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Baseline Fragmented QRS Increase The Risk of Major Arrhythmic Events in Brugada Syndrome: Systematic Review And Meta-Analysis

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Abbreviations

CI	Confidence interval
ECG	electrocardiogram
fQRS	Fragmented QRS
MAE	Major arrhythmic events
RR	Risk ratio
SCD	Sudden Cardiac Death

VF	Ventricular Fibrillation
sVT	Sustained Ventricular Tachycardia

Background: Fragmented QRS reflects disturbances in the myocardium predisposing the heart to ventricular tachyarrhythmias. Recent studies suggest that fragmented QRS (fQRS) is associated with worsen major arrhythmic events in Brugada syndrome. However, a systematic review and meta-analysis of the literature has not been done. We assessed the association between fQRS and major arrhythmic events in Brugada syndrome by a systematic review of the literature and a meta-analysis.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to May 2017. Included studies were published prospective or retrospective cohort studies that compared major arrhythmic events (ventricular fibrillation, sustained ventricular tachycardia, sudden cardiac arrest, or sudden cardiac arrest) in Brugada syndrome with fQRS versus normal QRS. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate risk ratios and 95% confidence intervals.

Results: Nine studies from January 2012 to May 2017 were included in this meta-analysis involving 2360 subjects with Brugada syndrome (550 fQRS and 1,810 non-fQRS). Fragmented QRS was associated with major arrhythmic events (pooled risk ratio =3.36, 95 % confidence interval: 2.09-5.38, $p < 0.001$, I^2=50.9%) as well as fatal arrhythmia (pooled risk ratio =3.09, 95 % confidence interval: 1.40-6.86, $p = 0.005$, I^2=69.7%)

Conclusions: Baseline fQRS increased major arrhythmic events up to 3-fold. Our study suggests that fQRS could be an important tool for risk assessment in patients with Brugada syndrome.

Brugada syndrome is characterized by a type 1 coved-pattern electrocardiogram (ECG) in the right precordial leads in patients without apparent structural heart abnormalities. The disease increases the risk of ventricular arrhythmias and sudden cardiac death (SCD) (1). However, risk stratification of Brugada syndrome remains unclear leading to a clinical challenge (2). A history of cardiac arrest is a strong predictor of recurrent ventricular fibrillation (VF) up to 35-48% at 4-10 years (3, 4). Malignant syncope is considered as a moderate predictor of spontaneous VF (4), whereas familial sudden cardiac death and the presence of a SCN5A mutation is less well-defined prognostic value (2). For the ECG risk stratification, the presence of spontaneous type I ECG increases the risk for VF in all previous multivariate analysis studies (4-6). Fragmented QRS (fQRS) has been reported as potential noninvasive tool for risk stratification in various cardiac conditions (7). In

Brugada syndrome, the presence of fQRS correlates with increased risk in most of the studies (5, 8-13). However, several studies did not show significant correlation (14, 15) thus the role of fQRS has been controversial (2). We performed a meta-analysis to assess the predictive value of fQRS in precordial leads (V1-V3) for the development of major arrhythmic events (MAE) in Brugada syndrome patient.

Methods

Search strategy

Two investigators (NP and NL) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to June 2017 using a search strategy (Figure 1) that included the terms for "fragmented QRS", "QRS fragmentation" and "Brugada". Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion criteria

The eligibility criteria included the following:

(1) Cohort study (prospective or retrospective) reporting incident of major arrhythmic events (MAE) including VF, sustained ventricular tachycardia (sVT), sudden cardiac arrest, or sudden cardiac death, in Brugada syndrome patient with and without fQRS

(2) Relative risk, hazard ratio, odds ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals or sufficient raw data for the calculation were provided.

(3) Brugada syndrome participants without fQRS were used as controls.

Study eligibility was independently determined by two investigators (NK and PC) and differences were resolved by mutual consensus. Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies (16).

Data extraction

A standardized data collection form was used to obtain the following information from

each study: title of study, name of first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose the outcomes of interest (fQRS and major arrhythmic events), and average duration of follow-up with confounders that were adjusted and adjusted effect estimates with 95% confidence interval 95% confidence intervals and covariates that were adjusted in the multivariable analysis.

To ensure accuracy, all investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles.

Statistical analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. The extracted studies were excluded from the analysis if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird (17). The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic and Q statistic. For the Q statistic, substantial heterogeneity was defined as $p<0.10$. The I^2 statistic ranges in value from 0 to 100% ($I^2<25\%$, low heterogeneity; $I^2=25\%–50\%$, moderate heterogeneity; and $I^2>50\%$, substantial heterogeneity) (18). A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using funnel plot and Egger's regression test (19) ($p<0.05$ was considered significant). All data analyses were performed using the Stata SE 14.1 software from StataCorp LP.

Sensitivity analysis

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed (20). We sequentially and cumulatively excluded studies that accounted for the largest share of heterogeneity until I^2 was less than 50%. We then examined whether relative risk estimates were consistent. In accordance with Cochrane, evidence of

publication bias was examined through funnel plots if there were more than 10 available studies. Funnel plot asymmetry was further confirmed with Egger's test. If asymmetry was present, we used the trim-and-fill method to adjust for publication bias. Potential bias from clinical characteristics were analyzed with subgroup analysis and were compared with meta-regression among European versus Japanese descendants, case-control versus cohort study design, and univariate versus multivariate analysis.

Results

Description of included studies

Our search strategy yielded 24 potentially relevant articles (10 articles from EMBASE and 14 articles from MEDLINE). After exclusion of 8 duplicated articles, 16 articles underwent title and abstract review. Two were excluded at this stage since they were not cohort studies, leaving 14 articles for full-length article review. Five studies were excluded, as they were abstract presentation, potential duplicated studied population, conducted in non-Brugada syndrome patient, and paced QRS study. Therefore, 4 retrospective and 5 prospective cohort studies with 550 fQRS and 1,810 non-fQRS Brugada syndrome pateints were included in this meta-analysis. The clinical characteristics are described in Table 1.

Quality assessment of included studies

The Newcastle-Ottawa scale (0 to 9) was used to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent higher study quality. The score of each study ranged from 7 to 9 which reflected high quality of included studies. Intra-study risks of bias including study population definition, outcome definition, independent assessment of the outcome, follow up duration, selective loss during follow up, and identified limitation, were evaluated among each included study and no intra-study risk of bias was identified.

Meta-analysis results

Nine studies (550 fQRS and 1,810 non-fQRS) were included for MAE. Every study revealed an increased risk of MAE (VF, sVT, SCA, or SCD) in Brugada syndrome patients with seven meeting statistical significance (5, 8-13). However, two studies did

not show significant association (14, 15). In our meta-analysis, fQRS in the precordial leads is significantly associated with the primary outcome of MAE (risk ratio [RR] = 3.36, 95 % confidence interval [CI]: 2.09-5.38, $p < 0.001$, I^2=50.9%) (Figure 2). To evaluate subgroup of fatal arrhythmia (VF, sVT, and appropriate shock) as an outcome, there were five studies (248 fQRS and 905 non-fQRS) which only reported fatal arrhythmia: all of five studies revealed an increased risk of fatal arrhythmia among patients with fQRS with three achieving statistical significance (5, 8, 12). The pooled analysis of the secondary outcome demonstrated a statistically significant increased risk of fatal arrhythmia in patients with fQRS (RR = 3.09, 95 % CI: 1.40-6.86, $p = 0.005$, I^2=69.7%) (Figure 2). The statistical heterogeneity was substantial with I^2 of 50.9 and 69.7% for the primary and secondary outcomes, respectively. No publication bias was found from Egger test (data not shown) and funnel plot (Figure 3). Sensitivity analysis to explore heterogeneity showed no significant change in our findings when omitting each study. Cumulative analysis indicated no substantial variation of RR by publication date. For exploratory subgroup analysis, we found no difference among European versus Japanese descendants (p=0.751), case-control versus cohort study design (p=0.431), and univariate versus multivariate analysis (p=0.801).

Discussion

Brugada syndrome is a inherited arrhythmic heart disease which increases the risk of ventricular arrhythmias and sudden cardiac death (SCD) (1). Recommended prevention strategies include exercise restriction, avoidance of excessive alcohol intake, anti-arrhythmic drugs, and ICD (21). Identifying those who would benefit from ICD is challenging but an essential part of clinical decision-making. Since there is no randomized control trials or strong evidence that can be used to help decide on ICD implantation in Brugada syndrome patients, recommendations are based on cohort studies which provide relationship between clinical characteristics and prognostic outcomes.

A history of cardiac arrest (3, 4), spontaneous type I ECG (4-6), and malignant syncope (4) are well-established significant prognosis predictor of MAE in Brugada syndrome. Fragmented QRS (fQRS) has also been reported as potential noninvasive tool for risk

stratification in Brugada syndrome (9). Initially, fQRS was reported to be correlated with myocardial scar and prognosis of old myocardial infarction (22). The prognostic value of fQRS was then broadened to prediction of MAE and SCD in ischemic heart disease, non-ischemic cardiomyopathy, and various heart disease patients (7, 22, 23).

In patients with Brugada syndrome, fQRS was reported to be appear in the right precordial leads and was correlated with MAE in symptomatic patients (9). A prospective cohort study reported by Priori et al. showed that fQRS was a potential predictor of MAE in Brugada syndrome patients even without a previous history of cardiac arrest (5). The presence of fQRS correlates with increased risk in most of the studies (5, 8-13). However, the role of fQRS has been controversial (2). Because of controversial results from previous studies, the prognostic value of fQRS in predicting MAE in Brugada syndrome had come into question (2).

In the present study, we evaluated the fQRS in patients with BrS by systemic review and meta-analysis. To our knowledge, our study is the first meta-analysis to assess the predictive value of fQRS in precordial leads (V1-V3) for the development of MAE in Brugada syndrome patient. Our findings confirm that fQRS is associated with an increased risk of MAE up to 3-fold.

Our meta-analysis summarized all available evidence of MAE in Brugada syndrome from nine studies, a total of 2,360 patients (550 fQRS and 1,810 non-fQRS). Our study revealed that Brugada syndrome patients with fQRS have statistically significant increased risk of MAE compared to those without fQRS (RR = 3.36, confidence interval [CI]: 2.09- 5.38, P<0.001) as well as fatal arrhythmia (RR = 3.09, 95 % CI: 1.40-6.86, p = 0.005). To prove the validity of the result, we perform a sensitivity analysis by excluding one study at a time. The results are similar to the main result. This result stresses the importance of integrating fQRS into risk stratification of HCM for SCD in clinical practice. Fragmented QRS could be considered as a possible important factor for implantable cardioverter defibrillator implantation in Brugada syndrome patient.

Limitation

Our study is not without limitations. We limited fQRS to precordial leads V1-V3. There was no available reported data to examine fQRS in non-precordial leads as a prognostic value of MAE and SCD. Different study populations and designs were included and thus might introduce potential sources of heterogeneity. However, we found no difference among exploratory subgroup analysis in European versus Japanese descendants, case-control versus cohort study design, and univariate versus multivariate analysis. We also did not demonstrate independent predictors of SCD in AF such as age, sex, diabetes, and hypertension because of insufficient data from included studies to perform meta-analysis in these subgroups. Theses factors might introduce potential sources of heterogeneity as well. Some heterogeneity exists among studies. Nonetheless, we used sensitivity analysis methods in the random-effects model and found no difference of the imputed risk ratio and its 95% confidence interval.

Conclusion

In conclusion, our meta-analysis demonstrated that fQRS in precordial leads is a valuable predictor of MAE and SCD in Brugada syndrome patients. Fragmented QRS could be considered as a possible important factor for implantable cardioverter defibrillator implantation in Brugada syndrome patient. Further study is needed to establish its potential role in identifying the Brugada syndrome patients at highest risk of SCD.

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Figure legends

Figure 1 Search methodology and selection process

Figure 2 Forest plot of the included studies assessing the association between fragmented QRS and major arrhythmic events and fatal arrhythmia

Figure 3 Funnel plot of fragmented QRS and major arrhythmic events. Circles represent observed published studies

Table legends

Table 1 The clinical characteristics and summary of included studies

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Table 1: The clinical characteristics and summary of included studies

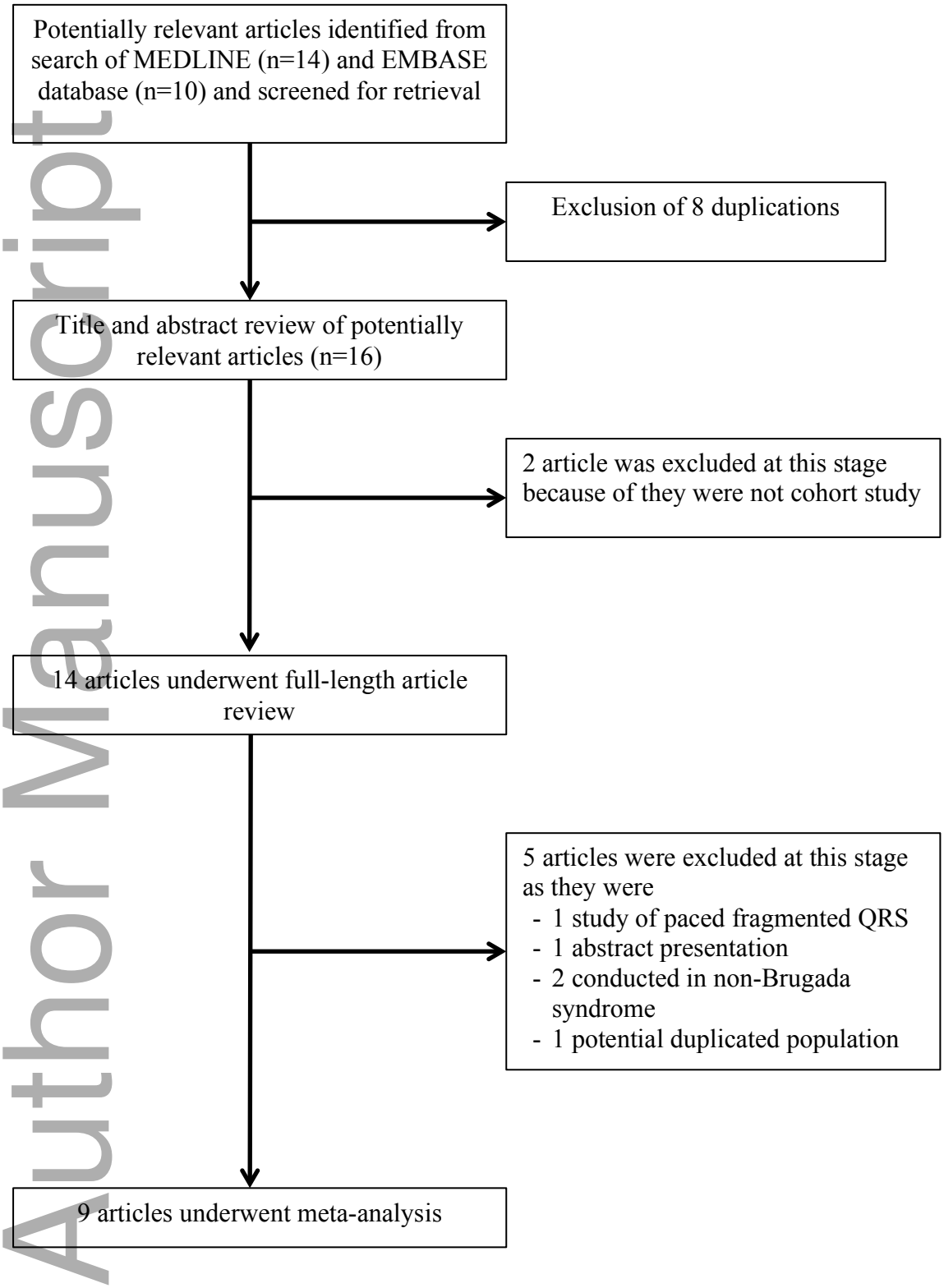
First Author	Country of Origin	Year	Study Type	Participant Description	Exclusion criteria	Total Population	Male (%)	Mean age (years)	fQRS Definition	fQRS (n)	Mean Duration of Follow up (months)	Outcome Definition	Conclusion by authors
Asmundis et al.	Belgium	2017	Prospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG	Underlying structural cardiac abnormalities	289	70	45±16	Abnormal fragmentation within the QRS complex as ≥ 4 spikes in I or ≥ 8 spikes in V1, V2, and V3	50	121.2±55.2	VF or SCD	fQRS was associated with VF/SCD
Calo et al.	Italy	2016	Prospective cohort study	Spontaneous type 1 Brugada pattern ECG	History of VF or aborted SCD	347	78.4	45±13.1	Fragmentation within the QRS complex, with ≥4 spikes in a single lead or ≥8 spikes in V1, V2, and V3	85	48±38	VF or SCD	fQRS was associated with VF/SCD
Conte et al.	Belgium	2016	Prospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG who underwent ICD therapy	Underlying structural cardiac abnormalities	176	67	40.7±16.7	Abnormal fragmentation within the QRS complex as ≥ 4 spikes in I or ≥ 8 spikes in V1,	29	95.2±51.10	Appropriate ICD shock to VF/sVT	fQRS was not associated with a higher rate of appropriate

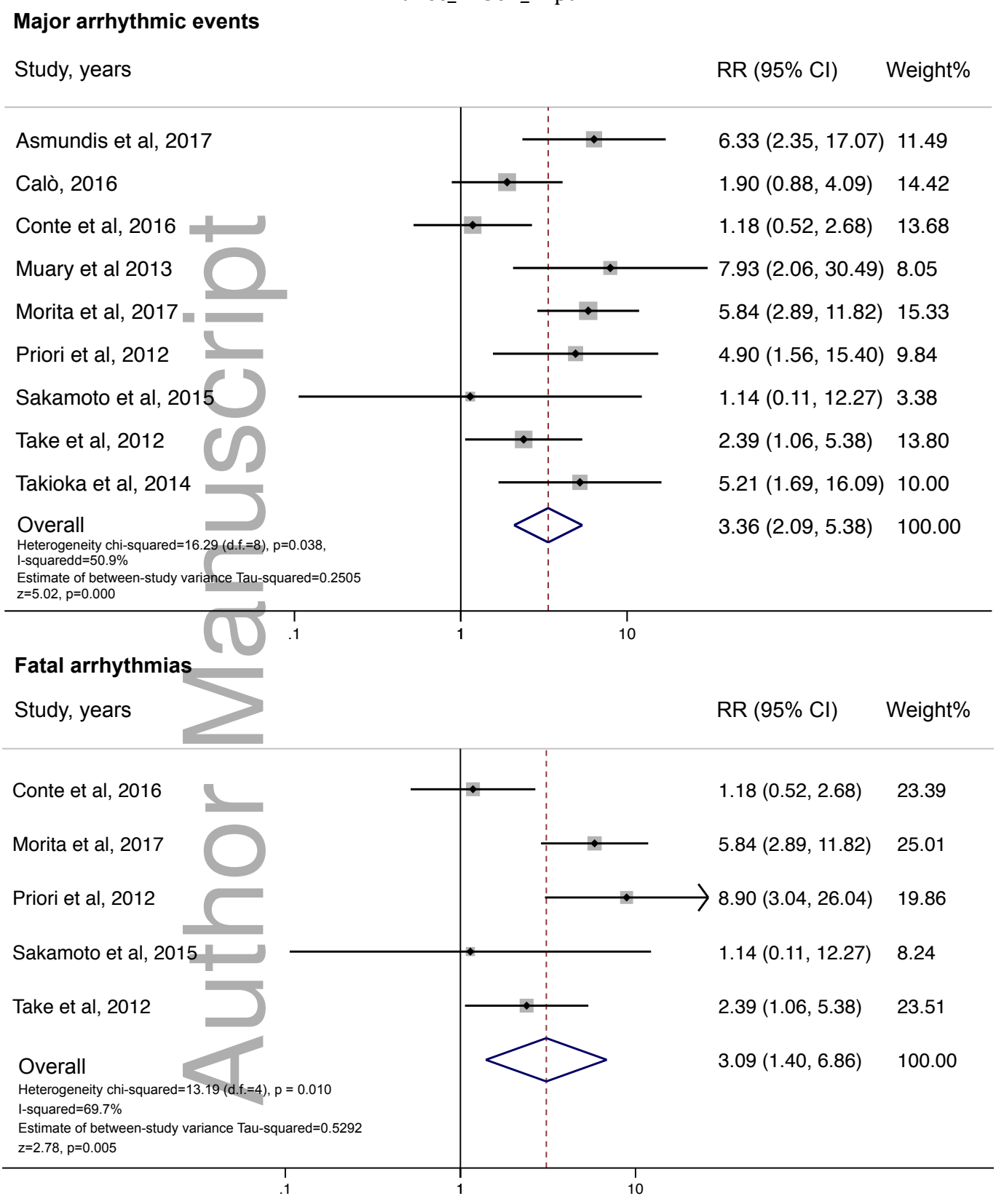
									V2, and V3				ICD shock
Maury et al.	France	2013	Retrospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG	N/A	325	79.4	47±13	Fragmented QRS in V1 to V3	8	48±34	SD	fQRS was associated with SDs
Morita et at.	Japan	2017	Retrospective cohort study	Spontaneous type 1 Brugada pattern ECG	Low quality of ECG recording and lack of ECG recording of V1 and V2	456	95	46.5±14	(1) ≥4 positive spikes in one of the leads V1 through V3 or (2) ≥8 positive spikes in all of V1, V2, and V3	229	89.5±62.1	VF	Patients with fQRS had a shorter time to arrhythmic events
Priori at al.	Italy	2012	Prospective cohort study	Patients ≥18 years old with spontaneous or drug induced type 1 Brugada pattern ECG who never had cardiac arrest and sVT	Structural cardiac abnormalities or cardiac diseases	308	80	45±12	≥ 2 spikes within the QRS complex in V1 to V3	25	36±8	VF or appropriate ICD	fQRS was associated with arrthymia events

Sakamoto et al.	Japan	2015	Prospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG	Taking antiarrhythmic drugs, abnormality in either the right or left ventricular morphology and/or function	129	94.6	52±12	(1) ≥4 positive spikes in one of the leads V1 through V3 or (2) ≥8 positive spikes in all of V1, V2, and V3	9	49.24	VF	fQRS was not associated VF
Take et al.	Japan	2012	Retrospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG with history of syncope	History of VF due to ischemic heart disease	84	97.6	47±12	Fragmented QRS in V1 to V3	37	48 ±48	VF or appropriate ICD	fQRS was associated with the occurrence of VF
Tokioka et al.	Japan	2014	Retrospective cohort study	Spontaneous or drug induced type 1 Brugada pattern ECG	N/A	246	95.9	47.6±13.6	Abnormal fragmentation within the QRS complex as ≥ 4 spikes in I or ≥ 8 spikes in V1, V2, and V3	78	45.1 ± 44.3	VF or SCD	VF/SCD episodes were more frequently observed in patients with fQRS than in those without fQRS

ECG: Electrocardiogram, ERP: Early repolarization pattern, fQRS: Fragmented QRS, ICD: Implantable cardioverter-defibrillator, N/A: Not applicable, SCD: Sudden cardiac death, SD: Sudden death, sVT: sustained ventricular tachycardia, VF: Ventricular tachycardia

Figure 1 Search methodology and selection process





*Note: RR; Risk Ratio, CI; Confidence Interval