Received: 30 June 2018 | Revised: 30 July 2018 | Accepted: 14 August 2018

DOI: 10.1002/joa3.12118

ORIGINAL ARTICLE

WILEY Journal of Arrhythmia Open Access

T_{peak}-T_{end}, T_{peak}-T_{end}/QT ratio and T_{peak}-T_{end} dispersion for risk stratification in Brugada Syndrome: A systematic review and meta-analysis

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Funding information
Croucher Foundation, Grant/Award Number: Clinical Assistant Professorship

Abstract

Background: Brugada syndrome is an ion channelopathy that predisposes affected subjects to ventricular tachycardia/fibrillation (VT/VF), potentially leading to sudden cardiac death (SCD). T_{peak}-T_{end} intervals, (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion have been proposed for risk stratification, but their predictive values in Brugada syndrome have been challenged recently.

Methods: A systematic review and meta-analysis was conducted to examine their values in predicting arrhythmic and mortality outcomes in Brugada Syndrome.

PubMed and Embase databases were searched until 1 May 2018, identifying 29 and 57 studies.

Results: Nine studies involving 1740 subjects (mean age 45 years old, 80% male, mean follow-up duration was 68 ± 27 months) were included. The mean T_{peak}-T_{end} interval was 98.9 ms (95% CI: 90.5-107.2 ms) for patients with adverse events (ventricular arrhythmias or SCD) compared to 87.7 ms (95% CI: 80.5-94.9 ms) for those without such events, with a mean difference of 11.9 ms (95% CI: 3.6-20.2 ms, $P = 0.005$; $I^2 = 86\%$). Higher (T_{peak}-T_{end})/QT ratios (mean difference = 0.019, 95% CI: 0.003-0.036, $P = 0.024$; $I^2 = 74\%$) and T_{peak}-T_{end} dispersion (mean difference = 7.8 ms, 95% CI: 2.1-13.4 ms, $P = 0.007$; $I^2 = 80\%$) were observed for the event-positive group.

Conclusion: T_{peak}-T_{end} interval, (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion were higher in high-risk than low-risk Brugada subjects, and thus offer incremental value for risk stratification.

KEYWORDS

Brugada syndrome, risk stratification, sudden cardiac death, T_{peak}-T_{end}, ventricular arrhythmia

1 | INTRODUCTION

Brugada syndrome is a used to describe the combination of specific ECG changes, the Brugada pattern, in addition to life threatening arrhythmias and sudden cardiac death (SCD).[1] Traditionally, it has been considered a congenital ion channelopathy linked to abnormalities in the cardiac sodium channel.[2,3] Recently, pathogenic mutations in other ion channels have been described. Mechanisms of arrhythmogenesis can be broadly divided into triggered activity and re-entry. Of these, re-entry is thought to be the predominant mechanism underlying increased arrhythmogenicity in Brugada syndrome requiring an increased spatial dispersion of repolarization. Such re-entrant activity may involve direct electrotonic activation during phase 2 of the cardiac action potential, as shown in pre-clinical studies using arterially perfused, canine wedge preparations,[4] or circus-type/spiral wave activity around an anatomical or functional obstacle. Regardless of the precise underlying mechanism for re-entry, this transmural dispersion of repolarization can be quantified electrocardiographically by the interval from the peak to the end of the T-wave (T_{peak}-T_{end} interval), (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion.[5,6]

However, not all studies have shown an association between higher T_{peak}-T_{end} intervals, (T_{peak}-T_{end})/QT ratio or T_{peak}-T_{end} dispersion with an arrhythmogenic phenotype in Brugada Syndrome. Recently, Mugnai and colleagues conducted one of the largest retrospective studies to date, including a total of 448 patients with spontaneous or drug induced type 1 Brugada pattern.[7] They found no statistically significant difference in all three indices between asymptomatic subjects and patients with syncope and malignant arrhythmias. Morita and colleagues also found in 471 patients no difference in T_{peak}-T_{end} intervals between patients with syncope or VT/VF and those who were asymptomatic.[8] These findings contrast with a meta-analysis published previously by some members of our group, which extracted and pooled odds or hazard ratios for the relationship between T_{peak}-T_{end} and arrhythmic and/or mortality outcomes in various clinical conditions, including Brugada Syndrome.[9] This demonstrated prolonged T_{peak}-T_{end} interval was associated with an increased risk of ventricular arrhythmias and SCD in Brugada Syndrome.

However, our previous study did not determine the absolute mean values for T_{peak}-T_{end}, nor was it possible to include the largest dataset from Mugnai and colleagues. Moreover, it did not investigate the utility of other indices such as (T_{peak}-T_{end})/QT ratio or T_{peak}-T_{end} dispersion. Therefore, we conducted a systematic review with meta-analysis into the relationships between T_{peak}-T_{end} interval, (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion and arrhythmic and/or mortality endpoints in Brugada Syndrome.

2 | METHODS

2.1 | Search strategy, inclusion and exclusion criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) statement. PubMed and Embase were searched for studies that investigated the association between T_{peak}-T_{end} or T_{peak}-T_{end} /QT with arrhythmic or mortality endpoints in Brugada syndrome. The following search terms were used for both databases: [“Tpeak-Tend” or “Tpeak-end” or “Tp-e” AND Brugada]. The databases were searched until 1 May 2018 without language restrictions. The following inclusion criteria were used: (a) the study was a case-control, prospective or

retrospective cohort study in human subjects with a Brugada phenotype, (b) T_{peak}-T_{end} intervals or (T_{peak}-T_{end}) /QT ratios were provided; (c) predefined adverse events (appropriate implantable cardioverter-defibrillator therapy [ICD], syncope, ventricular tachycardia/fibrillation [VT/VF], SCD, cardiovascular death [CVD], major adverse cardiac events [MACE]) or all-cause mortality were reported. In cases of incomplete data from the published studies, the original authors were contacted, but no replies were received.

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the included studies.[10] The NOS system evaluated the categories of study participant selection, results comparability, and quality of the outcomes. Specifically, the following characteristics were assessed: (a) representativeness of the exposed cohort; (b) selection of the non-exposed cohort; (c) ascertainment of exposure; (d) demonstration that outcome of interest was not present at the start of study; (e) comparability of cohorts based on study design or analysis; (f) assessment of outcomes; (g) follow-up periods that were sufficiently long for outcomes to occur; and (h) adequacy of follow-up of cohorts. This scale varied from zero to nine stars, which indicated that studies were graded as poor quality if the score was <5, fair if the score was 5-7, and good if the score was >8. Studies with a score equal to or higher than six were included. The details of the NOS quality assessment are shown in Tables S1 and S2.

2.2 | Data extraction and statistical analysis

Data from the different studies were entered in pre-specified spreadsheets in Microsoft Excel. All potentially relevant studies were retrieved as complete manuscripts, which were assessed fully to determine their compliance with the inclusion criteria. We extracted the following data from the included studies: (a) publication details: last name of first author, publication year and locations; (b) study design; (c) endpoint(s); (d) quality score; and (e) characteristics of the population including sample size, gender, age and number of subjects. Two reviewers (GT and MG) reviewed each included study independently. Disagreements were resolved by adjudication with input from a third reviewer (TL).

Adverse events were defined as ventricular arrhythmias (VT/VF), SCD, cardiovascular death, MACE or all-cause mortality. If more than one mortality endpoint was described, then SCD was preferentially used for analysis, followed by cardiovascular and all-cause mortality in this order. Mean differences between event-positive and event-negative groups, with 95% confidence intervals (CIs) for T_{peak}-T_{end} interval, (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion were extracted and subsequently combined to generate a pooled estimate.

Heterogeneity between studies was quantified using The Cochran's Q value and the I^2 statistic from the standard chi-square test, which describes the percentage of the variability in effect estimates resulting from heterogeneity. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if $I^2 < 50\%$. The random-effect model using the inverse variance heterogeneity method was used when $I^2 > 50\%$. To locate the origin of the heterogeneity, sensitivity analysis by excluding one study at a time, and subgroup analyses based on different disease conditions and different endpoints were performed. Funnel plots, Begg and Mazumdar rank correlation test and Egger's test were used to detect publication bias.

3 | RESULTS

Figure 1 shows a flow diagram detailing the above search terms with inclusion and exclusion criteria. A total of 29 and 57 entries were retrieved from PubMed and Embase, respectively. Nine studies met the inclusion criteria and were included in our final meta-analysis.[6,7,11-17] In this meta-analysis, a total of 1740 subjects with Brugada Syndrome were included (mean age 45 years old, 80% male). The mean follow-up duration was 68 ± 27 months. Of the entire cohort, 40% had a spontaneous Type 1 pattern and 19% were positive for SCN5a mutation. The baseline characteristics of these studies and of the study populations are shown in Table 1.

3.1 | T_{peak}-T_{end}

For determining T_{end}, the tangent method and the return of the voltage to baseline method were used. T_{peak}-T_{end} intervals from different leads and the maximum of these measurements have been presented by most studies. Regarding maximum T_{peak}-T_{end} intervals, the mean value for the event-positive group was 98.9 ms (95% CI: 90.5-107.2 ms) (Figure 2A) and event-negative group was 87.7 ms (95% CI: 80.5-94.9 ms) (Figure 2B). Five studies reported longer values in the event-positive compared to event-negative groups, whereas four studies reported no significant difference (Figure 2C). T_{peak}-T_{end} intervals were 11.9 ms longer (95% CI: 3.6-20.2 ms, $P = 0.005$) in event-positive patients than in event-negative patients. The Cochran's Q value was greater than the degrees of freedom (56 vs 8), indicating that the true effect size was different between studies.

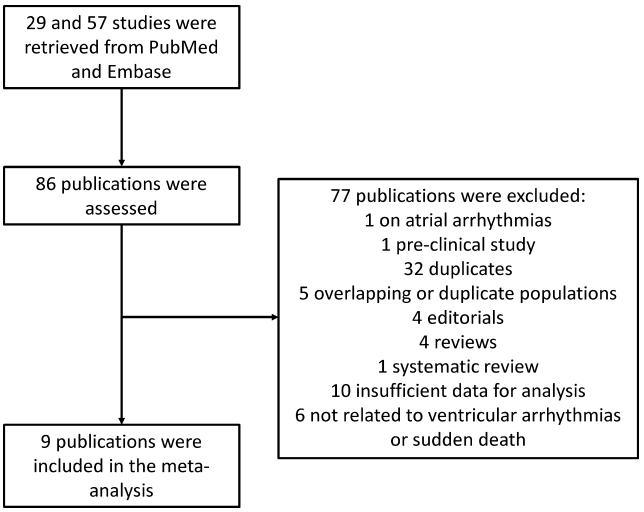

FIGURE 1 Flow diagram of the study selection process

TABLE 1 Characteristics of the nine studies included in this meta-analysis

First author/ year	Sample size (n)	T_{peak}-T_{end} measurement: method and leads	Age (SD)	No. of males (%)	No. of Sp. type 1 patients (%)	No. of SCN5a positive patients (%)	Endpoints	Comparisons	No. of patients with adverse events /without adverse events/%/% per year	Follow-up duration (months)	Quality score	Ref.
Morita 2017	471	Tangent method; V1, V2, V3, V5	47 (19)	447 (95)	118 (25)	27 (15)	Syncope or VT/VF	Syncope/VT/VF vs asymptomatic	145/326/31/4.09	91	7	16
Mugnai 2017	448	End of the T-wave; V1 to V6	45 (16)	273 (61)	96 (21)	55 (22)	Spontaneous VF or SCD	AT/SD vs asymptomatic	43/290/13/1.67	93	6	7
Kawazoe 2016	143	Tangent method; V1 to V6	46 (12)	140 (98)	84 (59)	–	VF	VF vs no VF	35/108/24/1.9	105	7	17
Zumhagen 2016	78	Tangent method; V1	45 (14)	57 (73)	22 (28)	17 (22)	Spontaneous VT/VF	VT/VF/aborted SCD vs asymptomatic/ syncope	22/54/29/-	–	6	14
Maury 2015	325	Tangent method; V1 to V4	47 (13)	260 (80)	143 (44)	43 (13)	Spontaneous VT/VF	AT/SD vs asymptomatic	26/226/10/2.50	48	7	11
Letsas 2010	23	End of the T-wave; V2, V6	43 (15)	19 (83)	10 (43)	–	Inducible VT/ VF	Inducible VT vs no inducible VT	17/6/74/16.15	55	6	12
Junttila 2008	200	End of the T-wave; V2, II	40 (16)	143 (72)	200 (100)	25 (50)	Syncope, VT/ VF, SCD	Syncope/VT/VF/ aborted SCD vs asymptomatic	66/134/33/-	–	7	15
Wang 2007	23	End of the T-wave; Max from V1 to V6	45 (8)	23 (100)	–	–	Spontaneous VT/VF	Syncope/VT/VF/ inducible VT vs asymptomatic	11/9/55/5.12	43	8	13
Castro Hevia 2006	29	Tangent method, Max from V1 to V6	41 (12)	25 (86)	15 (52)	–	Spontaneous VT/VF	Presyncope/syncope/ aborted SCD vs asymptomatic	12/17/41/3.81	43	8	6

SCD: sudden cardiac death; VT: ventricular tachycardia; VF: ventricular fibrillation; Sp.: spontaneous.

I^2 took a value of 86%, suggesting the presence of substantial heterogeneity. A funnel plot plotting standard errors against differences in means is shown in Figure S1. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0.3 with P = 0.30, which suggests no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 2.4, t-value 1.2; P = 0.25). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time, but this did not significantly influence the mean difference (Figure S2), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis. Subgroup analysis based on the method of T_{end} determination was performed. For the tangent method, the T_{peak}-T_{end} mean difference was 15.5 ms (95% CI: 3.9-27.2 ms; P = 0.009) and I^2 remained high at 90%. For full recovery of voltage to baseline, the mean difference was 6.0 ms (95% CI: 0.7-11.4 ms; P = 0.006) and I^2 remained high at 76%. Therefore, different methods of T_{end} determination did not introduce significant heterogeneity to the pooled effect estimate.

3.2 | (T_{peak}-T_{end})/QT ratio

Regarding maximum (T_{peak}-T_{end})/QT ratio, the mean value for the event-positive group was 0.221 (95% CI: 0.208-0.234) (Figure 3A) and event-negative group was 0.210 (95% CI: 0.205-0.214) (Figure 3B). Two studies reported higher values in Brugada subjects with positive events compared to those without such events, whereas four studies demonstrated no significance between the groups (Figure 3C). Pooling of the mean values demonstrated significantly higher (T_{peak}-T_{end})/QT ratios in the event-positive group than in the event-negative group (mean difference = 0.019, 95% CI: 0.003-0.036, P = 0.024). The Cochran's Q value was greater than the degrees of freedom (19 vs 5), indicating that the true effect size was different between studies. I^2 took a value of 74%, suggesting significant heterogeneity. A funnel plot plotting standard errors against differences in means is shown in Figure S3. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0.07 with P = 1, which suggested no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 3.5, t-value 1.1; P = 0.31). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time, but this did not significantly influence the mean difference (Figure S4), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis. Subgroup analysis based on the method of T_{end} determination was performed. For the tangent method, the mean difference of (T_{peak}-T_{end})/QT ratio was 0.03 (95% CI: 0.01-0.05; $P < 0.05$) and I^2 was lowered to 55%. For full recovery of voltage to baseline, the mean difference was only 0.004 (95% CI: −0.03 to 0.03 ms; P = 0.81) and I^2 remained high at 74%. Therefore, different method of T_{end} determination appeared to contribute partially to the heterogeneity of the pooled effect estimate. Moreover, statistical significance was achieved when the tangent method was used, but was lost when the return to baseline method was used, which may suggest the former approach may be more sensitive.

3.3 | T_{peak}-T_{end} dispersion

Regarding maximum T_{peak}-T_{end} dispersion, the mean value for the event-positive group was 40.8 ms (95% CI: 26.9-54.8 ms) (Figure 4A) and event-negative group was 29.7 ms (95% CI: 24.5-34.8 ms) (Figure 4B). Regarding T_{peak}-T_{end} dispersion, two studies reported longer values in event-positive group compared to event-negative groups, whereas three studies found no significant difference (Figure 4C). Overall, pooling of the data showed that T_{peak}-T_{end} dispersion was significantly higher in the event-positive than in the event-negative groups (mean difference = 7.8 ms, 95% CI: 2.1 to 13.4 ms, P = 0.007). The Cochran's Q value was greater than the degrees of freedom (20 vs 4), indicating that the true effect size was different between studies. I^2 took a value of 80%, suggesting significant heterogeneity. A funnel plot plotting standard errors against differences in means is shown in Figure S5. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of −2 with P = 0.62, which suggests no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept −5.4, t-value 0.8; P = 0.48). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time, but this did not significantly influence the mean difference between event-positive and event-negative groups (Figure S6), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis. Subgroup analysis based on the method of T_{end} determination was performed. For the tangent method, the mean difference of T_{peak}-T_{end} dispersion was 16.2 ms (95% CI: 7.9-24.5 ms; $P < 0.0001$) and I^2 was 65%. For full recovery of voltage to baseline, the mean difference was 0.4 ms (95% CI: −7.3 to 8.2 ms; P = 0.91) and I^2 was reduced to 19%. Therefore, different method of T_{end} determination contributed heterogeneity to the pooled effect estimate. Moreover, statistical significance was achieved when the tangent method was used, but was lost when the return to baseline method was used, which may suggest the former approach may be more sensitive.

3.4 | Comparisons between patients with and without SCN5A mutations

SCN5A is the commonest ion channel gene that is mutated in Brugada syndrome.[2,3] Separate meta-analyses were conducted to compare the different T_{peak}-T_{end} parameters between patients with and without SCN5A mutations. Two of the included studies provided sufficient information for such analyses.[7,14] No significant difference in T_{peak}-T_{end} (mean difference = 8.2 ms, 95% CI: −6.7 to 23.2 ms, P = 0.28; I^2 = 59%; Figure S7), T_{peak}-T_{end}/QT ratio (mean difference = −0.006 ms, 95% CI: −0.023 to 0.011 ms, P = 0.47; I^2 = 24%; Figure S8) or T_{peak}-T_{end} dispersion (mean difference = 5.2 ms, 95% CI: −2.9 to 13.2 ms, P = 0.21; I^2 = 31%; Figure S9) was observed between patients with and without SCN5A mutations.

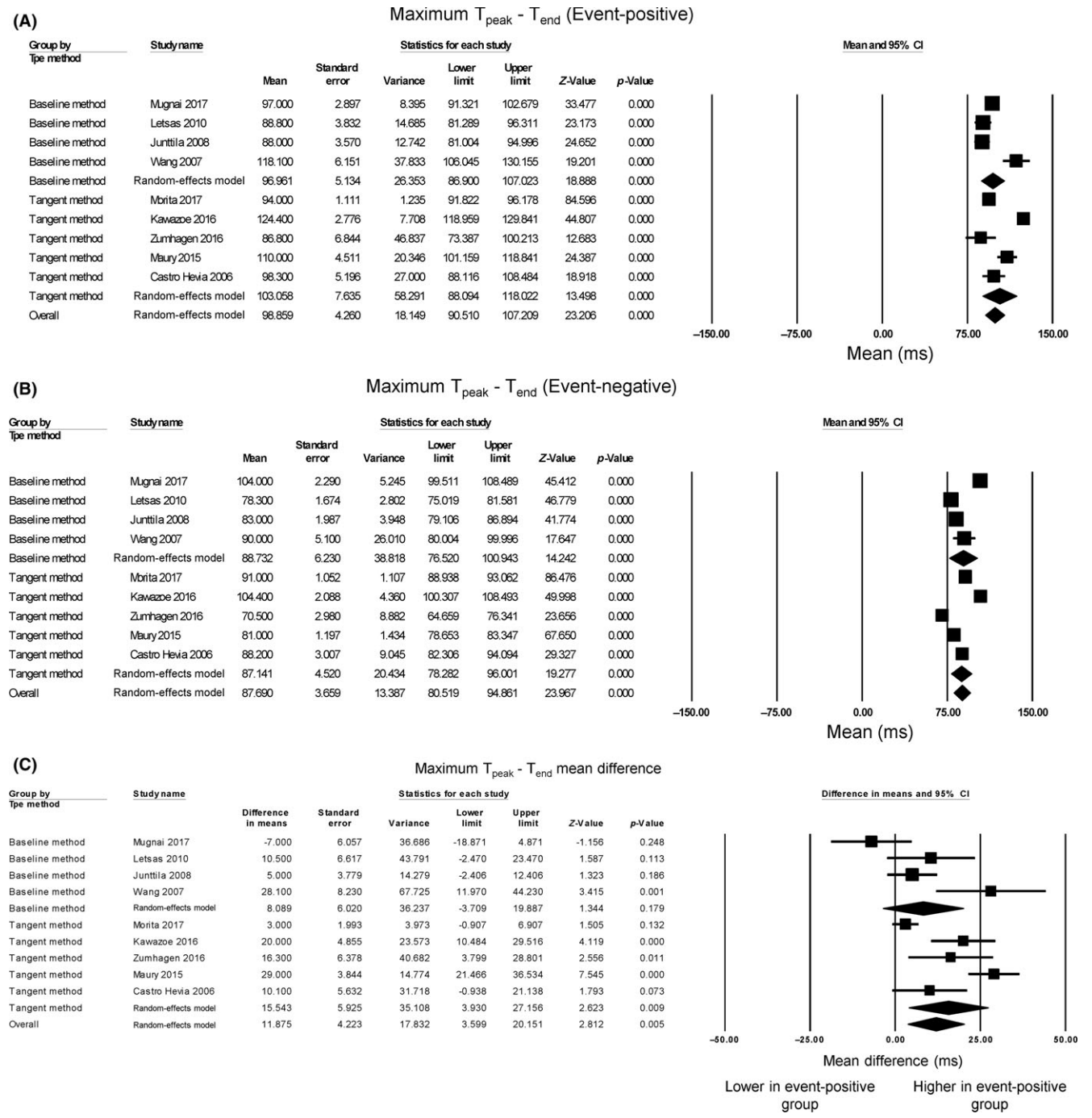

FIGURE 2 Forest plot demonstrating T_{peak}-T_{end} intervals obtained from event-positive (A) and event-negative (B) groups and the mean difference between both groups (C) in Brugada Syndrome

4 | DISCUSSION

The main findings of our meta-analysis, which included 1597 Brugada subjects, are (a) T_{peak}-T_{end} intervals, (b) (T_{peak}-T_{end})/QT ratio and (c) T_{peak}-T_{end} dispersion are higher in Brugada subjects with adverse cardiac events (ventricular tachy-arrhythmias and SCD) when compared to Brugada subjects free from such events.

The presence of pre-existing electrophysiological heterogeneities is important for mediating the normal, unidirectional spread of action potentials in the heart.[18,19] These are attributed to differences in repolarization times of the different cell types, which are responsible for generation of the T-wave on the electrocardiogram (ECG).[20,21] However, exacerbation of such differences has been associated with ventricular tachy-arrhythmias in different conditions, thereby generating a pro-arrhythmic phenotype. These include congenital ion channelopathies such as long QT syndrome and Brugada syndrome[22-24] and acquired cardiac diseases such as myocardial infarction.[25,26] These heterogeneities can occur locally or across the

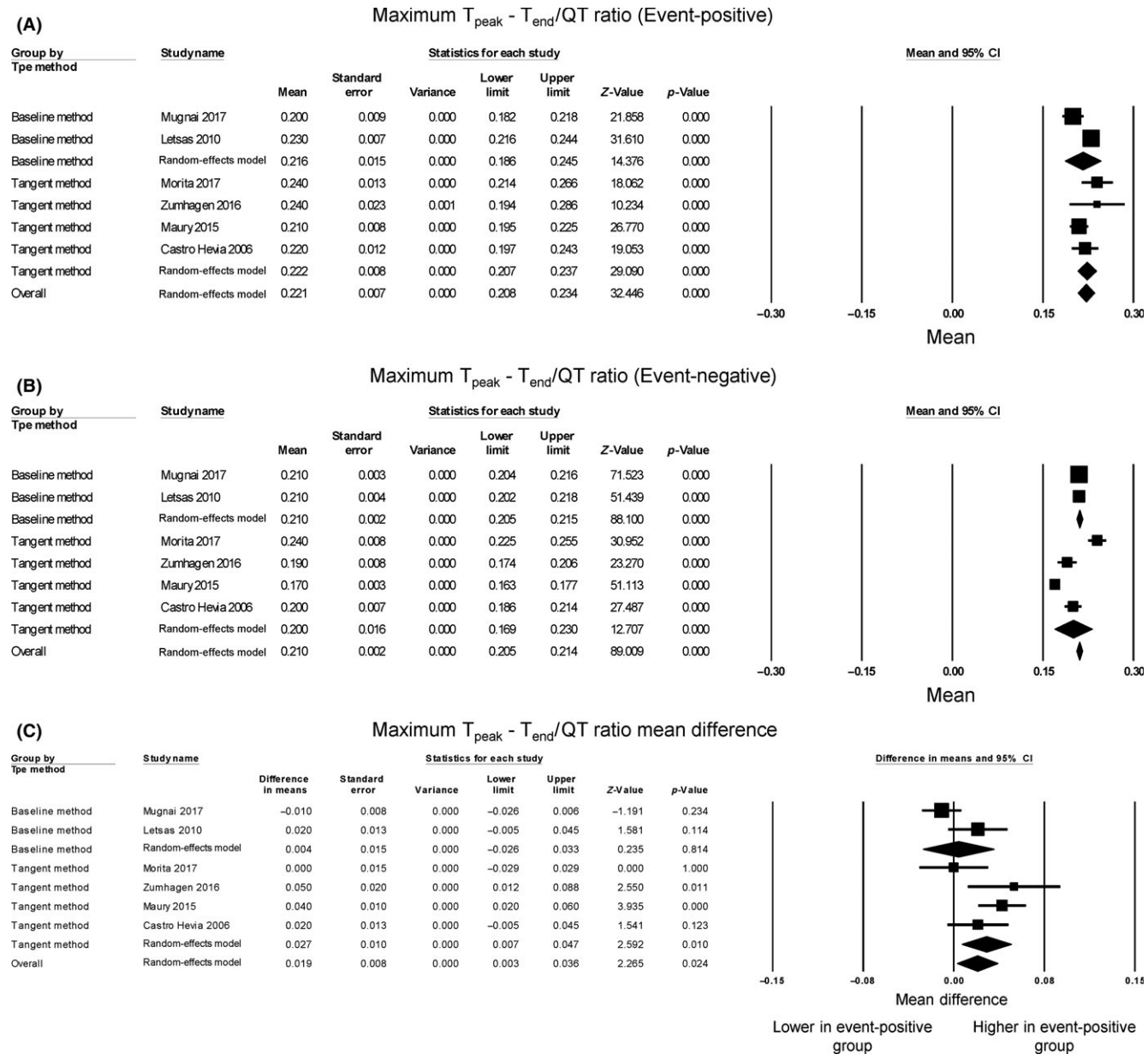

FIGURE 3 Forest plot demonstrating T_{peak}-T_{end}/QT ratios obtained from event-positive (A) and event-negative (B) groups and the mean difference between both groups (C) in Brugada Syndrome

myocardial wall,[27] potentially causing arrhythmias by inducing unidirectional conduction block and therefore circus-type or spiral wave re-entry.[28,29] Moreover, a greater epicardial-endocardial repolarization time difference may increase the propensity of phase 2 re-entry, which is hypothesized to generate extrasystolic activity in Brugada syndrome.[30] This occurs when sites with an action potential dome to sites which a dome morphology, leading to direct depolarization of the downstream sites.[31] Once an extrasystole is generated, together with a favorable re-entrant substrate, ventricular tachycardia and fibrillation can result.[32]

A number of electrocardiographic indices have been proposed for stratification of arrhythmic or mortality risk.[33,34] Of these, Yan and Antzelevitch were the first to propose the use of the difference between the peak and the end of the T-wave (the T_{peak}-T_{end} interval) as a measure of transmural dispersion of repolarization.[20,35-37] Subsequent clinical studies have demonstrated that, confirmed recently in a systematic review and meta-analysis from our group,[9] that T_{peak}-T_{end} prolongation significantly elevated the risk of ventricular tachyarrhythmias and/or SCD in heart failure, ischemic heart disease, Brugada syndrome, hypertension, and the general population. Recently, Mugnai and colleagues in a total of 448 subjects found no significant differences T_{peak}-T_{end} intervals, (T_{peak}-T_{end})/QT ratio or T_{peak}-T_{end} dispersion between patients with VT/VF requiring anti-tachycardia pacing or with sudden death, and those who were asymptomatic.[7] Similarly, in a separate population of 471 subjects, Morita and colleagues found no significance difference in T_{peak}-T_{end} intervals

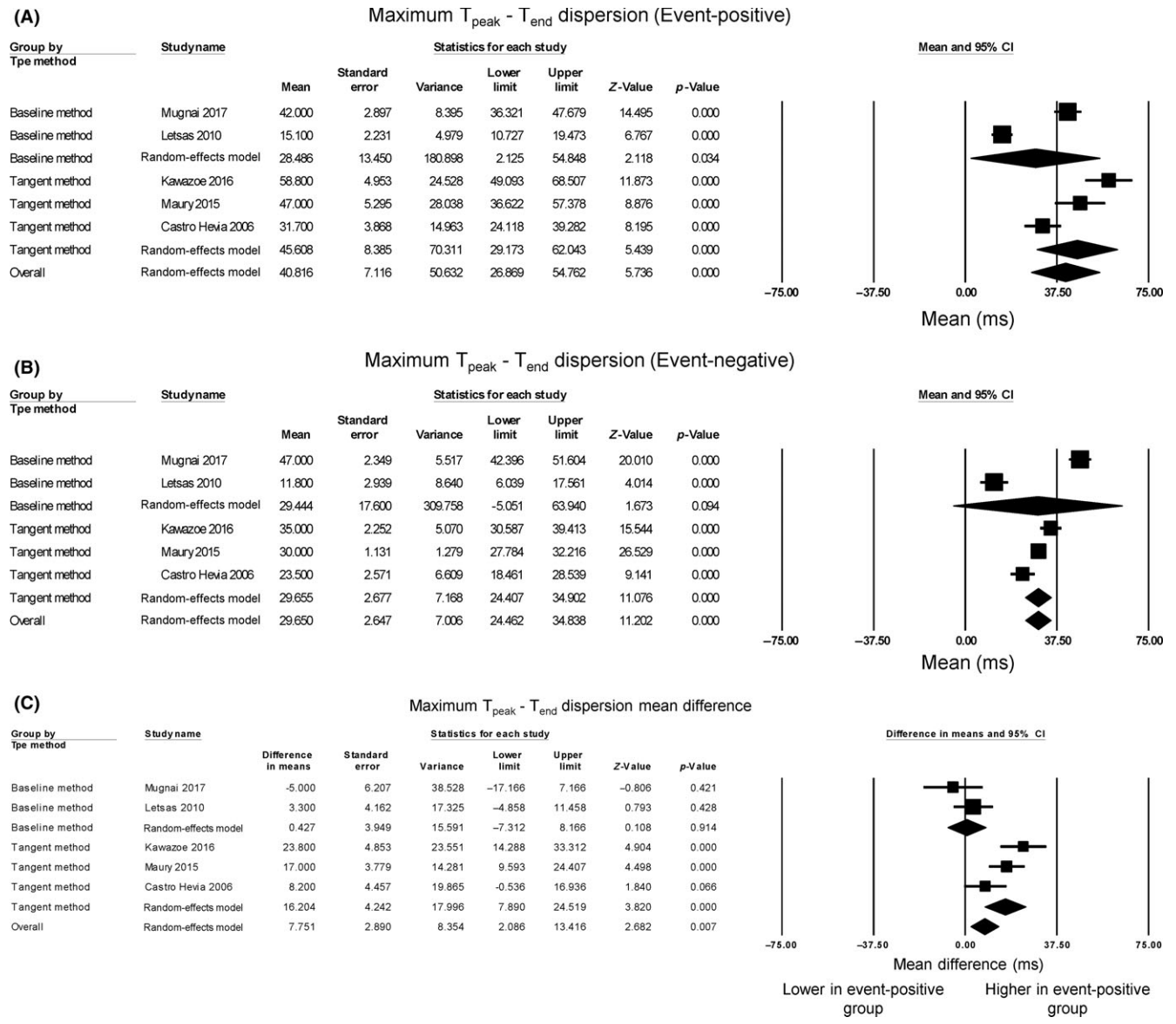

FIGURE 4 Forest plot demonstrating T_{peak}-T_{end} dispersion obtained from event-positive (A) and event-negative (B) groups and the mean difference between both groups (C) in Brugada Syndrome

between patients with syncope or VT/VF and asymptomatic patients.[16] Publication of these two studies prompted us to conduct this meta-analysis, which confirms the value of T_{peak}-T_{end} interval, (T_{peak}-T_{end})/QT ratio and T_{peak}-T_{end} dispersion, in distinguishing high-risk patients from low-risk patients.

In the Mugnai study, the largest study to date, the percentage of patients with adverse events were the lowest at 13%.[7] Male gender, a spontaneous Type 1 Brugada pattern and SCN5a mutation positive status were significantly associated with ventricular arrhythmias.[38] Therefore, the lower percentage of patients with adverse events can be explained by the lower percentage of Type 1 Brugada patients (21% vs 28%-100% in the remaining studies) and lower percentage male patients (61% vs 72%-100%) despite similar percentage with SCN5a positive status (22% vs 13%-50%). While these differences in patient characteristics affect the likelihood of adverse events occurring, they should not explain the lack of difference in T_{peak}-T_{end} intervals between event-positive and event-negative groups in the Morita study[16] or the Mugnai study. Interestingly, Mugnai and colleagues found a non-statistically significant lower T_{peak}-T_{end} intervals in event-positive groups. Of the remaining six studies, five studies had reported significantly higher T_{peak}-T_{end} intervals and one study reported no difference.[15] A recent epidemiological study reported a U-shaped relationship between T_{peak}-T_{end} intervals and increased mortality.[39] Autonomic modulation, which is part of Coumel's triad for arrhythmogenesis,[40] is known to modulate the re-entrant substrate. Increased activity of the parasympathetic nervous system may reduce T_{peak}-T_{end} intervals, which may also be pro-arrhythmic.[41] By contrast, exercise, during which sympathetic activity is increased, can exacerbate pre-existing heterogeneities, such as producing conduction slowing[42] and increasing the dispersion of repolarization.[43]

In our previous meta-analysis pooling together studies that reported odds ratios or hazard ratios, the average cut-off for T_{peak}-T_{end} was 95.8 ms across different clinical conditions.[9] The present meta-analysis pooling mean values for event-positive and -negative groups clearly indicates that the 100 ms cut-off is too high for Brugada syndrome. Our data would support a lower cut-off value between 88 and 99 ms to be used. This cut-off will also be method-dependent for determining T_{end} in the case of the T_{peak}-T_{end} intervals. Previously, it was shown that in a cohort of high-risk Brugada subjects, only 10 of 16 studies reported a T_{peak}-T_{end} longer than 100 ms, supporting our notion that this cut-off value may be too high.[44] Moreover, different studies measured T_{peak}-T_{end} from different leads. Some had measured it from all 12 leads and taken the mean values while others have done so for V1 to V3 only. While there is no consensus as to which leads are most appropriate for measurement, obtaining it from all 12 leads is likely to be less useful clinically due to the time-consuming nature. To simplify T_{peak}-T_{end} determination, we would thus propose measuring it from the right precordial leads given BrS is primarily a right ventricular disorder.

While it may appear that the difference in T_{peak}-T_{end} between high-risk and low-risk Brugada patients was only small, at around 12 ms, it should be emphasized that increased transmural dispersion of repolarization is only one mechanism by which re-entrant arrhythmogenesis is generated. Other mechanisms, such as reduced conduction velocity, increased dispersion of conduction[45] or dynamic substrates such as steep action potential restitution,[46] in which normal T_{peak}-T_{end} interval, T_{peak}-T_{end}/QT ratio or T_{peak}-T_{end} dispersion may be observed, also contribute to arrhythmogenesis in Brugada syndrome. Therefore, better risk stratification scores will need to incorporate a combination of repolarization and conduction indices. Moreover, some of these dynamic changes may not be detectable on the ECG and may require additional tests such as non-invasive ECG imaging (ECGi),[43] or only becomes detectable only under stressful conditions such as exercise.[43]

4.1 | Limitations

The following limitations of this meta-analysis should be noted. First, there is marked heterogeneity between the included studies. The method of T_{peak}-T_{end} determination across the studies was split even between the tangent method and full recovery of the voltage to baseline. Subgroup analysis based on the method used did not reduce the heterogeneity observed. Therefore, measurement method was unlikely to have significantly contributed to the heterogeneity observed. Moreover, the Letsas 2010 study[12] used a different endpoint of inducible VT compared to the remaining studies, but its exclusion did not significant affect the mean T_{peak}-T_{end} values for event-positive group, event-negative group, and mean difference between these groups. Second, retrospective studies may have more bias than prospective studies. Finally, it should be acknowledged that there is overlap between event-postiive and event-negative groups irrespective of the method of measuring T_{end}. This would suggest as a single measurement, T_{peak}-T_{end} is unlikely to be useful in its own right. Indeed, accurate risk stratification will require a composite scoring system assessing not only dispersion of repolarization, but that of conduction, clinical symptoms, family history, the type of Brugada pattern, genetic background, electrical and drug provocation testing as well as electrophysiological mapping.[38,41,45,47-49]

5 | CONCLUSIONS

T_{peak}-T_{end} interval, T_{peak}-T_{end}/QT ratio and T_{peak}-T_{end} dispersion were higher in high-risk than low-risk Brugada subjects, and thus offer incremental value for risk stratification.

ACKNOWLEDGEMENTS

GT thanks the Croucher Foundation of Hong Kong for the support of a clinical assistant professorship.

CONFLICTS OF INTERESTS

Authors declare no Conflict of Interests for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Tse G, Gong M, Li CKH, et al. T_{peak}-T_{end}, T_{peak}-T_{end}/QT ratio and T_{peak}-T_{end} dispersion for risk stratification in Brugada Syndrome: A systematic review and meta-analysis. *J Arrhythmia*. 2018;00:1–11. https://doi.org/10.1002/joa3.12118