risk score model in a single center such as that of the Sieira et al. (23) risk score model, this heterogeneity is not taken into consideration. Since the risk score model in this study was established by using cohorts across 8 countries and 16 centers, it ensures a better representation of a more generalized BrS cohort.

PROGRAMMED STIMULATION AND GENETIC TESTING. Due to the controversial nature of programmed ventricular stimulation as a risk factor for VA/SCD in BrS (2,6,18,20,24), it is not strongly recommended in clinical guidelines (10); only 406 patients (37%) in the current cohort underwent programmed ventricular stimulation as in other published studies (24), and 66% underwent SCN5A mutation testing, compatible with previous studies (6,23). Thereby, the findings from these investigations were not included in the development of the final risk score model during multivariate analysis. The risk score model of Sieira et al. (23) assigned inducible VA on programmed ventricular stimulation as a risk marker in their risk score model even though it was only determined on univariate analysis. In the current cohort, 37% (n = 406) of the patients underwent programmed ventricular stimulation versus 91% (n = 364) in the study by Sieira et al. (23), which still accounts for a large number of patients. On the univariate analysis in this study, this factor was not shown to be predictive of VA/SCD.

Programmed ventricular stimulation in this study was performed in accordance with the protocol of Wellens et al. (16), which involved triple extrastimuli and is consistent with that used by Sieira et al. (23). There is currently no clear consensus on what protocol is most appropriate for evaluating VA inducibility (18). This is further highlighted by the pooled

analysis by Sroubek et al. (18), whereby studies included use either single, double, or triple extrastimuli during programmed ventricular stimulation. This pooled analysis concluded that using triple extrastimuli during programmed ventricular stimulation as used in the creation of this model was not as specific as using double extrastimuli; however, they did show that VA induction using triple extrastimuli was significantly associated with cardiac arrest or appropriate ICD shock during follow-up. Sieira et al. (23) also used triple extrastimuli, which they showed was predictive of VA/SCD. Therefore, the lack of predictive power of a positive programmed ventricular stimulation in this study cannot solely be accounted for by the stimulation protocol used. This does, however, highlight a major limitation of incorporating findings from programmed ventricular stimulation into a risk score model. First, its role remains controversial and is not recommended routinely in the current guidelines. Second, if the stimulation protocol utilized is dictated by that used during the model development, this might require centers to alter their clinical practice to be able to adopt the model. The model created in this study incorporates markers that can be evaluated from clinical history and a baseline ECG and thus is not influenced by the limitations as discussed here.

Although we found no association with SCN5A mutation status and risk, it is recognized that specific mutations may be more malignant or specific haplotypes confer greater risk of VA events (e.g., Nav1.5 protein truncating mutations [23,25]).

ER AND PERIPHERAL BRUGADA ECG FEATURES. In this cohort, ER was shown to be associated with a higher risk of VA/SCD in patients with BrS, which is consistent with the findings of other studies in BrS (20–22) and idiopathic VF (26,27). The role of a type 1 Brugada ECG pattern in peripheral leads as a risk factor for VA/SCD in BrS has only been assessed in 1 other study (13). It is plausible that the presence of a type 1 Brugada/ER ECG pattern in peripheral leads is indicative of a higher "ER burden" and thereby accounts for the higher VA/SCD risk when present, analogous to prolonged repolarization in long QT syndrome (28).

SYNCOPE. PAR syncope alone was associated with significantly fewer events compared with the addition of 1 or more of the other 4 identified risk markers. PAR syncope alone was associated with a predicted risk of VA/SCD during follow-up of 5%. Because many large studies have not evaluated for the presence of all the risk markers identified in this study, it is unclear whether the other risk markers did coexist in these patients and that the high event rate identified is solely accounted for by the presence of a history of syncope. Patients with PAR syncope and none of the other study-identifiable risk factors fall in the predicted risk group >3%. In the current clinical guidelines, a Class IIa recommendation is provided for primary prevention ICD implantation in these patients. As shown in this study, if ICD implantation was restricted to patients above the predicted risk group >5%, not only is the NNT to prevent an event lower, but a smaller proportion of patients end up with ICD implantation without experiencing an event compared with the predicted risk group > 3%. However, as the predicted risk is just below the risk level >5%, clinicians should use their discretion along with guideline recommendations when deciding whether ICD implantation should be considered in these patients. The same argument applies with a spontaneous type 1 Brugada ECG pattern, which was associated with a predicted risk of 5.9% (which is just above 5%). This risk becomes significantly multiplied when combined with the other markers. The exact risk threshold to implant an ICD is at the discretion of the physician and shared decision-making with the patient.

CLINICAL IMPLICATIONS. The utilization of this score enables more accurate quantification of risk in asymptomatic BrS patients and risk thresholds to optimize ICD prescription. The risk score shows that in BrS at the 3% risk threshold, the NNT is 9 at 5 years. The exact thresholds selected will vary according to patient, physician-determined risk:benefit thresholds, and health policy.

STUDY LIMITATIONS. Due to the retrospective nature of this study, there is a risk of recall bias. However, to overcome the low incidence rate of VA/SCD in BrS and the need for long-term follow-up, using a multicenter international cohort enables establishment of a cohort that is more representative of a general BrS population. Because not all patients underwent programmed ventricular stimulation, VERP assessment, and genetic mutation testing, these factors were not included in the Cox regression model. However, the univariate analysis did not show a predictive role for these factors, and there was no significant difference in the VA/SCD rate in those with or without these factors, and thus they are unlikely to be of significance.

FUTURE DEVELOPMENTS. The incremental predictive value of environmental, social factors, including access to health care and genetic information, could be examined in future iterations of this model. The ultimate test of the usefulness of a prediction model is an impact study that determines whether the model improves decision-making, patient outcomes, and cost-effectiveness.

CONCLUSIONS

By reviewing major proposed risk factors in a multicenter BrS cohort over a long follow-up period, 4 factors were shown to play a significant role in the risk stratification of VA/SCD in BrS. A risk score model using these factors was strongly predictive of VA/SCD in BrS. Utilizing this model in clinical practice could improve the predictive accuracy of primary prevention ICD recommendations and allow individualized risk stratification.

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ADDRESS FOR CORRESPONDENCE: Dr. Pier D. Lambiase, Institute of Cardiovascular Science, University College London, The Barts Heart Centre, West Smithfield, London EC1A 7BE, United Kingdom. E-mail: p.lambiase@ucl.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Risk stratification for primary prevention of SCD in BrS is a significant challenge due to the low event rates and conflicting evidence. By reviewing 16 major proposed risk markers in a multicenter international BrS cohort over a long follow-up period, 4 markers (PAR syncope, type 1 spontaneous ECG, ER in the peripheral leads, and type 1 ECG Brugada pattern in peripheral leads) were shown to play a significant role in the risk stratification of VA/SCD in BrS. A risk score model using these markers revealed high sensitivity and specificity in predicting VA/SCD during follow-up.

TRANSLATIONAL OUTLOOK: Through this multicenter international study, it has been shown that 4 markers are associated with a higher risk of VA/SCD in patients with BrS during follow-up. A risk score model that incorporated these markers can be used in clinical practice to improve the predictive accuracy of primary prevention ICD recommendations and allow individualized risk stratification.

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KEY WORDS **Brugada syndrome, inherited channelopathy, sudden cardiac death, ventricular arrhythmia**

APPENDIX **For supplemental Methods, Results, figures, and tables, please see the online version of this paper.**