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The $T_{\text{peak}} - T_{\text{end}}$ interval as an electrocardiographic risk marker of arrhythmic and mortality outcomes: a systematic review with meta-analysis

Gary Tse MBBS PhD FIBMS FRSPH $^1$, Wing Tak Wong MPhil PhD $^2$, Mengqi Gong MD $^3$, Konstantinos P. Letsas MD FESC $^4$, Vassilis S Vassiliou MA MBBS MRCP FHEA FESC $^5$, Yat Sun Chan MBBS FRCP $^5$, Bryan P Yan MBBS FRCP FACC $^6$, Paula Whittaker MBChB MPH MMed MRCGP $^7$, Yunlong Xia MD PhD $^8$, Gan-Xin Yan MD PhD $^9$, Tong Liu MD PhD $^{10}$

$^1$ Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China; Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China; School of Health Sciences, University of Manchester, United Kingdom (tseg@cuhk.edu.hk)

$^2$ School of Life Sciences, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China (jack_wong@cuhk.edu.hk)

$^3$ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, People’s Republic of China (qituzi@vip.qq.com)

$^4$ Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, “Evangelismos” General Hospital of Athens, Athens, Greece (k.letsas@gmail.com)

$^5$ Norwich Medical School, University of East Anglia, Bob Champion Research & Education Building, James Watson Road, Norwich, UK; Royal Brompton Hospital and Imperial College London, UK (v.vassiliou@rbht.nhs.uk)

$^6$ Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China (cys644@ha.org.hk)

$^7$ Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China (bryan.yan@cuhk.edu.hk)

$^8$ Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, University of Manchester, United Kingdom (paula.whittaker@manchester.ac.uk)
Correspondence to

Dr. Gary Tse
Department of Medicine and Therapeutics
The Chinese University of Hong Kong,
Hong Kong, SAR, P.R. China
Email: tseg@cuhk.edu.hk

Prof. Tong Liu
Department of Cardiology,
Tianjin Institute of Cardiology,
Second Hospital of Tianjin Medical University,
Tianjin 300211, People’s Republic of China
Email: liutongdoc@126.com

Keywords: Tpeak - Tend; dispersion of repolarization; risk stratification; ventricular arrhythmia;
sudden cardiac death

Word count: 4529
Abstract

Importance: The T_{peak} – T_{end} interval, an electrocardiographic marker that reflects transmural dispersion of repolarization, has been proposed to predict the occurrence of ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD) in different clinical settings.

Objective: This comprehensive systematic review with meta-analysis was conducted to evaluate the significance of T_{peak} – T_{end} interval in predicting arrhythmic and/or mortality endpoints.

Data Sources: PubMed, Embase, Cochrane Library and CINAHL Plus databases through 30th November 2016.

Study selection: Case-control, prospective or retrospective observational studies in humans

and iv) odds ratios (ORs) or hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) or data necessary to calculate these were described. Human studies reporting odds or hazard ratios for arrhythmic and mortality outcomes.

Data Extraction and Synthesis: Two authors independently extracted and entered data into standardized spreadsheets.

Main Outcomes: The odds ratios or hazard ratios of adverse endpoint events [appropriate implantable cardioverter-defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death (SCD), cardiovascular death (CVD) or all-cause mortality.

Results: Of the 854 studies identified initially, 29 observational studies involving 154749 patients were included in our meta-analysis. T_{peak} – T_{end} interval prolongation with a mean cut-off point of 105.4 ± 17.3 was a significant predictor of the arrhythmic or mortality outcomes (odds ratio (OR): 1.13, 95% CI: 1.10 to 1.17, p < 0.001). When different end-points were analyzed, the ORs are as follows: VT/VF (OR: 1.09, 95% CI: 1.05 to 1.13, p < 0.0001) and SCD
(OR: 1.24, 95% CI 1.14 to 1.35, p < 0.0001). Subgroup analysis for each disease revealed that
the risk of VT/VF or death was highest for Brugada syndrome (OR: 5.69, 95% CI: 1.57 to 20.57,
p < 0.01), followed by ischemic heart disease (odds ratio: 1.06, 95% CI: 1.02 to 1.09, p = 0.001)
and heart failure (odds ratio: 1.07, 95% CI: 1.04 to 1.08, p < .0001). In the general population, a
prolonged $T_{\text{peak}} - T_{\text{end}}$ interval also predicted arrhythmic or mortality outcomes (odds ratio: 1.59,
95% CI: 1.21 to 2.09, p < .001).

Conclusions and relevance: This meta-analysis showed that the $T_{\text{peak}} - T_{\text{end}}$ interval is useful
risk stratification tool in different clinical settings as well as in the general population.
**Key Points**

**Question:** Is $T_{\text{peak}} - T_{\text{end}}$ interval a good predictor of ventricular tachycardia/ventricular fibrillation (VT/VF) and sudden cardiac death (SCD)?

**Findings:** In this systematic review and meta-analysis, prolonged $T_{\text{peak}} - T_{\text{end}}$ interval (>105 ms) was associated with a 13% increase in the risk of VT/VF and SCD.

**Meaning:** The $T_{\text{peak}} - T_{\text{end}}$ interval is a useful non-invasive electrocardiographic marker that can be used for risk stratification of VT/VF and SCD.
Introduction

Ventricular arrhythmias can take the form of monomorphic or polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). Both are life-threatening, potentially culminating in sudden cardiac death (SCD). SCD is a major health problem with a devastating impact on both economic and social issues. The prevalence of SCD is high with up to 60,000 deaths in the U.K. \(^1\), 200,000 deaths in the U.S. \(^2\) and 4 to 5 million deaths worldwide \(^3\), annually. Reliable stratification markers are therefore of paramount importance in order to identify high risk patients for SCD. Several electrocardiographic (ECG) markers related to increased risk of arrhythmias and SCD have been proposed \(^4\)-\(^6\). Traditional ECG markers of ventricular repolarization including the corrected QT (QT\(_c\)) interval \(^7\) and QT dispersion (QT\(_D\)) \(^8\) have been used for risk stratification in various clinical settings. Relatively new ECG markers of ventricular repolarization, such as the interval from the peak to the end of the T wave (T\(_{peak} - T_{end}\)) \(^9\), and the \((T_{peak} - T_{end})/QT\) ratio \(^10\), have been recently proposed to predict ventricular arrhythmic events and SCD \(^11\). These ECG markers have been validated in congenital ion channelopathies such as Long QT and Brugada syndromes \(^12\)-\(^14\), myocardial infarction \(^15\), cardiomyopathies \(^16\) and other diseases such as pulmonary embolism, hypertension and Chagas disease \(^17\),\(^18\). However, data are limited and controversial regarding the clinical utility of these ECG markers \(^19\)-\(^23\). The present systematic review and meta-analysis of the current literature aimed to investigate the prognostic significance of T\(_{peak} - T_{end}\) interval with respect to arrhythmic and mortality outcomes.

Method

Search strategy, inclusion and exclusion criteria
The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. MEDLINE, Embase, Cochrane library and CINAHL Plus were searched for studies that investigated the relationship between $T_{\text{peak}} - T_{\text{end}}$ interval with arrhythmic or mortality endpoints using the following terms: ["Tpeak – Tend" OR "Tpeak–Tend" OR “Tp - Te” OR “Tp-Te” OR “Tpeak-end” OR “Tp-e” OR "T(peak)-T(end)"
OR "T wave peak-to-end" OR "T peak-T end" OR "TPEc" OR "T-peak to T-end" OR "Tpeak-to-
tend"]. The search period was from the beginning of the databases (1965 for PubMed, 1910 for Embase, 1996 for Cochrane Library, 1937 for CINAHL Plus) through to 30th November 2016, with no language restrictions. The following inclusion criteria were applied: i) the design was a case-control, prospective or retrospective observational study in humans, ii) $T_{\text{peak}} - T_{\text{end}}$ interval durations were determined; iii) endpoint events [appropriate implantable cardioverter-defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death (SCD), cardiovascular death (CVD) or all-cause mortality were reported and iv) odds ratios (ORs) or hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) or data necessary to calculate these were described.

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS). The point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. 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 on the basis of the design or analysis; f) assessment of outcomes; g) follow-up period 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 they met <5 criteria, fair if they met 5 to 7 criteria, and good if they met >8 criteria. The details of the NOS quality assessment are shown in Supplementary Tables 1 and 2.

Data extraction and statistical analysis

Data from the different studies were entered in pre-specified spreadsheet in Microsoft Excel. All potentially relevant reports were retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. In this meta-analysis, the extracted data elements consisted of: i) publication details: last name of first author, publication year and locations; ii) study design; iii) follow-up duration; iv) definition of T_{peak} - T_{end} interval; v) lead(s) where the T_{peak} - T_{end} interval was measured; vi) endpoint(s); vii) the quality score; and viii) the characteristics of the population including sample size, gender, age and number of subjects. Meta-analyses of observational studies are challenging due to differences in study designs and inherent biases. This systematic review was therefore conducted in accordance to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Two reviewers (GT and MG) independently reviewed each included study and disagreements were resolved by adjudication with input from a third reviewer (TL).

The endpoints of the study were the occurrences of ventricular arrhythmias (VT/VF), SCD, cardiovascular death or all-cause mortality. The definition of these endpoints used in the different studies were analyzed. If more than one mortality endpoint was described, then SCD was preferentially used for analysis, followed by cardiovascular death and all-cause mortality. Multivariate adjusted odds ratios (OR) or hazard ratios (HR) with 95% confidence interval (CI) were extracted and analyzed for each study. When values from multivariate analysis were not
available, those from univariate analysis were used. When the latter were not provided, raw data were used to calculate unadjusted risk estimates where possible. Where arrhythmic or mortality outcomes were determined but ORs or HRs were not reported, we contacted the corresponding authors of the studies. HR value in multivariate Cox proportional hazards model was equated as OR. The pooled adjusted risk estimates from each study as the OR values with 95% CI were presented. The heterogeneity between studies was determined using Cochran's Q, the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the $I^2$ statistic from the standard chi-square test, which describes the percentage of the variability in effect estimates resulting from heterogeneity, rather than sampling error. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if no significant heterogeneity was found. Therefore, the random-effects model using the inverse variance heterogeneity method was used with $I^2 < 50\%$. To locate the origin of the heterogeneity, sensitivity analysis 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 assess for possible publication bias.

Results

A flow diagram detailing the above search terms with inclusion and exclusion criteria is depicted in Figure 1. A total of 401, 310, 27 and 122 entries were retrieved from PubMed, Embase, Cochrane Library and CINAHL Plus, respectively. Comparing with the entries extracted from the PubMed search, 143, 23 and 116 duplicate entries from the Embase, Cochrane library and CINAHL Plus searches were found and removed. This yielded 854 publications and further assessment demonstrated that 29 met the inclusion criteria $^{5,10,15,22,27-50}$. The Haarmark
2009 study was excluded due to non-symmetry of the reported confidence intervals. In the current systematic review, a total of 154946 patients were included. Three studies examined the risk in different patient populations (normotensive and hypertensive; dilated cardiomyopathy and ischemic cardiomyopathy; normal intraventricular conduction and intraventricular conduction delay). The $T_{\text{peak}} - T_{\text{end}}$ interval was examined in the following clinical settings: heart failure in 8 studies, Brugada syndrome in 6 studies, ischemic heart disease in 7 studies, pulmonary embolism in one study, Chagas disease in one study, hypertension in one study, intraventricular conduction delay in one study, dilated cardiomyopathy in one study and ischemic cardiomyopathy in one study. Five studies addressed the prognostic significance of $T_{\text{peak}} - T_{\text{end}}$ interval in the general population. The baseline characteristics of these studies are listed in Table 1. Fifteen were prospective studies and 14 were retrospective studies. The mean follow-up duration was 45 ± 48 months.

In the 28 studies, the total number of patients was 154946 (mean: 5164; range from 23 to 138404). The mean age was 58 ± 9 years old). The subjects were predominantly male (70 ± 15%). The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 105.3 ± 17.3 ms (range between 77.4 and 146.4 ms). All studies consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$ interval and increased risk of VT/VF or SCD (17 using multivariate analysis and 11 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval is associated with 1.13 times higher risk of VT/VF or SCD (95% CI: 1.10 to 1.16, $p < 0.0001$; Figure 2). The Cochrane’s $Q$ value was greater than the degrees of freedom (384 vs. 29), suggesting the true effect size was different among the various studies. Moreover, $I^2$ took a value of 92.5%, suggesting significant heterogeneity was present. Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures 3 and 4, respectively.
Begg and Mazumdar rank correlation suggested no significant publication bias (Kendal’s Tau value 0.21, p > 0.05). Egger’s test demonstrated significant asymmetry (intercept 3.6, t-value 7.8; $P < 0.0001$) 51.

To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time, and subgroup analyses based on different disease conditions and endpoints were performed. Sensitivity analysis by the leave-one-out method did not affect the overall odds ratio when each study was removed (Figure 5). When VF and SCD were analyzed as different endpoints, the ORs are the following: VT/VF (OR: 1.09, 95% CI: 1.05 to 1.13, p < 0.0001) and SCD (OR: 1.24, 95% CI 1.14 to 1.35, p < 0.0001). Subgroup analyses based on diagnosis were subsequently performed.

Heart failure

For heart failure, eight studies 27,31,35,38,40,41,45,48 consisting of 1912 patients (range from 84 to 572) with a mean age of 65 ± 7 years (70 ± 11% males) were included. The mean follow-up period was 21 ± 14 months. The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 106.3 ± 8.4 ms. All eight groups consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$ interval and increased risk of VT/VF or SCD (5 using multivariate analysis and 4 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval was associated with approximately 1.07 times the risk of these endpoints (95% CI: 1.04 to 1.11, $p < 0.0001$; Figure 6). The Cochrane’s Q value was greater than the degrees of freedom (56 vs. 7), which would suggest different true effect size among different studies. $I^2$ took a value of 87.5%, suggesting most of the observed variance reflects heterogeneity between studies.
**Brugada syndrome**

For Brugada syndrome, six studies involving 583 subjects were included (range from 23 to 325)\(^5,10,29,44,50\). The mean age was 44 ± 2 years old and 84 ± 9% of subjects were male. The mean follow-up period was 50 ± 8 months. The mean cut-off point for T\(_{\text{peak}}\) – T\(_{\text{end}}\) interval was 99.4 ± 15.2 ms. All six studies consistently reported a positive association between increased T\(_{\text{peak}}\) – T\(_{\text{end}}\) interval and increased risk of VT/VF or SCD (2 using multivariate analysis and 4 using univariate analysis). The pooled meta-analysis demonstrated that prolonged T\(_{\text{peak}}\) – T\(_{\text{end}}\) interval is associated with approximately 5.69 times the risk of these endpoints (95% CI: 1.57 to 20.57, p < 0.01; Figure 7). The Cochrane’s Q value was greater than the degrees of freedom (35 vs. 5), indicating that differing true effect sizes among the different studies. An \(I^2\) of 85.7% suggests high heterogeneity.

**Ischemic heart disease**

For ischemic heart disease, data from seven studies involving 3302 subjects were available\(^15,22,36,39,40,43,49\). As indicated above, the confidence intervals of the hazard ratio in the Haarmark 2009 study were non-symmetrical\(^43\). This study was therefore excluded from further analysis. In this sub-group analysis, data from the remaining six studies including 3201 subjects were used for the meta-analysis\(^15,22,36,39,40,49\). The mean age was 61 ± 5 years old (79 ± 5% males). The mean follow-up period was 20 ± 11 months. The mean cut-off point for T\(_{\text{peak}}\) – T\(_{\text{end}}\) interval was 112.8 ± 23.1 ms. All six studies consistently reported a positive association between increased T\(_{\text{peak}}\) – T\(_{\text{end}}\) interval and increased risk of VT/VF or SCD (three studies using
multivariate analysis and three studies using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval is associated with approximately 1.06 times the risk of these endpoints (95% CI: 1.02 to 1.09; $p = 0.001$) (Figure 8). The Cochrane’s Q value was greater than the degrees of freedom (48 vs. 4), indicating the true effect size were different among different studies. A $I^2$ value of 89.6% suggested that most of the observed variances reflect differences in true effect sizes.

General population

For the general population, five studies involving 141320 subjects (mean age 55 ± 9 years old, 87 ± 63% males) were included (ranges from 65 to 138404) [28,30,32,42,46]. The mean follow-up period was 87 ± 63 months. The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 113.6 ± 22.8 ms. All five studies consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$ interval and increased risk of VT/VF or SCD (2 using multivariate analysis and 3 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval is associated with approximately 7.6 times higher risk of reaching these endpoints (95% CI: 3.8 to 14.9, $p < 0.0001$; Figure 9). The Cochrane’s Q value was less than the degrees of freedom (3 vs. 4), suggesting that the true effect size were not significantly different between studies. A $I^2$ value of 84.0% suggests that high heterogeneity among studies.

Discussion

The cellular origin of the T-wave has been an area of intense study the previous decades [52-54]. The waveform has been attributed to electrophysiological characteristics of ventricular
cardiomyocytes located in the different regions of the myocardial wall, such as epicardium, mid-myocardium (M) and endocardium. $T_{\text{peak}} - T_{\text{end}}$ is defined as the interval between the peak of the T wave and the end of the T wave, representing the dispersion of repolarization. Initially, it was hypothesized that the $T_{\text{peak}} - T_{\text{end}}$ interval reflects the transmural dispersion of repolarization (TDR). Later work found that the end of epicardial repolarization coincided with $T_{\text{peak}}$ and end of M-cell repolarization coincided with $T_{\text{end}}$. Subsequent experiments in pigs demonstrated that $T_{\text{peak}}$ coincided with the earliest end of repolarization, whereas $T_{\text{end}}$ coincided with the latest end of repolarization. In other words, $T_{\text{peak}} - T_{\text{end}}$ was a measure of global dispersion of repolarization rather than TDR. $T_{\text{peak}} - T_{\text{end}}$ is also lead-dependent as the dispersion of repolarization varies with different cardiac regions. Therefore, for left ventricular diseases, measurements from lead V5 and for right ventricular diseases such as Brugada syndrome, measurements from lead V2, have been used for ECG interval analysis. In some studies, $T_{\text{peak}} - T_{\text{end}}$ were calculated from mean values of all 12 leads. Although the mechanism of the T wave generation remains controversial, as to whether it represents global or transmural dispersion of repolarization, a prolonged $T_{\text{peak}} - T_{\text{end}}$ interval has been associated with an increased incidence of ventricular tachyarrhythmias. Increased spatial dispersion of repolarization can produce unidirectional block, which predisposes to circus-type or spiral reentry. Moreover, this may reflect loss of the action potential dome in the epicardial region compared to the endocardial region. This is expected to increase the risk of phase 2 reentry.

The prognostic significance of $T_{\text{peak}} - T_{\text{end}}$ interval has been investigated in various clinical settings. A prolonged $T_{\text{peak}} - T_{\text{end}}$ interval has been associated with increased arrhythmogenicity in Long QT syndrome (LQTS1) and LQTS2 at baseline. Exercise is known to trigger ventricular arrhythmias in LQTS1 but not LQTS2. Greater increases in $T_{\text{peak}} - T_{\text{end}}$
interval were observed in LQTS1, suggesting that it could be a useful risk marker for arrhythmogenesis in this LQTS subtype. An accentuation of the $T_{\text{peak}} - T_{\text{end}}$ interval has been associated an increased propensity to develop Torsades de Pointes (TdP) in subjects with LQTS1. The $T_{\text{peak}} - T_{\text{end}}$ interval is also increased in Short QT syndrome (12). There are limited data regarding the utility of $T_{\text{peak}} - T_{\text{end}}$ interval in Brugada syndrome (10,13,14,50). A prolonged $T_{\text{peak}} - T_{\text{end}}$ interval has been associated with arrhythmic events in Brugada syndrome (50), which is consistent with pre-clinical data that TDR is involved in arrhythmogenesis in Brugada syndrome (68-71). Previous studies have underscored the prognostic significance of $T_{\text{peak}} - T_{\text{end}}$ interval in subjects with structural heart disease including hypertrophic cardiomyopathy (15) and myocardial infarction (14). The Copenhagen study found an inverted U relationship between $T_{\text{peak}} - T_{\text{end}}$ interval and the risk of all-cause and cardiovascular mortality, atrial fibrillation and heart failure (32). However, the ability of $T_{\text{peak}} - T_{\text{end}}$ interval to predict prognosis or arrhythmic events has not always been successful (19-21,23). Moreover, shortenings of this interval also predicted worsened survival rates (72).

In this study, we conducted a systematic review and meta-analysis into the ability of $T_{\text{peak}} - T_{\text{end}}$ to predict VT/VF and/or cardiovascular death, SCD or all-cause death. Our main findings are that prolonged $T_{\text{peak}} - T_{\text{end}} (>107.1 \pm 17.4 \text{ ms})$ is associated with a 1.16 fold increased risk in VT/VF, SCD, cardiovascular death or all-cause mortality when data from all pathological conditions were pooled. There was significant heterogeneity. Subgroup analyses were subsequently performed for each condition. The risk of VT/VF and/or SCD in Brugada syndrome was the highest with a 5.6 fold increase compared to 1.59 in the general population, 1.26 fold in ischemic heart disease and 1.07 fold in heart failure. Sensitivity analysis removing one study at a time did not alter the pooled odds ratio. Therefore, in the overall meta-analysis, the
heterogeneity is likely derived from the distinct patient populations with different diseases. In Brugada syndrome, both the depolarization and repolarization hypotheses have been proposed to explain the abnormal electrophysiological findings. As shown in our meta-analysis, a prolonged $T_{\text{peak}} - T_{\text{end}}$ interval displays the highest predictive ability for arrhythmic events in Brugada syndrome compared to other clinical conditions. This would lend weight towards abnormal repolarization being a significant contributor to arrhythmic substrate. On the contrary, in heart failure patients, there is only a small, albeit significant, increase in arrhythmic risk. This possibly suggests that increased dispersion of repolarization plays a moderated role in ventricular arrhythmogenesis, and other factors such as abnormal action potential restitution or conduction abnormalities being more important.

This systematic review with meta-analysis has several potential limitations. Firstly, publication bias in meta-analyses is frequently examined by checking for asymmetry in a funnel plot. In our case there was significant asymmetry, which may suggest some bias. However, it is known that effect estimates such as odd ratios used in this meta-analysis correlate with standard errors, and can produce spurious asymmetry in a funnel plot. Secondly, some studies included in our studies are retrospective studies, which may have more recall bias. Thirdly, although the overall number of patients included in this meta-analysis is large, for certain conditions such as Brugada syndrome a small number of patients (500 patients) were included potentially affecting or masking the true effect. Finally, our systematic review only included articles published in PubMed, Embase, Cochrane and CINAHL. It therefore might have missed articles that were not indexed in these search engines. Despite these limitations, there is strong evidence to suggest that increased $T_{\text{peak}} - T_{\text{end}}$ interval confers a higher risk of VT/VF or SCD in various clinical settings as well as in the general population.
**Figure legends**

Figure 1. Flow diagram of the study selection process.

Figure 2. Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or mortality outcomes in patient populations with different clinical conditions.

Figure 3. Funnel plot of standard errors against logarithms of odds ratios.

Figure 4. Funnel plot of precision measure against logarithms of odds ratios.

**Tables**

Table 1. Characteristics of the 28 studies included in the meta-analysis.

**Supplementary files**

Supplementary Figure 1. Sensitivity analysis using the leave-one-out method.

Supplementary Figure 2. Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or mortality outcomes in patients with heart failure.

Supplementary Figure 3. Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or mortality outcomes in patients with Brugada syndrome.

Supplementary Figure 4. Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or mortality outcomes in patients with ischemic heart disease.

Supplementary Figure 5. Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or mortality events in the general population.
Supplementary Table 1. NOS risk of bias scale for case-control studies.

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

References


401, 310, 27 and 122 publications were retrieved from PubMed, Embase, Cochrane Library and CINAHL Plus

143, 23 and 166 duplicate publications from Embase, Cochrane Library and CINAHL Plus were removed

854 publications were assessed

29 publications were included in the meta-analysis

825 publications were excluded (non-human studies, no T_{peak} – T_{end} reported, no odds or hazard ratios or data necessary to calculate were reported)

Figure 1
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**Figure 2**
Figure 3
Figure 4
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<th>Variables in multivariate model</th>
<th>Endpoints</th>
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Prior treatment includes: non-loop diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, QTc-interval prolonging drugs, myocardial infarction, valvular heart disease, hyperthyroidism, modified Charlson comorbidity index, LVH on ECG, QTc duration, heart rate.
<p>| Mugnai 2015 | P | IHD | 223 | 136 | V4, if not V5 then V6 | 64 | 77 | - | Composited fatal VT/VF SCD, non fatal VT/VF, arrhythmic death | 22 | 6 |
| Maury 2015 | R | BrS | 325 | 100 | V1 to V4 | 47 | 80 | Type 1 ST elevation in peripheral leads, syncope, Spontaneous Type 1 ST elevation, SCN5A mutation, first degree AVB, familial sudden death, QRS duration, fragmented QRS, inducibility at EPS VT/VF | 48 | 7 |
| Rosenthal 2015 | P | HF | 305 | 99 | V2 to V5 | 70 | 73 | - | VT/VF | 48 | 6 |</p>
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**Abbreviations:** P: Prospective; R: Retrospective; BrS: Brugada syndrome; HF: Heart Failure; GP: General Population; IHD: Ischemic Heart Disease; CVD: Cardiovascular Death; MAE: Major Adverse Events; SCD: Sudden Cardiac Death; VT: Ventricular Tachycardia; VF: Ventricular Fibrillation; \(\Delta T_{\text{peak}} - T_{\text{end}}\): change in \(T_{\text{peak}} - T_{\text{end}}\) following cardiac resynchronization therapy.