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Can QTc Prolongation >10 msec Predict Sudden Cardiac Death?

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ABSTRACT

Context: Currently, specific clinical studies are mandated before drug approval to ensure accurate evaluation of the risk of drug-induced arrhythmias. The underlying assumption for this requirement is that QTc-interval prolongation ≥10 msec leads to an increase in the risk of torsade de pointes (TdP). However, the evidence for such a correlation remains debatable.

Objective: To challenge the notion of increased TdP risk with QTc-interval prolongation ≥10msec and to explore whether sudden cardiac death (SCD), a potential surrogate for TdP, is correlated with increases from baseline QTc or to high baseline values.

Design, Setting, and Patients: The incidence of SCD in the population was derived from data in the Rotterdam Study cohort observed between 1997 and 2004 (n=282).

Main Outcome Measures: Trend-analysis was applied to evaluate SCD rates in patients showing increasing, decreasing and no change in QTc-interval measurements. A sensitivity analysis was also performed on the impact of the time span between death and last ECG measurement.

Results: Incidence rates of SCD increased significantly with higher baseline QTc values. This increase was independent of the time elapsed between the last ECG and death. In contrast to current belief, the incidence rates in subjects showing QTc prolongation <10 msec and ≥10 msec varied from 4.6 to 4.0 cases per 1000 person years (p<0.261).

Conclusions: QTc-interval prolongation by ≥10 msec does not appear to affect the incidence rate of SCD. Instead, increased rates were found to better correlate with high baseline QTc values. Despite the limited size of the cohort, these findings prompt for careful revision of the guidelines for evaluating the pro-arrhythmic risk of new medicines.
8.1 INTRODUCTION

Approximately 50% of all cardiac deaths are estimated to be of sudden nature. Sudden cardiac death (SCD) is defined as “natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour after the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected”. Irrespective of other triggering conditions, ventricular arrhythmias associated with an acquired long-QT syndrome (LQTS) are considered a risk factor for SCD. In addition, it is also assumed that QT-interval prolongation can provoke torsades de pointes (TdP), which in turn can either resolve spontaneously or deteriorate into ventricular fibrillation and potentially into SCD.

The alleged link between LQTS and SCD has become a real concern for the medical community given that a variety of drugs have been recognised to possess substantial pro-arrhythmic potential by inducing QTc-interval prolongation and consequently increasing the risk of TdP. Whilst the mechanism by which prolonged QTc-intervals can degrade into fatal arrhythmias is well described in various publications, there is still an ongoing debate in the literature on the clinical significance of its prolongation. Yet, QTc-interval prolongation has become one of the most common causes of post-market withdrawal as well as restriction of use of drugs.

Several large population-based studies evaluating the association between the heart-rate corrected QT-interval and mortality in apparently healthy persons did not find a consistent association between the length of the QTc-interval and total or cardiovascular mortality. Only few of these studies specifically explored events such as sudden cardiac death and when they did, the number of cases was often too small to detect statistically significant differences. Nevertheless, SCD has been found to be associated with high values of QTc-interval in a study conducted by Straus et al. In view of the potential implications of drug-induced LQTS, the use of QTc-interval prolongation has been proposed as a marker of cardiovascular risk for both pre- and post-market studies, regardless of the supporting evidence.
To mitigate such risks, the European Agency for Evaluation of Medicinal Products (EMA) was the first to issue a “points to consider” document from the Committee for Proprietary Medicinal Products (CPMP) in 1997. In the early 2000s, regulatory scrutiny continued to increase, leading to the development of the latest guideline from the International Conference on Harmonisation (ICH), topic E14, which introduced the requirement for a thorough-QT (TQT) study. A TQT study will only be considered negative for a new chemical entity (NCE) if the 95% upper interval of the largest time-matched QTc measurements after active treatment does not include 10 msec after adjusting for baseline and placebo effects. Yet, the guideline states that it is not clear whether arrhythmia development is more closely related to an increase in the absolute QT or QTc.

Irrespective of the premises adopted by regulatory agencies and recent advancements in the detection of QT-interval prolongation, it remains unclear whether TdP and SCD are indeed correlated with each other in a cause-and-effect manner. As a result, any meaningful attempt to further implement QT-interval as a prognostic marker of cardiovascular risk must take into consideration the basic operating characteristics of working variables, i.e., its sensitivity and specificity to detect the signal of interest. Among other things, it is of interest to investigate whether increases in QTc values, calculated as changes from baseline measurements or absolute measured QTc values, are associated with SCD using traditional epidemiological methodologies. The aim of this study was therefore to explore whether the incidence rate of SCD is correlated with high baseline values or increases from baseline QTc-interval.

### 8.2 METHODS

**Protocol design and study population**

This study was conducted using the Rotterdam Study cohort. All inhabitants of a suburb in Rotterdam, Ommoord, aged 55 years and over (n = 10275), were invited to participate. Of these, 7983 (78%) gave their written informed consent and took part in the baseline examination. Objectives and methods of the Rotterdam Study have been described in detail elsewhere. During baseline assessment, all participants were visited at home for a standardised questionnaire and 7151 were subsequently examined at the
research centre. A second, third and fourth follow up visit took place between 1993 and 2004. In addition to follow-up examinations, the cohort was continuously monitored for major morbidity and mortality through linkage with general practitioner and municipality records. Drug prescriptions dispensed to participants have been stored in the database by automated pharmacy procedures. All participants in the Rotterdam Study with at least two consecutive ECG assessments were included in this analysis.

**Sudden cardiac death assessment**

In case of a fatal event, general practitioners (GP) filled in a questionnaire describing the circumstances of the death, including time since the occurrence of first symptoms, most likely cause of death according to the physician, actual time and place of death. All questionnaires and a copy of the medical records were used to assess if the death could be classified as a sudden cardiac death. If death was witnessed and occurred within one hour after the start of symptoms, we assumed it to be a sudden cardiac death, without additional review of the medical records for a medical history of cardiovascular disease or the presence of cardiovascular risk factors. In case of an un-witnessed death, evidence of cardiac causes was searched for using all available information. Two research physicians coded all reported events independently according to the International Classification of Diseases, 10th edition (ICD-10, sudden cardiac death: I.46). In case of disagreement, consensus was sought. Finally, a cardiologist, whose judgment was considered decisive, reviewed all events.

**ECG interpretation and measurements**

A 10 sec 12-lead resting ECG (on average 8-10 beats) was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs were processed by the Modular ECG Analysis System (MEANS), which determines the QT-interval from the start of the QRS complex until the end of the T wave. The Bazett’s formula (QTc[b]=QT/sqrt(RR)) was used to correct for heart rate differences. Digitally stored ECGs from 6134 and 4415 participants who visited the research centre were available at the time of the first and second visit (86% vs. 70% of the study population), respectively.
The immediate last QTc value on record prior to the case of SCD was used as the measurement associated with death. QTc values were categorised into bins of 10 msec increments as shown in Table 1. For calculating changes in QTc-interval the immediate two last consecutive values on record were used. Two analyses were performed using the differences in QTc (delta QTc). The first one was meant to explore the directionality of the two consecutive measurements: downward (negative delta) where $\Delta$QTc<0, flat (zero delta) with $\Delta$QTc=0, and upward (positive delta) where $\Delta$ QTc>0. The second analysis was based on a subsequent dichotomisation of delta QTc values into less than 10 msec and those equal or greater than 10 msec. In all those cases in which measurements could not be obtained or were missing, the patient was excluded from this investigation.

Statistical analysis

The incidence rate of sudden cardiac death was determined by dividing the total number of sudden cardiac death cases by the total number of person-years accumulated in the study population. 95% confidence intervals were calculated based on a Poisson distribution.

Trend analysis of the incidence rates was then performed. SCD rates for delta QTc of <10 msec and ≥10 msec were compared with negative, zero and positive changes between consecutive measurements. In addition, a sensitivity analysis was performed to assess parameter precision at different time lapses between death and last ECG measurement at 6, 12, 18, 24, 30 and 36 months.

Binomial proportions testing was performed to determine if the proportions of SCD cases with QTc values above and below the population median QTc value were significant using $p < 0.05$ as a statistical significance level. This consisted of comparing the ratios between the number of deaths associated with QTc-intervals that are below the median QTc value of the entire population versus the number of deaths associated with QTc-intervals that are above the population median QTc value. Furthermore, logistic regression calculations were done to determine if predictor variables or regression coefficients in this analysis, namely bins of QTc-intervals, delta QTc of <10 msec or ≥10msec, and delta QTc of < 0, =0 or >0, were correlated with the probability of occurrence of SCD. A $p$-value < 0.05 was also chosen as threshold for statistical significance.
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Table 1. QTc categories and the corresponding QTc values in increment bins of 10msec. The incidence rates are shown for each category with its corresponding confidence intervals.
8.3 RESULTS

Out of 6680 subjects with an ECG measurement, 282 cases of SCD were identified of which 147 cases were witnessed. Only 38 subjects were taking QTc-prolonging medications at the time of the last ECG measurement prior to death. No clear pattern has emerged from exploring the sequences of ECG measurements over time, as shown in the top panel in Figure 1 for seven randomly selected subjects who experienced SCD. The median QTc value associated with all the QTc values included in the analysis is 434 msec. There were 162 SCD cases out of 3235 QTc measurements above the median value, 118 cases out of 3315 measurements below the median value and 2 cases out of 91 measurements at the median value. Based on the binomial proportions test it was concluded that the differences between the two groups were statistically significant ($p = 0.004574$). The overall distributions of all QTc measurements associated with cases of SCD and non SCD show that the fatal event can occur at normal, borderline and prolonged values, as defined by the Committee for Proprietary Medicinal Products (Figure 1, middle and bottom panels). 19

In contrast, incidence rates did increase with higher baseline QTc values ($p < 0.001$) as shown in Table 1. This increase was consistently observed irrespective of the time elapsed between the last ECG measurement and death (Figure 2). When delta QTc values are compared with regard to its direction of fluctuation, the trend over time is uncorrelated ($p = 0.195$). In Figure 3, negative, zero and positive delta QTc values were compared for 6, 12, 18, 24, 30, and 36 months between last ECG measurement and death. Remarkably, shown in Figure 4, the magnitude of the changes in QTc-interval, $< 10$ msec or $\geq 10$ msec, was not correlated to incidence rates of SCD with results varying from 4.6 to 4.0 cases per 1000 person years respectively ($p = 0.261$). $\Delta$ QTc values were also compared for 6, 12, 18, 24, 30, and 36 months between last ECG measurement and death with insignificant results.
Figure 1. Four consecutive ECG measurements of seven randomly selected subjects prior to SCD (top panel). The x-axis denotes the four measurements (visit) between 1990-2004. Density distribution of last ECG measurements before SCD (middle panels). Density distribution of last ECG measurements of non SCD cases (bottom panels). The definition of “normal”, “borderline”, and “prolonged” QTc values are taken from the European regulatory guidelines. 19
Figure 2. Top panel - Incidence rates of sudden cardiac death by increment bins of 10 msec QTc-intervals \( (p < 0.00000235) \). Bottom panels - Sensitivity analysis of incidence rates of sudden cardiac death. Each sub-panel shows the time lapse between the last measurement and death. \( N \) denotes the number of subjects included in the analysis.
Figure 3. Incidence rates of sudden cardiac death by defining delta QTc as decreasing (negative delta), maintained (zero delta) and increasing (positive delta) (p = 0.195). The x-axis shows the time lapse between the last measurement and death.

Figure 4. Incidence rates of sudden cardiac death by defining ∆QTc as < 10 msec and > 10 msec (p = 0.261). The x-axis shows the time lapse between the last measurement and death.
8.4 DISCUSSIONS

A prolonged QT-interval has been considered an attractive non-invasive risk factor for SCD. In this study, we showed that the incidence rate of SCD is better correlated with high absolute baseline QTc-interval values. A prolongation by $\geq 10$ msec did not significantly affect the incidence rate of SCD given there were only 182 cases with two consecutive QTc measurements prior to death.

Even though no consistent evidence has been demonstrated for increased risk of total or cardiovascular mortality or sudden death, the results from this study do agree with previous epidemiological studies. Recently, Straus et al., found that prolonged QTc-intervals are associated with threefold increased risk of sudden cardiac death after adjustment for age, sex, body mass index, hypertension, cholesterol/HDL ratio, diabetes mellitus, myocardial infarction and heart failure in the same population used in this present study. In another study, a QTc-interval $> 440$ msec was found to double the risk of sudden cardiac death. Analogous conclusions have been drawn by the Amsterdam study and by Dekker et al. Furthermore, inferences can also be made from data showing that the relative risk for arrhythmic death is higher when resting heart rate is greater or equal to 84 bpm, and that TdP is rarely associated with QTc-intervals less than 500 msec.

On the other hand, our findings contrast with the Framingham study, which did not demonstrate an association of baseline QTc with sudden death. However, the population was considerably younger at time of enrolment (ages 30-65 years) and thus, the majority of baseline ECGs were recorded in patients probably before changes in risk become significant or cardiac disease is still subclinical. Other attempts to characterise the determinants of SCD have been less successful due to the limited number of SCD cases or because of issues with the sensitivity and specificity of the analysis.

Despite the lack of evidence corroborating the link between QT/QTC-interval prolongation and TdP, QT-interval has been used as a surrogate marker for cardiovascular safety risks. When corrected for heart rate, the QT-interval read from an electrocardiogram is a direct marker of ventricular action potential duration and represent the time taken for the heart to return to its resting state following the preceding contraction that pumps blood around
the body. Albeit imperfect, it is at present the best available surrogate maker for the risk of TdP, which can potentially lead to SCD. From the sensitivity analysis performed in our study, SCD incidence rates were found to be independent from the time elapsed since last ECG measured and death. This implies that using the absolute QTc values to determine the risk of SCD may be relatively more reliable.\textsuperscript{28,29}

Most importantly, our findings appear to contradict the hypothesis underlying the current requirements by ICH topic E14 guideline on the evaluation of cardiovascular risk for non antiarrhythmic drugs, in which safety is defined by a threshold for an upper interval delta prolongation value of 10 msec. From our analysis, the association between a delta 10 msec change in QTc and SCD is not statistically significant, nor reliable. Thus, two important concepts will need to be addressed in future revisions of the ICH E14 guideline: the threshold of 10 msec and the usage of delta QTc values.

There are also challenges in interpreting the significance of mean changes ($\Delta$QT) from baseline without understanding inter-individual differences in drug exposure.\textsuperscript{30} For example, the mean increases in peak QTc-interval were 9 and 22 msec following single oral doses of, respectively, 10 mg and 50 mg thioridazine\textsuperscript{31}, whilst 15 msec and 17 msec increases relative to placebo were found with 400 mg and 800 mg of single oral doses of moxifloxacin.\textsuperscript{32} In this context, the assumption of a constant increase in the risk of pro-arrhythmia does not seem to be substantiated by clinical data. In fact, pharmacokinetic-pharmacodynamic analysis reveals clear differences in the slope of the concentration-effect relationships of compounds showing QTc-prolonging effects.\textsuperscript{33}

Thus far, the risk of TdP as well as SCD has all pointed to an association with absolute QTc measurements. Based on our results, it appears that drug-induced changes in QTc may not increase the cardiovascular risks unless the measured QTc value falls within a range of values with a higher risk.\textsuperscript{34}

It should be noted that our estimates were not adjusted for other cardiovascular risk factors, such as age, gender, smoking status, body mass index, diabetes and cardiac-related comorbidities, and that we used the most recent regulatory guidelines to classify QTc prolongation.\textsuperscript{35} We have assumed random distribution in the measurement error and negligible confounding effect of drug-induced T-wave changes, which may complicate
the measurement of the QT-interval. Yet, it should be emphasised that the absolute risk of sudden cardiac death does show an increase with age. 36,37

In summary, our findings corroborate an association between heart-rate corrected (QTc)-interval and the risk of sudden cardiac death (SCD). Given the growing relevance of QTc prolongation in drug development, our results clearly raise questions about the rationale for the evaluation of the pro-arrhythmic potential of novel compounds. Whilst it may not be feasible to establish a cut-off range for QTc-intervals without taking into account additional factors contributing to an increase in the risk of SCD, it seems evident that clinically effective risk management policies should consider baseline QT/QTc-interval as a strong prognostic factor for pro-arrhythmias. We strongly recommend revisiting the current guidelines for the evaluation of cardiovascular safety. The assumption of a comparable risk of TdP across the population for an increase in QTc-interval of ≥10 msec cannot be sustained.

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