

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

3 Short title: Systematic review of $T_{\text{peak}} - T_{\text{end}}$ for risk stratification
4

5 Gary Tse MBBS PhD FESC FACC ^{1,2,3}, Mengqi Gong MD ⁴, Wing Tak Wong MPhil PhD ⁵,
6 Stamatis Georgopoulos MD ⁶, Konstantinos P. Letsas MD FESC ⁶, Vassilios S Vassiliou MA
7 MBBS MRCP PhD FHEA FESC ⁷, Yat Sun Chan MBBS FRCP FACC ¹, Bryan P Yan MBBS
8 FRCP FACC ¹, Sunny Hei Wong MBChB DPhil MRCP ^{1,2}, William KK Wu MMedSc MPhil
9 PhD FRCPath ^{2,8}, Ana Ciobanu MD PhD ⁹, Guangping Li, MD, PhD ⁴, Jayaprakash Shenthar
10 MD ¹⁰, Ardan M. Saguner MD ¹¹, Sadeq Ali-Hasan-Al-Saegh, MD ¹², Aishwarya Bhardwaj MD
11 ¹³, Abhishek C. Sawant, MD MPH ¹³, Paula Whittaker MBChB MPH MMed MRCP ³,
12 Yunlong Xia MD PhD ¹⁴, Gan-Xin Yan MD PhD ¹⁵, Tong Liu MD PhD ⁴
13

14 ¹ Department of Medicine and Therapeutics, Faculty of Medicine, Chinese University of Hong
15 Kong, Hong Kong, SAR, P.R. China;

16 ² Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong
17 Kong, Hong Kong, SAR, P.R. China;

18 ³ School of Health Sciences, University of Manchester, United Kingdom

19 ⁴ Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of
20 Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University,
21 Tianjin 300211, People's Republic of China

22 ⁵ School of Life Sciences, Chinese University of Hong Kong, Hong Kong, SAR, P.R. China

23 ⁶ Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, “Evangelismos”
24 General Hospital of Athens, Athens, Greece

25 ⁷ Norwich Medical School, University of East Anglia, Bob Champion Research & Education
26 Building, James Watson Road, Norwich, UK; Royal Brompton Hospital and Imperial College
27 London, UK

28 ⁸ Department of Anaesthesia and Intensive Care, State Key Laboratory of Digestive Disease,
29 LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China

30 ⁹ Department of Cardiology, Theodor Burghele Clinical Hospital, Carol Davila University of
31 Medicine and Pharmacy, Bucharest, Romania

32 ¹⁰ Electrophysiology Unit Sri Jayadeva Institute of Cardiovascular Sciences and Research B G
33 Road, 9th Block, Jayanagar, Bangalore - 560069 India

34 ¹¹ Department of Cardiology, University Heart Center, Zurich, Switzerland

35 ¹² Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

36 ¹³ Division of Cardiology, Department of Internal Medicine, State University of New York at
37 Buffalo)

38 ¹⁴ Department of Cardiovascular Medicine, First Affiliated Hospital of Dalian Medical
39 University, Dalian, P.R. China

40 ¹⁵ Lankenau Institute for Medical Research and Lankenau Medical Center, Wynnewood,
41 Pennsylvania, USA; Beijing Anzhen Hospital, Capital Medical University, Beijing, China

42

43 *Correspondence to*

44 *Assistant Professor Gary Tse*

45 Department of Medicine and Therapeutics

46 The Chinese University of Hong Kong,

47 Hong Kong, SAR, P.R. China

48 Email: tseg@cuhk.edu.hk

49 Telephone: +852 2632 3125

50

51 *Associate Professor Tong Liu*

52 Department of Cardiology,

53 Tianjin Institute of Cardiology,

54 Second Hospital of Tianjin Medical University,

55 Tianjin 300211, People's Republic of China

56 Email: liutongdoc@126.com

57 Keywords: Tpeak - Tend; dispersion of repolarization; risk stratification; ventricular arrhythmia;

58 sudden cardiac death

59 Word count: 4220 excluding references

60

61 **Abstract**

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

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

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

69 **Results:** Of the 854 studies identified initially, 33 observational studies involving 155856
70 patients were included in our meta-analysis. $T_{\text{peak}} - T_{\text{end}}$ interval prolongation (mean cut-off:
71 103.3 ± 17.4 ms) was a significant predictor of the arrhythmic or mortality outcomes (odds ratio
72 (OR): 1.14, 95% CI: 1.11 to 1.17, $p < 0.001$). When different end-points were analyzed, the ORs
73 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,
74 $p < 0.0001$), cardiovascular death (1.40, 95% CI 1.19 to 1.64, $p < 0.0001$), and all-cause
75 mortality (4.56, 95% CI 0.62 to 33.68, $p < 0.0001$). Subgroup analysis for each disease revealed
76 that the risk of VT/VF or death was highest for Brugada syndrome (OR: 5.68, 95% CI: 1.57 to
77 20.53, $p < 0.01$), followed by hypertension (OR: 1.52, 95% CI: 1.26 to 1.85, $p < .0001$), heart
78 failure (OR: 1.07, 95% CI: 1.04 to 1.11, $p < .0001$) and ischemic heart disease (OR: 1.06, 95%
79 CI: 1.02 to 1.10, $p = 0.001$). In the general population, a prolonged $T_{\text{peak}} - T_{\text{end}}$ interval also
80 predicted arrhythmic or mortality outcomes (OR: 1.59, 95% CI: 1.21 to 2.09, $p < 0.001$).

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

83

84 **Introduction**

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

103

104 **Method**

105 *Search strategy, inclusion and exclusion criteria*

106 The meta-analysis was performed according to the Preferred Reporting Items for
107 Systematic Reviews and Meta-Analyses statement ²⁴. MEDLINE, Embase, Cochrane library and
108 CINAHL Plus were searched for studies that investigated the relationship between $T_{\text{peak}} - T_{\text{end}}$
109 interval with arrhythmic or mortality endpoints using the following terms: [" $T_{\text{peak}} - T_{\text{end}}$ " OR
110 " $T_{\text{peak}}-T_{\text{end}}$ " OR " $T_{\text{p}} - T_{\text{e}}$ " OR " $T_{\text{p}}-T_{\text{e}}$ " OR " $T_{\text{peak}}-end$ " OR " $T_{\text{p}}-e$ " OR "T(peak)-T(end)"
111 OR "T wave peak-to-end" OR "T peak-T end" OR "TPEc" OR "T-peak to T-end" OR "Tpeak-to-
112 tend"]. The search period was from the beginning of the databases (1965 for PubMed, 1910 for
113 Embase, 1996 for Cochrane Library, 1937 for CINAHL Plus) through to 30th November 2016,
114 with no language restrictions. The following inclusion criteria were applied: i) the design was a
115 case-control, prospective or retrospective observational study in humans, ii) $T_{\text{peak}} - T_{\text{end}}$ interval
116 durations were determined; iii) endpoint events [appropriate implantable cardioverter-
117 defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death
118 (SCD), cardiovascular death (CVD) or all-cause mortality were reported and iv) odds ratios
119 (ORs) or hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) or data
120 necessary to calculate these were described.

121 The quality assessment of these studies included in our meta-analysis was performed
122 using the Newcastle–Ottawa Quality Assessment Scale (NOS) ²⁵. The point score system
123 evaluated the categories of study participant selection, comparability of the results, and quality of
124 the outcomes. The following characteristics were assessed: a) representativeness of the exposed
125 cohort; b) selection of the non-exposed cohort; c) ascertainment of exposure; d) demonstration
126 that outcome of interest was not present at the start of study; e) comparability of cohorts on the
127 basis of the design or analysis; f) assessment of outcomes; g) follow-up period sufficiently long

128 for outcomes to occur; and h) adequacy of follow-up of cohorts. This scale varied from zero to
129 nine stars, which indicated that studies were graded as poor quality if they met <5 criteria, fair if
130 they met 5 to 7 criteria, and good if they met >8 criteria. The details of the NOS quality
131 assessment are shown in Supplementary Tables 1 and 2.

132

133 *Data extraction and statistical analysis*

134 Data from the different studies were entered in pre-specified spreadsheet in Microsoft
135 Excel. All potentially relevant reports were retrieved as complete manuscripts and assessed for
136 compliance with the inclusion criteria. In this meta-analysis, the extracted data elements
137 consisted of: i) publication details: last name of first author, publication year and locations; ii)
138 study design; iii) follow-up duration; iv) definition of $T_{\text{peak}} - T_{\text{end}}$ interval; v) lead(s) where the
139 $T_{\text{peak}} - T_{\text{end}}$ interval was measured; vi) endpoint(s); vii) the quality score; and viii) the
140 characteristics of the population including sample size, gender, age and number of subjects.
141 Meta-analyses of observational studies are challenging due to differences in study designs and
142 inherent biases. This systematic review was conducted in accordance to PRISMA statement ²⁶
143 and registered with PROSPERO (Review number 52916). Two reviewers (GT and MG)
144 independently reviewed each included study and disagreements were resolved by adjudication
145 with input from a third reviewer (TL).

146 The endpoints of the study were the occurrences of ventricular arrhythmias (VT/VF),
147 SCD, cardiovascular death or all-cause mortality. The definition of these endpoints used in the
148 different studies were analyzed. If more than one mortality endpoint was described, then SCD
149 was preferentially used for analysis, followed by cardiovascular death and all-cause mortality.
150 Multivariate adjusted odds ratios (OR) or hazard ratios (HR) with 95% confidence interval (CI)

151 were extracted and analyzed for each study. When values from multivariate analysis were not
152 available, those from univariate analysis were used. When the latter were not provided, raw data
153 were used to calculate unadjusted risk estimates where possible. Where arrhythmic or mortality
154 outcomes were determined but ORs or HRs were not reported, we contacted the corresponding
155 authors of the studies. HR value in multivariate Cox proportional hazards model was equated as
156 OR. The pooled adjusted risk estimates from each study as the OR values with 95% CI were
157 presented.

158 The heterogeneity between studies was determined using Cochran's Q, the weighted sum
159 of squared differences between individual study effects and the pooled effect across studies, and
160 the I^2 statistic from the standard chi-square test, which describes the percentage of the variability
161 in effect estimates resulting from heterogeneity, rather than sampling error. $I^2 > 50\%$ was
162 considered to reflect significant statistical heterogeneity. A fixed effects model was used if $I^2 <$
163 50% , otherwise the random-effects model using the inverse variance heterogeneity method was
164 used. To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time,
165 and subgroup analyses based on different disease conditions and different endpoints were
166 performed. Funnel plots, Begg and Mazumdar rank correlation test and Egger's test were used to
167 assess for possible publication bias.

168

169 **Results**

170 A flow diagram detailing the above search terms with inclusion and exclusion criteria is
171 depicted in Figure 1. A total of 401, 310, 27 and 122 entries were retrieved from PubMed,
172 Embase, Cochrane Library and CINAHL Plus, respectively. Comparing with the entries
173 extracted from the PubMed search, 143, 23 and 116 duplicate entries from the Embase, Cochrane

174 library and CINAHL Plus searches were found and removed. This yielded 854 publications and
175 further assessment demonstrated that 30 met the inclusion criteria ^{5, 10, 15, 22, 27-50}. Three groups
176 provided their data on odds ratio (OR) or hazard ratio (HR), and these studies were also included.
177 Thus, in the final meta-analysis, 33 studies were included.

178 A total of 155856 patients were included. Three studies examined the risk in different
179 patient populations (normotensive and hypertensive; dilated cardiomyopathy and ischemic
180 cardiomyopathy; normal intraventricular conduction and intraventricular conduction delay). The
181 $T_{\text{peak}} - T_{\text{end}}$ interval was examined in the following clinical settings: heart failure in eight studies
182 ^{27, 31, 35, 38, 40, 41, 45, 48}, ischemic heart disease in eight studies ^{15, 22, 36, 39, 40, 43, 49, 53}, Brugada
183 syndrome in six studies ^{5, 10, 29, 34, 44, 50}, hypertension in two studies ^{30, 51}, pulmonary embolism in
184 one study ³³, Chagas disease in one study ³⁷, intraventricular conduction delay in one study ⁴²,
185 dilated cardiomyopathy in one study ⁴⁰ and ischemic cardiomyopathy in one study ⁴⁰. Five
186 studies addressed the prognostic significance of $T_{\text{peak}} - T_{\text{end}}$ interval in the general population ^{28,}
187 ^{30, 32, 42, 46}. The baseline characteristics of these studies are listed in Table 1. Fifteen were
188 prospective studies and 14 were retrospective studies. The mean follow-up duration was 42 ± 48
189 months.

190 In the 33 studies, the total number of patients was 155856 (mean: 4329; range from 23 to
191 138404). The mean age was 62 ± 11 years old). The subjects were predominantly male (69%).
192 The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 103.3 ± 17.4 ms (range between 77.4 and
193 146.4 ms). All studies consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$
194 interval and increased risk of VT/VF or SCD (17 using multivariate analysis and 16 using
195 univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval
196 is associated with 1.14 times higher risk of VT/VF or SCD (95% CI: 1.11 to 1.17, $p < 0.0001$;

197 Figure 2). The Cochran's Q value was greater than the degrees of freedom (432 vs. 34),
198 suggesting the true effect size was different among the various studies. Moreover, I^2 took a value
199 of 92%, suggesting significant heterogeneity was present. Funnel plot plotting standard errors or
200 precision against the logarithms of the odds ratio are shown in Figures 3 and 4, respectively.
201 Begg and Mazumdar rank correlation suggested no significant publication bias (Kendal's Tau
202 value 0.15, $p > 0.05$). Egger's test demonstrated significant asymmetry (intercept 3.5, t-value 8.1;
203 $P < 0.0001$)⁵². When HR and OR were analyzed separately, the data were as follows: HR = 1.12
204 (95% CI: 1.09 to 1.16, $p < 0.0001$; Figure A1); OR = 1.23 (95% CI: 1.14 to 1.32, $p < 0.0001$;
205 Figure A2).

206 To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a
207 time, and subgroup analyses based on different disease conditions and endpoints were
208 performed. Sensitivity analysis by the leave-one-out method did not affect the overall odds ratio
209 when each study was removed. VT/VF and different mortality measures were subsequently
210 analyzed as different end-points. For spontaneous and inducible VT/VF, the OR was 1.10 (95%
211 CI: 1.06 to 1.13, $p < 0.0001$) (Figure A3). Exclusion of three studies reporting inducible VT/VF
212 did not significantly alter the pooled OR (1.09, 95% CI: 1.06 to 1.13; Figure A4). For mortality
213 endpoints, the ORs were: SCD (1.27, 95% CI 1.17 to 1.39, $p < 0.0001$; Figure A5),
214 cardiovascular death (1.40, 95% CI 1.19 to 1.64, $p < 0.0001$; Figure A6), and all-cause mortality
215 (4.56, 95% CI 0.62 to 33.68, $p < 0.0001$; Figure A7). Subgroup analyses based on diagnosis were
216 subsequently performed.

217

218 *Heart failure*

219 For heart failure, eight studies^{27, 31, 35, 38, 40, 41, 45, 48} consisting of 1912 patients (range from
220 84 to 572) with a mean age of 64 ± 13 years (72% males) were included. The mean follow-up
221 period was 21 ± 14 months. The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 106.3 ± 8.4 ms.
222 All eight groups consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$
223 interval and increased risk of VT/VF or SCD (7 using multivariate analysis and 1 using
224 univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval
225 was associated with approximately 1.07 times the risk of these endpoints (95% CI: 1.04 to 1.11,
226 $p < 0.0001$; Figure A8). The Cochran's Q value was greater than the degrees of freedom (56 vs.
227 6), which would suggest different true effect size among different studies. I^2 took a value of
228 88%, suggesting most of the observed variance reflects heterogeneity between studies.

229

230 *Ischemic heart disease*

231 For ischemic heart disease, data from eight studies involving 3402 subjects were included
232 in the sub-group analysis^{15, 22, 36, 39, 40, 43, 49, 53}. The mean age was 63 ± 12 years old (77% males).
233 The mean follow-up period was 18 ± 12 months. The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval
234 was 109.6 ± 20.4 ms. All eight studies consistently reported a positive association between
235 increased $T_{\text{peak}} - T_{\text{end}}$ interval and increased risk of VT/VF or SCD (three studies using
236 multivariate analysis and five studies using univariate analysis). The pooled meta-analysis
237 demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval is associated with approximately 1.06 times the
238 risk of these endpoints (95% CI: 1.02 to 1.10; $p < 0.001$) (Fig. A9). The Cochran's Q value was
239 greater than the degrees of freedom (51 vs. 6), indicating the true effect size were different
240 among different studies. A I^2 value of 89.6% suggested that most of the observed variances
241 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 $T_{\text{peak}} - T_{\text{end}}$ interval was
247 95.8 ± 16.3 ms. All six studies consistently reported a positive association between increased
248 $T_{\text{peak}} - T_{\text{end}}$ 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 $T_{\text{peak}} - T_{\text{end}}$
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 $T_{\text{peak}} - T_{\text{end}}$ interval was $96.7 \pm$
259 36.3 ms. Both studies consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$
260 interval and increased risk of VT/VF or SCD in multivariate analysis. The pooled meta-analysis
261 demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ 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

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

265

266 *General population*

267 For the general population, five studies involving 148215 subjects (mean age 62 ± 11
268 years old, 43% males) were included (ranges from 65 to 138404) ^{28, 30, 32, 42, 46}. The mean follow-
269 up period was 111 ± 55 months. The mean cut-off point for $T_{\text{peak}} - T_{\text{end}}$ interval was 99.8 ± 27.6
270 ms. All five studies consistently reported a positive association between increased $T_{\text{peak}} - T_{\text{end}}$
271 interval and increased risk of VT/VF or SCD (2 using multivariate analysis and 3 using
272 univariate analysis). The pooled meta-analysis demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ interval
273 is associated with approximately 1.6 times higher risk of reaching these endpoints (95% CI: 1.2
274 to 2.1, $p < 0.0001$; Figure A12). The Cochran's Q value was less than the degrees of freedom (25
275 vs. 4), indicating that differing true effect sizes among the different studies. An I^2 value of 84.0%
276 suggests a high heterogeneity among studies.

277

278 **Discussion**

279 The main findings of this study are the following:

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

- 283 ii. Subgroup analyses demonstrated that the risk of VT/VF and/or SCD in Brugada
284 syndrome was the highest with a 5.6 fold increase compared to 1.52 in
285 hypertension, 1.07 in heart failure and 1.06 in ischemic heart disease.
- 286 iii. In the general population, a prolonged $T_{\text{peak}} - T_{\text{end}}$ interval was also predictive of
287 arrhythmic or mortality outcomes with an OR of 1.59.

288 The cellular origin of the T-wave has been an area of intense study the previous decades
289 ⁵⁴⁻⁵⁶. The waveform has been attributed to electrophysiological characteristics of ventricular
290 cardiomyocytes located in the different regions of the myocardial wall, such as epicardium, mid-
291 myocardium (M) and endocardium ⁵⁷. $T_{\text{peak}} - T_{\text{end}}$ is defined as the interval between the peak of
292 the T wave and the end of the T wave, representing the dispersion of repolarization ⁹. Initially, it
293 was hypothesized that the $T_{\text{peak}} - T_{\text{end}}$ interval reflects the transmural dispersion of repolarization
294 (TDR). Later work found that the end of epicardial repolarization coincided with T_{peak} and end of
295 M-cell repolarization coincided with T_{end} ⁵⁸. Subsequent experiments in pigs demonstrated that
296 T_{peak} coincided with the earliest end of repolarization, whereas T_{end} coincided with the latest end
297 of repolarization. In other words, $T_{\text{peak}} - T_{\text{end}}$ was a measure of global dispersion of
298 repolarization rather than TDR ^{9, 59-61}. $T_{\text{peak}} - T_{\text{end}}$ is also lead-dependent as the dispersion of
299 repolarization varies with different cardiac regions ⁶². Therefore, for left ventricular diseases,
300 measurements from lead V5 and for right ventricular diseases such as Brugada syndrome,
301 measurements from lead V2, have been used for ECG interval analysis. In some studies, $T_{\text{peak}} -$
302 T_{end} were calculated from mean values of all 12 leads. Although the mechanism of the T wave
303 generation remains controversial, as to whether it represents global or transmural dispersion of
304 repolarization, a prolonged $T_{\text{peak}} - T_{\text{end}}$ interval has been associated with an increased incidence
305 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 $T_{\text{peak}} - T_{\text{end}}$. The occurrence of TWA is expected to increase the spatial dispersion of
311 repolarization. Indeed, microvolt TWAs have been associated with the duration of $T_{\text{peak}} - T_{\text{end}}$ 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 $T_{\text{peak}} - T_{\text{end}}$ interval has been investigated in various
317 clinical settings. A prolonged $T_{\text{peak}} - T_{\text{end}}$ 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 $T_{\text{peak}} - T_{\text{end}}$
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 $T_{\text{peak}} - T_{\text{end}}$ interval has been
322 associated an increased propensity to develop Torsades de Pointes (TdP) in subjects with LQTS1
323 ¹². The $T_{\text{peak}} - T_{\text{end}}$ interval is also increased in Short QT syndrome (12). There are limited data
324 regarding the utility of $T_{\text{peak}} - T_{\text{end}}$ interval in Brugada syndrome ^{10, 13, 14, 50}. A prolonged $T_{\text{peak}} -$
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 $T_{\text{peak}} - T_{\text{end}}$ interval in
328 subjects with structural heart disease including hypertrophic cardiomyopathy and myocardial

329 infarction. The Copenhagen study found an inverted U relationship between $T_{\text{peak}} - T_{\text{end}}$ interval
330 and the risk of all-cause and cardiovascular mortality, atrial fibrillation and heart failure ³².
331 However, the ability of $T_{\text{peak}} - T_{\text{end}}$ interval to predict prognosis or arrhythmic events has not
332 always been successful ^{19-21, 23}. Moreover, shortenings of this interval also predicted worsened
333 survival rates ⁷⁴.

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

337 In Brugada syndrome, both the depolarization and repolarization hypotheses have been
338 proposed to explain the abnormal electrophysiological findings ^{71, 75}. This would lend weight
339 towards abnormal repolarization being a significant contributor to arrhythmic substrate. On the
340 contrary, in heart failure patients, there is only a small, albeit significant, increase in arrhythmic
341 risk. This possibly suggests that increased dispersion of repolarization plays a moderated role in
342 ventricular arrhythmogenesis, and other factors such as abnormal action potential restitution ⁷⁶ or
343 conduction abnormalities may be more important ⁷⁷.

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

352 will terminate the re-entrant activity ⁷⁹. Prolonged $T_{\text{peak}} - T_{\text{end}}$ interval will increase the
353 likelihood of generating unidirectional conduction block, but other factors, such as slowed
354 conduction and increased dispersion of conduction are also important but not reflected in the
355 $T_{\text{peak}} - T_{\text{end}}$ interval. A recent meta-analysis showed that another measure of repolarization, the
356 QT interval, predicted mortality ⁸⁰. The results were more dramatic, reporting a 24% increase in
357 the risk of SCD with every 50 millisecond increase in the QT interval.

358

359 **Cut-off points for different conditions**

360 Of the different study populations, the degree of $T_{\text{peak}} - T_{\text{end}}$ prolongation for significant
361 elevations in arrhythmic risk for the general population is the greatest with a cut-off point of
362 113.6 ms. For some diseased states, the cut-off value is much lower. Thus, for Brugada
363 syndrome and heart failure, the cut-off values for $T_{\text{peak}} - T_{\text{end}}$ duration were 95.8 ms and 106.3
364 ms, respectively. Interestingly, the cut-off for ischemic heart disease patients was not
365 significantly different from that of the general population, with a value of 109.6 ms. Whilst the
366 $T_{\text{peak}} - T_{\text{end}}$ could provide additional information for risk stratification, at the moment it should
367 not be used on its own in estimating arrhythmia risk. However, it could provide incremental
368 information regarding risk stratification in more complex patients and when the risk estimation
369 based on conventional parameters might be difficult to calculate.

370

371 **Limitations**

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

374 probabilities are low, hazard ratios and odds ratios can be equated ⁸¹. Nonetheless, we have
375 performed additional analysis by pooling HRs and ORs separately. Secondly, a significant
376 heterogeneity among studies was noted. Sensitivity analysis removing one study at a time did not
377 alter the pooled odds ratio. Therefore, in the overall meta-analysis, the heterogeneity is likely
378 derived from the distinct patient populations with different diseases. Thirdly, publication bias in
379 meta-analyses is frequently examined by checking for asymmetry in a funnel plot. In our case
380 there was significant asymmetry, which may suggest some bias. However, it is known that effect
381 estimates such as odd ratios used in this meta-analysis correlate with standard errors, and can
382 produce asymmetry in a funnel plot. Fourthly, some studies included in our studies are
383 retrospective studies, which may have more recall bias. Finally, although the overall number of
384 patients included in this meta-analysis is large, for certain conditions such as Brugada syndrome
385 a small number of patients (500 patients) were included potentially affecting or masking the true
386 effect. Finally, our systematic review only included articles published in PubMed, Embase,
387 Cochrane and CINAHL. It therefore might have missed articles that were not indexed in these
388 search engines.

389

390 **Tables**

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

392

393 **Appendices**

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

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

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

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

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

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

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

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

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

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

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

413 **Figure A12.** Forest plot demonstrating the association between $T_{\text{peak}} - T_{\text{end}}$ and arrhythmic or
414 mortality events in the general population.

415 **Supplementary Table 1.** NOS risk of bias scale for case-control studies.

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

417

418 **Acknowledgements**

419 GT and SW thank the Croucher Foundation of Hong Kong for supporting his clinical assistant
420 professorship.

421

422 **Funding**

423 This work was supported by the Croucher Foundation of Hong Kong. The funding body played
424 no role in the preparation or content of this manuscript.

425

426 **References**

- 427 **1.** NICE. Implantable cardioverter defibrillators for arrhythmias. Review of technology appraisal 11.
428 National Institute for Health and Clinical Excellence (NICE) 2007.
- 429 **2.** Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk
430 factors. *Nat Rev Cardiol* 2010;7:216-225.
- 431 **3.** Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J.
432 Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis*
433 2008;51:213-228.
- 434 **4.** Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, Janssens S, Nuyens D. Evaluation of
435 Index of Cardio-Electrophysiological Balance (iCEB) as a New Biomarker for the Identification of
436 Patients at Increased Arrhythmic Risk. *Ann Noninvasive Electrocardiol* Aug 25 2016.
- 437 **5.** Zumhagen S, Zeidler EM, Stallmeyer B, Ernsting M, Eckardt L, Schulze-Bahr E. Tpeak-Tend
438 interval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. *Europace* Mar 3 2016.
- 439 **6.** Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart*
440 *Rhythm* Mar 2009;6:S8-14.
- 441 **7.** Surawicz B. The QT interval and cardiac arrhythmias. *Annu Rev Med* 1987;38:81-90.
- 442 **8.** Elming H, Holm E, Jun L, Torp-Pedersen C, Kober L, Kircshoff M, Malik M, Camm J. The
443 prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality
444 and morbidity in a population of Danish citizens. *Eur Heart J* Sep 1998;19:1391-1400.
- 445 **9.** Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global
446 dispersion of ventricular repolarization: evaluations using monophasic action potential mapping
447 of the epi- and endocardium in swine. *J Interv Card Electrophysiol* Nov 2005;14:79-87.
- 448 **10.** Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas
449 Molina R, Quinones Perez MA, Fayad Rodriguez Y. Tpeak-Tend and Tpeak-Tend dispersion as risk

- 450 factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome.
451 J Am Coll Cardiol May 2 2006;47:1828-1834.
- 452 **11.** Tse G, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers
453 of sudden cardiac death. *Europace* 2016.
- 454 **12.** Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, Mabuchi T, Konno T, Kaneda T,
455 Mabuchi H. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new
456 index for arrhythmogenicity. *Clin Sci (Lond)* Dec 2003;105:671-676.
- 457 **13.** Watanabe H, Makiyama T, Koyama T, et al. High prevalence of early repolarization in short QT
458 syndrome. *Heart Rhythm* May 2010;7:647-652.
- 459 **14.** Zumhagen S, Zeidler EM, Stallmeyer B, Ernsting M, Eckardt L, Schulze-Bahr E. Tpeak-Tend
460 interval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. *Europace* Mar 3 2016 (in
461 press).
- 462 **15.** Erikssen G, Liestol K, Gullestad L, Haugaa KH, Bendz B, Amlie JP. The terminal part of the QT
463 interval (T peak to T end): a predictor of mortality after acute myocardial infarction. *Ann*
464 *Noninvasive Electrocardiol* Apr 2012;17:85-94.
- 465 **16.** Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, Itoh H, Iwaki T, Oe K, Konno T,
466 Mabuchi H. T-peak to T-end interval may be a better predictor of high-risk patients with
467 hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion.
468 *Clin Cardiol* Jul 2002;25:335-339.
- 469 **17.** Tokatli A, Kilicaslan F, Alis M, Yiginer O, Uzun M. Prolonged Tp-e Interval, Tp-e/QT Ratio and Tp-
470 e/QTc Ratio in Patients with Type 2 Diabetes Mellitus. *Endocrinol Metab (Seoul)* Mar
471 2016;31:105-112.
- 472 **18.** Ozdemir R, Isguder R, Kucuk M, Karadeniz C, Ceylan G, Katipoglu N, Yilmazer MM, Yozgat Y,
473 Mese T, Agin H. A Valuable Tool in Predicting Poor Outcome due to Sepsis in Pediatric Intensive
474 Care Unit: Tp-e/QT Ratio. *J Trop Pediatr* Apr 16 2016.
- 475 **19.** Zabel M, Klingenheben T, Franz MR, Hohnloser SH. Assessment of QT Dispersion for Prediction
476 of Mortality or Arrhythmic Events After Myocardial Infarction. Results of a Prospective, Long-
477 term Follow-up Study 1998;97:2543-2550.
- 478 **20.** Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic
479 value. *J Electrocardiol* Nov-Dec 2008;41:575-580.
- 480 **21.** Yi G, Poloniecki J, Dickie S, Elliott PM, Malik M, McKenna WJ. Is QT dispersion associated with
481 sudden cardiac death in patients with hypertrophic cardiomyopathy? *Ann Noninvasive*
482 *Electrocardiol* Jul 2001;6:209-215.
- 483 **22.** Mugnai G, Benfari G, Fede A, Rossi A, Chierchia GB, Vassanelli F, Menegatti G, Ribichini FL.
484 Tpeak-to-Tend/QT is an independent predictor of early ventricular arrhythmias and arrhythmic
485 death in anterior ST elevation myocardial infarction patients. *Eur Heart J Acute Cardiovasc Care*
486 Oct 2016;5:473-480.
- 487 **23.** Porthan K, Viitasalo M, Toivonen L, Havulinna AS, Jula A, Tikkanen JT, Vaananen H, Nieminen
488 MS, Huikuri HV, Newton-Cheh C, Salomaa V, Oikarinen L. Predictive value of
489 electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval
490 for sudden cardiac death in the general population. *Circ Arrhythm Electrophysiol* Aug
491 2013;6:690-696.
- 492 **24.** Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group
493 P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)
494 2015 statement. *Systematic Reviews* 2015;4:1.
- 495 **25.** Marshall SC, Molnar F, Man-Son-Hing M, Blair R, Brosseau L, Finestone HM, Lamothe C, Korner-
496 Bitensky N, Wilson KG. Predictors of driving ability following stroke: a systematic review. *Top*
497 *Stroke Rehabil* Jan-Feb 2007;14:98-114.

- 498 **26.** Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and
499 meta-analyses: the PRISMA statement. *BMJ* 2009;339.
- 500 **27.** Xue C, Hua W, Cai C, Ding LG, Liu ZM, Fan XH, Zhao YZ, Zhang S. Acute and Chronic Changes and
501 Predictive Value of Tpeak-Tend for Ventricular Arrhythmia Risk in Cardiac Resynchronization
502 Therapy Patients. *Chin Med J (Engl)* 20th Sep 2016;129:2204-2211.
- 503 **28.** Chua KC, Rusinaru C, Reinier K, Uy-Evanado A, Chugh H, Gunson K, Jui J, Chugh SS. Tpeak-to-
504 Tend interval corrected for heart rate: A more precise measure of increased sudden death risk?
505 *Heart Rhythm* Nov 2016;13:2181-2185.
- 506 **29.** Rivard L, Roux A, Nault I, et al. Predictors of Ventricular Arrhythmias and Sudden Death in a
507 Quebec Cohort With Brugada Syndrome. *Can J Cardiol* Nov 2016;32:1355.e1351-1355.e1357.
- 508 **30.** Bombelli M, Maloberti A, Raina L, Facchetti R, Boggioni I, Pizzala DP, Cuspidi C, Mancia G, Grassi
509 G. Prognostic relevance of electrocardiographic Tpeak-Tend interval in the general and in the
510 hypertensive population: data from the Pressioni Arteriose Monitorate E Loro Associazioni
511 study. *J Hypertens* Sep 2016;34:1823-1830.
- 512 **31.** Sen O, Yilmaz S, Sen F, Balci KG, Akboga MK, Yayla C, Ozeke O. T-peak to T-end Interval Predicts
513 Appropriate Shocks in Patients with Heart Failure Undergoing Implantable Cardioverter
514 Defibrillator Implantation for Primary Prophylaxis. *Ann Noninvasive Electrocardiol* Jun 6 2016.
- 515 **32.** Bachmann TN, Skov MW, Rasmussen PV, et al. Electrocardiographic Tpeak-Tend interval and risk
516 of cardiovascular morbidity and mortality: Results from the Copenhagen ECG study. *Heart
517 Rhythm* Apr 2016;13:915-924.
- 518 **33.** Icli A, Kayrak M, Akilli H, Aribas A, Coskun M, Ozer SF, Ozdemir K. Prognostic value of Tpeak-
519 Tend interval in patients with acute pulmonary embolism. *BMC Cardiovasc Disord* Sep 03
520 2015;15:99.
- 521 **34.** Maury P, Sacher F, Gourraud JB, et al. Increased Tpeak-Tend interval is highly and independently
522 related to arrhythmic events in Brugada syndrome. *Heart Rhythm* Dec 2015;12:2469-2476.
- 523 **35.** Rosenthal TM, Stahls PF, 3rd, Abi Samra FM, Bernard ML, Khatib S, Polin GM, Xue JQ, Morin DP.
524 T-peak to T-end interval for prediction of ventricular tachyarrhythmia and mortality in a primary
525 prevention population with systolic cardiomyopathy. *Heart Rhythm* Aug 2015;12:1789-1797.
- 526 **36.** Tatlisu MA, Ozcan KS, Gungor B, Ekmekci A, Cekirdekci EI, Arugarlan E, Cinar T, Zengin A, Karaca
527 M, Eren M, Erdinler I. Can the T-peak to T-end interval be a predictor of mortality in patients
528 with ST-elevation myocardial infarction? *Coron Artery Dis* Aug 2014;25:399-404.
- 529 **37.** Armaganijan L, Moreira DA, Nolasco de Araujo RR, Puzzi MA, Munhoz FP, Carvalho MJ, Gallo LN,
530 Franca JI, Lopes RD. The usefulness of T-wave peak to T-wave end interval in identifying
531 malignant arrhythmias in patients with Chagas disease. *Hellenic J Cardiol* Nov-Dec 2013;54:429-
532 434.
- 533 **38.** Itoh M, Yoshida A, Fukuzawa K, Kiuchi K, Imamura K, Fujiwara R, Suzuki A, Nakanishi T,
534 Yamashita S, Matsumoto A, Hirata K. Time-dependent effect of cardiac resynchronization
535 therapy on ventricular repolarization and ventricular arrhythmias. *Europace* Dec 2013;15:1798-
536 1804.
- 537 **39.** Xiao WT, Wang XP, Gao CY, Yan JJ, Li MW, Zhang Y, Liu JJ. [Predictive value of corrected QT
538 interval, corrected Tp-e interval and Tp-e/QT ratio on malignant arrhythmia events in acute ST-
539 segment elevation myocardial infarction patients undergoing thrombolysis]. *Zhonghua Xin Xue
540 Guan Bing Za Zhi* Jun 2012;40:473-476.
- 541 **40.** Pei J, Li N, Gao Y, Wang Z, Li X, Zhang Y, Chen J, Zhang P, Cao K, Pu J. The J wave and fragmented
542 QRS complexes in inferior leads associated with sudden cardiac death in patients with chronic
543 heart failure. *Europace* Aug 2012;14:1180-1187.

- 544 **41.** Morin DP, Saad MN, Shams OF, Owen JS, Xue JQ, Abi-Samra FM, Khatib S, Nelson-Twakor OS,
545 Milani RV. Relationships between the T-peak to T-end interval, ventricular tachyarrhythmia, and
546 death in left ventricular systolic dysfunction. *Europace* Aug 2012;14:1172-1179.
- 547 **42.** Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J,
548 Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk
549 of sudden cardiac death. *Circ Arrhythm Electrophysiol* Aug 2011;4:441-447.
- 550 **43.** Haarmark C, Hansen PR, Vedel-Larsen E, Pedersen SH, Graff C, Andersen MP, Toft E, Wang F,
551 Struijk JJ, Kanters JK. The prognostic value of the Tpeak-Tend interval in patients undergoing
552 primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J*
553 *Electrocardiol* Nov-Dec 2009;42:555-560.
- 554 **44.** Wang JF, Shan QJ, Yang B, Chen ML, Zou JG, Chen C, Xu DJ, Cao KJ. [Tpeak-Tend interval and risk
555 of cardiac events in patients with Brugada syndrome]. *Zhonghua Xin Xue Guan Bing Za Zhi* Jul
556 2007;35:629-632.
- 557 **45.** Lellouche N, De Diego C, Akopyan G, Boyle NG, Mahajan A, Cesario DA, Wiener I, Shivkumar K.
558 Changes and predictive value of dispersion of repolarization parameters for appropriate therapy
559 in patients with biventricular implantable cardioverter-defibrillators. *Heart Rhythm* Oct
560 2007;4:1274-1283.
- 561 **46.** Watanabe N, Kobayashi Y, Tanno K, Miyoshi F, Asano T, Kawamura M, Mikami Y, Adachi T, Ryu S,
562 Miyata A, Katagiri T. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J*
563 *Electrocardiol* Jul 2004;37:191-200.
- 564 **47.** Aiba T, Shimizu W, Inagaki M, Satomi K, Taguchi A, Kurita T, Suyama K, Aihara N, Sunagawa K,
565 Kamakura S. Excessive increase in QT interval and dispersion of repolarization predict recurrent
566 ventricular tachyarrhythmia after amiodarone. *Pacing Clin Electrophysiol* Jul 2004;27:901-909.
- 567 **48.** Aoki S, Sakakibara M, Yamaguchi S, Yokoi T, Takeuchi S, Iwakawa N, Takenaka M, Kitagawa K,
568 Jinno Y. TPEAK TO TEND INTERVAL IS A SHORT TERM PROGNOSTIC FACTOR OF CARDIAC DEATH
569 IN ACUTE HEART FAILURE SYNDROME PATIENTS WITH REDUCED EJECTION FRACTION. *Journal of*
570 *the American College of Cardiology* 2015;65.
- 571 **49.** Hetland M, Haugaa KH, Sarvari SI, Erikssen G, Kongsgaard E, Edvardsen T. A novel ECG-index for
572 prediction of ventricular arrhythmias in patients after myocardial infarction. *Ann Noninvasive*
573 *Electrocardiol* Jul 2014;19:330-337.
- 574 **50.** Letsas KP, Weber R, Astheimer K, Kalusche D, Arentz T. Tpeak-Tend interval and Tpeak-Tend/QT
575 ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype.
576 *Europace* Feb 2010;12:271-274.
- 577 **51.** Ciobanu A, Gheorghe GS, Ababei M, Deaconu M, Iliesiu AM, Bolohan M, Paun N, Nicolae C,
578 Nanea IT. Dispersion of ventricular repolarization in relation to cardiovascular risk factors in
579 hypertension. *Journal of medicine and life* Oct-Dec 2014;7:545-550.
- 580 **52.** Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple,
581 graphical test. *BMJ* Sep 13 1997;315:629-634.
- 582 **53.** Shenthar J, Deora S, Rai M, Nanjappa Manjunath C. Prolonged Tpeak-end and Tpeak-end/QT
583 ratio as predictors of malignant ventricular arrhythmias in the acute phase of ST-segment
584 elevation myocardial infarction: a prospective case-control study. *Heart Rhythm* Mar
585 2015;12:484-489.
- 586 **54.** Burgess MJ. Relation of ventricular repolarization to electrocardiographic T wave-form and
587 arrhythmia vulnerability. *Am J Physiol* Mar 1979;236:H391-402.
- 588 **55.** Yan GX, Martin J. Electrocardiographic T wave: a symbol of transmural dispersion of
589 repolarization in the ventricles. *J Cardiovasc Electrophysiol* Jun 2003;14:639-640.
- 590 **56.** Ziegler RF. The T wave of the electrocardiogram: methods of measurement and interpretation.
591 *Arq Bras Cardiol* Jun 1966;19:173-196.

- 592 **57.** Drouin E, Charpentier F, Gauthier C, Laurent K, Le Marec H. Electrophysiologic characteristics of
593 cells spanning the left ventricular wall of human heart: evidence for presence of M cells. *J Am*
594 *Coll Cardiol* Jul 1995;26:185-192.
- 595 **58.** Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko VV, Burashnikov A, Di
596 Diego J, Saffitz J, Thomas GP. The M cell: its contribution to the ECG and to normal and
597 abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* Aug 1999;10:1124-1152.
- 598 **59.** Xia Y, Liang Y, Kongstad O, Liao Q, Holm M, Olsson B, Yuan S. In vivo validation of the
599 coincidence of the peak and end of the T wave with full repolarization of the epicardium and
600 endocardium in swine. *Heart Rhythm* Feb 2005;2:162-169.
- 601 **60.** Opthof T, Coronel R, Wilms-Schopman FJ, Plotnikov AN, Shlapakova IN, Danilo P, Jr., Rosen MR,
602 Janse MJ. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave:
603 Tp-e interval does not reflect transmural dispersion. *Heart Rhythm* Mar 2007;4:341-348.
- 604 **61.** Opthof T, Coronel R, Janse MJ, Rosen MR. A wedge is not a heart. *Heart Rhythm* 2007;4:1116-
605 1119.
- 606 **62.** Bieganowska K, Sawicka-Parobczyk M, Bieganowski M, Piskorski J. Tpeak-Tend Interval in 12-
607 Lead Electrocardiogram of Healthy Children and Adolescents Tpeak-Tend Interval in Childhood.
608 *Annals of Noninvasive Electrocardiology* 2013;18:344-351.
- 609 **63.** Lubinski A, Lewicka-Nowak E, Kempa M, Baczynska AM, Romanowska I, Swiatecka G. New
610 insight into repolarization abnormalities in patients with congenital long QT syndrome: the
611 increased transmural dispersion of repolarization. *Pacing Clin Electrophysiol* Jan 1998;21:172-
612 175.
- 613 **64.** Gilmour RF, Jr. Restitution, heterogeneity and unidirectional conduction block: New roles for old
614 players. *Heart Rhythm* Apr 2009;6:544-545.
- 615 **65.** Wiegerinck RF, van Veen TA, Belterman CN, Schumacher CA, Noorman M, de Bakker JM, Coronel
616 R. Transmural dispersion of refractoriness and conduction velocity is associated with
617 heterogeneously reduced connexin43 in a rabbit model of heart failure. *Heart Rhythm* Aug
618 2008;5:1178-1185.
- 619 **66.** Coronel R, Wilms-Schopman FJ, Opthof T, Janse MJ. Dispersion of repolarization and
620 arrhythmogenesis. *Heart Rhythm* Apr 2009;6:537-543.
- 621 **67.** Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada
622 R, Antzelevitch C. Ionic mechanisms responsible for the electrocardiographic phenotype of the
623 Brugada syndrome are temperature dependent. *Circ Res* Oct 29 1999;85:803-809.
- 624 **68.** Tse G. Mechanisms of Cardiac Arrhythmias. *J Arrhythm* 2015;32:75-81.
- 625 **69.** Takenaka K, Ai T, Shimizu W, Kobori A, Ninomiya T, Otani H, Kubota T, Takaki H, Kamakura S,
626 Horie M. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2
627 forms of the long-QT syndrome. *Circulation* Feb 18 2003;107:838-844.
- 628 **70.** Tse G, Sun B, Wong ST, Tse V, Yeo JM. Ventricular anti-arrhythmic effects of hypercalcaemia
629 treatment in hyperkalaemic, Langendorff-perfused mouse hearts. *Biomed Rep* 2016 (in press).
- 630 **71.** Tse G, Wong ST, Tse V, Yeo JM. Depolarization vs. repolarization: what is the mechanism of
631 ventricular arrhythmogenesis underlying sodium channel haploinsufficiency in mouse hearts?
632 *Acta Physiol (Oxf)* Apr 16 2016.
- 633 **72.** Tse G. (Tpeak-Tend)/QRS and (Tpeak-Tend)/(QT x QRS): novel markers for predicting arrhythmic
634 risk in Brugada syndrome. *Europace* 2016 (in press).
- 635 **73.** Tse G, Yan BP. Novel arrhythmic risk markers incorporating QRS dispersion: QRSd x (Tpeak -
636 Tend)/QRS and QRSd x (Tpeak - Tend)/(QT x QRS). *Ann Noninvasive Electrocardiol* Aug 18 2016.
- 637 **74.** Smetana P, Schmidt A, Zabel M, Hnatkova K, Franz MR, Huber K, Malik M. Analysis of tpe-
638 interval for prediction of long term prognosis in cardiovascular disease. *Heart Rhythm*;3:S188-
639 S189.

- 640 **75.** Tse G, Liu T, Li KH, Laxton V, Chan YW, Keung W, Li RA, Yan BP. Electrophysiological mechanisms
641 of Brugada syndrome: insights from pre-clinical and clinical studies. *Front Physiol* 2016;7:467.
642 **76.** Tse G, Wong STT, V., Lee YT, Lin HY, Yeo JM. Cardiac dynamics: alternans and arrhythmogenesis.
643 *J Arrhythm* 2016.
644 **77.** Choy L, Yeo JM, Tse V, Chan SP, Tse G. Cardiac disease and arrhythmogenesis: mechanistic
645 insights from mouse models. *Int J Cardiol Heart Vasc* 2016;12:1-10.
646 **78.** Takasugi N, Goto H, Takasugi M, Verrier RL, Kuwahara T, Kubota T, Toyoshi H, Nakashima T,
647 Kawasaki M, Nishigaki K, Minatoguchi S. Prevalence of Microvolt T-Wave Alternans in Patients
648 With Long QT Syndrome and Its Association With Torsade de Pointes. *Circ Arrhythm*
649 *Electrophysiol* Feb 2016;9:e003206.
650 **79.** Mines GR. On dynamic equilibrium in the heart. *J Physiol* 1913;46:349-383.
651 **80.** Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic
652 QT interval and mortality: a meta-analysis. *Epidemiology (Cambridge, Mass)* 2011;22:660-670.
653 **81.** Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev*
654 1987;9:1-30.

655

656

657

658 **Figure 1.** Flow diagram of the study selection process.

659

660

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

663

664

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

666

667

668

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

670

671