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

Gary Tse, MBBS, PhD, FESC, FACC, FRCP (Glasg),[*†‡] Mengqi Gong, MD,[§] Wing Tak Wong, MPhil, PhD,[‖] Stamatis Georgopoulos, MD,[¶] Konstantinos P. Letsas, MD, FESC, FEHRA,[¶] Vassilios S. Vassiliou, MA, MBBS, MRCP, PhD, FHEA, FESC,[#**] Yat Sun Chan, MBBS, FRCP, FACC,[*] Bryan P. Yan, MBBS, FRCP, FACC,[*] Sunny Hei Wong, MBChB, DPhil, MRCP,[*†] William K.K. Wu, MMedSc, MPhil, PhD, FRCPath,[†††] Ana Ciobanu, MD, PhD,[‡‡] Guangping Li, MD, PhD,[§] Jayaprakash Shenthar, MD,[§§] Ardan M. Saguner, MD,[‖‖] Sadeq Ali-Hasan-Al-Saegh, MD,[¶¶] Aishwarya Bhardwaj, MD,[##] Abhishek C. Sawant, MD, MPH,[##] Paula Whittaker, MBChB, MPH, MMed, MRCGP,[‡] Yunlong Xia, MD, PhD,[***] Gan-Xin Yan, MD, PhD,[†††‡‡‡] Tong Liu, MD, PhD[§]

*From the *Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China, †Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China, ‡School of Health Sciences, University of Manchester, Manchester, United Kingdom, §Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, People's Republic of China, ‖School of Life Sciences, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China, ¶Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, "Evangelismos" General Hospital of Athens, Athens, Greece, #Norwich Medical School, University of East Anglia, Norwich, United Kingdom, **Royal Brompton Hospital and Imperial College London, London, United Kingdom, ††Department of Anaesthesia and Intensive Care, State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China, ‡‡Department of Cardiology, Theodor Burghele Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, §§Electrophysiology Unit, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore, India, ‖‖Department of Cardiology, University Heart Center, Zurich, Switzerland, ¶¶Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, ##Division of Cardiology, Department of Internal Medicine, State University of New York at Buffalo, Buffalo, New York, ***Department of Cardiovascular Medicine, First Affiliated Hospital of Dalian Medical University, Dalian, People's Republic of China, †††Lankenau Institute for Medical Research and Lankenau Medical Center, Wynnewood, Pennsylvania, and ‡‡‡Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China.*

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

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

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

RESULTS Of the 854 studies identified initially, 33 observational studies involving 155,856 patients were included in our meta-analysis. $T_{peak} - T_{end}$ interval prolongation (mean cutoff value 103.3 ± 17.4 ms) was a significant predictor of the arrhythmic or mortality outcomes (odds ratio [OR] 1.14; 95% confidence interval [CI] 1.11–1.17; $P < .001$). When different end points were analyzed,

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Address reprint requests and correspondence: Dr Gary Tse, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, SAR, People's Republic of China. E-mail address: tseg@cuhk.edu.hk.

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the ORs were as follows: VT/VF, 1.10 (95% CI 1.06–1.13; $P < .0001$); sudden cardiac death, 1.27 (95% CI 1.17–1.39; $P < .0001$); cardiovascular death, 1.40 (95% CI 1.19–1.64; $P < .0001$); and all-cause mortality, 4.56 (95% CI 0.62–33.68; $P < .0001$). Subgroup analysis for each disease revealed that the risk of VT/VF or death was highest for Brugada syndrome (OR 5.68; 95% CI 1.57–20.53; $P < .01$), followed by hypertension (OR 1.52; 95% CI 1.26–1.85; $P < .0001$), heart failure (OR 1.07; 95% CI 1.04–1.11; $P < .0001$), and ischemic heart disease (OR 1.06; 95% CI 1.02–1.10; $P = 0.001$).

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

KEYWORDS $T_{peak} - T_{end}$; Dispersion of repolarization; Risk stratification; Ventricular arrhythmia; Sudden cardiac death

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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 4–5 million deaths worldwide 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.[1] Traditional ECG markers of ventricular repolarization including the corrected QT interval and QT dispersion 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 ($T_{peak} - T_{end}$) and the ($T_{peak} - T_{end}$)/QT ratio, have been recently proposed to predict ventricular arrhythmic events and SCD. These ECG markers have been validated in congenital ion channelopathies such as long QT and Brugada syndromes, myocardial infarction, cardiomyopathies, and other diseases such as pulmonary embolism, hypertension, and Chagas disease. However, data are controversial regarding the predictive value of these ECG markers. The present systematic review and meta-analysis of the current literature aimed to investigate the prognostic significance of the $T_{peak} - T_{end}$ interval with respect to arrhythmic and mortality outcomes.

Method

Search strategy and 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 the $T_{peak} - T_{end}$ interval and arrhythmic or mortality end points 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, and 1937 for CINAHL Plus) to November 30, 2016, with no language restrictions. The following inclusion criteria were applied: (1) the design was a case-control, prospective, or retrospective observational study in humans; (2) $T_{peak} - T_{end}$ interval durations were determined; (3) end point events (appropriate implantable cardioverter-defibrillator therapy, VT/VF, SCD, cardiovascular death, or all-cause mortality) were reported; and (4) 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. 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: (1) representativeness of the exposed cohort; (2) selection of the nonexposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts. This scale varied from 0 to 9 stars, which indicated that studies were graded as poor quality if they met <5 criteria, fair if they met 5–7 criteria, and good if they met >8 criteria. The details of the Newcastle-Ottawa Quality Assessment Scale quality assessment are presented in Supplemental Tables 1 and 2.

Data extraction and statistical analysis

Data from the different studies were entered into the prespecified 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 (1) publication details: last name of first author, publication year, and locations; (2) study design; (3) follow-up duration; (4) definition of $T_{peak} - T_{end}$ interval; (5) lead(s) where the $T_{peak} - T_{end}$ interval was measured; (6) end point(s); (7) the quality score; and (8) the characteristics of the population including sample size, sex, age, and number of patients. Meta-analyses of observational studies are challenging because of differences in study designs and inherent biases. This systematic review was conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[2] and registered with PROSPERO (review number 52916). Two reviewers (G.T. and M.G.) independently reviewed each included study, and disagreements were resolved by adjudication with input from a third reviewer (T.L.).

The end points of the study were the occurrences of ventricular arrhythmias (VT/VF), SCD, cardiovascular death, or all-cause mortality. The definitions of these end points used in different studies were analyzed. If >1 mortality end point was described, then SCD was preferentially used for the analysis, followed by cardiovascular death and all-cause mortality. Multivariate-adjusted ORs or HRs with 95% CIs 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. The HR value in the multivariate Cox proportional hazards model was equated to the OR value. The pooled adjusted risk estimates from each study as the OR values with 95% CIs were presented.

Heterogeneity between studies was determined using Cochran 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 χ^2 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 statistically significant 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 1 study at a time and subgroup analyses based on different disease conditions and different end points were performed. Funnel plots, Begg and Mazumdar rank correlation test, and Egger test were used to assess 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. Compared 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.[3–30] Three groups provided their data on OR or HR, and these studies were also included.[30–33] Thus, in the final meta-analysis, 33 studies were included.

A total of 155,856 patients were included. Three studies examined the risk in different patient populations (normotensive and hypertensive; dilated cardiomyopathy and ischemic cardiomyopathy; and normal intraventricular conduction and intraventricular conduction delay). The $T_{peak} - T_{end}$ interval was examined in the following clinical settings: heart failure in 8 studies,[3,7,12,15,18,19,23,27] ischemic heart disease in 8 studies,[13,16–18,21,28,29,32] Brugada syndrome in 6 studies,[5,8,11,22,24,30] hypertension in 2 studies,[6,31] pulmonary embolism in 1 study,[10] Chagas disease in 1 study,[14] intraventricular conduction delay in 1 study,[20] dilated cardiomyopathy in 1 study,[18] and ischemic cardiomyopathy in 1 study.[18] Five studies[4,6,9,20,25] addressed the prognostic significance of the $T_{peak} - T_{end}$ interval in the general population. The baseline characteristics of these studies are listed in Supplemental Table 3. Fifteen were prospective studies, and 14 were retrospective studies. The mean follow-up duration was 42 ± 48 months.

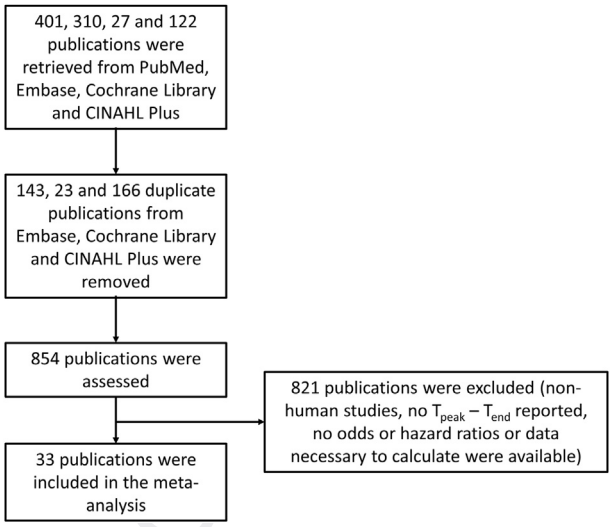

Figure 1 Flow diagram of the study selection process. Q6

In the 33 studies, the total number of patients was 155,856 (mean 4329; range 23–138,404). The mean age was 62 ± 11 years. The patients were predominantly men (69%). The mean cutoff point for the $T_{peak} - T_{end}$ interval was 103.3 ± 17.4 ms (range 77.4–146.4 ms). All studies consistently reported a positive association between the increased $T_{peak} - T_{end}$ interval and the increased risk of VT/VF or SCD (17 using multivariate analysis and 16 using univariate analysis). The pooled meta-analysis demonstrated that a prolonged $T_{peak} - T_{end}$ interval is associated with 1.14 times higher risk of VT/VF or SCD (95% CI 1.11–1.17; $P < .0001$) (Figure 2). The Cochran Q value was greater than the degrees of freedom (432 vs 34), suggesting that the true effect size was different among the various studies. Moreover, I^2 took a value of 92%, suggesting that significant heterogeneity was present. Funnel plots of standard errors and precision measure against logarithms of ORs are shown in Figures 3 and 4, respectively. The Begg and Mazumdar rank correlation test suggested no significant publication bias (Kendal $\tau = 0.15$; $P > .05$). The Egger test demonstrated a significant asymmetry (intercept 3.5; $t = 8.1$; $P < .0001$).[34] When HR and OR were analyzed separately, data were as follows: HR 1.12 (95% CI 1.09–1.16; $P < .0001$) (Supplemental Figure 1); OR 1.23 (95% CI 1.14–1.32; $P < .0001$) (Supplemental Figure 2).

To locate the origin of the heterogeneity, sensitivity analysis excluding 1 study at a time and subgroup analyses based on different disease conditions and end points were performed. The results are shown in the Supplemental Appendix (Supplemental Figures 3–12).

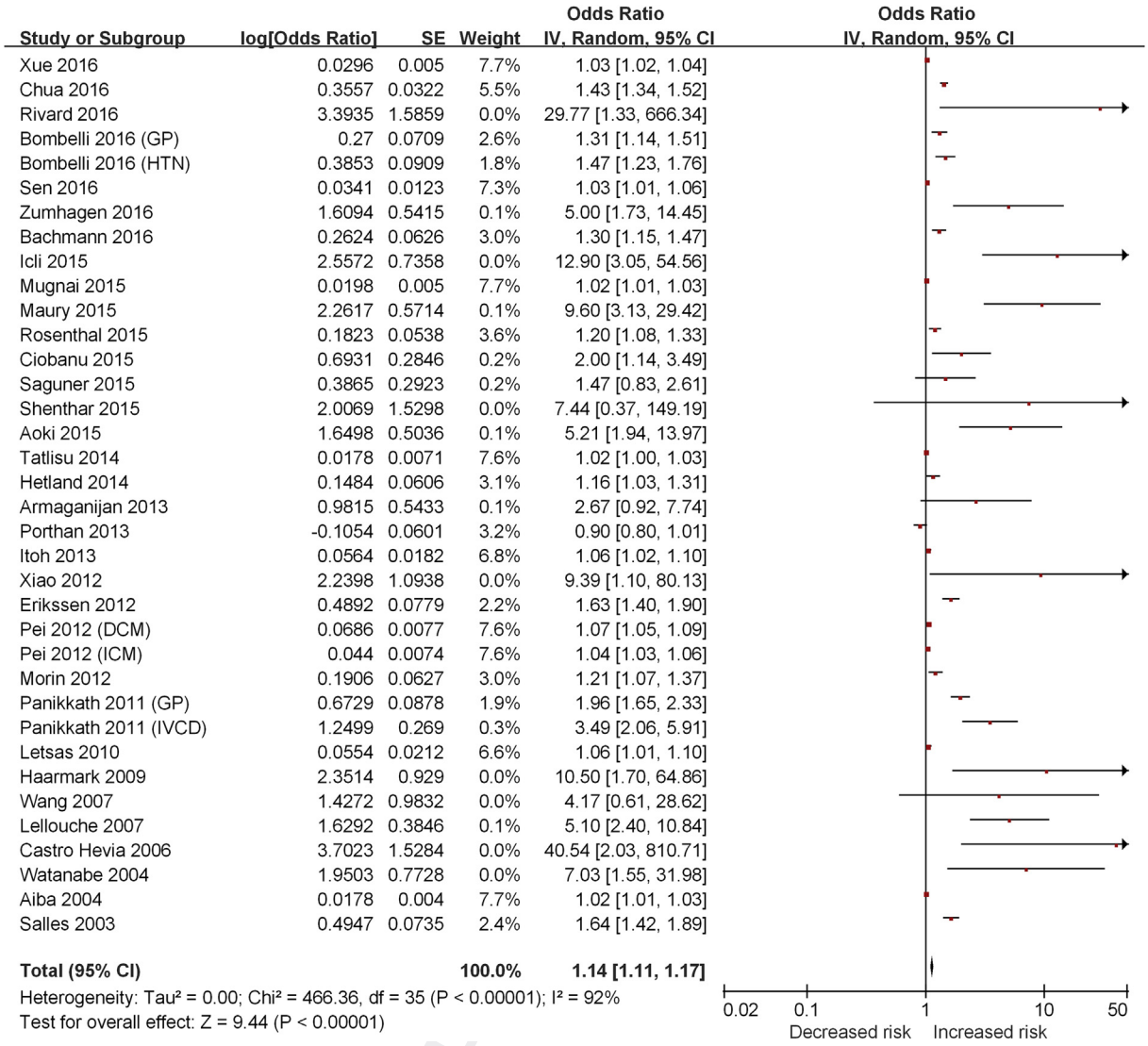

Figure 2 Forest plot demonstrating the association between $T_{peak} - T_{end}$ and arrhythmic or mortality outcomes in patient populations with different clinical conditions.

Discussion

The main findings of this study are the following:

1. A prolonged $T_{peak} - T_{end}$ interval 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.
2. 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 with 1.52 in hypertension, 1.07 in heart failure, and 1.06 in ischemic heart disease.
3. 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 in the recent decades.[35] The waveform has been attributed to electrophysiological characteristics of ventricular cardiomyocytes located in the different regions of the myocardial wall, such as epicardium, midmyocardium, and endocardium. The $T_{peak} - T_{end}$ interval represents the dispersion of repolarization. Several ECG parameters such as QT interval, QT dispersion, and T-wave alternans (TWA) are associated with $T_{peak} - T_{end}$. The occurrence of TWA is expected to increase the spatial dispersion of repolarization. Indeed, microvolt TWAs have been associated with the duration of $T_{peak} - T_{end}$. The mechanism of TWA generation is multifactorial but has traditionally been described by the restitution hypothesis. The TWA magnitude is likely a function of heterogeneity in Ca^{2+} alternans that can drive APD alternans. Conversely, a steep spatial gradient of repolarization can convert spatially concordant alternans to spatially discordant alternans.

The prognostic significance of the $T_{peak} - T_{end}$ interval has been investigated in various clinical settings. 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.

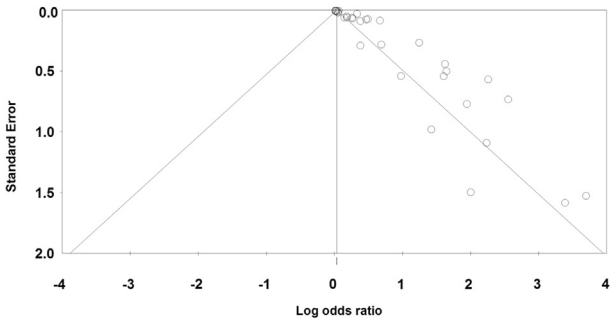

Figure 3 Funnel plot of standard errors against logarithms of odds ratios.

In Brugada syndrome, both the depolarization and repolarization hypotheses have been proposed to explain the abnormal electrophysiological findings. Our meta-analytical data support the notion that abnormal repolarization is a significant contributor to arrhythmic substrate. On the contrary, in patients with heart failure, there is only a small, albeit significant, increase in arrhythmic risk. This possibly suggests that increased dispersion of repolarization plays a moderate role in ventricular arrhythmogenesis, and other factors such as abnormal action potential restitution or conduction abnormalities may be more important.

It should be noted that the results are not dramatic. On the basis of this meta-analysis, we would advocate that a different cutoff value should be considered for each cardiac pathology that should also be considered alongside other factors known to associate with cardiac risk, such as QT interval, QT dispersion, or TWA. Increased dispersion of repolarization, which is reflected by the prolonged $T_{peak} - T_{end}$ intervals, is only 1 mechanism by which reentrant mechanism is generated. Indeed, in Mines' seminal work on circus-type reentry, his proposal included 3 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 reentrant activity. A 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.

Cutoff 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 cutoff point of 113.6 ms. For some disease states, the cutoff value is much lower. Thus, for Brugada syndrome and heart failure, the cutoff values of $T_{peak} - T_{end}$ duration were 95.8 and 106.3 ms, respectively. Interestingly, the cutoff for patients with ischemic heart disease was not significantly different from that for the general population, with a value of 109.6 ms. While the $T_{peak} - T_{end}$ interval 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 for risk stratification in more complex patients and when the risk estimation based on conventional parameters might be difficult to calculate.

Study limitations

This systematic review with meta-analysis has several potential limitations. First, HRs were equated as ORs. When event rates or probabilities are low, it is appropriate to treat HRs as ORs. Nonetheless, we have performed additional analysis by pooling HRs and ORs separately. Second, significant heterogeneity among studies was noted. Sensitivity analysis removing 1 study at a time did not alter the pooled OR. Therefore, in the overall meta-analysis, heterogeneity is likely derived from the distinct patient populations with different diseases. Third, publication bias in meta-analyses

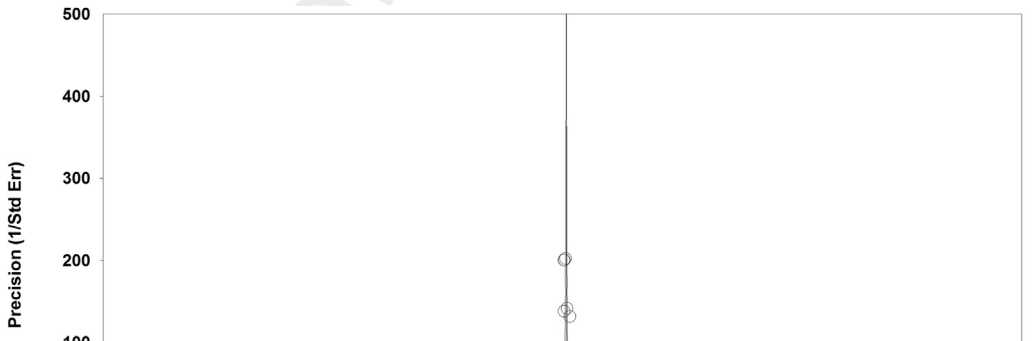

Figure 4 Funnel plot of precision measure against logarithms of odds ratios.

is frequently examined by checking for asymmetry in a funnel plot. In our case there was a significant asymmetry, which may suggest some bias. However, it is known that effect estimates such as ORs used in this meta-analysis correlate with standard errors and can produce asymmetry in a funnel plot. Fourth, some studies included in our studies are retrospective studies, which may have more recall bias. Fifth, 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 included articles published only in PubMed, Embase, Cochrane Library, and CINAHL Plus. It therefore might have missed articles that were not indexed in these search engines. Q10

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2017.05.031.

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