





SYSTEMATIC REVIEW AND META-ANALYSIS

Standard ECG in Brugada Syndrome as a Marker of Prognosis: From Risk Stratification to Pathophysiological Insights

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BACKGROUND: The 12-lead ECG plays a key role in the diagnosis of Brugada syndrome (BrS). Since the spontaneous type 1 ECG pattern was first described, several other ECG signs have been linked to arrhythmic risk, but results are conflicting.

METHODS AND RESULTS: We performed a systematic review to clarify the associations of these specific ECG signs with the risk of syncope, sudden death, or equivalents in patients with BrS. The literature search identified 29 eligible articles comprising overall 5731 patients. The ECG findings associated with an incremental risk of syncope, sudden death, or equivalents (hazard ratio ranging from 1.1–39) were the following: localization of type 1 Brugada pattern (in V2 and peripheral leads), first-degree atrioventricular block, atrial fibrillation, fragmented QRS, QRS duration >120 ms, R wave in lead aVR, S wave in L1 (≥ 40 ms, amplitude ≥ 0.1 mV, area ≥ 1 mm²), early repolarization pattern in inferolateral leads, ST-segment depression, T-wave alternans, dispersion of repolarization, and Tzou criteria.

CONCLUSIONS: At least 12 features of standard ECG are associated with a higher risk of sudden death in BrS. A multiparametric risk assessment approach based on ECG parameters associated with clinical and genetic findings could help improve current risk stratification scores of patients with BrS and warrants further investigation.

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Key Words: arrhythmias ■ arrhythmic risk stratification ■ Brugada syndrome ■ electrocardiogram

The 12-lead ECG plays a pivotal role in the diagnosis of Brugada syndrome (BrS). ECG signs of right bundle branch block with persistent elevation of the ST-segment and T-wave inversion in the right precordial leads were first identified in 1953 by Osher and Wolff as a normal variant ECG pattern.¹ A few decades later, an association between this ECG pattern and sudden cardiac death (SCD) was described in young adults without cardiac disease, and in 1992 Pedro and Josep Brugada outlined a new “distinct clinical and electrocardiographic

syndrome.”^{2,3} Despite increasing knowledge of the epidemiology and pathogenesis of BrS, the risk stratification remains challenging. Clinical signs such as a previous unexplained syncope and spontaneous type 1 ECG pattern in patients with a history of aborted cardiac death or sustained ventricular tachycardia (VT) are to date the only objective data to identify patients at high arrhythmic risk.³ Presence of a family history of SCD is of uncertain value.⁴ The predictive role of electrophysiological examination to evaluate the arrhythmic risk in these patients remain

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CLINICAL PERSPECTIVE

What Is New?

- Despite increasing knowledge of the epidemiology and pathogenesis of Brugada syndrome, risk stratification remains challenging.
- Several different ECG markers of ventricular depolarization and repolarization have emerged over time but with variable and conflicting results.
- We quantitatively evaluated the incremental risk of 12 different ECG signs identified as high-risk markers in Brugada syndrome.

What Are the Clinical Implications?

- A multiparametric risk assessment approach based on ECG parameters associated with clinical and genetic findings could help improve the current risk stratification scores of Brugada syndrome and warrants further investigation.

Non-standard Abbreviations and Acronyms

AVB	atrioventricular block
BrS	Brugada syndrome
ER	early repolarization
fQRS	fragmented QRS
SCD	sudden cardiac death
SCN5A	sodium voltage-gated channel alpha subunit 5
Tp-e	Tpeak-Tend
TWA	T-wave alternans

uncertain,⁵⁻⁹ and it should be used with caution.¹⁰ Unfortunately, even genetic analysis of BrS has not yet made a significant contribution to risk stratification. Currently the single most frequent gene involved in the pathogenesis of the syndrome is *SCN5A* (sodium voltage-gated channel alpha subunit 5), but it is found in only 25% of patients with BrS.^{11,12} Mutations in the *SCN5A* gene causing truncation or inactivation of the Nav1.5 protein combined with a history of SCD in young relatives are so far the only clinical-genetic data with prognostic significance.¹¹

Several studies have investigated the prognostic value of qualitative and quantitative ECG features in the presence of the Brugada pattern, but with conflicting results. A possible explanation relates to the dynamic nature of the ECG pattern in BrS, which limits the prognostic value of ECG in these patients. We performed a systematic review of the literature on the spectrum of ECG signs associated with negative

prognosis in BrS to quantify the incremental risk of each sign and to unravel the electrogenetic and pathophysiologic mechanisms underlying the different ECG features.

METHODS

The authors declare that all supporting data are available within the article (and its supplementary files).

Search Strategy

We conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹³⁻¹⁵ Two reviewers (A.B., F.V.) elaborated the search strategy in November 2019. The search terms used were the following: ((ECG) OR (EKG) OR (electrocardiogram) OR (electrocardiographic)) AND ((sign) OR (predictor) OR (marker)) AND (Brugada) AND ((sudden death) OR (death) OR (syncope) OR (arrhythmia) OR (ventricular fibrillation) OR (ventricular tachycardia)). The databases analyzed were PubMed and EMBASE. Only articles published in English and in peer-reviewed journals were eligible for inclusion. A total of 3 independent reviewers (A.B., F.V., M.S.) analyzed the records and decided those that warranted full-text analysis. The same reviewers (A.B., F.V., M.S.) independently analyzed the references of all the evaluated articles to identify other articles not found through the database search. Disagreement was resolved by consensus. The protocol of this systematic review was registered in the PROSPERO international prospective register for systematic reviews (registration number CRD42019123794).

Selection Criteria

Studies were eligible for selection only if they (1) were an observational or interventional trial in patients with BrS and (2) contained data on ECG signs and arrhythmic events, syncope, cardiac arrest, SCD, and/or implantable cardioverter defibrillator (ICD) interventions during follow-up. We excluded (1) duplicate reports, (2) reports with a duplicated sample size, (3) case report/series, (4) review articles, and (5) articles with no outcome of interest.

Data Extraction and End Points

The reviewers recorded the following information for each article: journal, year of publication, sample characteristics including events at enrollment, outcome, ECG signs related to prognosis with hazard ratios (HRs) or odds ratios (ORs), and sensitivity/specificity when available. The primary outcome of the systematic review was to synthesize the relationship of specific ECG signs of BrS with “arrhythmic risk” defined as the

risk of syncope, cardiac arrest, SCD, or appropriate ICD interventions during follow-up.

Quality Assessment and Data Synthesis

A total of 2 unblinded reviewers (A.B., F.V.) analyzed the quality of the full texts based on the methodological index for non-randomized studies (MINORS) criteria,¹⁶ resolving any discrepancies by consensus (Table S1). No study was excluded because of the analysis. The reviewers provided a descriptive synthesis of the results.

RESULTS

The literature search identified 231 records. After screening, we excluded 194 articles because of a lack of outcomes of interest (Figure 1). The remaining 29 articles were analyzed as full-text and were included in

the qualitative analysis (Table).^{6,17-44} The Table1 reports the following details of the articles: journal and year of publication, number of patients, number of events, study type, and enrollment period. Figure 2 summarizes the ECG markers analyzed by each study with outcomes.

We found 12 different ECG signs associated with an incremental arrhythmic risk such as syncope, cardiac arrest, SCD, or appropriate ICD interventions during follow-up (HR ranging from 1.1–39). These signs were localization of type 1 Brugada pattern outside the right precordial leads, first-degree atrioventricular block (AVB), atrial fibrillation (AF), fragmented QRS (fQRS), QRS duration >120 ms, R wave in lead aVR, S wave in L1 (≥ 40 ms, amplitude ≥ 0.1 mV, area ≥ 1 mm²), early repolarization (ER) pattern in inferolateral leads, ST-segment depression, T-wave alternans (TWA), dispersion of repolarization, and Tzou criteria. These ECG

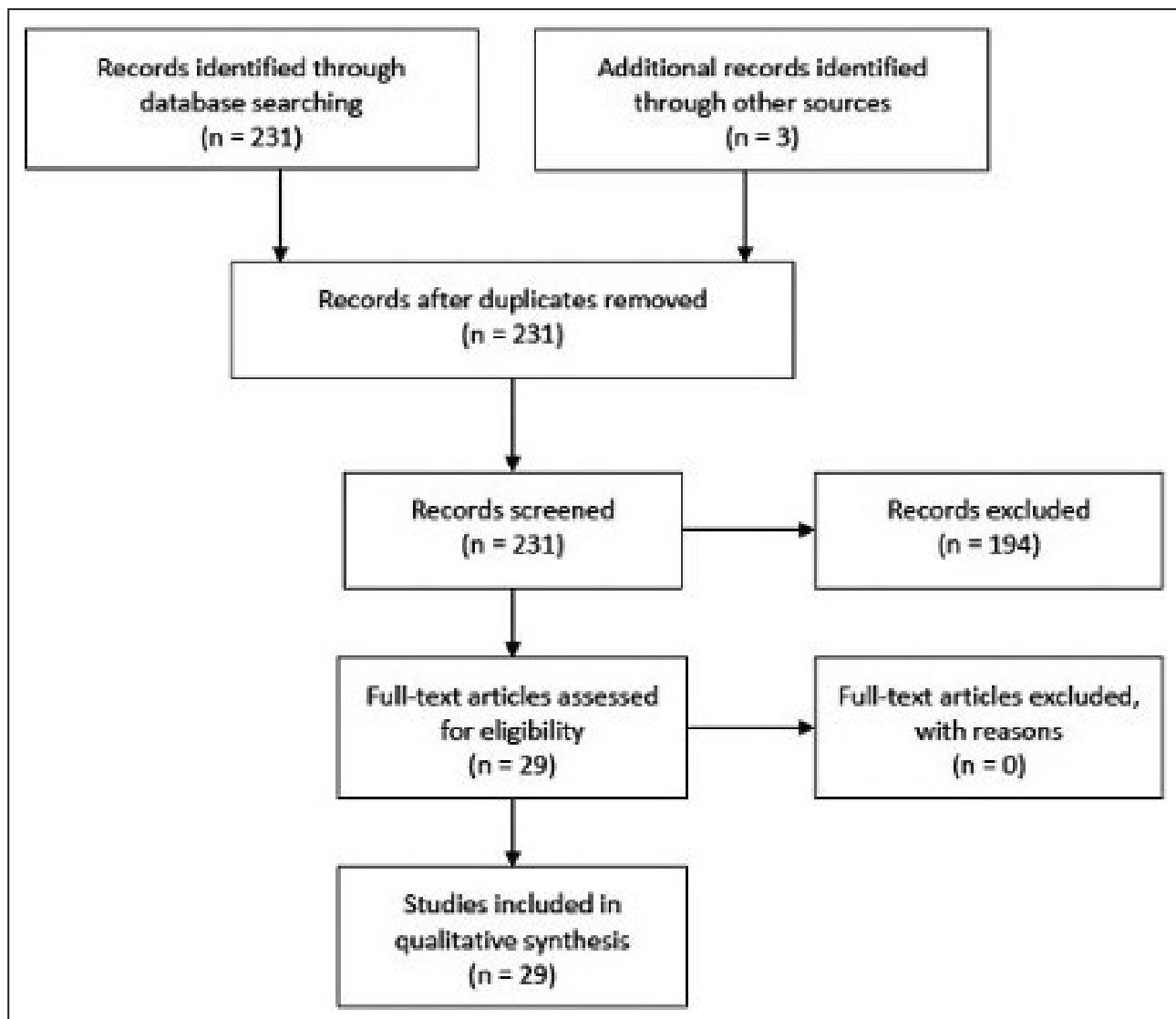


Figure 1. Summary of the search strategy.

Table. Description of the Studies Included

First Author	Journal	Year	Center	No. of Patients	No. of Events	Study Type/ Enrollment Period	Pattern Type	Patient Type	ECG Signs	Outcomes
Migliore et al ²³	<i>Europace</i>	2019	Consortium	272	17 patients had ≥1 major arrhythmic events (appropriate ICD shocks, n=13 and SCD, n=4)	Retrospective February 1995–June 2015	Spontaneous and induced	Mixed	First-degree AVB	Combined end point (SCD, CA, ICD appropriate intervention)
Delise et al ¹⁷	<i>Europace</i>	2018	Consortium	26	26 patients experienced SCD/aSCD	Retrospective 2010–2016	Spontaneous and induced	Symptomatic (all with aborted cardiac arrest)	Drug-induced type 1	ICD shocks
Morita et al ²⁶	<i>J Cardiovasc Electrophysiol</i>	2018	Okayama University Graduate Okayama, Japan	471	41 patients experienced VF	Retrospective	Spontaneous and induced	Mixed	RR, PQ, QRS, QT, Tp-e, ST level, AF, first- degree AVB, spontaneous type 1 ECG, ER, fQRS	VTA
Mughai et al ⁴³	<i>Am J Cardiol</i>	2017	Heart Rhythm Management Centre of UZ Brussels, Belgium	448	43 patients had VTA	Retrospective	Spontaneous and induced	Mixed	Tp-e, Tp-e/ QT, Tp-e dispersion, QTc, and QTd	VF; SCD
Ragab et al ⁴⁴	<i>J Cardiovasc Electrophysiol</i>	2018	Consortium Evaluation of Cardiogenetic Disease and Effectiveness of Screening of Screening (ENCODER project)	147	30 patients had VTA	Retrospective	Spontaneous and induced	Mixed	Tzou criteria (V1R>0.15 mV, V6S>0.15 mV, and V6SR>0.2); (2) prominent S wave in lead I, lead II, and lead III; (3) SII>SIII; and (4) prominent Q wave in lead III	VT; VF; ICD shocks

(Continued)

Table. Continued

First Author	Journal	Year	Center	No. of Patients	No. of Events	Study Type/ Enrollment Period	Pattern Type	Patient Type	ECG Signs	Outcomes
Ragab et al ³¹	<i>Am J Cardiol</i>	2017	Consortium of Evaluation of Cardiogenetic Disease and Effectiveness of Screening (ENCODER project)	132	VTA occurred in a total of 9 patients, and 4 patients developed VF. Five patients who initially presented with an OHCA or syncope had recurrent VT/VF	Retrospective	Spontaneous and induced; 14% type 2 pattern	Mixed	R wave in lead aVR; (R wave > 0.3 mV in lead aVR)	VTA
Sakamoto et al ³⁸	<i>Heart Vessels</i>	2017	Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Japan	81	11 patients experienced VF	Prospective April 2012–January 2015	Spontaneous and induced	Mixed	TWA, HRV	VF
Sakamoto et al ³⁹	<i>Heart Vessels</i>	2016	Department of Cardiovascular Medicine, Osaka City University Graduate School of Medicine, Japan	129	16 patients experienced VF. Appropriate ICD therapies were 140 according to VF	Retrospective	Spontaneous and induced	Mixed	Maximum TWA 3L-V2 during night	VF
Calò et al ²⁵	<i>J Am Coll Cardiol</i>	2016	Consortium	347	39 patients developed syncope, and 32 developed VF/SCD	Prospective 1999–nr	Spontaneous	Mixed	S wave (≥ 0.1 mV and/or ≥ 40 ms) in lead I and AF	VF/SCD
Maury et al ²²	<i>Am J Cardiol</i>	2013	Consortium	325	10 patients had SD, 55 had unexplained syncope 56 had inducible VTA	Retrospective 1996–2010	Spontaneous and induced	Mixed	Tpe of ≥ 100 lead V1 to lead V4	VTA

(Continued)

Table. Continued

First Author	Journal	Year	Center	No. of Patients	No. of Events	Study Type/ Enrollment Period	Pattern Type	Patient Type	ECG Signs	Outcomes
Crea et al ³⁵	<i>Ann Noninvasive Electrocardiol</i>	2015	Clinical and Experimental Medicine, University Hospital of Messina, Italy	87	nr	Retrospective	nr	nr	ST-segment depression (≥ 0.1 mV with duration ≥ 0.08 s) in the inferior leads	...
Uchinura-Makita et al ³⁷	<i>J Cardiovasc Electrophysiol</i>	2014	Hiroshima University Hospital, Japan	45	5 patients experienced VF	Retrospective 2001–2011	Spontaneous and induced	Mixed	TWA	VF
Kawata et al ³⁸	<i>Heart Rhythm</i>	2013	Okayama University Hospital, Japan	49	27 patients experienced VF	Retrospective	Spontaneous and induced	Symptomatic	ER (defined as J-point elevation ≥ 0.1 mV in inferior or lateral leads)	VTA
Rollin et al ²¹	<i>Heart Rhythm</i>	2013	Consortium	323	26 patients experienced SD/appropriate ICD shocks	Retrospective 1996–2010	Spontaneous and induced	Mixed	Type 1 ECG in the peripheral leads (at least 1)	VTA
Maury et al ⁴²	<i>Heart Rhythm</i>	2015	Consortium	325	10 patients had SD, 55 had unexplained syncope 56 had inducible VTA	Retrospective	Spontaneous and induced	Mixed	RBBB, LBBB, LAFB, LPFB, aVR sign, PR interval, P wave	SCD/ICD appropriate intervention
Priori et al ⁶	<i>J Am Coll Cardiol</i>	2012	Consortium	308	13 patients had appropriate ICD shocks and 1 OHCA	Prospective 2004–2009	Spontaneous and induced	Mixed	Spontaneous type 1 ECG, fQRS	VTA
Ohkubo et al ²⁹	<i>Int Heart J</i>	2011	Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan	35	No events	Retrospective 1995–2009	Spontaneous and induced	Mixed	QRS duration measured from lead V2	VTA/syncope
Nishii et al ¹⁹	<i>Circ J</i>	2010	Consortium	108	15 patients experienced appropriate ICD shocks	Retrospective 1997–2009	Spontaneous and induced	Mixed	Spontaneous type 1	ICD shock

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Table. Continued

First Author	Journal	Year	Center	No. of Patients	No. of Events	Study Type/ Enrollment Period	Pattern Type	Patient Type	ECG Signs	Outcomes
Nakano et al ¹⁸	<i>Europace</i>	2010	Hiroshima University Hospital, Japan	52	8 patients had appropriate ICD shocks	Retrospective 2000–2008	Spontaneous and induced	Mixed	Spontaneous type 1 ECG in lead V2	VF
Probst et al ²⁰	<i>Circulation</i>	2010	Consortium	1029	44 patients experienced appropriate ICD shocks, and 7 SD	Prospective	Spontaneous and induced	Mixed	Type 1 ECG pattern in right precordial leads	SCD or ICD shocks
Letsas et al ⁴¹	<i>Europace</i>	2010	Abteilung Rhythmologie, Herz-Zentrum, Bad Krozingen, Germany	23	No events	nr	nr	nr	Tp-e interval and Tp-e/QT in V2 e V6	VT/VF
Shimeno et al ³⁴	<i>Circ J</i>	2009	Department of Internal Medicine and Cardiology, Osaka City University Graduate School of Medicine, Osaka, Japan	58	No events	Prospective 2002–2007	Spontaneous (type 2) and induced	Mixed	Descending rate of the ST segment	Positive drug provocative test
Sarkozy et al ³²	<i>Circ Arrhythmia Electrophysiol</i>	2009	Consortium	280	14 patients had aSD, 68 had unexplained syncope	Retrospective 1992–2007	Spontaneous and induced	Mixed	Spontaneous inferior-lateral ER	VF
Morita et al ²⁷	<i>Circulation</i>	2008	Okayama University, Japan	115	13 patients had VF, 28 had unexplained syncope	Prospective	Spontaneous	Mixed	fQRS	VF
Tada et al ³⁶	<i>J Cardiovasc Electrophysiol</i>	2008	Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan	77	14 patients experienced VF	Prospective 2000–2006	Spontaneous	Mixed	TWA (after drug provocative test)/late potentials	VF

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Table. Continued

First Author	Journal	Year	Center	No. of Patients	No. of Events	Study Type/ Enrollment Period	Pattern Type	Patient Type	ECG Signs	Outcomes
Takagi et al ²⁴	<i>J Cardiovasc Electrophysiol</i>	2007	Consortium Japan Idiopathic Ventricular Fibrillation Study (J-IVFS)	188	61 patients experienced SD or VF	Prospective 2002–2006	Spontaneous and induced	Mixed	I–J interval in lead V2≥90 ms and QRS duration in lead V6≥90 ms	
Babai Bigi et al ³⁰	<i>Heart Rhythm</i>	2007	Cardiology Department, Shiraz University of Medical Sciences, Shiraz, Iran	24	3 patients had aSD, 10 had unexplained syncope	Retrospective 2000–2006	Spontaneous and induced	Mixed	R wave amplitude or R/q ratio in lead aVR	Composite end point (syncope, aborted SCD, VTA)
Juhani Junttila et al ²⁸	<i>J Cardiovasc Electrophysiol</i>	2007	Consortium	200	Syncope, n=33; VT/VF, n=6; SD, n=27	Retrospective	Spontaneous	Mixed	QRS duration measured from lead II or lead V2	Syncope, VT/VF, SCD
Castro Hevia et al ⁴⁰	<i>J Am Coll Cardiol</i>	2006	Cardiovascular Surgery and Cardiology Institute, Havana, Cuba	29	nr	Prospective 1995–2004	Spontaneous and induced	Mixed	Tp-e and Tp-e dispersion	not available

AF indicates atrial fibrillation; aSCD, aborted sudden cardiac death; CA, cardiac arrest; ER, early repolarization; fQRS, fragmented; HRV, heart rate variability; QRS ICD, implantable cardioverter defibrillator; LAFB, left anterior fascicular block; LBBB, left bundle-branch block; LPFB, left posterior fascicular block; OHCA, out hospital cardiac arrest; RBBB, right bundle-branch block; SCD, sudden cardiac death; Tp-Te, T-peak T-end; TWA, T-wave alternans; VF, ventricular fibrillation; VT, ventricular tachycardia; and VTA, ventricular arrhythmias.

First Author	Year	Center	Number of patients	Study type	ECG pattern	Type 1 ECG pattern	First grade AVB	Swave in lead I	Fragment QRS	Trou criteria	R wave in aVR	Repolarization dispersion	TWA	ER pattern	ST depression	QRS duration	AF	Study endpoint	Multivariable analysis (hazard ratio/odds ratio or relative risk [95% confidence interval], P value)
Migliore F ¹⁷	2018	Consortium	272	Retrospective	S/D-I	X	X											SCD or ICD shocks	HR: 4.65 (2.3-9.1) 0.002
Defina P ¹⁷	2018	Consortium	24	Retrospective	S/D-I	X												ICD shocks	N/A
Marita H ¹⁶	2018	Okayama University Okayama, Japan	471	Retrospective	S/D-I				X			X		X				VF	HR: 12.66 [2.40-235.49] 0.0009 HR: 3.33 [1.45-8.13] 0.0045
Mugnai G ¹¹	2018	Centre of UZ Brussels, Belgium	448	Retrospective	S/D-I							X						VF; SCD	HR: 3.03 [1.26-9.01] 0.011 HR: 1.26 [0.29-5.64] 0.76
Ragab AAY ¹⁴	2018	Consortium	147	Retrospective	S/D-I			X		X								VF or ICD shocks	HR: 4.15 [1.2-16.9] 0.025 HR: 3.7 [1.0-13.58] 0.049
Ragab AAY ¹⁵	2017	Consortium	132	Retrospective	S/D-I						X							VF	OR: 4.8 [1.79-13.27]
Sakamoto S ¹⁸	2016	Osaka City University Japan	81	Prospective	S/D-I								X					VF	OR: 10.4 [1.08-250] 0.043
Sakamoto S ¹⁹	2015	Osaka City University Japan	129	Retrospective	S/D-I								X					VF	OR: 9 [1.1-232] 0.04
Calò L ²¹	2016	Consortium	347	Prospective	S			X									X	SCD or ICD shocks	HR: 39.1 [5.34-287.1] <0.0001 HR: 3.7 [1.59-8.73] 0.002 HR: 9.6 [3.13-29.4] 0.0001
Mazny P ²²	2015	Consortium	325	Retrospective	S/D-I							X						VF	HR: 3.91 [1.1-13.5] 0.032
Crea P ¹⁸	2015	Hospital of Messina, Italy	87	Retrospective	S										X			N/A	N/A
Uchimura-Makita Y ¹⁷	2014	Hiroshima University Hospital, Japan	45	Retrospective	S/D-I								X					VF	OR: 2.594 [1.199-5.672] 0.018
Kawata H ²³	2013	Okayama University Hospital, Japan	49	Retrospective	S/D-I									X				VT or VF	0.0019
Rallin A ²¹	2013	Consortium	323	Retrospective	S/D-I	X												SCD or ICD shocks	OR: 4.58 [1.7-12.32] 0.0025
Mazny P ²²	2013	Consortium	325	Retrospective	S/D-I		X											SCD or ICD shocks	2.41 [1.01-5.73] 0.046
Priest SG ⁶	2012	Consortium	308	Prospective	S/D-I	X			X									SCD or ICD shocks	HR: 6.466 [2.111-18.558] 0.001
Ohkubo K ¹⁴	2011	Nihon University Tokyo, Japan	35	Retrospective	S/D-I													VT or VF	0.012
Nishii N ¹⁹	2010	Consortium	108	Retrospective	S/D-I	X												ICD shock	OR: 6.72 0.021
Nakano Y ¹⁸	2010	Hiroshima University Hospital, Japan	52	Retrospective	S/D-I	X												VF	Relative risk: 24.3 [3.27-33.3] 0.002
Prabst V ²⁰	2010	Consortium	1029	Prospective	S/D-I	X												SCD or ICD shocks	HR: 1.8 [1.03-3.3] 0.04
Letas KP ¹⁵	2009	Herz-Zentrum, Bad Kreuznach, Germany	23	Prospective	S/D-I							X						VT/VF inducibility	N/A
Shimono K ¹⁶	2009	Osaka City University Osaka, Japan	58	Prospective	S/D-I										X			Positive drug provocative test	N/A
Sarkozy A ¹¹	2009	Consortium	200	Retrospective	S/D-I									X				N/A	N/A
Marita H ¹⁷	2008	Okayama University, Japan	115	Prospective	S				X									VF	<0.001
Tada T ¹⁶	2008	Okayama University, Japan	77	Retrospective	S/D-I								X					VF	HR: 22.21 [3.29-149.928] 0.001
Takagi M ¹⁴	2007	Japan JVFPS Study	188	Prospective	S/D-I													SCD or VF	HR: 4.21 [1.3-11.8] 0.01
Bibani Bigi Ad ¹⁴	2007	Shiraz University, Shiraz, Iran	24	Retrospective	S/D-I						X							SCD or VF	0.01
Juhani Junttila M ²⁴	2007	Consortium	200	Retrospective	S													VF or SCD	HR: 2.7 [1.3-5.8] 0.011
Castro-Hewitt J ¹⁶	2006	Havana, Cuba	29	Prospective	S/D-I							X						ICD shocks	0.006

VTA: ventricular arrhythmias; VT: ventricular tachycardia; VF: ventricular fibrillation; SCD: sudden cardiac death; S: spontaneous; D-I: drug induced

Figure 2. Summary of the studies included and the main outcomes.

D-I, drug induced; S, spontaneous; SCD, sudden cardiac death; VF, ventricular fibrillation; VTA, ventricular arrhythmias; and VT: ventricular tachycardia.

signs and their putative electrogenetic mechanisms are summarized in Figure 3. Representative ECG pictures can be found in Figures S1 to S5.

DISCUSSION

In this systematic review of the literature on Brugada ECG pattern (BrS type 1 ECG), we quantitatively evaluated the incremental risk related to a spectrum of ECG features and provide some insights into the pathophysiology of BrS. Before discussing the different ECG signs and their relative prognostic implications, the following general points need to be considered:

1. Unlike other channelopathies in which the extent of the primary pathogenetic alteration is directly related to the prognosis (typically the length of QT in long QT syndromes), in the case of BrS, the severity of the ST-T alterations of the type 1 pattern has not a defined role for the prognosis.
2. The diagnosis of BrS is based on a single element of standard ECG, the so-called type 1 pattern. However, a very broad spectrum of ECG changes is present, with variable frequency and clinical

significance. This makes the disease—which still lacks precise nosographic boundaries—even more challenging and intriguing.

3. To explain such a broad spectrum of ECG manifestations, it is necessary to hypothesize other mechanisms besides the main mechanism underlying the type 1 ECG Brugada pattern, such as the epi-endocardial gradient in myocells of the right ventricular outflow tract (RVOT) attributed to loss of function of the sodium current.

Spontaneous Type 1 ECG Pattern in Leads Other Than the Right Precordial

The type 1 ECG pattern is defined for diagnostic purposes as an ST-segment elevation ≥ 2 mm in ≥ 1 right precordial lead (V1–V3) followed by a concave or straight ST segment with a negative symmetric T wave.⁴⁵ A spontaneous type 1 ECG pattern in the right precordial leads is the only ECG sign with a clearly established association to arrhythmic risk.¹⁷ A retrospective analysis of 54 patients with BrS enrolled at Hiroshima University Hospital with and without histories of ventricular fibrillation (VF) demonstrated that the spontaneous type 1 ECG pattern

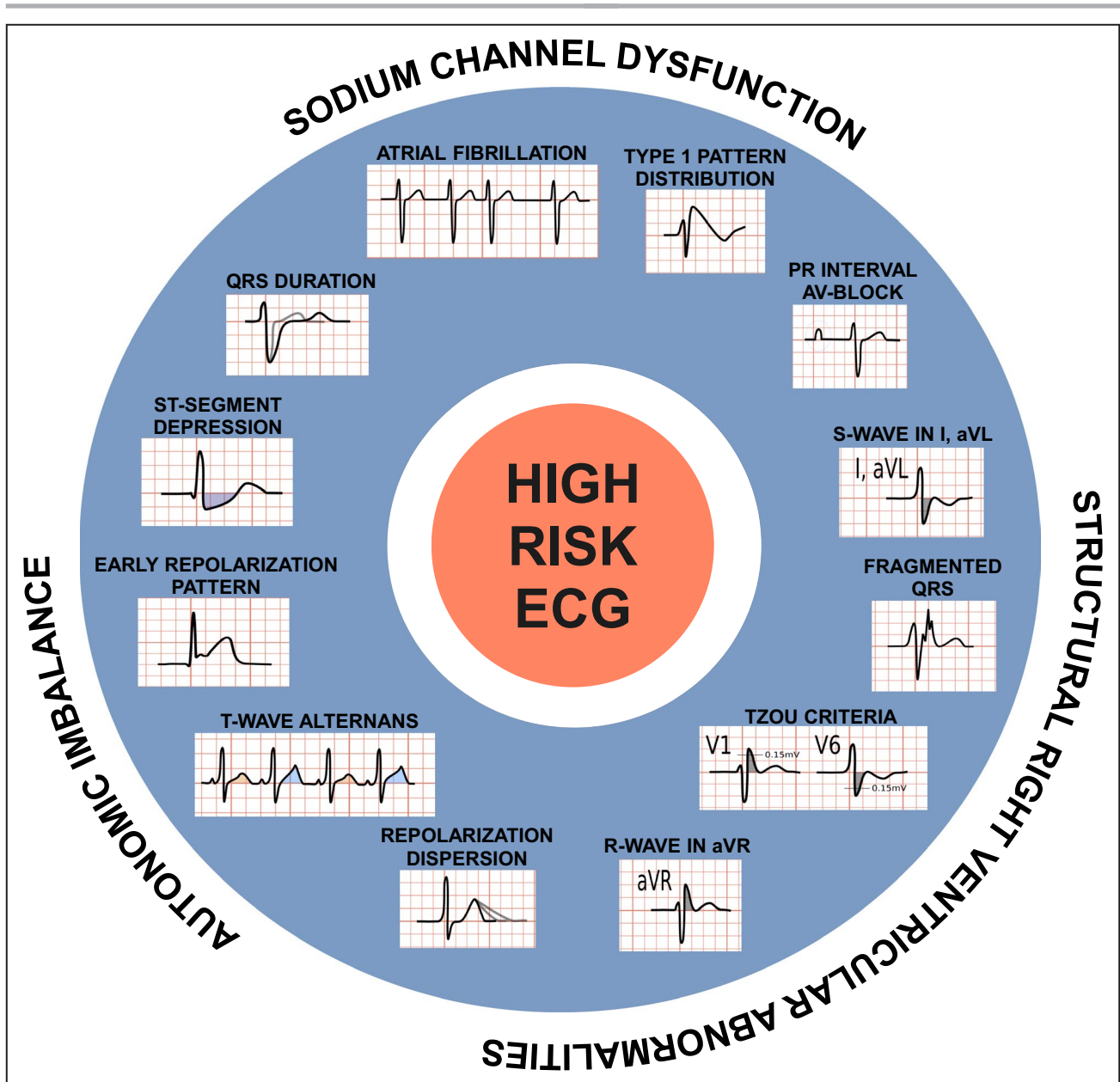


Figure 3. Schematic representation of the ECG markers analyzed for BrS. BrS indicates Brugada syndrome.

in lead V2 was an independent predictor of VF.¹⁸ In a prospective study investigating the association between *SCN5A* mutations and VF in patients with BrS, Nishii et al¹⁹ showed a strong correlation between *SCN5A* mutations, spontaneous type 1 ECG and VF recurrence. Results from the FINGER BrS registry showed that symptoms and spontaneous type 1 pattern were the only risk factors predictive of arrhythmic events in BrS.²⁰ In the PRELUDE (programmed electrical stimulation predictive value) registry, Priori et al⁶ prospectively demonstrated in 308 asymptomatic patients with spontaneous or drug-induced type 1 ECG pattern that the spontaneous type 1

pattern was an independent and strong predictor of arrhythmic events (HR, 4.2).

The type 1 Brugada pattern has also been investigated in other leads besides the right precordial leads. Rollin et al²¹ retrospectively analyzed 323 asymptomatic patients with BrS and found a higher rate of SCD and appropriate ICD therapy in patients with a spontaneous or drug-induced type 1 pattern in at least 1 peripheral lead compared with those without peripheral lead abnormalities (OR, 4.58; 95% CI, 1.7–12.32; *P*=0.0025). Interestingly, they also showed that patients with type 1 ECG in the peripheral leads more often had *SCN5A* gene mutations, higher

J-wave amplitude in the right precordial leads, and a slower heart rate.⁴⁶ Although it is well known that the ECG pattern in BrS is dynamic and influenced by time, these data suggest that its finding also in leads other than the right precordial may be the expression of a higher grade of SCN5A channel dysfunction and thus of a greater volume of tissue experiencing the electrogenic alteration.

First-Degree AVB

First-degree AVB is seen at presentation in 16.5% to 40% of patients with BrS.^{22,23} The relevance of the PR interval in BrS is a consequence of the strong association between mutation in the SCN5A gene and sodium channel dysfunction causing atrio-ventricular (AV) conduction disturbance. SCN5A mutations have a wide phenotypic spectrum of clinical presentations other than BrS, including dysfunction of the cardiac conduction system at different levels, AF, sick sinus syndrome, and even Lenègre-Lev disease.²²

Two studies analyzed the role of a prolonged PR interval, defined as PR \geq 200 ms, in predicting tachyarrhythmia events. In a multicenter study on 325 patients with BrS, spontaneous type 1 ECG pattern and first-degree AVB (PR \geq 200 ms) were associated with an increased risk of SCD and appropriate ICD therapies.²² Migliore et al²³ confirmed this finding in a study on 272 patients with BrS with spontaneous or drug-induced type 1 Brugada ECG pattern. At multivariate analysis, spontaneous type 1 ECG pattern and first-degree AVB (PR $>$ 200 ms) at baseline were strongly linked to SCD and appropriate ICD interventions (HR, 4.65; 95% CI, 2.34–19.1; $P=0.002$). Considering this evidence, it is plausible to look at PR interval prolongation as a marker of greater impairment of the sodium currents in the conduction system beyond the RVOT involvement.

Atrial Fibrillation

Paroxysmal AF is more frequent than spontaneous AF in patients with BrS, and the presence of spontaneous AF is associated with a more severe phenotype.⁴⁷ Prevalence of AF in patients with BrS ranges from 5% to 15%.^{24,25}

A total of 3 studies evaluated the correlation between AF and higher incidence of ventricular arrhythmias in patients with BrS. The Japan Idiopathic Ventricular Fibrillation Study showed in 188 consecutive symptomatic patients with BrS that the presence of a previous history of AF was higher in patients who experienced VF.²⁴ In a recent study, this finding was confirmed in 347 consecutive patients with type 1 ECG pattern and no previous cardiac arrest, where a history of AF was an independent risk factor for VF/SCD (HR, 3.70; 95% CI, 1.59–8.73; $P=0.0024$).²⁵

Morita et al²⁶ showed that the presence of paroxysmal AF in patients with BrS with previous VF or syncope is a strong predictor for VF recurrence. The presence of AF or other conduction disorders is usually linked to a more aggressive phenotype. Similar to PR interval prolongation, the presence of AF is related to severe impairment of sodium channels and may be the expression of a diffuse extension of the sodium current impairments beyond the RVOT and into the atrial myocardium.

Fragmented QRS

Fragmented QRS (fQRS) is defined as an abnormal fragmentation within the QRS complex characterized by multiple notching of the R and S waves or the presence of more than 1 R' wave. This ECG finding may underlie the presence of myocardial fibrosis.^{26,48} It has been hypothesized that in BrS the presence of fQRS represents an epicardial repolarization heterogeneity of the RVOT or even of structural alterations (myocarditis/fibrofatty infiltration) resulting in a substrate for VF. High prevalence of fQRS is reported in both asymptomatic (6%–20%) and symptomatic (30%–40%) patients with BrS.^{6,26,27} In animal models, delayed electrical activation of a large ventricular mass can cause multiple spikes on the QRS complex in the surface ECG. A strong association between fQRS in the V1 to V3 leads, presence of SCN5A mutations, and syncope was reported in 115 asymptomatic and symptomatic patients with BrS.²⁷ The same authors showed in a population of 471 patients with BrS that fQRS predicted VF recurrence in both symptomatic and asymptomatic patients (asymptomatic HR, 5.88; 95% CI, 1.55–38.26 [$P=0.007$]; symptomatic HR, 8.15; 95% CI, 2.87–34.18 [$P<0.0001$]); in addition, fQRS was confirmed as an independent predictor of prognosis in symptomatic patients.²⁶

We believe that the presence of fQRS may be a marker of concomitant structural alteration and repolarization heterogeneity with inhomogeneous conduction of action potentials through the myocardium, thus its presence should be interpreted as a sign of a deeply altered substrate.

QRS Duration

The importance of a prolonged QRS duration in BrS is linked to the “depolarization hypothesis,” according to which abnormal depolarization coexists with repolarization abnormalities in determining the arrhythmic substrate. The prolonged QRS in this hypothesis is attributed to sodium current dysfunction mainly in the conduction system and specifically in the His-Purkinje system. Junttila et al²⁸ found a strong correlation in patients with BrS between prolonged QRS duration (<120 ms) in leads II and V2 and prior symptoms such

as syncope. In the same study, prolonged QRS duration (≥ 120 ms) in V2 was strongly associated with a history of SCD, VF, and VT (OR, 2.6; 95% CI, 1.4–4.8; $P=0.004$).²⁸ A Japanese study on 35 patients with BrS confirmed these correlations.²⁹

Once again, the involvement of the conduction system in BrS expressed by the QRS prolongation is linked to poor prognosis.

R Wave in Lead aVR

The importance of the aVR lead consists in its ability to explore the RVOT. A critical analysis of the morphology of this lead in BrS can provide a series of useful information. In 2007, Babai Bigi et al³⁰ first identified the aVR sign in 24 male patients with mixed BrS. The authors defined as a significant aVR sign an R wave ≥ 0.3 mV or R/q ratio ≥ 0.75 in the aVR lead. Despite the small cohort of patients, in the presence of the type 1 ECG pattern, the aVR sign appeared to be associated with syncope, VT/VF, and aborted SCD.³⁰ This initial finding was not confirmed in 2 larger studies, where the aVR sign was not related to syncope, VT/VF, or aborted SCD.^{22,28} In 2017, a retrospective Dutch study on 132 patients with BrS from the ENCODER (Evaluation of Cardiogenetic Disease and Effectiveness of Screening) project found an R wave >0.3 mV in the aVR lead to be an independent predictor for ventricular tachyarrhythmia development (OR, 4.8; 95% CI, 1.79–13.27; $P=0.002$) but with moderate sensitivity and specificity (area under the curve, 0.7; sensitivity, 63%; specificity, 77%).³¹ A positive aVR sign was highly prevalent in patients with BrS who were asymptomatic (26%) and symptomatic (60%). A high R wave in the aVR lead may be the sign of a pronounced conduction defect in the RVOT.

S Wave in the Lateral Leads

Lateral leads such as L1 and aVL are complementary to aVR in the exploration of RVOT depolarization and repolarization. The depolarization of the RVOT and basal region of the ventricles generates the third electrocardiographic vector of the QRS complex. Delayed depolarization in those areas leads to a deep S wave in L1 and aVL. In a prospective study on 347 consecutive patients with BrS with spontaneous type 1 ECG pattern, Calò et al²⁵ found that the presence of an S wave in lead I ≥ 40 ms (HR, 39.1; 95% CI, 5.34–287.1; $P<0.0001$) with amplitude ≥ 0.1 mV (HR, 13.3; 95% CI, 4.05–43.72; $P<0.0001$) and area ≥ 1 mm² (HR, 17.1; 95% CI, 1.59–8.69; $P<0.0001$) strongly predicted VF and SCD during follow-up with good sensitivity (S amplitude >0.1 mV, 90.6%; S duration >40 ms, 96.9%) but low specificity.²⁵ Moreover, an S wave ≥ 0.1 mV and/or ≥ 40 ms in lead I was found to be significantly more frequent in patients with BrS

who were symptomatic than patients with BrS who were asymptomatic (prevalence 96% versus 55%, respectively).^{25,50} In the same study focused on an inflammation hypothesis in BrS, 30 patients underwent electroanatomic mapping and RVOT endomyocardial biopsy, and the evidence showed a higher rate of myocardial inflammation in patients who were symptomatic with a positive electrophysiological study than in patients who were asymptomatic. The presence of a pronounced S wave in the lateral leads is caused by the same process underlying a high R wave in aVR, probably a zonal conduction block in the RVOT.

ER Pattern

An ER pattern, defined as a J-point elevation of at least 1 mm above the baseline terminal QRS notching in at least 2 consecutive inferior or lateral leads, is a common electrocardiographic sign in the general population, with an estimated prevalence of 1% to 5% in healthy adults.⁵¹ In the past, it was considered a benign electrocardiographic finding, but several reports have recently suggested an association between idiopathic VF and ER in the inferior and/or lateral leads of the ECG.⁵²

In 2009, Sarkozy et al³² investigated the prevalence and characteristics of spontaneous or drug-induced inferolateral repolarization abnormalities in a large unselected population of patients with BrS. Patients with inferolateral spontaneous ER more frequently had a spontaneous type 1 ECG pattern, had a more severe phenotype, and were less likely to be asymptomatic at first presentation.

Kawata et al³³ investigated the prevalence and prognostic significance of ER in the inferolateral leads in 49 patients with BrS with documented VF and ICD implanted for secondary prevention. ER was observed persistently or intermittently in nearly half of the patients (in at least 1 but not in all ECGs). During follow-up, recurrence of VF occurred in all patients with a persistent ER pattern, in 75% of the patients with an intermittent ER pattern, and in 44% of those without ER. The presence of either persistent or intermittent ER in an inferolateral lead was an independent predictor of fatal arrhythmic events (persistent ER: HR, 4.88; 95% CI, 2.02–12.7 [$P=0.0004$]; intermittent ER: HR, 2.50; 95% CI, 1.03–6.43 [$P=0.04$]).

ST-Segment Depression

ST-segment depression is more frequently associated with acute coronary syndromes attributed to either acute ischemia or acute myocardial infarction. This electrocardiographic pattern, however, can also appear in patients with nonischemic events such as left bundle branch block and left ventricular hypertrophy and in patients with therapeutic digitalis levels.

In 2009, Shimeno et al³⁴ first studied ST-segment behavior in patients with BrS. They systematically measured the amplitude of the ST segment 20 ms and 40 ms after the r' wave and found the descending rate of the ST segment to be a noninvasive predictor of positive provocative drug testing. The positive and negative predictive values of the descending rate of the ST segment in lead V2 in the third intercostal space (defined as the difference between the amplitude of the peak of the r' wave and the amplitude 20 ms after the r' wave divided by the difference between the amplitude of r' wave and the bottom of the ST segment) were 92.3% and 81.8%, respectively. Crea et al³⁵ analyzed the ECG features in the inferior leads in a cohort of 87 patients with type 1 spontaneous ECG Brugada pattern. ST-segment depression (≥ 0.1 mV with duration ≥ 0.08 s) was present in 41 cases (47%). Notably, in 21 patients, the Brugada type 1 pattern was recognizable only at the second or third intercostal space: 10 of them (48%) presented a significant ST depression in the inferior leads. The origin of this particular sign is difficult to interpret from a pathophysiological point of view and is still under debate.

T-Wave Alternans

TWA is not discernible from standard ECG but usually derived from ECG-Holter. The definition of TWA is the beat-to-beat variation in the shape or amplitude of the T wave. In several heart diseases, TWA is a strong predictor of SCD. The pathophysiology of TWA is not yet clearly established, but several studies have demonstrated that it reflects a spatial or temporal dispersion of repolarization that may predispose to a higher risk of ventricular tachyarrhythmia, including polymorphic VT or VF.⁵⁴

Macroscopic TWA sometimes appears after the administration of a sodium channel blocker or during a febrile state in patients with BrS. Tada et al³⁶ investigated the association between the presence of TWA after pilsicainide administration and the occurrence of adverse events such as syncope or spontaneous VF and identified TWA as an independent predictor of spontaneous VF. This association between VF and TWA was confirmed by Uchimura-Makita et al (OR, 7.217; 95% CI, 2.503–35.504; $P=0.002$) with good sensitivity and specificity.³⁷

Sakamoto et al further investigated the utility of TWA as a risk stratification marker of arrhythmia events and found significantly greater max-TWA (measured at the third intercostal spaces) during the night in patients with a history of syncope or VF.^{38,39} Multivariate analysis revealed that a max-TWA ≥ 20 μ V during the night and a previous history of VF were independent predictors of future VF episodes. The authors suggested that max-TWA may be a useful predictor of VF in patients with BrS.

Dispersion of Repolarization

Transmural dispersion of repolarization within the ventricular myocardium has been suggested as 1 of the main features characterizing arrhythmogenesis in BrS; several studies have investigated different parameters of dispersion of repolarization as possible predictors of arrhythmic risk in patients with BrS^{40–43}:

1. Tpeak-Tend (Tp-e) interval, defined as the time difference between the peak and the end of the T wave in the precordial leads during a single beat
2. Tp-e dispersion
3. Tp-e maximum value
4. Tp-e/QT ratio
5. QTc prolongation and QT dispersion

Castro Hevia et al⁴⁰ tested the Tp-e interval in patients with BrS and showed that the Tp-e interval and Tp-e dispersion were significantly prolonged in patients with arrhythmia recurrences. The study demonstrated also a significant correlation between previous events, QTc prolongation in V2, Tp-e, and Tp-e dispersion and the occurrence of life-threatening arrhythmic events, suggesting that these parameters may be useful for risk stratification of patients with BrS.

In patients with spontaneous or drug-induced type 1 BrS pattern who underwent programmed ventricular stimulation,⁴¹ those with inducible VT/VF displayed an increased Tp-e interval in leads V2 and V6 and a greater Tp-e /QT ratio in lead V6.

The utility of Tp-e interval as a marker of arrhythmic risk in BrS was further investigated in patients with BrS with spontaneous or drug-induced type 1 BrS pattern.⁴² Tp-e measured in V1 to V4, Tp-e maximum value, and Tp-e dispersion were significantly higher in patients with SCD/appropriate ICD therapies or in patients with syncope compared with patients who were asymptomatic. At multivariate analysis, a maximum Tp-e ≥ 100 ms was independently related to arrhythmic events (OR, 9.61; 95% CI, 3.13–29.41; $P<0.0001$).

Recently, Morita et al²⁶ showed that the Tp-e interval (≥ 95 ms) was a predictor of VF in patients who were asymptomatic and symptomatic, whereas a long QT interval (≥ 420 ms) was a predictor of VF in the symptomatic group only.

Mugnai et al⁴³ evaluated the association between parameters of dispersion of repolarization (Tp-e, Tp-e/QT, Tp-e dispersion, QTc, and QTd) and VF/SCD in a large cohort of patients with type 1 BrS but found no significant differences in Tp-e, Tp-e/QT, Tp-e/QT ratio, maximum Tp-e, and Tp-e dispersion between patients who were asymptomatic and those with syncope and malignant arrhythmias.

All of these ECG signs reflect transmural dispersion of repolarization among different myocardial regions and appear to be related to electrical instability and/or structural alterations in BrS as in other cardiovascular diseases.

Tzou Criteria

Tzou criteria—defined as V1R >0.15 mV, V6S >0.15 mV, and V6 S:R>0.2—have been described as predictive of malignant arrhythmias in patients with nonischemic cardiomyopathy.⁵² The presence, in patients with BrS, of a right anterosuperior area of conduction block determining an rS pattern in lead V1 and a prominent S wave in lead V6 prompted an investigation of the utility of Tzou criteria for predicting arrhythmic events in patients with BrS.⁴⁴ In 147 patients with BrS (79% with spontaneous pattern), 20% of them developed ventricular tachyarrhythmia (either documented history or de novo). Positive Tzou criteria were present in 37 patients (25%), 63% of whom were symptomatic. Multivariable regression analysis revealed the independent predictive value of Tzou criteria for ventricular arrhythmias. On the other hand, Calò et al²⁵ in their study on 347 patients with spontaneous type 1 Brugada pattern found no significant difference in any of the Tzou criteria between patients subdivided into 3 groups according to the presence or not of syncope and/or documented VF/SCD.

The presence of Tzou criteria seems to be related to a right anterosuperior conduction block, therefore it may express the presence of a conduction block in the RVOT (identified by high R wave in aVR and large and deep S wave in DI–aVL).

LIMITATIONS

A major limitation of this study is the heterogeneity of the input data because of differences in methodology, population, and ethnicity. Variabilities in the ascertainment of ECG markers and adjudication of the outcomes may affect the quality of the overall data.

Our systematic review considered the overall data of the published series. We didn't go into detail about specific issues regarding subgroups such as women and children, who have a very challenging risk profile.^{53–55} In addition, many of the pathophysiological mechanisms proposed in these studies are hypothetical, that is, not based on experimental data. Therefore, further rigorous studies are needed to confirm these hypotheses.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Controversies still exist about the risk stratification of BrS and BrS type 1 ECG. Clinical findings, such as

a history of syncope, aborted cardiac death, or sustained VT, remain the only clear means to identify patients with high arrhythmic risk. The predictive role of electrophysiological study with programmed ventricular stimulation in patients with BrS is still debated.⁵⁶ Family history of SCD is of uncertain value and the results of genetic analysis are often confounding. Given that 12-lead ECG analysis is 1 of the major diagnostic tools in this syndrome, several different ECG markers of ventricular depolarization and repolarization have emerged over time but with variable and conflicting results.

In this review, we discussed 12 different ECG signs identified as high-risk markers in patients with BrS: localization of type 1 Brugada pattern (in V2 and peripheral leads), first-degree AVB, AF, fragmented QRS, QRS duration >120 ms, R wave >0.3 mV in lead aVR, S wave in L1 (≥ 40 ms, amplitude ≥ 0.1 mV, area ≥ 1 mm²), ER pattern in inferolateral leads, ST-segment depression, TWA, dispersion of repolarization, and Tzou criteria. A multi-parametric risk assessment approach based on ECG parameters associated with clinical and genetic findings could help improve current risk stratification scores of patients with BrS^{57–59} and warrants further investigation.

In addition to prognostic hints, ECG signs within the Brugada pattern can provide useful insights into the complex pathophysiology of this entity.

ARTICLE INFORMATION

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Supplementary Material

Table S1
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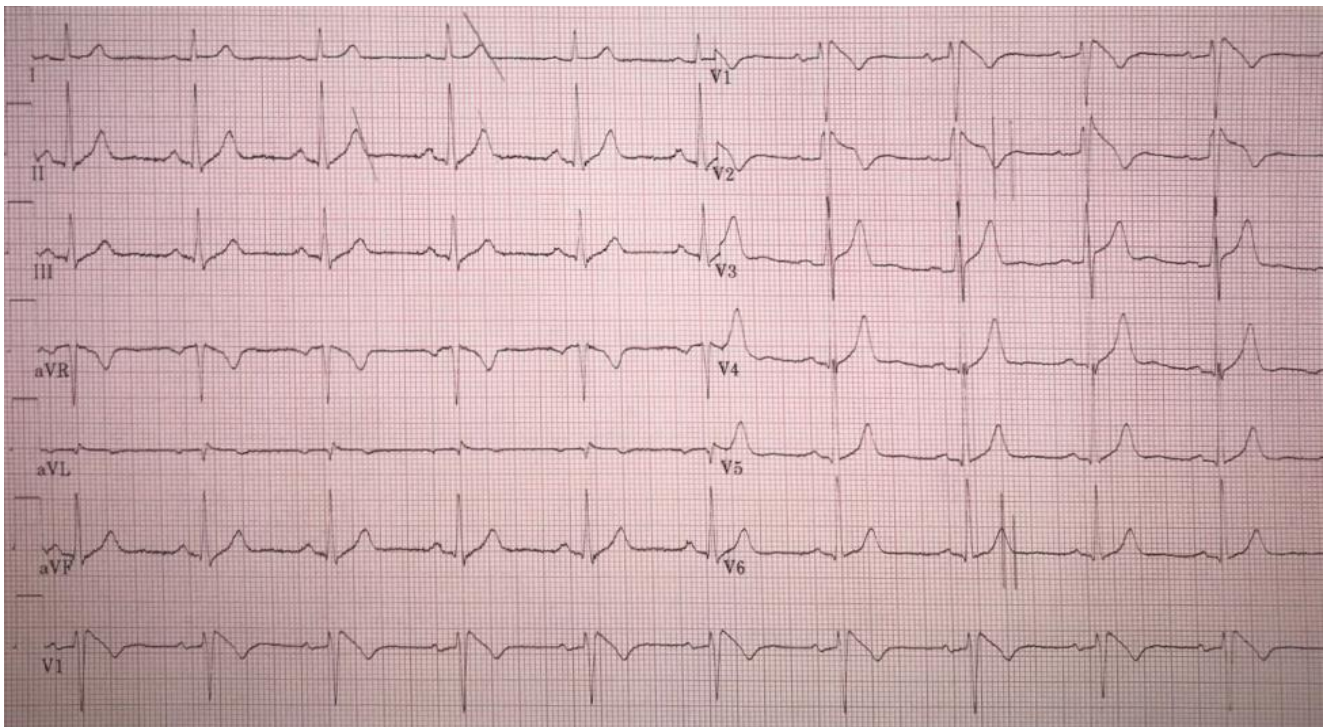
Supplemental Material

Table S1. Quality assessment of observational study included in the systematic review with MINORS criteria.

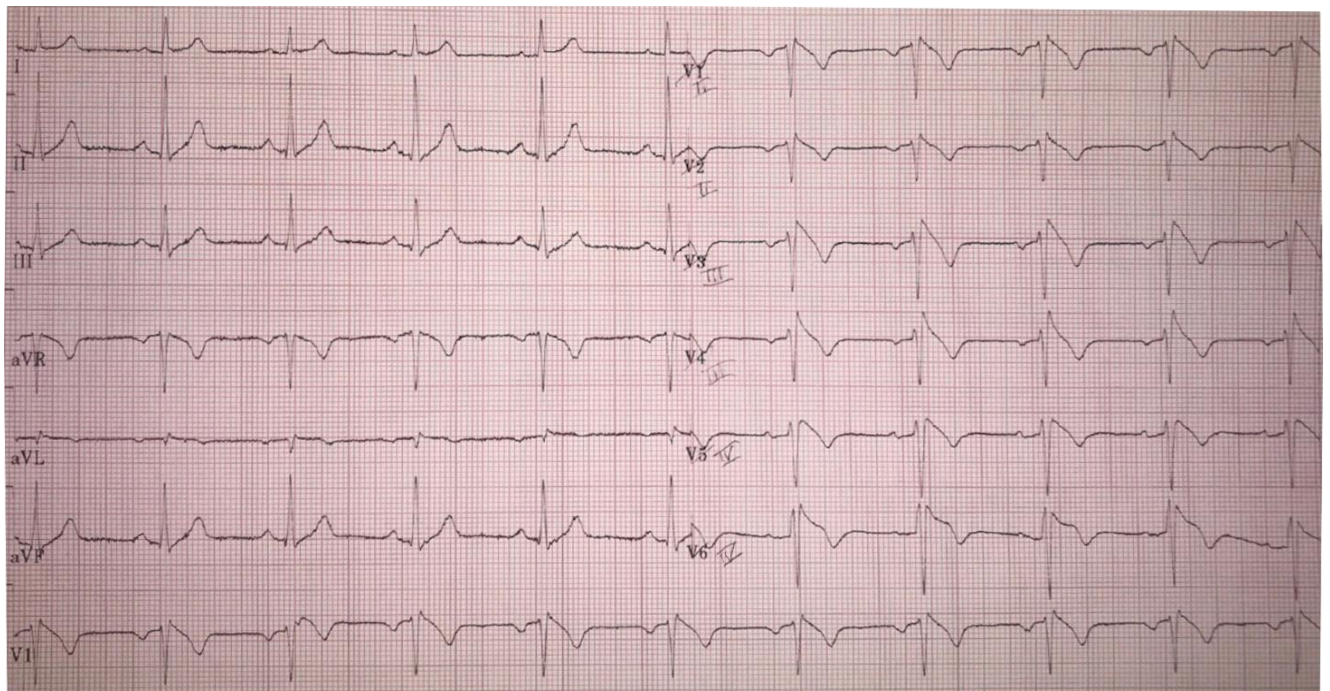
References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
<i>Migliore et al.</i> ²³	2	1	0	2	2	2	1	0	0	0	0	2
<i>Delise et al.</i> ¹⁷	2	2	0	2	2	2	2	0	0	0	0	1
<i>Morita et al.</i> ²⁶	2	2	0	2	2	0	1	0	0	0	0	2
<i>Mugnai et al.</i> ⁴³	2	2	0	2	2	0	1	0	0	0	0	1
<i>Ragab et al.</i> ⁴⁴	2	1	0	2	2	0	1	0	0	0	0	1
<i>Ragab et al.</i> ³¹	2	1	0	2	2	0	1	0	0	0	0	2
<i>Sakamoto et al.</i> ³⁸	2	2	2	2	2	2	2	2	0	0	0	2
<i>Probst et al.</i> ²⁰	2	2	2	2	2	2	1	0	0	1	0	2
<i>Sakamoto et al.</i> ³⁹	2	2	0	2	2	0	1	0	0	0	0	2
<i>Calò et al.</i> ²⁵	2	1	2	2	2	1	1	2	0	0	0	2
<i>Maury et al.</i> ²²	2	1	0	2	2	2	1	0	0	0	0	2
<i>Crea et al.</i> ³⁵	2	2	0	0	0	0	2	0	0	0	0	1
<i>Uchimura-Makita et al.</i> ³⁷	2	2	0	2	2	2	2	0	0	0	0	2
<i>Kawata et al.</i> ³³	2	2	0	2	2	0	2	0	0	0	0	2
<i>Rollin et al.</i> ²¹	2	1	0	2	2	2	1	0	0	0	0	2
<i>Maury et al.</i> ⁴²	2	1	0	2	2	0	1	0	0	0	0	1
<i>Priori et al.</i> ⁶	2	1	2	2	2	2	2	2	0	0	0	2
<i>Ohkubo et al.</i> ²⁹	2	2	0	2	2	2	2	0	0	0	0	1
<i>Nishii et al.</i> ¹⁹	2	2	0	2	2	2	1	0	0	0	0	1
<i>Nakano et al.</i> ¹⁸	2	1	0	2	2	2	2	0	0	0	0	2
<i>Letsas KP et al.</i> ⁴¹	2	1	0	2	2	0	2	0	0	0	0	1
<i>Shimeno et al.</i> ³⁴	2	2	2	1	1	2	2	2	0	0	0	1
<i>Sarkozy et al.</i> ³²	2	1	0	2	2	2	1	0	0	0	0	1
<i>Morita et al.</i> ²⁷	2	2	2	2	2	0	1	2	0	0	0	1
<i>Tada et al.</i> ³⁶	2	2	2	2	2	2	2	2	0	0	0	2
<i>Takagi et al.</i> ²⁴	2	2	2	0	0	2	1	2	0	0	0	2
<i>Babai Bigi et al.</i> ³⁰	2	2	0	2	2	2	2	0	0	0	0	1
<i>Juhani Junttila et al.</i> ²⁸	2	1	0	2	2	0	1	0	0	0	0	2
<i>Castro Hevia et al.</i> ⁴⁰	2	2	2	0	0	2	2	2	0	0	0	2

Q: question. In every item the following points were assigned: "Not reported (0 point)", "Reported but inadequate (1 point), or "Reported and adequate (2 point)". Q1: A clearly stated aim; Q2: Inclusion of consecutive patient; Q3: Prospective collection of data; Q4: Endpoints appropriate to the aim of the study; Q5: Unbiased assessment of the study endpoint; Q6: Follow-up period appropriate to the aim of the study; Q7: Loss to follow up less than 5%; Q8: Prospective calculation of the study size; Q9: An adequate control group; Q10: Contemporary groups; Q11: Baseline equivalence of groups. Q12: Adequate statistical analyse

Figure S1. Case 1.



A

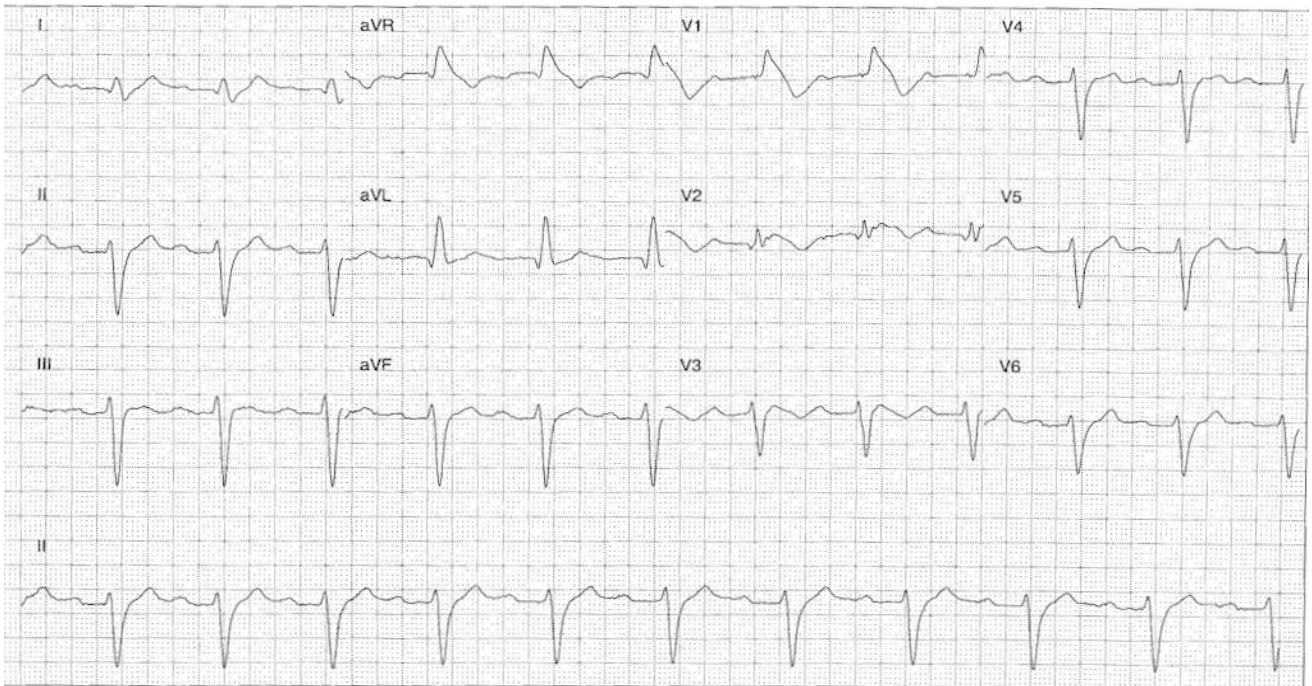


B

Case 1: these two ECGs are from the same asymptomatic 22 years old male with no history of familial sudden death. Normal echocardiogram and cardiac MRI. No gene mutations found. **A:** (standard 12

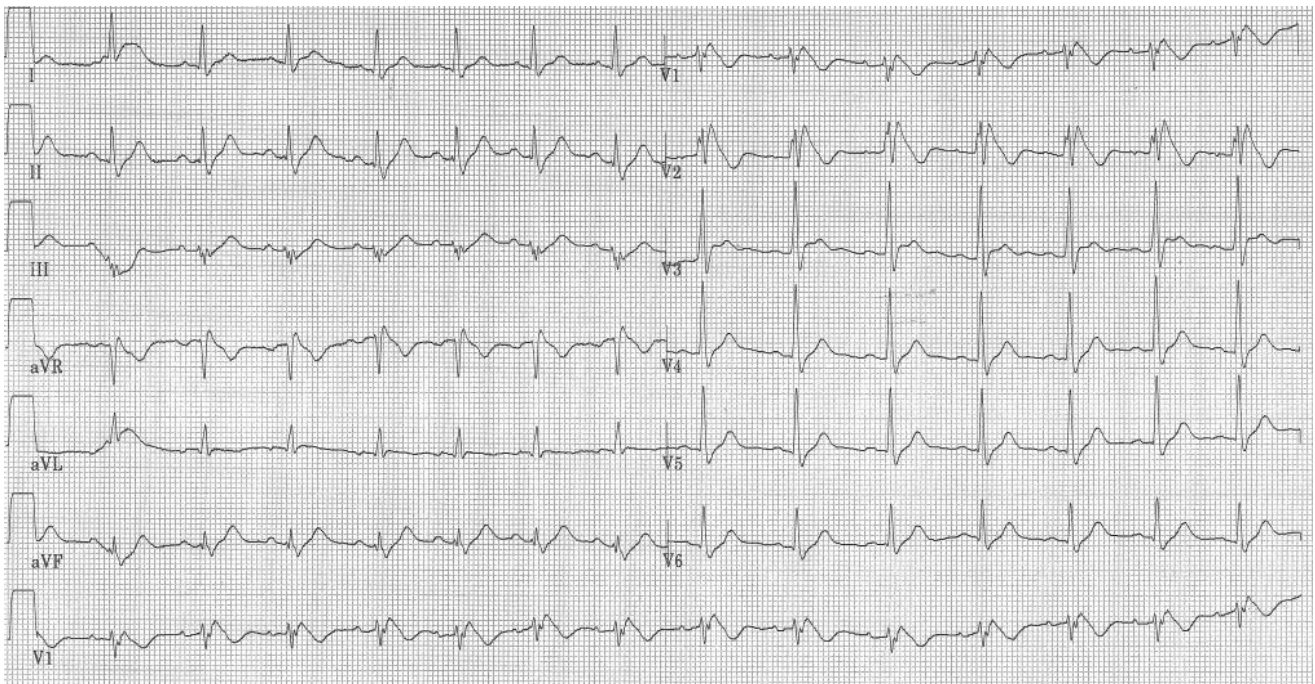
lead ECG) normal sinus rhythm, normal PR interval and QRS complex (duration and axis), ST segment elevation ≥ 2 mm in right precordial leads (V1–V2) followed by a concave or straight ST segment with a negative symmetric T-wave (type 1 Brugada pattern). **B:** (V1 and V2 along the 2nd, 3rd, 4th intercostal space) type 1 Brugada pattern expressed in all the modified precordial leads. In Case 1 ECG there are no additional arrhythmic signs inside the type 1 Brugada pattern. We can identify this as a “low risk pattern”.

Figure S2. Case 2.



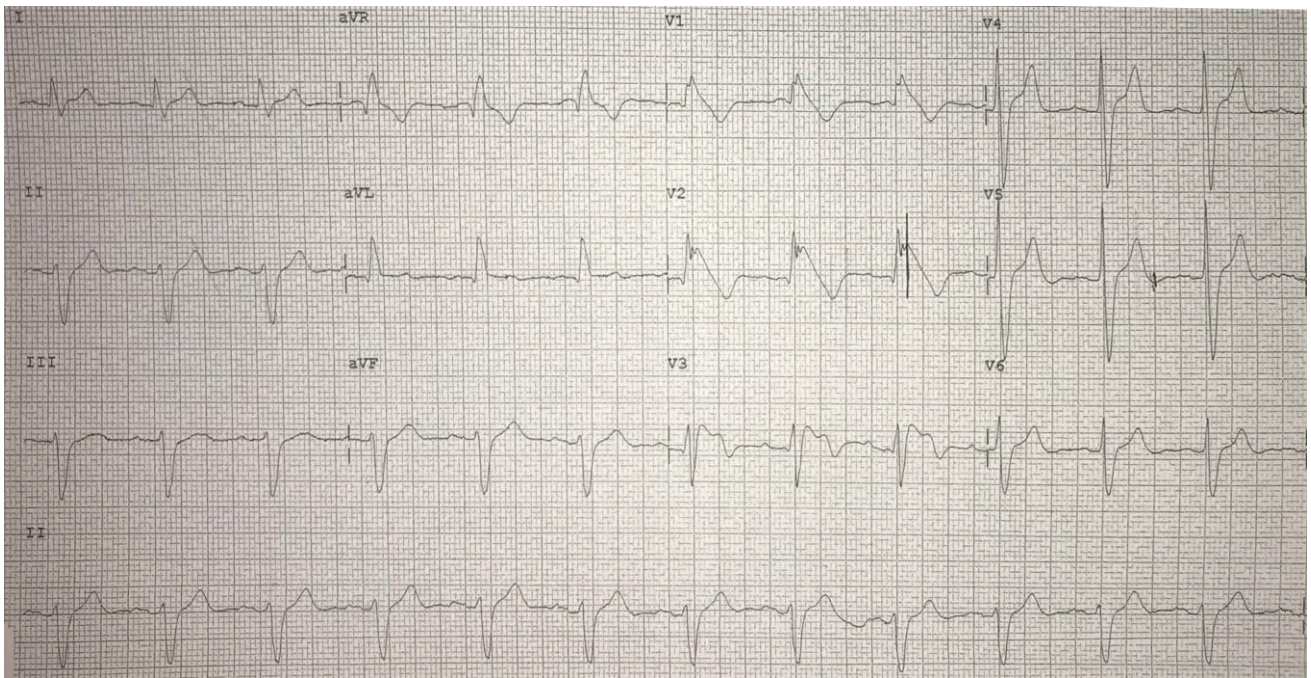
Case 2: 51 years old male with previous cardiac arrest. Multiple appropriate ICD interventions on VT/VF (one per year). Mild left ventricular hypertrophy at echocardiogram and cardiac MRI. SCN5A and Myosin gene mutations were found. **Figure S2:** (standard 12 lead ECG) normal sinus rhythm, first degree atrio-ventricular block (PR interval 340 ms), prolonged QRS duration (160 ms), left anterior hemiblock, type 1 Brugada pattern in V2 but also in lead aVR. In this ECG we have multiple arrhythmic signs as first degree AV block, prolonged QRS duration and type 1 Brugada pattern in the peripheral leads. We can identify this as “high risk pattern”.

Figure S3. Case 3.



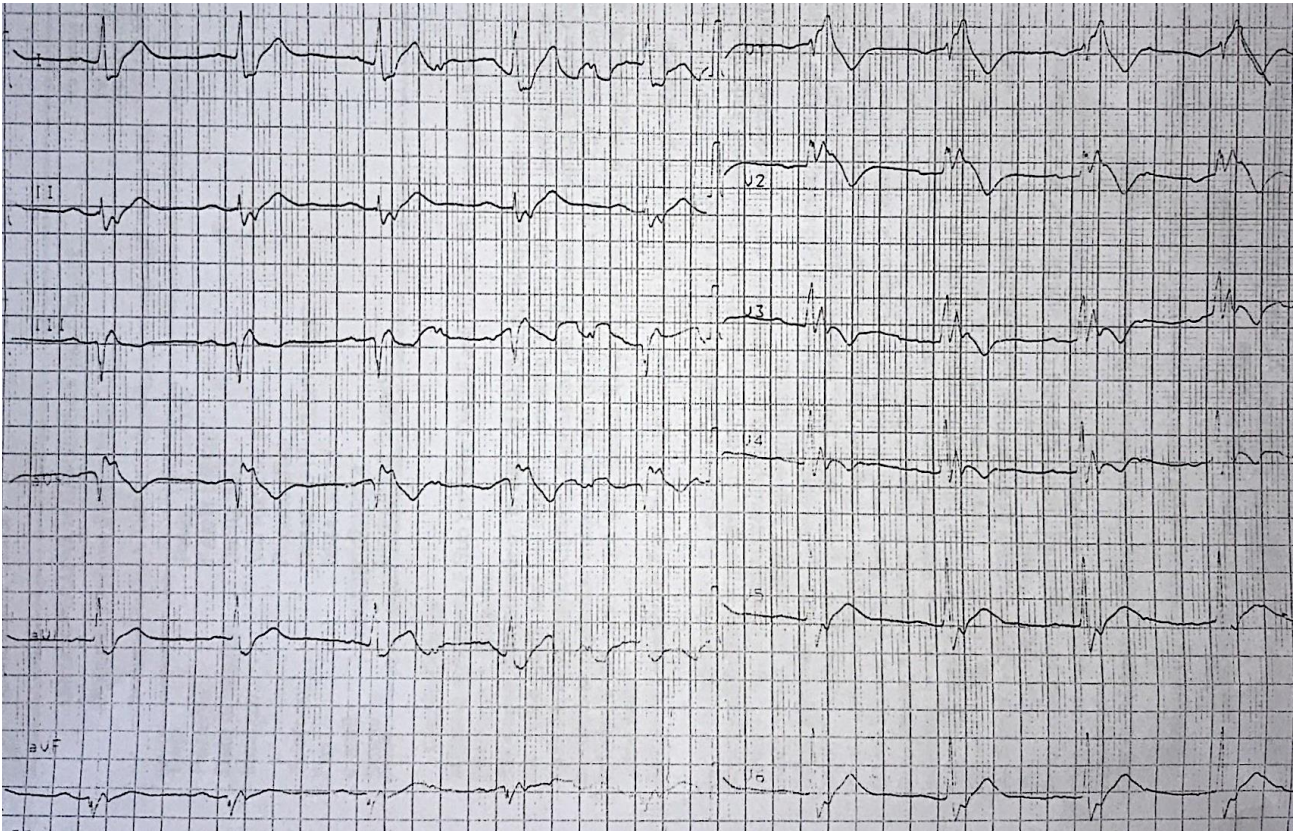
Case 3: 43 years old male with aborted cardiac death. He had multiple appropriate ICD interventions on polymorphic ventricular tachycardia. Father and paternal grandfather with sudden cardiac deaths in their forties. Normal echocardiogram and cardiac MRI. Novel pathogenic mutation in the lamin A/C gene was found⁶¹. **Figure S3:** (standard 12 lead ECG): normal sinus rhythm; normal PR interval, prolonged QRS interval in V2 (135 ms), multiple notching of QRS complex in right precordial leads, tall R wave in lead aVR, deep S wave in V5 - V6 and DI, type 1 Brugada pattern in V1 - V2. In this ECG we have multiple arrhythmic signs as prolonged QRS duration in V2, fragmented QRS, aVR sign and deep S wave in lateral leads. We can identify this as “high risk pattern”.

Figure S4. Case 4.



Case 4: 74 years old man with ICD placed when he was 55 years old after ventricular arrhythmias induced during programmed electrical stimulation. He had only one appropriate ICD intervention for VF in his follow-up. He has paroxysmal atrial fibrillation. No family history of sudden cardiac death. Normal echocardiogram. No gene mutations found. **Figure S4:** (standard 12 lead ECG) normal sinus rhythm, first degree atrio-ventricular block (PR interval 220 ms), prolonged QRS duration (140 ms), left anterior hemiblock, fragmented QRS in right precordial leads, tall R wave in lead aVR, profound S wave in V5 - V6 and DI, Tzou criteria, type 1 Brugada pattern in V1 - V2 and type 2 Brugada pattern in V3. In this ECG, similar to Case 2 ECG, we have multiple arrhythmic signs as first degree AV block, prolonged QRS duration, fragmented QRS, aVR sign, Tzou criteria and deep S wave in lateral leads. We can identify this as “high risk pattern”.

Figure S5. Case 5.



Case 5: 55 years old man with aborted sudden cardiac while sleeping. No ICD interventions during follow-up. No history of familiar sudden death. Normal echocardiogram and cardiac MRI. SCN5A gene mutation was found. **Figure S5:** (standard 12 lead ECG) normal sinus rhythm, first degree atrio-ventricular block (PR interval 240 ms), prolonged QRS duration in V2 and DII (180 ms), fragmented QRS in right precordial leads, tall and prolonged R wave in lead aVR, deep S wave in V5 - V6 and DI - aVL, Tzou criteria, high depolarization dispersion, type 1 Brugada pattern in V1 - V2. Here we have almost all the arrhythmic signs as first degree AV block, prolonged QRS duration, fragmented QRS, aVR sign, Tzou criteria and deep S wave in lateral leads. We can identify this as a “very high risk pattern”.