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

Short title: Systematic review of $T_{peak} - T_{end}$ for risk stratification

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Abstract

Background: The $T_{peak} - T_{end}$ interval, an electrocardiographic marker reflecting transmural dispersion of repolarization, has been used to predict ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD) in different clinical settings.

Objective: This systematic review and meta-analysis evaluated the significance of $T_{peak} - T_{end}$ interval in predicting arrhythmic and/or mortality endpoints.

Methods: PubMed, Embase, Cochrane Library and CINAHL Plus databases were searched through 30th November 2016.

Results: Of the 854 studies identified initially, 33 observational studies involving 155856 patients were included in our meta-analysis. $T_{peak} - T_{end}$ interval prolongation (mean cut-off: 103.3 ± 17.4 ms) was a significant predictor of the arrhythmic or mortality outcomes (odds ratio (OR): 1.14, 95% CI: 1.11 to 1.17, $p < 0.001$). When different end-points were analyzed, the ORs are as follows: VT/VF (1.10, 95% CI: 1.06 to 1.13, $p < 0.0001$), SCD (1.27, 95% CI 1.17 to 1.39, $p < 0.0001$), cardiovascular death (1.40, 95% CI 1.19 to 1.64, $p < 0.0001$), and all-cause mortality (4.56, 95% CI 0.62 to 33.68, $p < 0.0001$). Subgroup analysis for each disease revealed that the risk of VT/VF or death was highest for Brugada syndrome (OR: 5.68, 95% CI: 1.57 to 20.53, $p < 0.01$), followed by hypertension (OR: 1.52, 95% CI: 1.26 to 1.85, $p < .0001$), heart failure (OR: 1.07, 95% CI: 1.04 to 1.11, $p < .0001$) and ischemic heart disease (OR: 1.06, 95% CI: 1.02 to 1.10, $p = 0.001$). In the general population, a prolonged $T_{peak} - T_{end}$ interval also predicted arrhythmic or mortality outcomes (OR: 1.59, 95% CI: 1.21 to 2.09, $p < 0.001$).

Conclusion: The $T_{peak} - T_{end}$ interval is useful risk stratification tool in different diseases and in the general population.

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 identifying 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 controversial regarding the predictive value 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 [24]. MEDLINE, Embase, Cochrane library and CINAHL Plus were searched for studies that investigated the relationship between $T_{peak} - T_{end}$ 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) $T_{peak} - T_{end}$ 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) [25]. 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 conducted in accordance to PRISMA statement [26] and registered with PROSPERO (Review number 52916). 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 $I^2 < 50\%$, otherwise the random-effects model using the inverse variance heterogeneity method was used. 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 30 met the inclusion criteria [5, 10, 15, 22, 27-50]. Three groups provided their data on odds ratio (OR) or hazard ratio (HR), and these studies were also included. Thus, in the final meta-analysis, 33 studies were included.

A total of 155856 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 $T_{peak} - T_{end}$ interval was examined in the following clinical settings: heart failure in eight studies [27, 31, 35, 38, 40, 41, 45, 48], ischemic heart disease in eight studies [15, 22, 36, 39, 40, 43, 49, 53], Brugada syndrome in six studies [5, 10, 29, 34, 44, 50], hypertension in two studies [30, 51], pulmonary embolism in one study [33], Chagas disease in one study [37], intraventricular conduction delay in one study [42], dilated cardiomyopathy in one study [40] and ischemic cardiomyopathy in one study [40]. Five studies addressed the prognostic significance of $T_{peak} - T_{end}$ interval in the general population [28, 30, 32, 42, 46]. 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 42 ± 48 months.

In the 33 studies, the total number of patients was 155856 (mean: 4329; range from 23 to 138404). The mean age was 62 ± 11 years old). The subjects were predominantly male (69%). The mean cut-off point for $T_{peak} - T_{end}$ interval was 103.3 ± 17.4 ms (range between 77.4 and 146.4 ms). All studies consistently reported a positive association between increased $T_{peak} - T_{end}$ interval and increased risk of VT/VF or SCD (17 using multivariate analysis and 16 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{peak} - T_{end}$ interval is associated with 1.14 times higher risk of VT/VF or SCD (95% CI: 1.11 to 1.17, $p < 0.0001$;

Figure 2). The Cochran's Q value was greater than the degrees of freedom (432 vs. 34), suggesting the true effect size was different among the various studies. Moreover, I^2 took a value of 92%, 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 0.15, $p > 0.05$). Egger's test demonstrated significant asymmetry (intercept 3.5, t-value 8.1; $P < 0.0001$) [52]. When HR and OR were analyzed separately, the data were as follows: HR = 1.12 (95% CI: 1.09 to 1.16, $p < 0.0001$; Figure A1); OR = 1.23 (95% CI: 1.14 to 1.32, $p < 0.0001$; Figure A2).

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. VT/VF and different mortality measures were subsequently analyzed as different end-points. For spontaneous and inducible VT/VF, the OR was 1.10 (95% CI: 1.06 to 1.13, $p < 0.0001$) (Figure A3). Exclusion of three studies reporting inducible VT/VF did not significantly alter the pooled OR (1.09, 95% CI: 1.06 to 1.13; Figure A4). For mortality endpoints, the ORs were: SCD (1.27, 95% CI 1.17 to 1.39, $p < 0.0001$; Figure A5), cardiovascular death (1.40, 95% CI 1.19 to 1.64, $p < 0.0001$; Figure A6), and all-cause mortality (4.56, 95% CI 0.62 to 33.68, $p < 0.0001$; Figure A7). 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 64 ± 13 years (72% males) were included. The mean follow-up period was 21 ± 14 months. The mean cut-off point for $T_{peak} - T_{end}$ interval was 106.3 ± 8.4 ms. All eight groups consistently reported a positive association between increased $T_{peak} - T_{end}$ interval and increased risk of VT/VF or SCD (7 using multivariate analysis and 1 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{peak} - T_{end}$ interval was associated with approximately 1.07 times the risk of these endpoints (95% CI: 1.04 to 1.11, $p < 0.0001$; Figure A8). The Cochran's Q value was greater than the degrees of freedom (56 vs. 6), which would suggest different true effect size among different studies. I^2 took a value of 88%, suggesting most of the observed variance reflects heterogeneity between studies.

Ischemic heart disease

For ischemic heart disease, data from eight studies involving 3402 subjects were included in the sub-group analysis [15, 22, 36, 39, 40, 43, 49, 53]. The mean age was 63 ± 12 years old (77% males). The mean follow-up period was 18 ± 12 months. The mean cut-off point for $T_{peak} - T_{end}$ interval was 109.6 ± 20.4 ms. All eight studies consistently reported a positive association between increased $T_{peak} - T_{end}$ interval and increased risk of VT/VF or SCD (three studies using multivariate analysis and five studies using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{peak} - T_{end}$ interval is associated with approximately 1.06 times the risk of these endpoints (95% CI: 1.02 to 1.10; $p < 0.001$) (Fig. A9). The Cochran's Q value was greater than the degrees of freedom (51 vs. 6), 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.

242

243 *Brugada syndrome*

244 For Brugada syndrome, six studies involving 583 subjects were included (range from 23
245 to 325) [5, 10, 29, 34, 44, 50]. The mean age was 46 ± 11 years old and 80% of subjects were male. The
246 mean follow-up period was 50 ± 8 months. The mean cut-off point for $T_{peak} - T_{end}$ interval was
247 95.8 ± 16.3 ms. All six studies consistently reported a positive association between increased
248 $T_{peak} - T_{end}$ interval and increased risk of VT/VF or SCD (2 using multivariate analysis and 4
249 using univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{peak} - T_{end}$
250 interval is associated with approximately 5.68 times the risk of these endpoints (95% CI: 1.57 to
251 20.53, $p < 0.001$; Fig. A10). The Cochran's Q value was greater than the degrees of freedom (35
252 vs. 5), indicating that differing true effect sizes among the different studies. An I^2 of 86%
253 suggests high heterogeneity.

254

255 *Hypertension*

256 For hypertension, two studies involving 881 subjects were included (range from 57 to
257 824) [30, 51]. The mean age was 51 ± 11 years old and 55% of subjects were male. The mean
258 follow-up period was 192 months. The mean cut-off point for $T_{peak} - T_{end}$ interval was 96.7 ±
259 36.3 ms. Both studies consistently reported a positive association between increased $T_{peak} - T_{end}$
260 interval and increased risk of VT/VF or SCD in multivariate analysis. The pooled meta-analysis
261 demonstrated that prolonged $T_{peak} - T_{end}$ interval is associated with approximately 1.52 times the
262 risk of these endpoints (95% CI: 1.26 to 1.85, $p < 0.01$; Fig. A10). The Cochran's Q value was

greater than the degrees of freedom (1.1 vs. 1), indicating that differing true effect sizes among the different studies. An I^2 of 6% suggests a low heterogeneity.

General population

For the general population, five studies involving 148215 subjects (mean age 62 ± 11 years old, 43% males) were included (ranges from 65 to 138404) [28, 30, 32, 42, 46]. The mean follow-up period was 111 ± 55 months. The mean cut-off point for $T_{peak} - T_{end}$ interval was 99.8 ± 27.6 ms. All five studies consistently reported a positive association between increased $T_{peak} - T_{end}$ 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 $T_{peak} - T_{end}$ interval is associated with approximately 1.6 times higher risk of reaching these endpoints (95% CI: 1.2 to 2.1, $p < 0.0001$; Figure A12). The Cochran's Q value was less than the degrees of freedom (25 vs. 4), indicating that differing true effect sizes among the different studies. An I^2 value of 84.0% suggests a high heterogeneity among studies.

Discussion

The main findings of this study are the following:

i. A prolonged $T_{peak} - T_{end}$ is associated with a 1.14 fold increased risk in VT/VF, SCD, cardiovascular death or all-cause mortality when data from all pathological conditions were pooled with significant heterogeneity among studies;

ii. Subgroup analyses demonstrated that the risk of VT/VF and/or SCD in Brugada syndrome was the highest with a 5.6 fold increase compared to 1.52 in hypertension, 1.07 in heart failure and 1.06 in ischemic heart disease.

iii. In the general population, a prolonged $T_{peak} - T_{end}$ interval was also predictive of arrhythmic or mortality outcomes with an OR of 1.59.

The cellular origin of the T-wave has been an area of intense study the previous decades [54-56]. 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 [57]. $T_{peak} - T_{end}$ is defined as the interval between the peak of the T wave and the end of the T wave, representing the dispersion of repolarization [9]. Initially, it was hypothesized that the $T_{peak} - T_{end}$ interval reflects the transmural dispersion of repolarization (TDR). Later work found that the end of epicardial repolarization coincided with T_{peak} and end of M-cell repolarization coincided with T_{end} [58]. Subsequent experiments in pigs demonstrated that T_{peak} coincided with the earliest end of repolarization, whereas T_{end} coincided with the latest end of repolarization. In other words, $T_{peak} - T_{end}$ was a measure of global dispersion of repolarization rather than TDR [9, 59-61]. $T_{peak} - T_{end}$ is also lead-dependent as the dispersion of repolarization varies with different cardiac regions [62]. 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, $T_{peak} - T_{end}$ 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 $T_{peak} - T_{end}$ interval has been associated with an increased incidence of ventricular tachyarrhythmias [5, 10, 15, 22, 27-50, 63]. Increased spatial dispersion of repolarization

306 can produce unidirectional block, which predisposes to circus-type or spiral reentry [60, 64-66].
307 Moreover, this may reflect loss of the action potential dome in the epicardial region compared to
308 the endocardial region. This is expected to increase the risk of phase 2 reentry [67, 68]. Several ECG
309 parameters, such as QT interval, QT dispersion and T-wave alternans (TWA) are associated with
310 $T_{peak} - T_{end}$. The occurrence of TWA is expected to increase the spatial dispersion of
311 repolarization. Indeed, microvolt TWAs have been associated with the duration of $T_{peak} - T_{end}$ [4].
312 The mechanism of TWA generation is multi-factorial but has traditionally been described by the
313 restitution hypothesis [5]. The TWA magnitude is likely a function of the heterogeneity in Ca^{2+}
314 alternans which can drive APD alternans. Conversely, a steep spatial gradient of repolarization
315 can convert spatially concordant alternans to spatially discordant alternans.

316 The prognostic significance of $T_{peak} - T_{end}$ interval has been investigated in various
317 clinical settings. A prolonged $T_{peak} - T_{end}$ interval has been associated with increased
318 arrhythmogenicity in Long QT syndrome (LQTS)1 and LQTS2 at baseline [69]. Exercise is known
319 to trigger ventricular arrhythmias in LQTS1 but not LQTS2. Greater increases in $T_{peak} - T_{end}$
320 interval were observed in LQTS1, suggesting that it could be a useful risk marker for
321 arrhythmogenesis in this LQTS subtype. An accentuation of the T_{peak} - T_{end} interval has been
322 associated an increased propensity to develop Torsades de Pointes (TdP) in subjects with LQTS1
323 [12]. The $T_{peak} - T_{end}$ interval is also increased in Short QT syndrome (12). There are limited data
324 regarding the utility of T_{peak} - T_{end} interval in Brugada syndrome [10, 13, 14, 50]. A prolonged $T_{peak} -$
325 T_{end} interval has been associated with arrhythmic events in Brugada syndrome [50], which is
326 consistent with pre-clinical data that TDR is involved in arrhythmogenesis in Brugada syndrome
327 [70-73]. Previous studies have underscored the prognostic significance of $T_{peak} - T_{end}$ interval in
328 subjects with structural heart disease including hypertrophic cardiomyopathy and myocardial

infarction. The Copenhagen study found an inverted U relationship between $T_{peak} - T_{end}$ interval and the risk of all-cause and cardiovascular mortality, atrial fibrillation and heart failure [32]. However, the abitily of $T_{peak} - T_{end}$ 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 [74].

As shown in our meta-analysis, a prolonged $T_{peak} - T_{end}$ interval displays the highest predictive ability for arrhythmic events in Brugada syndrome compared to other clinical conditions.

In Brugada syndrome, both the depolarization and repolarization hypotheses have been proposed to explain the abnormal electrophysiological findings [71, 75]. 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 [76] or conduction abnormalities may be more important [77].

It should be noted that the results are not dramatic. Based on this meta-analysis we would advocate that a different cut-off value should be considered for each cardiac pathology which should also be considered alongside other known factors known to associate with cardiac risk such as such as QT interval, QT dispersion or T wave alternans [78]. Increased dispersion of repolarization, which is reflected by the prolonged $T_{peak} - T_{end}$ intervals, is only one mechanism by which re-entrant mechanism is generated. Indeed, in Mines' seminal work on circus-type re-entry, his proposal included three criteria: the presence of unidirectional conduction block, a distinct pathway along which the cardiac excitation can propagate, and interruption of the circuit

will terminate the re-entrant activity [79]. Prolonged $T_{peak} - T_{end}$ interval will increase the likelihood of generating unidirectional conduction block, but other factors, such as slowed conduction and increased dispersion of conduction are also important but not reflected in the $T_{peak} - T_{end}$ interval. A recent meta-analysis showed that another measure of repolarization, the QT interval, predicted mortality [80]. The results were more dramatic, reporting a 24% increase in the risk of SCD with every 50 millisecond increase in the QT interval.

Cut-off points for different conditions

Of the different study populations, the degree of $T_{peak} - T_{end}$ prolongation for significant elevations in arrhythmic risk for the general population is the greatest with a cut-off point of 113.6 ms. For some diseased states, the cut-off value is much lower. Thus, for Brugada syndrome and heart failure, the cut-off values for $T_{peak} - T_{end}$ duration were 95.8 ms and 106.3 ms, respectively. Interestingly, the cut-off for ischemic heart disease patients was not significantly different form that of the general population, with a value of 109.6 ms. Whilst the $T_{peak} - T_{end}$ could provide additional information for risk stratification, at the moment it should not be used on its own in estimating arrhythmia risk. However, it could provide incremental information regarding risk stratification in more complex patients and when the risk estimation based on conventional parameters might be difficult to calculate.

Limitations

This systematic review with meta-analysis has several potential limitations. Firstly, hazard ratios were equated as odds ratios. It has been suggested that when event rates or

probabilities are low, hazard ratios and odds ratios can be equated [81]. Nonetheless, we have performed additional analysis by pooling HRs and ORs separately. Secondly, a significant heterogeneity among studies was noted. 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. Thirdly, 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 asymmetry in a funnel plot. Fourthly, some studies included in our studies are retrospective studies, which may have more recall bias. Finally, 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.

Tables

Table 1. Characteristics of the 33 studies included in the meta-analysis.

Appendices

Figure A1. Forest plot demonstrating the hazard ratios for studies examining the relationship between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes.

Figure A2. Forest plot demonstrating the odds ratios for studies examining the relationship between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes.

Figure A3. Forest plot demonstrating the odds ratios for studies reporting inducible or spontaneous VT/VF outcomes.

Figure A4. Forest plot demonstrating the odds ratios for studies reporting spontaneous VT/VF outcomes.

Figure A5. Forest plot demonstrating the odds ratios for studies reporting sudden cardiac death.

Figure A6. Forest plot demonstrating the odds ratios for studies reporting cardiovascular death.

Figure A7. Forest plot demonstrating the odds ratios for studies reporting all-cause mortality.

Figure A8. Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes in patients with heart failure.

Figure A9. Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes in patients with ischemic heart disease.

Figure A10. Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes in patients with Brugada syndrome.

Figure A11. Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes in patients with hypertension.

Figure A12. Forest plot demonstrating the association between $T_{peak} - T_{end}$ 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.

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Figure 1. Flow diagram of the study selection process.

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661 **Figure 2.** Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or

662 mortality outcomes in patient populations with different clinical conditions.

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

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

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