Systematic Review and Meta-Analysis

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Risk factors for cardiac events in patients with Brugada syndrome

A PRISMA-compliant meta-analysis and systematic review

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Abstract

Introduction: Inconsistent results have been reported about the risk stratification of patients with Brugada syndrome. We have summarized the evidence regarding the strength of association between 6 risk factors (family history of sudden cardiac death [SCD] or syncope, inducible ventricular arrhythmias on electrophysiology study [EPS], spontaneous type 1 Brugada electrocardiogram [ECG], male sex, family history of SCD, and sodium voltage-gated channel alpha subunit 5 [*SCN5A*] gene mutation) and subsequent cardiac events in Brugada syndrome patients.

Methods: Pubmed, Ovid, Embase, and the Cochrane Library were searched for studies published between January 1992 and March 2016. Only prospective studies (27 studies, 4494 patients) that reported estimates with 95% confidence intervals (CIs) of cardiac events for the 6 risk factors were included.

Results: Family history of SCD or syncope (risk ratio [RR] 4.97, 95% CI 3.96–6.23, $P < 0.001$), inducible ventricular arrhythmia on EPS (RR 3.56, 95% CI 1.30–9.74, $P = 0.01$), and spontaneous type 1 Brugada ECG (RR 4.07, 95% CI 2.23–7.41, $P < 0.001$) were associated with an increased risk of future cardiac events. Spontaneous type 1 Brugada ECG was associated with an elevated risk of future cardiac events in patients without a family history of SCD.

Conclusions: Inducible ventricular arrhythmias on EPS, spontaneous type 1 Brugada ECG, and family history of SCD or syncope indicate a high risk of future cardiac events in patients with Brugada syndrome. Spontaneous type 1 Brugada ECG significantly increased the risk of future cardiac events in patients without family history of SCD.

Abbreviations: CIs = confidence intervals, EPS = electrophysiology study, NOS = Newcastle-Ottawa Scale, PVS = programmed ventricular stimulation, RR = risk ratio, SCD = sudden cardiac death, *SCN5A* = sodium voltage-gated channel alpha subunit 5.

Keywords: Brugada syndrome, cardiac events, meta-analysis, risk factors, systematic review

1. Introduction

In 1992, the Brugada brothers first described a clinical syndrome associated with ventricular fibrillation and a high risk of sudden cardiac death (SCD).[1] This syndrome was characterized by typical ST-segment elevation in the right precordial leads (V1–V3) accompanied by a right bundle branch block.[1,2] Brugada syndrome, as it is now known, usually occurs during adulthood and rarely during childhood; the average age at the time of SCD is 41 ± 15 years.[3] The prevalence of Brugada syndrome is higher in Asian countries than in Western countries.[2] Brugada syndrome accounts for 12% of all SCDs and 20% of all SCDs in patients with structurally normal hearts.[3] Three spontaneous electrocardiogram (ECG) patterns can be observed in patients with Brugada syndrome: Type 1 is characterized by coved ST-segment elevation (≥0.2 mV) followed by a negative T wave. Type 2 is characterized by a saddleback ST-segment configuration; the beginning of the J wave coincides with the peak of the ST-segment elevation, which gradually descends. Type 3 is characterized by either a saddleback or a coved ST-segment elevation followed by a positive T wave.[3] In addition, characteristic drug-induced ECGs are observed in patients with Brugada syndrome.

Implantable cardioverter-defibrillators (ICDs) can effectively prevent SCD in patients with Brugada syndrome. Previous studies have evaluated the risk factors for future cardiac events in

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patients with Brugada syndrome to guide the recommendation for ICD implantation.[4–7] In 2008, Nof and Antzelevitch[4] concluded that male sex and inducible ventricular arrhythmias on electrophysiology study (EPS) were risk factors for SCD. The results of their study showed that men had a 5.5-fold higher risk of SCD than did women, and patients with inducible ventricular arrhythmia on EPS had an 8-fold higher risk of SCD than did patients without this risk factor. They also found that a family history of SCD was a risk factor for SCD in patients with Brugada syndrome.[4] In 2006, a meta-analysis by Gehi et al[5] revealed that factors such as male sex, a history of syncope or SCD, and a spontaneous type 1 ECG pattern predicted a more malignant natural history. In contrast, factors such as inducible ventricular arrhythmia on EPS, sodium voltage-gated channel alpha subunit 5 (*SCN5A*) gene mutation, and a family history of SCD did not increase the risk of future cardiac events.[5] In 2007, a study on the role of programmed ventricular stimulation (PVS) in patients with Brugada syndrome could not identify a significant role of PVS.[6] Furthermore, a study by Brugada et al[7] reported that patients with inducible ventricular arrhythmias on EPS did have a high risk of future cardiac events, and should undergo risk stratification.

It is important to have a comprehensive understanding of the risk stratification of patients with Brugada syndrome, so as to guide ICD implantation. To better understand the implications of risk factors such as a history of SCD or syncope, inducible ventricular arrhythmias on EPS, spontaneous type 1 ECG pattern, male sex, a family history of SCD, and *SCN5A* gene mutation in patients with Brugada syndrome, we performed an updated systematic review and meta-analysis, and quantitatively assessed the risk factors in patients with Brugada syndrome.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This systematic review and meta-analysis was done according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[8] Ethics approval was not necessary for this study, as only de-identified pooled data from individual studies were analyzed. An extensive database search was performed to identify all trials concerning patients with Brugada syndrome, from January 1992 to March 2016. Relevant studies were identified by searching the following data sources (from January 1992 to March 2016): Pubmed, Ovid, Embase, and the Cochrane Library. The query terms "Brugada" and "Brugada syndrome" were used to identify all suitable trials. To identify any other relevant studies, we hand searched all the reference lists from the identified trials and review articles. Some articles or original data were also obtained by author contact.

The literature search, data extraction, and quality assessment were performed independently by 2 reviewers (WW and LT) who reached a consensus on all of the items with a standard method. All the data were assessed for internal consistency, and disagreements were resolved by discussion among the investigators. The study inclusion criteria and exclusion criteria were as follows: the studies selected for analysis were written in English; the studies were prospective cohort studies; the studies included more than 10 patients; the studies included information about patient characteristics such as average age, proportion of male patients, and nationality of patients; risk factors such as a history of syncope or SCD, male sex, a family history of SCD, Brugada ECG type, EPS outcomes, and *SCN5A* mutation; and cardiac events such as syncope and SCD; the follow-up time with identified patients was greater than 6 months; patients with structural cardiac disease were excluded from this meta-analysis; and if multiple studies from a same research group were suitable for inclusion, only the most recent comprehensive study was used.

2.2. Data collection and quality assessment

The following information was extracted from each suitable study: year of publication, nationality of patients, number of patients, average age of patients, type of Brugada ECG, average follow-up time, risk factors, and total number of cardiac events. The risk factors in these studies included a history of syncope or SCD, male sex, a family history of SCD, spontaneous type 1 Brugada ECG, inducible ventricular arrhythmias on EPS, and presence of *SCN5A* gene mutation. Cardiac events were defined as follows: SCD induced by arrhythmia, syncope caused by arrhythmia, and occurrence of ventricular tachycardia arrhythmia or ventricular fibrillations. The standard information was extracted into a spreadsheet.

To estimate the quality of the included cohort studies, we used the Newcastle-Ottawa Scale (NOS).[9] The NOS scores ranged between 0 and 9, and were based on the following items: selection (4 items), comparability (1 item), and outcome (3 items). The data extraction and quality assessment were conducted independently by 2 authors. The information was examined and adjudicated independently by an additional author referring to the original studies.

2.3. Statistical analysis

The risk ratios (RRs) and 95% confidence intervals (CIs) were calculated from the number of events, which was extracted from each trial before data pooling. Summary estimates of the RRs were obtained using statistical software. The data were analyzed by the Mantel–Haenszel method, which is based on a fixed-effects model, when there was no significant heterogeneity among the studies. The DerSimonian and Laird meta-analytic statistical method, which is based on a random-effects model, was used for all summary estimates of the predictors of future cardiac events when there was significant heterogeneity among the studies.[10] Heterogeneity among the studies was assessed using the Q test and Higgins I^2 test. $P > 0.10$ indicated no significant heterogeneity, whereas $P \leq 0.10$ indicated significant heterogeneity for the Q statistic.[11,12] Sensitivity analyses were undertaken to determine the stability of the overall effects.[13] Subgroup analyses were conducted on the basis of spontaneous type 1 ECG, inducible ventricular arrhythmia on EPS, family history of SCD, and male sex. The Egger[14] and Begg[15] tests were also used to statistically assess publication bias. All reported P values were 2-sided, and P values <0.05 were considered statistically significant for all the included studies. Statistical analyses were performed using the Stata software (version 12.0; Stata Corporation, TX).

3. Results

The results of the study selection process are shown in Fig. 1. The initial electronic research identified 7146 articles; of these, 7071 studies that were duplicates or irrelevant were excluded. A total of 75 potentially eligible studies were selected; after reviewing the full text of each study and browsing the results, we eliminated a further 46 articles that did not meet the inclusion criteria. In addition, 2 articles were eliminated because their data were

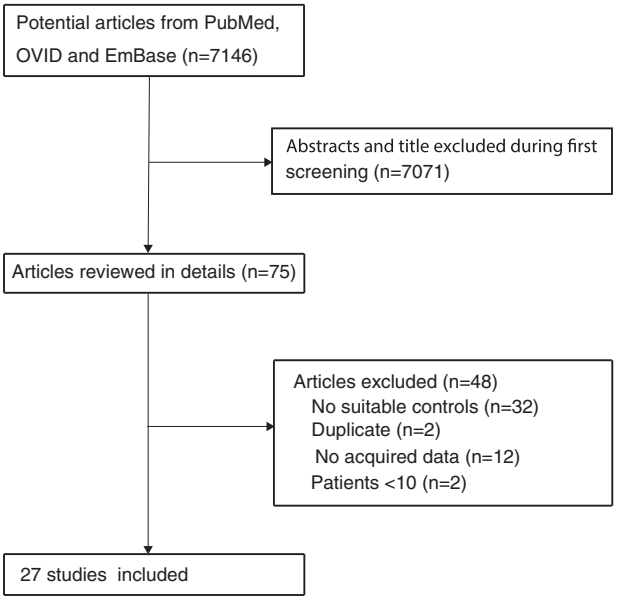

Figure 1. Flow chart of the study selection process.

identically used in a more recent, comprehensive study. Thus, finally, 27 studies with a total of 4494 patients were included in this systematic review and meta-analysis.[16–42]

Table 1 summarizes the characteristics of the included studies. These 27 articles included 1 or more risk factors, and all the studies were performed between January 2002 and December 2014. Furthermore, 71% of the patients were from Europe, 16% from Asia, and 13% from other countries. The ages of the patients ranged from 3 to 63 years, and the follow-up times ranged from 7 to 492 months in these studies. The relative percentages of male and female patients in the studies were 79% and 21%, respectively. Five studies included patients only with either spontaneous type 1 Brugada ECG or drug-induced Brugada ECG, whereas other studies included types 1, 2, or 3 Brugada ECGs. All the articles that provided prospective data about the predesigned risk factors for predicting cardiac events are outlined in Table 1. The risk factors included in the 27 studies were as follows: history of syncope or SCD in 24 studies, inducible ventricular arrhythmia on EPS in 9 studies, spontaneous type 1 Brugada ECG in 8 studies, male sex in 10 studies, family history of SCD in 7 studies, and *SCN5A* gene mutation in 2 studies. Table 2 summarizes the univariate RRs and the differences in the absolute risk of cardiac events during the follow-up time, for the risk factors studied. The NOS was used for estimating the quality of all the 27 cohort studies. Overall, 10 studies had a score of 7, 12 studies had a score of 6, and 5 studies had a score of 5 (Table 1).

A total of 24 studies comprising 4398 patients provided data about the factor of history of SCD or syncope. Considering that the heterogeneity among these studies was mild ($P=0.143$, $I^2=24.0\%$), the statistical analysis was performed with a fixed-effects model. The summary RR was found to be 4.97 (95% CI 3.96–6.23, $P<0.001$), demonstrating that this risk factor was associated with an increased risk of future cardiac events (Fig. 2).

A total of 9 studies comprising 1213 patients provided extractable data about the factor of inducible ventricular arrhythmia on EPS. Owing to the significant heterogeneity among these studies ($P=0.001$, $I^2=69.0\%$), a random-effects model was used for the pooled analysis. The summary RR was found to be 3.56 (95% CI 1.30–9.74, $P=0.013$), demonstrating that an inducible ventricular arrhythmia on EPS was associated with an increased risk of future cardiac events (Fig. 3A).

A total of 8 studies comprising 830 patients provided extractable data about the factor of spontaneous type 1 Brugada ECG. Because of significant heterogeneity among the studies ($P=0.003$, $I^2=67.8\%$), a random-effects model was used for the pooled analysis. The summary RR was found to be 2.78 (95% CI 1.00–7.71, $P=0.050$). After removing the study by Delise et al[18] for sensitivity analysis, the result changed from significant heterogeneity among the former 8 studies to no heterogeneity among the latter 7 studies ($P=0.507$, $I^2=0.0\%$). The new summary RR was found to be 4.07 (95% CI 2.23–7.41, $P<0.001$), indicating that the factor of spontaneous type 1 Brugada ECG was associated with a statistically increased risk of future cardiac events (Fig. 3B).

A total of 10 studies comprising 883 patients provided extractable data about the factor of male sex. Significant heterogeneity was observed among the studies ($P=0.010$, $I^2=58.5\%$); therefore, a random-effects model was selected for the pooled analysis. The summary RR was found to be 1.31 (95% CI 0.51–3.37, $P=0.576$), demonstrating that the factor of male sex had little or no effect on the risk of future cardiac events (Fig. 4A).

A total of 7 studies comprising 989 patients provided suitable data about the factor of family history of SCD. No heterogeneity was observed among the studies ($P=0.589$, $I^2=0.0\%$); therefore, a fixed-effects model was used for the pooled analysis. The summary RR was found to be 0.88 (95% CI 0.56–1.39, $P=0.589$), demonstrating that this factor was not associated with an increased risk of future cardiac events (Fig. 4B).

A total of 2 studies comprising 221 patients provided data on the risk of cardiac events associated with the factor of *SCN5A* gene mutation. No heterogeneity was observed among the studies ($P=0.733$, $I^2=0.0\%$); therefore, a fixed-effects model was used for the pooled analysis. The summary RR was found to be 0.62 (95% CI 0.28–1.39, $P=0.246$), indicating that the factor of *SCN5A* gene mutation had no significant effect on future cardiac events (Fig. 4C).

A total of 6 studies comprising 2295 patients without a history of SCD were included for subgroup analysis. Four risk factors, namely, spontaneous type 1 ECG, inducible ventricular arrhythmia on EPS, a family history of SCD, and male sex, were included in the subgroup analyses. The data are presented in Table 3. The risk of cardiac events was analyzed for patients with spontaneous type 1 Brugada ECG. The summary RR was found to be 2.64 (95% CI 1.22–5.22, $P=0.01$), demonstrating that this factor was associated with an increased risk of future cardiac events. For the risk of cardiac events in patients with inducible ventricular arrhythmia on EPS, the summary RR was found to be 2.72 (95% CI 0.97–7.62, $P=0.06$), indicating that this factor did not significantly increase the risk of future cardiac events. In addition, the summary RRs were found to be 0.59 (95% CI 0.20–1.68, $P=0.32$) for the factor of family history of SCD and 2.33 (95% CI 0.53–10.28, $P=0.26$) for the factor of male sex. Finally, the Egger and Begg test results showed no evidence of publication bias for the 6 risk factors.

4. Discussion

Recent studies indicate that ICD implantation is associated with a high rate of complications[16,17,43]; hence, ICD implantation is not suitable for all patients with Brugada syndrome. The

Table 1

Characteristics of patients in the includedstudies.

Article year	Patients (n)	Area	Average follow-up, mos	Average age, yrs	ECG Type	Risk factor	Total events(n)	NOS
2010[19]	1029	FINGER	31.9	46	I	SM	51	5
2003[22]	443	USA Belgium Spain	31	42.4	NA	SM EPS	65	6
2011[23]	24	Tunisian	26	40.8	I II	SM	1	5
2007[24]	30	Netherlands Germany France	37	7.5	I II III	sex SM SP *SCN5A*	3	7
2007[25]	166	Japan	37	53	NA	SM	13	6
2014[26]	90	in northeastern Thailand	57.6	46	NA	SM	25	7
2003[16]	15	Korean	19	44	NA	SM sex EPS FH	6	6
2014[27]	40	Belgium	83	8	I II	NA	2	5
2013[28]	41	Japan	76	48	NA	SM	5	6
2011[29]	33	USA	7.9	46.4	I II III	SM	2	7
2002[30]	334	Spain Belgium	33	42	NA	SM	74	6
2007[31]	47	Holland Belgium	47.5	44.5	I II III	sex SM SP FH EPS	7	7
2005[20]	212	Netherlands Germany France	40	45	I	SM SP FH EPS	9	7
2009[32]	330	Japan	48.7	51.4	NA	SM	24	6
2012[33]	43	Denmark	43	48	NA	NA	9	5
2006[34]	12	IRAN	27.8	46.5	NA	SM sex	2	5
2002[21]	200	Italy	492	41	NA	sex SM *SCN5A* FH EPS	22	6
2012[35]	25	Gulf	41.2	32	I II	SM sex	3	6
2013[17]	378	France Japan	77	46	NA	SM	46	7
2008[36]	59	Israel	45	44.1	I II III	SM	5	6
2014[37]	69	Korean	59	46.2	I II III	SM	19	6
2013[38]	69	Japan	43	30	I	SM sex FH EPS SP	8	7
2011[18]	320	Italy	40	43	I	SM SP EPS	17	7
2009[39]	166	Italy	30	45	I	SM EPS SP Sex FH	9	6
2011[40]	280	Belgium Spain	59	41	I II	sex SM SP FH	18	7
2010[41]	26	international	60.7	43.2	I II III	SM sex SP	2	6
2002[42]	13	Japan	36	52.4	NA	sex EPS	1	7

EPS = electrophysiological study, FH = family history of SCD, N = patients numbers, NA = not applicable, *SCN5A* = *SCN5A* gene mutation, SM = symptom (sudden cardiac death or syncope), SP = spontaneous type1 ECG.

survivors of cardiac arrest are recommended to apply ICD therapy, which is attributed to the assessment of ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia to confirm the cause of the event and rule out any completely reversible causes (level of evidence: A). In addition, the criteria of level A evidence for ICD therapy is not available to patients without a history of suffering from SCD.[3] It is important to have a more comprehensive understanding of the risk stratification of patients with Brugada syndrome, so as to guide therapy with ICD implantation. The present quantitative review, including more than 4400 individuals, suggests that risk factors such as inducible ventricular arrhythmias on EPS, spontaneous type 1 Brugada ECG, and history of SCD or syncope are associated with an increased risk of cardiac events, and that patients with such factors should undergo ICD implantation to prevent SCD. The findings of this study are not consistent with the results of some other trials.[4–6] The results in this study revealed that patients with a history of SCD or syncope and those with inducible ventricular arrhythmias on EPS had 4.97-fold and 3.56-fold increased risks of cardiac events, respectively. In addition, patients with spontaneous type 1 Brugada ECG had a 2.78-fold increased risk of cardiac events. However, the risk of cardiac events did not statistically increase in patients with the following risk factors: male sex, family history of SCD, or *SCN5A* gene mutation.

In this study, a history of SCD or syncope was associated with an increased risk of future cardiac events. The HRS (Heart Rhythm Society)/EHRA (European Heart Rhythm Association)/APHRS (Asia Pacific Heart Rhythm Society) Expert Consensus Statement for ICD implantation in patients with Brugada syndrome states that ICD therapy is indicated for patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia (level of evidence: A).[3] Subgroup analyses in patients without a family history of SCD showed that spontaneous type 1 ECG was associated with an elevated risk of future cardiac events. A few researchers have focused on the risk factors for future cardiac events in asymptomatic patients with Brugada syndrome. One study[18] has indicated that it is not a single clinical factor, but multiple factors such as history of syncope or SCD, family history of SCD, and inducible ventricular arrhythmias on EPS that could help identify whether a patient without previous cardiac arrest is at a high risk of future cardiac events.[18] A recent study reported that in asymptomatic patients, a spontaneous diagnostic ECG pattern or inducible ventricular arrhythmias during PVS were associated with an increased risk of future cardiac events.[19] No consensus has as yet been reached on the risk factors for future cardiac events in patients without a history of SCD.

We found that inducible ventricular arrhythmias on EPS were associated with a greater risk of future cardiac events in patients with Brugada syndrome. However, the risk of cardiac events did not statistically increase with this factor in previous studies.[5,6] Therefore, the value of this risk factor for predicting cardiac events in patients with Brugada syndrome remains controversial. In 2007, a study on the role of PVS in patients with Brugada syndrome concluded that the results were unable to identify a

Table 2

Summary risk ratio and difference in risk of events (syncope, sudden cardiac death) rate in patients.

Risk factor	Summary relative risk (95% CI)	Summary risk difference (%) (95% CI)	Average follow-up, mos	N (studies)	N (patients)	PI^2
Men	1.31 [0.51, 3.37]	0.07 [0.01, 0.13]	81	11	883	0.58 58%
History of SCD and syncope	4.97 [3.96, 6.23]	0.15 [0.13,0.17]	40	24	4398	$P<0.00001$ 24%
Inducible at EPS	3.56 [1.30, 9.74]	0.12 [0.04,0.21]	32	9	1213	0.01 69%
Family history of SCD	0.88 [0.56, 1.39]	−0.01 [−0.05,0.03]	40	7	1035	0.36 0%
Spontaneous type 1 Brugada ECG	2.78 [1.00, 7.71]	0.08 [0.01, 0.16]	44	8	280	0.05 68%
SCN5A mutation	0.62 [0.28, 1.39]	−0.05 [−0.13, 0.03]	39	2	221	0.25 0%

CI = confidence interval, ECG = electrocardiogram, EPS = electrophysiological study, N = number, SCD = sudden cardiac death, *SCN5A* = sodium voltage-gated channel alpha subunit 5.

significant role for PVS.[6] The studies conducted by Eckardt et al[20] and Priori et al[21] supported the idea that patients with inducible ventricular arrhythmias on EPS did not have a high risk of future cardiac events. Conversely, Shimizu[45] suggested that Brugada syndrome patients who had a history of syncope and inducible ventricular arrhythmias on EPS had a high risk of future cardiac events, and had sufficient evidence (class 1) for ICD implantation. Brugada et al[22] reported that patients with inducible ventricular arrhythmias on EPS did have a high risk of future cardiac events, and should undergo risk stratification. The differences in the findings of the aforementioned studies may be attributable to differences in the number of trials and patients, which may have contributed to the value of risk stratification in patients with Brugada syndrome. The present meta-analysis included 9 articles comprising 1213 patients, which provided more sufficient data than did former studies.

The relationship between spontaneous type 1 Brugada ECG and future cardiac events was not initially obvious in our study.

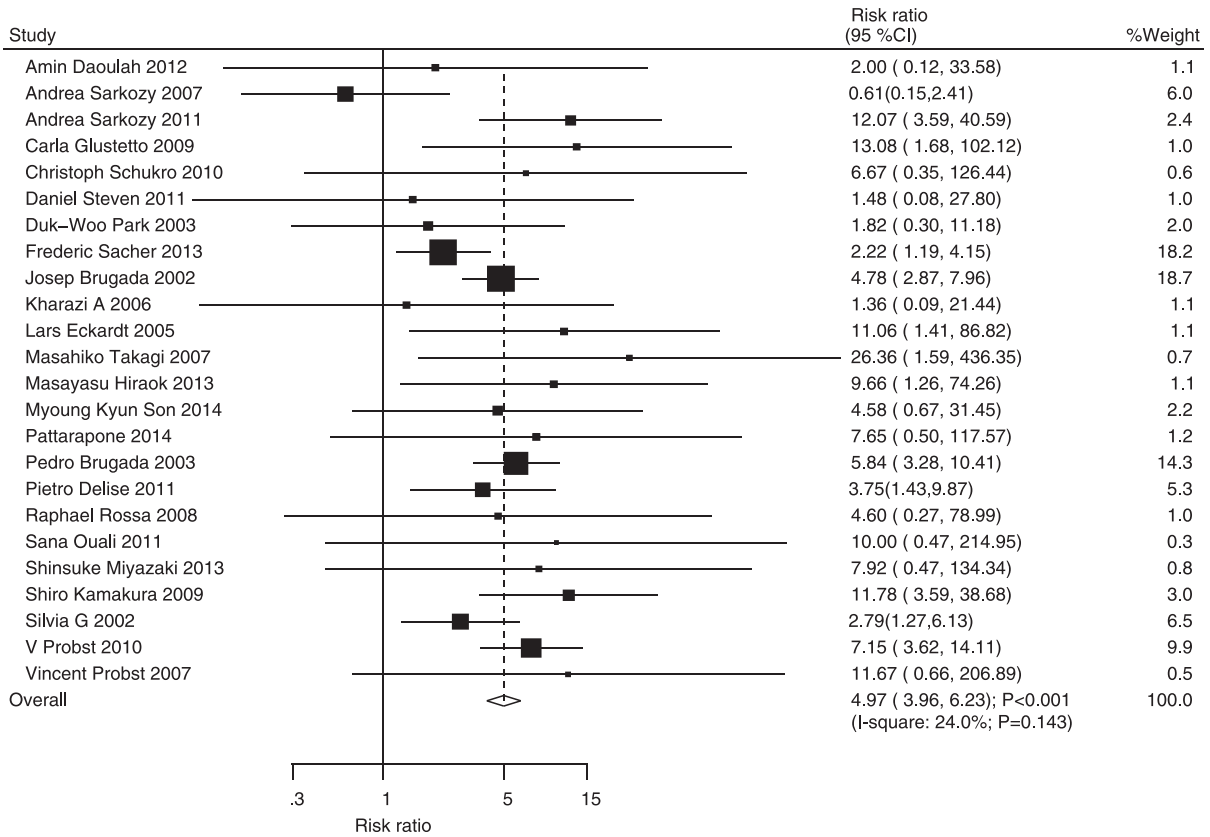

Figure 2. Forest plots of RR with 95% CI for the factor of SCD or syncope. CI = confidence interval, FE = fixed-effects model, RE = random-effects model, RR = risk ratio, SCD = sudden cardiac death.

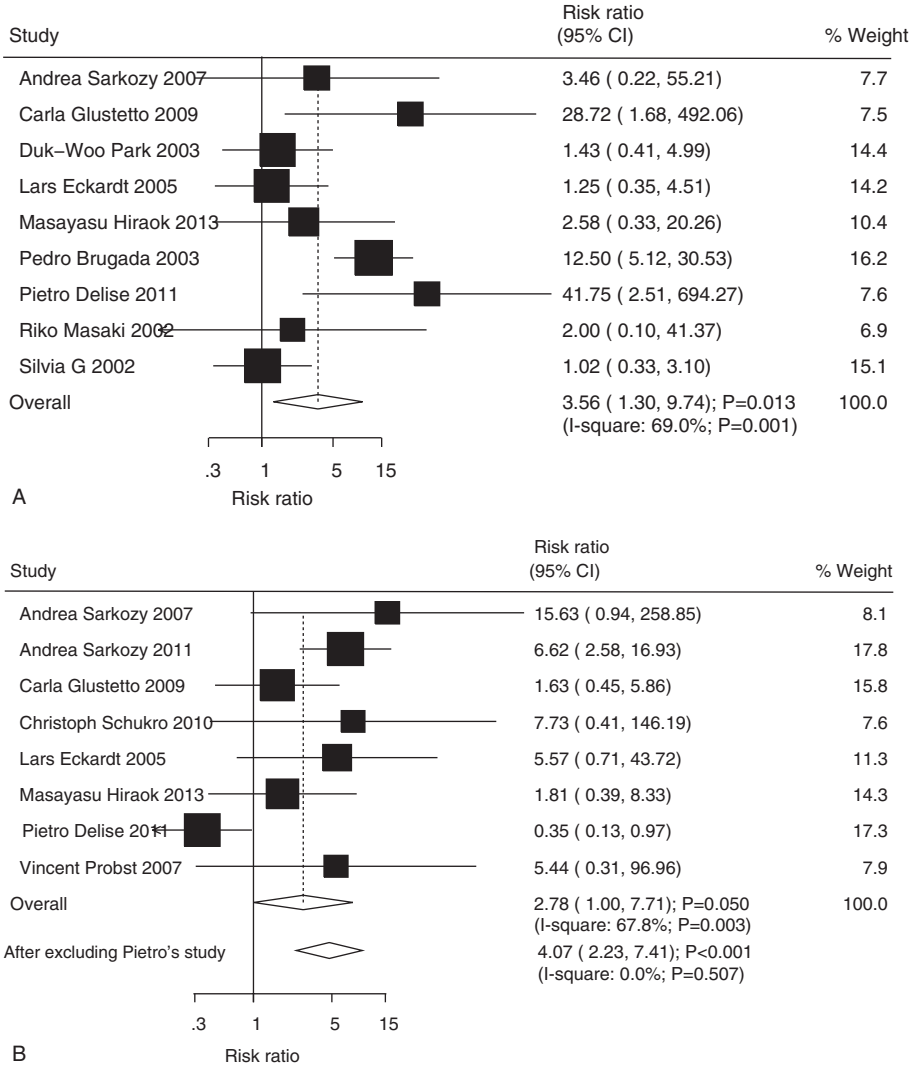

Figure 3. Forest plots of RR with 95% CI for the factors of inducible ventricular arrhythmia on EPS (A) and spontaneous type 1 Brugada ECG (B). CI = confidence interval, ECG = electrocardiogram, EPS = electrophysiological study, FE = fixed-effects model, RE = random-effects model, RR = risk ratio.

The summary RR for this factor was 2.78 (95% CI 1.00–7.71, $P = 0.050$) in our study. It is worth noting that we found significant heterogeneity among the studies reporting on this factor ($I^2 = 67.8\%$). The analysis was repeated after removing the study by Delise et al, and the outcome thus obtained was consistent with that of a 2006 meta-analysis. The new RR was 4.07 (95% CI 2.23–7.41, $P < 0.001$). Although this result was consistent with the previous study, a small difference between the former study and this meta-analysis persisted. Only spontaneous type 1 Brugada ECG was assessed in this meta-analysis, whereas 3 types of spontaneous Brugada ECG patterns were included in the former study, and only drug-induced Brugada ECG patterns were eliminated. Furthermore, Rollin et al[44] concluded that type 1 ST elevation in the peripheral ECG leads can be seen in 10% of patients with Brugada syndrome, and is an independent predictor of a malignant arrhythmic event.

The findings of this meta-analysis suggested that the risk of cardiac events was not statistically increased in male patients. However, previous meta-analyses have reported inconsistent results. In 2008, Nof and Antzelevitch[4] concluded that male sex was a risk factor for SCD, as they found that men had a 5.5-fold higher risk of SCD than did women. In 2006, a meta-analysis by Gehi et al[5] showed that male sex predicted a more malignant natural history. More recently, a study by Brugada et al[2] concluded that male patients were more often symptomatic than female patients, probably owing to the influence of hormones and ion-channel distribution across the heart. However, male sex was found not to be associated with the risk of cardiac events in Brugada syndrome patients in this study because only a few studies that focused on this factor were included in this meta-analysis.

In this study, a family history of SCD was found not to be associated with the risk of future cardiac events. This result was consistent with the results of 2 other studies. In 2008, Nof and Antzelevitch[4] concluded that a family history of SCD is not associated with a worse prognosis because a positive family history of SCD did not predict a more malignant outcome. In 2006, a meta-analysis by Gehi et al[5] indicated that a family history of SCD did not predict a more malignant natural history.

Two studies about the influence of *SCN5A* gene mutation on future cardiac events in Brugada syndrome patients were included in this meta-analysis. The results indicated that *SCN5A*

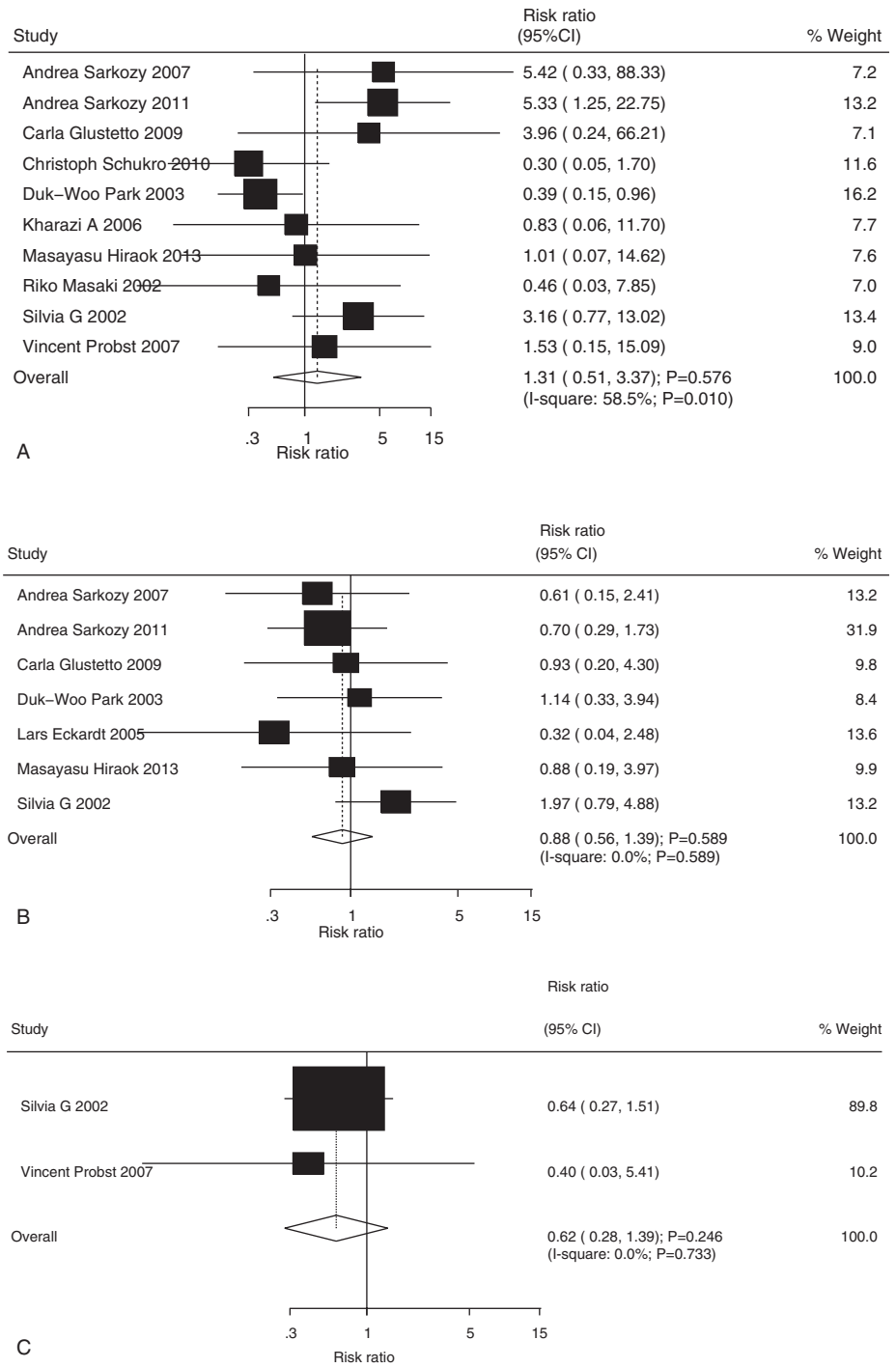

Figure 4. Forest plots of RR with 95% CI for the factors of male sex (A), history of SCD (B), and *SCN5A* gene mutation (C). CI = confidence interval, FE = fixed-effects model, RE = random-effects model, RR = risk ratio, SCD, sudden cardiac death, *SCN5A* = sodium voltage-gated channel alpha subunit 5.

gene mutation did not increase the risk of future cardiac events. The accuracy of this conclusion is limited by the low percentage of patients who were included in the present study.

The limitations of this study are as follows:

1. The patients in all of the studies were European or Asian, but none of the patients were Chinese. Hence, the clinical implications might be limited in the Chinese population.
2. Most of the studies selected for this meta-analysis had a limited number of female patients.
3. The studies in this meta-analysis included pediatric, middle-aged, and older patients. Because no subgroup analyses or further classification of these patients was done, the age characteristics could not be obtained.
4. More detailed characteristics were not reported about patients who had cardiac events during the follow-up period. As a result, we could not confirm whether the risk factors analyzed here were independent predictors for future cardiac events. In addition, assessing the interactive influence among the factors was not possible.

Table 3

The data in subgroup analysis of patients without history of SCD.

Publication year	First author		EPS+	EPS−	Male	Female	Family history+	Family history−	Spontaneous type 1 ECG+	Spontaneous type 1 ECG−	*SCN5A*+	*SCN5A*−
2003	PEDRO BRUGADA	A	152	211	NR	NR	NR	NR	NR	NR	NR	NR
		CE	25	4	NR	NR	NR	NR	NR	NR	NR	NR
2007	Vincent Probst	A	3	3	15	13	9	19	15	13	15	6
		CE	1	0	2	1	0	3	3	0	1	1
2003	Duk-Woo Park	A	4	3	7	0	5	2	4	3	NR	NR
		CE	0	1	1	0	1	0	1	0	NR	NR
2007	Andrea Sarkozy	A	38	8	35	11	26	21	23	24	NR	NR
		CE	7	0	7	0	3	4	5	2	NR	NR
2009	Shiro Kamakura	A	104	76	NR	NR	NR	NR	138	136	NR	NR
		CE	3	2	NR	NR	NR	NR	4	1	NR	NR
2006	Kharazi A	A	4	5	8	1	3	6	2	7	NR	NR
		CE	0	1	1	0	0	1	0	1	NR	NR
2014	Myoung Kyun Son	A	NR	NR	NR	NR	NR	NR	24	7	NR	NR
		CE	NR	NR	NR	NR	NR	NR	12	7	NR	NR
2011	Pietro Delise	A	96	149	NR	NR	NR	NR	174	146	NR	NR
		CE	13	0	NR	NR	NR	NR	NR	NR	NR	NR
2010	V. Probst	A	137	232	NR	NR	NR	NR	268	386	NR	NR
		CE	4	3	NR	NR	NR	NR	6	4	NR	NR

A = asymptomatic (no sudden cardiac death or syncope), CE = cardiac events (sudden death), ECG = electrocardiogram, EPS = electrophysiological study, NR = not recorded, *SCN5A* = sodium voltage-gated channel alpha subunit 5.

5. Multivariate analysis of these risk factors was not performed.

In conclusion, our findings show that Brugada syndrome patients with inducible ventricular arrhythmias on EPS, spontaneous type 1 Brugada ECG, or a history of SCD or syncope have a higher risk of future cardiac events as compared with other patients with Brugada syndrome. Furthermore, the subgroup analyses in this study indicated that spontaneous type 1 Brugada ECG significantly increased the risk of future cardiac events in patients without a history of SCD. However, other risk factors such as family history of SCD, male sex, and *SCN5A* gene mutation did not independently increase the risk of future cardiac events. These results might have clinical implications for the management of patients with Brugada syndrome, including risk stratification and the determination of the suitability of primary prevention with ICD implantation. Further clinical studies of patients with Brugada syndrome are still needed to improve the management of this patient population.

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