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

Gary Tse MPH, PhD, FESC, FACC, FHRS, FRCP1,2,3 | Mengqi Gong BS4
Christien Ka Hou Li1,2,5 | Keith Sai Kit Leung BSc (Hons) LIBMS1,2,3,6
Stamatis Georgopoulos MD7 | George Bazoukis MSc, MD7
Konstantinos P. Letsas MD, FESC, FEHRA7 | Abhishek C. Sawant MD, MPH8
Giacomo Mugnai MD, PhD9 | Martin C.S. Wong MPH, MD, FESC, FACC, FFPH10
Gan Xin Yan MD, PhD11,12 | Pedro Brugada MD, PhD9 | Gian-Battista Chierchia MD, PhD9
| Carlo de Asmundis MD, PhD9 | Adrian Baranchuk MD, FACC, FRCPC, FCCS13 | Tong Liu MD, PhD4 | International Health Informatics Study (IHIS) Network

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 Tpeak-Tend 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 (Tpeak-Tend)/QT ratios (mean difference = 0.019, 95% CI: 0.003-0.036, \( P = 0.024; \ i^2 = 74\%\)) and Tpeak-Tend 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:** Tpeak-Tend interval, (Tpeak-Tend)/QT ratio and Tpeak-Tend 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, Tpeak-Tend, ventricular arrhythmia

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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-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 cusc-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 (Tpeak-Tend interval), (Tpeak-Tend)/QT ratio and Tpeak-Tend dispersion.\(^5,6\)

However, not all studies have shown an association between higher Tpeak-Tend intervals, (Tpeak-Tend)/QT ratio or Tpeak-Tend 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 Tpeak-Tend 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 Tpeak-Tend and arrhythmic and/or mortality outcomes in various clinical conditions, including Brugada Syndrome.\(^9\) This demonstrated prolonged Tpeak-Tend 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 Tpeak-Tend, 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 (Tpeak-Tend)/QT ratio or Tpeak-Tend dispersion. Therefore, we conducted a systematic review with meta-analysis into the relationships between Tpeak-Tend interval, (Tpeak-Tend)/QT ratio and Tpeak-Tend 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 (PRISMA) statement. PubMed and Embase were searched for studies that investigated the association between Tpeak-Tend or Tpeak-Tend /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) $T_{\text{peak}}$-$T_{\text{end}}$ intervals or ($T_{\text{peak}}$-$T_{\text{end}}$)/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. 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 $T_{\text{peak}}$-$T_{\text{end}}$ interval, ($T_{\text{peak}}$-$T_{\text{end}}$)/QT ratio and $T_{\text{peak}}$-$T_{\text{end}}$ 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. 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 $T_{\text{peak}}$-$T_{\text{end}}$

For determining $T_{\text{end}}$, the tangent method and the return of the voltage to baseline method were used. $T_{\text{peak}}$-$T_{\text{end}}$ intervals from different leads and the maximum of these measurements have been presented by most studies. Regarding maximum $T_{\text{peak}}$-$T_{\text{end}}$ 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). $T_{\text{peak}}$-$T_{\text{end}}$ 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.

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**FIGURE 1** Flow diagram of the study selection process
TABLE 1  Characteristics of the nine studies included in this meta-analysis

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Sample size (n)</th>
<th>(T_{\text{peak}}\text{-}T_{\text{end}}) measurement and leads</th>
<th>Age (SD)</th>
<th>No. of males (%)</th>
<th>Sample type 1 patients (%)</th>
<th>No. of SCN5a positive patients (%)</th>
<th>Endpoints</th>
<th>Comparisons</th>
<th>No. of patients with adverse events /without adverse events/% per year</th>
<th>Follow-up duration (months)</th>
<th>Quality score</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morita 2017</td>
<td>471 Tangent method; V1, V2, V3, V5</td>
<td>47 (19) 447 (95) 118 (25) 27 (15)</td>
<td>Syncope or VT/VF</td>
<td>Syncope/VT/VF vs asymptomatic</td>
<td>145/326/314.09</td>
<td>91</td>
<td>7</td>
<td>16</td>
<td></td>
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<tr>
<td>Mugnai 2017</td>
<td>448 End of the T-wave; V1 to V6</td>
<td>45 (16) 273 (61) 96 (21) 55 (22)</td>
<td>Spontaneous VF or SCD</td>
<td>AT/SD vs asymptomatic</td>
<td>43/290/131.67</td>
<td>93</td>
<td>6</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawazoe 2016</td>
<td>143 Tangent method; V1 to V6</td>
<td>46 (12) 140 (98) 84 (59) –</td>
<td>VF</td>
<td>VF vs no VF</td>
<td>35/108/24/1.9</td>
<td>105</td>
<td>7</td>
<td>17</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zumhagen 2016</td>
<td>78 Tangent method; V1</td>
<td>45 (14) 57 (73) 22 (28) 17 (22)</td>
<td>Spontaneous VT/VF</td>
<td>VT/VF/aborted SCD vs asymptomatic/syncope</td>
<td>22/54/2/–</td>
<td>–</td>
<td>6</td>
<td>14</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Maury 2015</td>
<td>325 Tangent method; V1 to V4</td>
<td>47 (13) 260 (80) 143 (44) 43 (13)</td>
<td>Spontaneous VT/VF</td>
<td>AT/SD vs asymptomatic</td>
<td>26/226/10/2.50</td>
<td>48</td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letsas 2010</td>
<td>23 End of the T-wave; V2, V6</td>
<td>43 (15) 19 (83) 10 (43) –</td>
<td>Inducible VT/VF</td>
<td>Inducible VT vs no inducible VT</td>
<td>17/67/4/16.15</td>
<td>55</td>
<td>6</td>
<td>12</td>
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<tr>
<td>Junttila 2008</td>
<td>200 End of the T-wave; V2, V1</td>
<td>40 (15) 143 (72) 200 (100) 25 (50)</td>
<td>Syncope, VT/VF, SCD</td>
<td>Syncope/VT/VF/aborted SCD vs asymptomatic</td>
<td>66/134/33/–</td>
<td>–</td>
<td>7</td>
<td>15</td>
<td></td>
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<tr>
<td>Wang 2007</td>
<td>23 End of the T-wave; Max from V1 to V6</td>
<td>45 (8) 23 (100) – –</td>
<td>Spontaneous VT/VF</td>
<td>Syncope/VT/VF/inducible VT vs asymptomatic</td>
<td>11/9/55/5.12</td>
<td>43</td>
<td>8</td>
<td>13</td>
<td></td>
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<tr>
<td>Castro Hevia 2006</td>
<td>29 Tangent method, Max from V1 to V6</td>
<td>41 (12) 25 (86) 15 (52) –</td>
<td>Spontaneous VT/VF</td>
<td>Presyncope/syncope/aborted SCD vs asymptomatic</td>
<td>12/17/41/3.81</td>
<td>43</td>
<td>8</td>
<td>6</td>
<td></td>
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SCD: sudden cardiac death; VT: ventricular tachycardia; VF: ventricular fibrillation; Sp.: spontaneous.
The return to baseline method was used, which may suggest the former approach may be more sensitive.

3.3 | T\textsubscript{\text{peak}} - T\textsubscript{end} dispersion

Regarding maximum T\textsubscript{\text{peak}} - T\textsubscript{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\textsubscript{\text{peak}} - T\textsubscript{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\textsubscript{\text{peak}} - T\textsubscript{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. \( \hat{I}^2 \) took a value of 80%, suggesting significant heterogeneity. A funnel plot pooling 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 (Figure S2), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis. Subgroup analysis based on the method of \( T_{\text{end}} \) determination was performed. For the tangent method, the \( T_{\text{peak}} - T_{\text{end}} \) mean difference was 15.5 ms (95% CI: 3.9-27.2 ms; \( P = 0.009 \)) and \( \hat{I}^2 \) 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 \( \hat{I}^2 \) remained high at 76%. Therefore, different methods of \( T_{\text{end}} \) determination did not introduce significant heterogeneity to the pooled effect estimate.

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 \( T_{\text{peak}} - T_{\text{end}} \) 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 \( T_{\text{peak}} - T_{\text{end}} \) (mean difference = 8.2 ms, 95% CI: -6.7 to 23.2 ms, \( P = 0.28 \); \( \hat{I}^2 = 59\% \); Figure S7), \( T_{\text{peak}} - T_{\text{end}} / \text{QT ratio} \) (mean difference = -0.006 ms, 95% CI: -0.023 to 0.011 ms, \( P = 0.47 \); \( \hat{I}^2 = 24\% \); Figure S8) or \( T_{\text{peak}} - T_{\text{end}} \) dispersion (mean difference = 5.2 ms, 95% CI: -2.9 to 13.2 ms, \( P = 0.21 \); \( \hat{I}^2 = 31\% \); Figure S9) was observed between patients with and without SCN5A mutations.
DISCUSSION

The main findings of our meta-analysis, which included 1597 Brugada subjects, are (a) $T_{\text{peak}}-T_{\text{end}}$ intervals, (b) $(T_{\text{peak}}-T_{\text{end}})/QT$ ratio and (c) $T_{\text{peak}}-T_{\text{end}}$ dispersion are higher in Brugada subjects with adverse cardiac events (ventricular tachyarrhythmias 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.\textsuperscript{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).\textsuperscript{20,21} However, exacerbation of such differences has been associated with ventricular tachyarrhythmias in different conditions, thereby generating a pro-arrhythmic phenotype. These include congenital ion channelopathies such as long QT syndrome and Brugada syndrome\textsuperscript{22-24} and acquired cardiac diseases such as myocardial infarction.\textsuperscript{25,26} These heterogeneities can occur locally or across the
myocardial wall, potentially causing arrhythmias by inducing unidirectional conduction block and therefore circus-type or spiral wave re-entry. 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. This occurs when sites with an action potential dome to sites which a dome morphology, leading to direct depolarization of the downstream sites. Once an extrasystole is generated, together with a favorable re-entrant substrate, ventricular tachycardia and fibrillation can result.

A number of electrocardiographic indices have been proposed for stratification of arrhythmic or mortality risk. 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. Subsequent clinical studies have demonstrated that, confirmed recently in a systematic review and meta-analysis from our group, $T_{peak} - T_{end}$ 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. Similarly, in a separate population of 471 subjects, Morita and colleagues found no significance difference in $T_{peak} - T_{end}$ intervals between the peak and the end of the T-wave (the $T_{peak} - T_{end}$ interval) as a measure of transmural dispersion of repolarization.

### 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.
between patients with syncope or VT/VF and asymptomatic patients. Publication of these two studies prompted us to conduct this meta-analysis, which confirms the value of Tpeak-Tend interval,\((T_{\text{peak}}-T_{\text{end}})/QT\) ratio and Tpeak-Tend 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%. Male gender, a spontaneous Type 1 Brugada pattern and SCN5a mutation positive status were significantly associated with ventricular arrhythmias. 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 Tpeak-Tend intervals between event-positive and event-negative groups in the Morita study or the Mugnai study. Interestingly, Mugnai and colleagues found a non-statistically significant lower Tpeak-Tend intervals in event-positive groups. Of the remaining six studies, five studies had reported significantly higher Tpeak-Tend intervals and one study reported no difference. A recent epidemiological study reported a U-shaped relationship between Tpeak-Tend intervals and increased mortality. Autonomic modulation, which is part of Coumel’s triad for arrhythmogenesis, is known to modulate the re-entrant substrate. Increased activity of the parasympathetic nervous system may reduce Tpeak-Tend intervals, which may also be pro-arrhythmic. By contrast, exercise, during which sympathetic activity is increased, can exacerbate pre-existing heterogeneities, such as producing conduction slowing and increasing the dispersion of repolarization.

**FIGURE 4** Forest plot demonstrating Tpeak-Tend dispersion obtained from event-positive (A) and event-negative (B) groups and the mean difference between both groups (C) in Brugada Syndrome.
In our previous meta-analysis pooling together studies that reported odds ratios or hazard ratios, the average cut-off for \( T_{peak}^\text{Tend} \) 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 \( T_{peak}^T_{end} \) 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 end-point 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-positive 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.

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CONFLICTS OF INTERESTS

Authors declare no Conflict of Interests for this article.

ORCID

Gary Tse http://orcid.org/0000-0001-5510-1253
George Bazoukis http://orcid.org/0000-0003-1009-9772
Giacomo Mugnai http://orcid.org/0000-0003-4733-9418
Carlo de Asmundis http://orcid.org/0000-0001-9351-0760
Adrian Baranchuk http://orcid.org/0000-0002-3042-6569

REFERENCES


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 end-point 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-positive 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.


SUPPORTING INFORMATION

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

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