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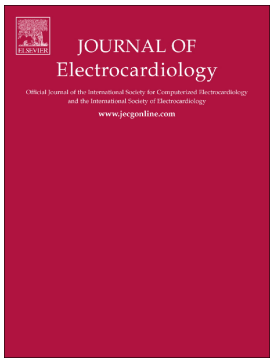

Meta-analysis of Tpeak–Tend and Tpeak–Tend/QT ratio for risk stratification in congenital long QT syndrome

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Meta-analysis of $T_{peak} - T_{end}$ and $T_{peak} - T_{end}$/QT ratio for risk stratification in congenital long QT syndrome

Short title: T_{peak}-T_{end} indices in congenital long QT syndrome: a meta-analysis

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Abstract

Background and Objectives: Congenital long QT syndrome (LQTS) predisposes affected individuals to ventricular tachycardia/fibrillation (VF/VF), potentially resulting in sudden cardiac death. The $T_{peak} - T_{end}$ interval and the $T_{peak} - T_{end}$ / QT ratio, electrocardiographic markers of dispersion of ventricular repolarization, were proposed for risk stratification but their predictive values in LQTS have been controversial. A systematic review and meta-analysis was conducted to examine the value of $T_{peak} - T_{end}$ intervals and $T_{peak} - T_{end}$ / QT ratios in predicting arrhythmic and mortality outcomes in congenital LQTS.

Method: PubMed and Embase databases were searched until 9th May 2017, identifying 199 studies.

Results: Five studies on long QT syndrome were included in the final meta-analysis. $T_{peak} - T_{end}$ intervals were longer (mean difference [MD]: 13 ms, standard error [SE]: 4 ms, P = 0.002; I^2 = 34%) in congenital LQTS patients with adverse events [syncope, ventricular arrhythmias or sudden cardiac death] compared to LQTS patients without such events. By contrast, $T_{peak} - T_{end}$ / QT ratios were not significantly different between the two groups (MD: 0.02, SE: 0.02, P = 0.26; I^2 = 0%).

Conclusion: This meta-analysis showed that $T_{peak} - T_{end}$ interval is significant higher in individuals who are at elevated risk of adverse events in congenital LQTS, offering incremental value for risk stratification.

Keywords: Tpeak – Tend; Tpeak – Tend / QT; dispersion of repolarization; risk stratification; ventricular arrhythmia; sudden cardiac death

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Introduction

Congenital long QT syndrome (LQTS) increases the risk of ventricular tachycardia/fibrillation (VT/VF), potentially leading to sudden cardiac death (SCD). However, patients with prolonged QT intervals are heterogeneous in that only a subset develop these adverse events, and risk stratification in this condition remains difficult. Traditional electrocardiographic markers for risk prediction have largely focused on abnormal repolarization, of which the archetypal examples are QT [1] and QT_c [2]. Other markers [3], such as QT dispersion (QT_d) [4, 5], interval from the peak to the end of the T wave [6] ($T_{peak} - T_{end}$ interval) and $T_{peak} - T_{end}$ / QT ratio [7] were developed to improve risk stratification.

Prolongation in the $T_{peak} - T_{end}$ interval increases arrhythmic risk because increased dispersion of repolarization predisposes to the occurrence of unidirectional block and therefore reentry [8-11]. However, $T_{peak} - T_{end}$ varies with different species and heart rate, has significant inter-individual variability [12]. It was found that dividing it by the QT interval yielded a parameter, $T_{peak} - T_{end}$ / QT ratio, that had a relatively constant normal range between 0.17 and 0.23 [12]. Much of the work on dispersion of repolarization were conducted by Yan and Antzelevitch in animal models and electrocardiographic correlates of repolarization dispersion were subsequently used for risk stratification in humans [12]. However, the predictive value of $T_{peak} - T_{end}$ interval or $T_{peak} - T_{end}$ / QT ratio in LQTS remains controversial. A recent meta-analysis examined the prognostic value of $T_{peak} - T_{end}$ interval by pooling together the odds or hazard ratios for arrhythmic or mortality outcomes when this interval is prolonged, but it did not examine the absolute values of this index, nor did it investigate LQTS in the subgroup analyses [13]. Thus, many studies have reported $T_{peak} - T_{end}$ interval or $T_{peak} - T_{end}$ / QT ratio in LQTS. For $T_{peak} - T_{end}$ interval, three studies did not report a significant difference in duration between

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LQTS patients who suffered from adverse events compared to those who did not [14, 15]. For $T_{peak} - T_{end}$ / QT ratio was a significant predictor of *torsade de pointes* in univariate analysis, but lost its significance in multivariate analysis [16]. By contrast, $T_{peak} - T_{end}$ / QT ratio was not significantly higher in LQTS patients who suffered from ventricular arrhythmias compared to LQTS patients without such events. Given these conflicting findings, the aim of this study is to conduct a systematic review with meta-analysis into the association between $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$ / QT ratio and arrhythmic and/or mortality endpoints in LQTS.

Methods

Search strategy, inclusion and exclusion criteria

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISM) statement [17]. PubMed and Embase were searched for studies that investigated the association between $T_{peak} - T_{end}$ or $T_{peak} - T_{end}$ / QT with arrhythmic or mortality endpoints in long QT syndrome. The following search terms were used for both databases: [“Tpeak–Tend” 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 “Tpe” "TPEc" OR "T-peak to T-end" OR "Tpeak-to-Tend" AND "long QT"]. The search period was from the beginning of the database through to 9th May 2017 without language restrictions. The following inclusion criteria were used: i) the study was conducted on humans, ii) $T_{peak} - T_{end}$ intervals or $T_{peak} - T_{end}$ / QT ratios were provided; iii) endpoint events [appropriate implantable cardioverter-defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death (SCD), cardiovascular death (CVD), major adverse cardiac events (MACE) or all-cause mortality were reported.

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The quality assessment of these studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS) [18]. 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 based on study design or analysis; f) assessment of outcomes; g) follow-up periods that were sufficiently long for outcomes to occur; and h) adequacy of follow-up of cohorts. This scale varied from zero to nine stars, which indicated that studies were graded as poor quality if the score was <5, fair if the score was 5 to 7, and good if the score was >8. Studies with a score equal to or higher than six were included. The details of the NOS quality assessment are shown in **Supplementary Tables 1 and 2**. No studies were excluded based on the quality score.

Data extraction and statistical analysis

Data from the different studies were entered in pre-specified spreadsheets in Microsoft Excel. All potentially relevant studies were retrieved as complete manuscripts and assessed fully to determine whether they met 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) endpoint(s); iv) the quality score; and v) the characteristics of the population including sample size, gender, age and number of subjects. Two reviewers (GT and CW) reviewed each included study independently. Disagreements were resolved by adjudication with input from a third reviewer (TL).

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The endpoints of the studies are occurrences of ventricular arrhythmias (VT/VF), sudden cardiac death, cardiovascular death, major adverse cardiac events (MACE) or all-cause mortality. If more than one endpoint is described, then SCD is preferentially used for analysis, followed by cardiovascular death and all-cause mortality. Mean differences with 95% confidence interval (CI) for $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$/QT ratio were extracted from each study and subsequently pooled.

The heterogeneity between studies was determined using Cochran's Q value, the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which describes the percentage of the variability in effect estimates resulting from heterogeneity, rather than sampling error. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. A fixed effects model was used if no significant heterogeneity was found. The random-effects model using the inverse variance heterogeneity method was used with $I^2 < 50\%$. To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time, and subgroup analyses based on different disease conditions and different endpoints were performed. Funnel plots, Begg and Mazumdar rank correlation test and Egger's test were used to assess for possible publication bias.

Results

Figure 1 shows a flow diagram detailing the above search terms with inclusion and exclusion criteria. A total of 97 and 116 entries were retrieved from Pubmed and Embase, respectively. Five studies were relevant for congenital long QT syndrome (LQTS) and were included in our final meta-analysis [14, 15, 19-21]. In this meta-analysis, a total of 388 patients were

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included (mean age 35 years old, range from 7 to 38; 37% male). **Table 1** shows the baseline characteristics of these studies and of the study populations.

Regarding $T_{peak} - T_{end}$ intervals, two studies reported longer values in event-positive group compared to event-negative groups, whilst the remaining three studies demonstrated no significant prolongation (**Figure 2**). The $T_{peak} - T_{end}$ intervals for event-negative and event-positive groups were 96 ± 8 and 114 ± 11, respectively, with a significant mean difference of 13 ± 4 ms (P = 0.002). The Cochran's Q value was greater than the degrees of freedom (6 vs. 4), indicating that the true effect size was different between studies. I^2 took a value of 34%, suggesting a low level of heterogeneity. A funnel plot plotting standard errors against differences in means is shown in **Supplementary Figure 1**. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0.2 with P = 0.62, which suggests no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 1.5, t-value 1.2; P = 0.32). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time. However, this did not significantly influence the mean difference (**Supplementary Figure 2**), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis.

For $T_{peak} - T_{end}$ / QT ratio**,** none of the four studies included in the analysis reported any significant difference between event-positive and event-negative groups (**Figure 3**). The $T_{peak} - T_{end}$ / QT ratio for event-negative and event-positive groups were 0.19 ± 0.01 and 0.21 ± 0.01, respectively, with no significant difference between the groups (mean difference: 0.02 ± 0.02; P = 0.26). The Cochran's Q value was less than the degrees of freedom (0.2 vs. 3), indicating that the true effect size was not significantly different between the included studies. I^2 took a value of 0%, suggesting no heterogeneity. A funnel plot plotting standard errors against differences in

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means is shown in **Supplementary Figure 3**. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's Tau took a value of 0 with P = 1.00, which suggests no publication bias. Egger's test demonstrated no significant asymmetry (intercept 0.1, t-value 0.3; P = 0.81). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time to calculate the pooled OR. However, this did not significantly influence the mean difference (**Supplementary Figure 4**), suggesting that no single study was responsible for the heterogeneity observed in this meta-analysis.

Discussion

Our main findings are that $T_{peak} - T_{end}$ intervals are longer and $T_{peak} - T_{end}$ / QT ratios are higher, in congenital LQTS patients suffering from adverse events compared to those who without these events.

Pre-existing heterogeneities in the heart are crucial for ensuring unidirectional spread of action potentials conducted through the cardiac conduction system [22, 23]. These are due to differences in repolarization times of the different cell types, which are responsible for inscription of the T-wave on the electrocardiogram (ECG) [24, 25]. However, exacerbation of these heterogeneities has been linked to ventricular arrhythmogenesis in a variety of conditions. These include congenital ion channelopathies such as LQTS and Brugada syndrome [26-28], acquired causes of LQTS [29] and short QT syndrome [30], as well as other diseases such as diabetes mellitus, hypertension and myocardial infarction [31-34]. These heterogeneities can occur locally or across the myocardial wall [35], potentially causing arrhythmias by inducing unidirectional conduction block and therefore circus-type or spiral wave re-entry [36, 37]. Pre-clinical experiments have

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associated higher degrees of transmural dispersion of repolarization (TDR) with arrhythmogenesis observed in long QT and Brugada syndromes [38, 39].

A number of electrocardiographic indices have been developed for risk stratification [40, 41]. The $T_{peak} - T_{end}$ interval was first proposed by Yan and Antzelevitch as an electrocardiographic surrogate marker of TDR [24, 42-44]. This was based on observations in coronary-perfused wedge preparations, in which the end of repolarization of the epicardium coincided with the T_{peak} and end of repolarization of M-cells coincided with T_{end} [45]. Subsequent experiments in pigs suggest that T_{peak} coincided with the *earliest* end of repolarization and T_{end} coincided with the *latest* end of repolarization. However, given that the U-wave also represents the repolarizing current, T_{end} will likely reflect the majority of repolarization [46-48]. Together, $T_{peak} - T_{end}$ is a surrogate marker for global dispersion of repolarization [6, 9, 49, 50].

In clinical studies, an increase in $T_{peak} - T_{end}$ interval has been associated with ventricular arrhythmias in LQTS type 1 and type 2 [51, 52], Brugada syndrome [53] and other cardiac conditions such as myocardial infarction [54]. $T_{peak} - T_{end}$ interval can be normalized to the QT interval, yielding $T_{peak} - T_{end}$ / QT ratio, which is equivalent to heart rate correction by Bazett's formula, with a relatively constant range of 0.17 to 0.23 [12]. This is thought to be a more sensitive index of arrhythmia risk than $T_{peak} - T_{end}$ interval, as it provides an estimate of dispersion of repolarization relative to total duration of repolarization, which would eliminate the confounding effects of heart rate and QT interval variability. Despite several studies have demonstrated the predictive value of $T_{peak} - T_{end}$ / QT ratio [12, 16, 32, 51, 55-57], three studies failed to demonstrate its value in LQTS and SQTS [16, 58, 59]. Only one of the included studies compared the performance of $T_{peak} - T_{end}$ intervals to traditional repolarization markers. Firstly, Samol and colleagues reported a sensitivity of 83% and a specificity of 73% at a cut-off value of 87ms with an area

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under the curve (AUC) of 0.80±0.07) for the prediction of adverse clinical events by $T_{peak} - T_{end}$ [20]. This compared to a comparable sensitivity of 82% but lower specificity of 68% with AUC of 0.86 ± 0.07 for QTc with a cut-off of 488 ms. It would appear that $T_{peak} - T_{end}$ has a higher specificity with similar sensitivity of discriminating high-risk patients when compared to QT_c. These need to be confirmed by larger studies. More complex derivations of these repolarization intervals have been proposed [60, 61], but whether these provide incremental value for risk stratification is controversial [62, 63].

However, incorporating conduction parameters into repolarization indices would likely improve risk stratification, since the likelihood of re-entry depends on both conduction velocity and refractory period, together determining the wavelength of excitation [64]. This can be estimated electrocardiographically [40, 65, 66]. Moreover, dispersion of conduction can predispose to unidirectional block. This can be observed as fragmentation in the QRS complex, whose prognostic value has been confirmed in Brugada syndrome [67]. Fragmented QRS has been observed in LQTS [68, 69], but whether it will be useful as a risk marker remains to be evaluated prospectively.

Limitations

The following strengths should be noted. Firstly, this is the only meta-analysis to date analyzing the predictive of $T_{peak} - T_{end}$ intervals and $T_{peak} - T_{end}$ / QT ratios for adverse clinical outcomes in congenital LQTS. Secondly, only a small degree of heterogeneity for the meta-analysis on mean difference of $T_{peak} - T_{end}$ intervals between event-positive and event-negative groups in congenital LQTS. This was despite different sub-types of congenital LQTS being included, suggesting that $T_{peak} - T_{end}$ intervals may be universally applicable regardless of the

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underlying ion channel that is mutated. However, some limitations remain. Firstly, the percentage of male patients and age differed between the studies. As this was a study-level meta-analysis, it was not possible to ascertain the impact of these factors on $T_{peak} - T_{end}$ intervals. Secondly, $T_{peak} - T_{end}$ intervals vary with lead positions and therefore measurement of these intervals from different leads can introduce a source of heterogeneity. Thirdly, their methods of determination, such as measurement from a single T-wave, averaged values of T-waves or median complexes, also differ. Fourthly, the definition of T_{end} also differs between studies. Three studies used the tangent method by taking the intersection of a tangent to the steepest downslope of the dominant repolarization wave with the isoelectric line, one study used the point at which the T-wave crossed the isoelectric line, and one study did not specify the method of T_{end} determination. Fifthly, there is considerable inter-observer variability. Interestingly, a previous study noted that for patients with LQTS, more than 80% of arrhythmia experts but less than 50% of cardiologists and less than 40% of non-cardiologists calculated the QTc correctly, and that interobserver agreement was excellent among QT experts, but moderate among arrhythmia experts and low among cardiologists and non-cardiologists [70]. It also demonstrated underestimation of the QTc for LQTS patients and overestimation of this interval for healthy patients [70]. Finally, recall bias may have been present in the retrospective studies, which could have also contributed to some of the heterogeneity observed. Nevertheless, the aim of this study is to determine the prognostic value of $T_{peak} - T_{end}$ intervals, which we have confirmed in our meta-analysis.

Conclusions

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This meta-analysis shows that $T_{peak} - T_{end}$ interval and $T_{peak} - T_{end}$ / QT ratio can distinguish high-risk patients with congenital LQTS from those who are at low-risk of adverse cardiac events. Further prospective studies with similarly definition of $T_{peak} - T_{end}$ interval from the same observers are needed to elucidate whether these indices provide additional value for risk stratification when compared to traditional repolarization indices such as the QTc interval.

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Additional information

No conflicts of interest declared.

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Tables

Table 1 Characteristics of the ten studies included in this meta-analysis

First author / Year	Study design	Population	Lead for $T_{peak} - T_{end}$ measurement	Method of T_{end} measurement	Sample size (n)	Age	% Male	Endpoints	No. of patients with any positive events	Syncope	Ventricular arrhythmia	SCA / SCD	Reference
Krych 2017	Retrospective	Congenital LQT7 (KCNJ2)	V2 or V3	Not specified	25	30	52	Syncope, CA, PVC > 2000 / 24 hours, PVT, BiVT	14	-	-	-	[19]
Samol 2016	Prospective	Congenital LQT1 (KCNQ1), 2 (KCNH2),8 (CACNA1c) and unknown subtype	V1	Tangent method	34	31	32	Syncope, TdP, SCA	12	12	7 (TdP)	4 (SCA)	[20]
Couderc 2011	Retrospective	Drug-induced and congenital LQTS (KCNH2)	II	Tangent method	143	38	39	SCA, SCD	74	77	-	11 (SCA), 3 (SCD)	[15]
Couderc 2010	Retrospective	Drug-induced and congenital LQTS (subtypes not described)	All 12 leads	Tangent method	8	7	63	TdP	5	-	5	-	[14]
Kanters 2008	Retrospective	Congenital LQT1 (KCNQ1), 2 (KCNH2), 3 (SCN5A)	V5	The point at which T-wave crosses isoelectric line	95	37	34	Syncope	45	45	-	-	[21]

Abbreviations: LQT: long QT; CA: cardiac arrest; SCA: sudden cardiac arrest; SCD: Sudden cardiac death; ICD: implantable cardioverter-defibrillator; PVC: premature ventricular complex; VT: Ventricular tachycardia; PVT: polymorphic VT; BiVT: bidirectional VT;

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Figures

Figure 1. Flow diagram of the study selection process.

Figure 2. Forest plot demonstrating the mean differences for between $T_{peak} - T_{end}$ intervals obtained from event-positive and event-negative groups in LQTS.

Figure 3. Forest plot demonstrating the mean differences for between $T_{peak} - T_{end}$/QT ratios from in event-positive and event-negative groups in LQTS.

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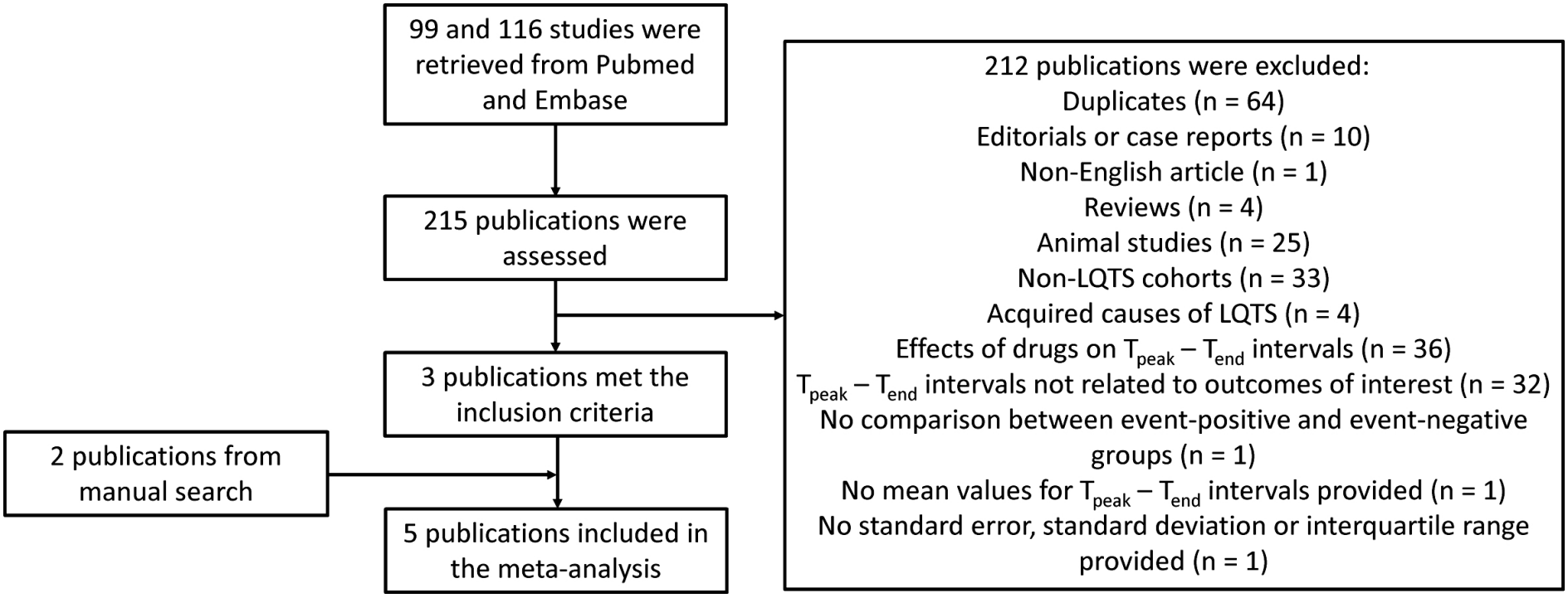
99 and 116 studies were retrieved from Pubmed and Embase
215 publications were assessed
3 publications met the inclusion criteria
2 publications from manual search
5 publications included in the meta-analysis
212 publications were excluded:
Duplicates (n = 64)
Editorials or case reports (n = 10)
Non-English article (n = 1)
Reviews (n = 4)
Animal studies (n = 25)
Non-LQTS cohorts (n = 33)
Acquired causes of LQTS (n = 4)
Effects of drugs on $T_{peak} – T_{end}$ intervals (n = 36)
$T_{peak} – T_{end}$ intervals not related to outcomes of interest (n = 32)
No comparison between event-positive and event-negative groups (n = 1)
No mean values for $T_{peak} – T_{end}$ intervals provided (n = 1)
No standard error, standard deviation or interquartile range provided (n = 1)

Figure 1

$T_{peak} - T_{end}$

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Krych 2017	29.000	10.690	114.281	8.047	49.953	2.713	0.007
Samol 2016	19.900	9.099	82.789	2.067	37.733	2.187	0.029
Couderc 2011	3.000	5.824	33.917	-8.415	14.415	0.515	0.606
Couderc 2010	14.000	32.391	1049.167	-49.485	77.485	0.432	0.666
Kanters 2008	19.000	10.248	105.031	-1.087	39.087	1.854	0.064
	12.779	4.056	16.451	4.830	20.729	3.151	0.002

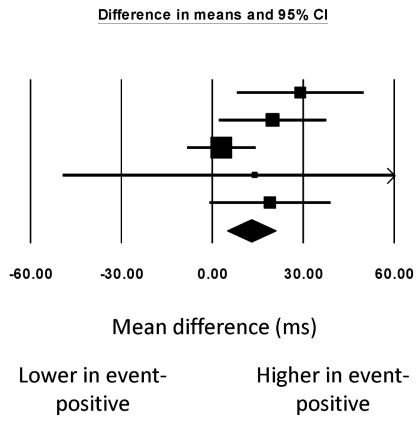

Figure 2

$T_{peak} - T_{end}$ / QT ratio

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Statistics for each study				
Krych 2017	0.056	0.087	0.008	-0.114	0.226	0.645	0.519
Samol 2016	0.018	0.018	0.000	-0.017	0.053	1.017	0.309
Couderc 2011	0.009	0.058	0.003	-0.104	0.123	0.164	0.870
Couderc 2010	-0.008	0.221	0.049	-0.441	0.424	-0.038	0.970
	0.019	0.017	0.000	-0.014	0.051	1.119	0.263

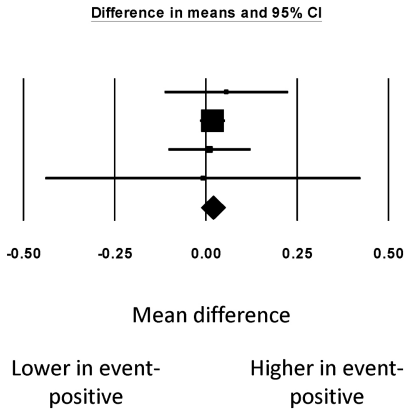

Figure 3