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Spontaneous type 1 pattern, ventricular arrhythmias and sudden cardiac death in Brugada Syndrome: an updated systematic review and meta-analysis

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Brugada syndrome (BrS) is primary electrical disorder characterized by ST segment elevation with right bundle branch block morphology in patients with apparent structurally normal hearts.[1] It predisposes affected individuals to ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD).[2] A number of studies have identified risk factors that are associated with a more malignant course of disease. These include male gender, syncope, a spontaneous type 1 ECG pattern, family history of SCD, family history of Brugada syndrome, loss-of-function mutations in the SCN5a gene, inducible VT/VF during programmed electrical stimulation. Of these risk factors, many studies have demonstrated that the presence of a spontaneous type 1 pattern is associated with a significantly higher risk of VT/VF or SCD, but other studies have demonstrated a lack of significant predictive value.

Three meta-analyses have addressed the prognostic value of a spontaneous type 1 Brugada pattern. Firstly, Letsas, *et al*.[3] examined its predictive value in six studies involving 2219 asymptomatic patients only, demonstrating a 3.6-fold increase in the risk of future arrhythmic events. Secondly, Wu, *et al*.[4] examined only prospective studies (n = 8) that included 1150 patients, demonstrating a 4-fold increase in the risk. Finally, Gehi, *et al*.[5] examined also only prospective studies (n = 3) in 935 patients, demonstrating a relative risk of 4.7. In this study, we performed an updated systematic review and meta-analysis, which includes the largest number of studies and patient numbers.

PubMed and Embase were searched for studies that investigated the association between a spontaneous type 1 Brugada pattern on the ECG and ventricular arrhythmias and SCD in Brugada syndrome. The following search terms were used for both databases: "Brugada syndrome spontaneous type 1". The search period was from the beginning of the database through to 30th June 2017 without language restrictions. The following inclusion criteria were used: (1) the study was a case-control, prospective or retrospective cohort study in human subjects with a Brugada phenotype; and (2) data on the relationship between a type 1 pattern and adverse events (appropriate implantable cardioverter defibrillator shocks, VT/VF, and SCD) were reported.

A total of 139 and 10 entries were retrieved from PubMed and Embase, respectively. After reference trawling and excluding overlapping populations, a total of 6561 Brugada patients from 24 studies were included.[6–29] The mean age was 44 ± 16 years and 73% of the patients were male, with a mean follow-up of 50 ± 36 months. Table 1 shows the baseline characteristics of these studies and the study populations. Quality analysis of the included studies

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Table 1. Characteristics of the studies included in this meta-analysis.

Studies	Study design	Sample size (*n*)	Age	Males	Endpoints	Follow-up duration (months)	Univariate or multivariate	Multivariate variables
Kitamura T, *et al*.[8]	R	304	30	169	VT/VF	91	U	-
Sieira J, *et al*.[9]	P	400	41	233	SCD + ICD Shock	81	U	-
Andorin A, *et al*.[13]	R	106	11	58	SCD + ICD Shock + VT/VF	54	M	Age and ICD
Casado-Arroyo R, *et al*.[11]	P	447	45	336	SCD + ICD Shock + VT/VF	50	U	-
Kawazoe H, *et al*.[12]	R	143	46	140	VF	83	U	-
Rivard L, *et al*.[10]	R	105	46	83	aSCD + appropriate ICD shocks	60	M	Max Tp-e and QRS in lead 6
Conte G, *et al*.[16]	P	176	43	118	Appropriate ICD shocks	84	U	-
Dores H, *et al*.[15]	R	55	42	30	Appropriate ICD shocks	74	U	-
Maury P, *et al*.[14]	R	325	47	258	SCD + appropriate ICD shocks	48	M	Sp1 ST elevation, SCN5A mutation, family history of SCD, QRS duration, Max Tp-e
Okamura H, *et al*.[17]	R	218	46	211	SCD + appropriate ICD shocks	78	M	Sp1, Syncope, inducibility of VF (PES+)
Son MK, *et al*.[19]	R	69	48	68	Appropriate/inappropriate ICD shocks	57	M	Age, presence of palpitations, sVT before implantation of ICD
Tokioka K, *et al*.[18]	R	246	48	236	SCD + ICD Shock + VF	45	U	-
Hiraoka M, *et al*.[20]	P	460	52	432	SCD + VF	43	U	-
Daoulah A, *et al*.[21]	R	25	32	25	Appropriate ICD shocks	41	NA	-
Delise P, *et al*.[23]	P	320	43	258	SCD + VF	40	M	Syncope, basal type 1 ECG
Nishii N, *et al*.[22]	P	108	49	10	Appropriate ICD shocks	72	U	-
Probst V, *et al*.[25]	R	1029	45	745	SCD + appropriate ICD shocks	32	M	Symptoms at diagnosis (aSCD/asymptomatic/syncope), Sp1, age, gender, EPS
Richter S, *et al*.[24]	P	186	43	115	aSCD + appropriate ICD shocks + VF	57	U	
Giustetto C, *et al*.[27]	P	166	42	138	aSCD + appropriate ICD shocks + VF	30	U	-
Kamakura S, *et al*.[26]	R	330	51	315	SCD + VF	49	U	-
Benito B, *et al*.[28]	P	384	46	272	SCD + VF	58	M	Gender, previous AF, symptoms at diagnosis (syncope, aSCD), Sp1, EPS
Eckardt L, *et al*.[29]	R	212	45	152	Appropriate ICD shocks + VF	40	U	-
Brugada J, *et al*.[6]	P	547	41	408	SCD + VF	24	M	Gender, Sp1, syncope, EPS (inducible)
Priori SG, *et al*.[7]	P	200	41	152	Cardiac arrest	34	U	-

AF: atrial fibrillation; aICD: appropriate implantable cardioverter defibrillator; aSCD: aborted sudden cardiac death; EPS: electrophysiological study; ICD: implantable cardioverter defibrillator; M: multivariate; NA: not available; P: prospective; R: retrospective; sVT: sustained ventricular tachycardia; U: univariate; VF: ventricular fibrillation.

by using the Newcastle-Ottawa Scale was shown in Table 2. The main finding of our meta-analysis is that the presence of a spontaneous type 1 pattern on the ECG confers 2.3 times the risk of ventricular arrhythmias or SCD in Brugada syndrome. There was a low level of heterogeneity ($I^2 = 42\%$) with significant publication bias (Kendall's tau = 0.37, $P < 0.05$).

The ECG is a simple and non-invasive test that provides information on cardiac electrophysiological properties of the test subjects. A spontaneous Brugada pattern indicates the presence of both depolarization and repolarization abnor-

Table 2. NOS risk of bias scale for included cohort studies.

Studies	Selection				Outcome				
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability	Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up	Total score (0–9)
Priori SG, *et al*.[7]	1	0	1	0	0	1	1	1	5
Brugada J, *et al*.[6]	1	0	1	1	0	1	1	1	6
Benito B, *et al*.[28]	1	0	1	1	0	1	1	1	6
Delise P, *et al*.[23]	1	0	1	1	2 (gender, family history of SCD)	1	1	1	8
Probst V, *et al*.[25]	1	0	1	1	0	1	1	1	6
Nishii N, *et al*.[22]	1	0	1	1	0	1	1	1	6
Daoulah A, *et al*.[21]	1	0	1	0	0	1	1	1	5
Hiraoka M, *et al*.[20]	1	0	1	1	2 (gender, family history of SCD)	1	1	1	8
Son MK, *et al*.[19]	1	0	1	0	1 (gender)	1	1	1	6
Tokioka K, *et al*.[18]	1	0	1	0	1 (family history of SCD)	1	1	1	6
Conte G, *et al*.[16]	1	0	1	1	2 (gender, family history of SCD)	1	1	1	8
Dores H, *et al*.[15]	1	0	1	0	2 (gender, family history of SCD)	1	1	1	7
Okamura H, *et al*.[17]	1	0	1	0	2 (gender, family history of SCD)	1	1	1	7
Andorin A, *et al*.[13]	1	0	1	1	2 (gender, family history of SCD)	1	1	1	8
Casado-Arroyo R, *et al*.[11]	1	0	1	1	2 (gender, family history of SCD)	1	1	1	8
Kawazoe H, *et al*.[12]	1	0	1	0	2 (gender, family history of SCD)	1	1	1	7
Rivard L, *et al*.[10]	1	0	1	1	1 (gender)	1	1	1	7
Kitamura T, *et al*.[8]	1	0	1	0	2 (gender, family history of SCD)	1	1	1	7
Sieira, *et al*.[9]	1	0	1	1	1 (gender)	1	1	1	7

NOS: Newcastle-Ottawa scale; SCD: sudden cardiac death.

malities at baseline, which represent substrates for re-entrant arrhythmogenesis.[30–32] This is in contrast to the presence of a type 2 or type 3 Brugada pattern, which can be converted to a type 1 pattern using drug challenge.[33] In addition to this type 1 characteristic pattern, detailed analyses of conduction and repolarization intervals from the 12-lead ECG can aid risk stratification.[34–37] For example, a recent meta-analysis has demonstrated that prolonged T_{peak}–T_{end} intervals, which represent a higher dispersion of repolarization, whilst another showed that fragmented QRS complex,[38] which indicates dispersion of conduction, are associated with higher risk of ventricular arrhythmias and sudden death in Brugada syndrome. Our meta-analysis shows patients with spontaneous type 1 Brugada pattern are at a high risk of adverse events. The ECG is a valuable tool that can aid clinicians to identify such high-risk individuals, who will require primary prevention by implantable cardioverter-defibrillator insertion.

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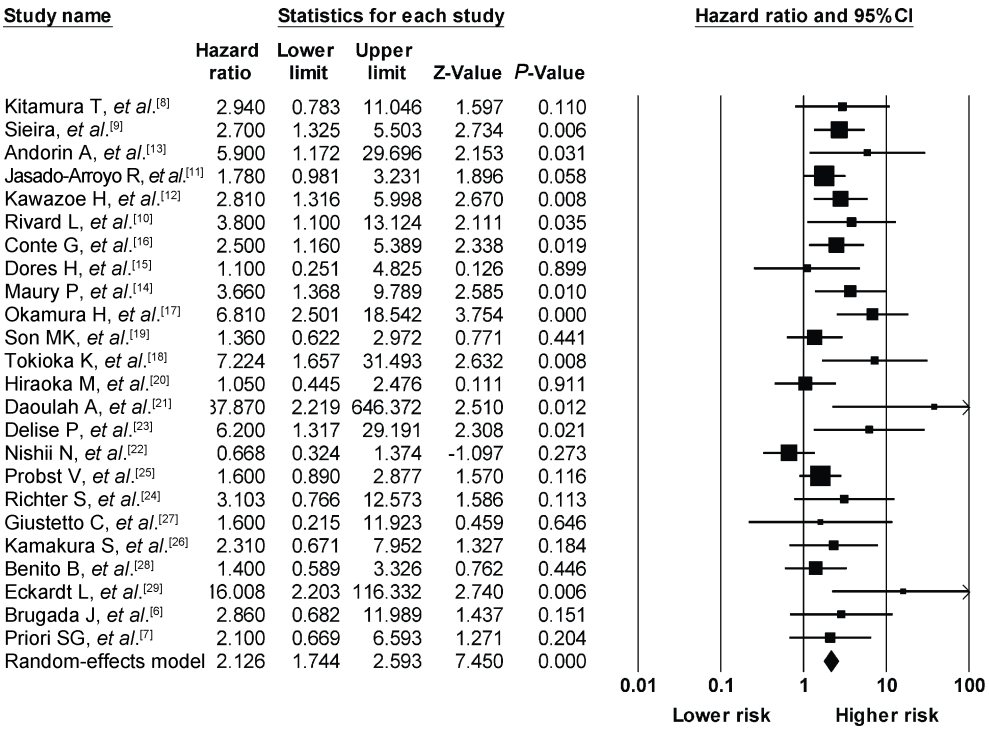

Figure 1. Forest plot demonstrating the hazard ratios for ventricular arrhythmias and sudden cardiac death with a spontaneous type 1 Brugada pattern.

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