Defining QT/QTc Prolongation During ST-Elevation Myocardial Infarction and Reperfusion

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Abstract. *Before novel drugs are approved, the US FDA mandates an adequate safety evaluation, including evaluation of measurable QT interval changes. Defining the safety profile of drugs for patients in disease states is a particular challenge, including patients suffering ST-elevation myocardial infarction (STEMI). Although STEMI therapies are effective in restoring perfusion at the epicardial level, ongoing cellular injury "downstream" can result in adverse arrhythmic events and remains an area of active research. To determine if therapies administered during STEMI create an increased safety risk, QT behavior from the disease itself needs to be quantified sufficiently to define boundary conditions evaluative of acute arrhythmic risk. We conducted a feasibility study to define the expected QT range during STEMI and reperfusion. Four cardiologists each measured QT and RR in a random sample of 44 subjects selected from a larger database of 24-hour, continuously recorded, 12-lead electrocardiograms (ECG) previously analyzed for ST-segment deviation. Seven pre-specified time points related to ST deviation were utilized. QTcF mean estimates were computed at each time point using repeated measures analysis, demonstrating the range, accuracy, and variation across different periods of ST deviation and the consistency across readers. More than 1,400 ECGs were measured with mean QTcF estimates by decreasing ST deviation from 416±5.2 to 431±5.2 msec, demonstrating a significant negative correlation between ST-segment deviation and QTcF (p=0.02). Intra-observer correlation among each pair of readers ranged from 0.87 to 0.94 and 0.90 to 0.99 for QT and RR, respectively. Study results could provide a global first-in-kind reference standard for patients in a disease state, complementing the existing standards utilized for thorough QT studies in normal volunteers. This STEMI ST-QT reference standard would further inform drug safety research and development paths in actual population of use STEMI studies. Boundaries around the mean QT for risk related to drugs given during STEMI would enable outliers to be characterized as safety concerns for proarrhythmic risk.*

Keywords: ST-segment; QT interval; STEMI; reperfusion

1. Introduction

While QT prolongation is an imperfect biomarker for proarrhythmic risk, a qualitative relationship exists between prolonged QT and the development of arrhythmias such as torsade de point (TdP). The United States (US) Food and Drug Administration (FDA) uses this biomarker as the gold standard for cardiac safety evaluation of new molecular entities (NME). QT studies for FDA submission are routinely performed in healthy volunteers, limiting the information available on cardiovascular safety in actual populations of use. Even more complex is the interpretation of drug-induced QT changes in a population of use whose disease state independently effects repolarization measured as QT interval, such as patients treated with drugs targeting reperfusion injury during ST elevation MI (STEMI). A reliable standard of the disease's impact on QT would be valuable for understanding whether NME exposure during STEMI promotes more QT prolongation than would be expected for STEMI alone. Such a standard would be a first in kind, and if available in the public domain, could be useful to the cardiac safety evaluation of NMEs intended for STEMI care.

Before a NME can be approved for clinical use, the FDA and the International Congress on Harmonisation (ICH) guidelines mandate an appropriate cardiac safety evaluation, including evaluation of such "off-target" effects as prolongation of myocellular action potentials leading to measurable changes in the QT or heart rate-corrected (QTc) interval. The evaluation of a novel drug's effect on cardiac repolarization is usually performed during early clinical development after pharmacokinetics of the drug are known in healthy volunteers to assess cardiac risk and determine if the effect of a novel drug on the QT/QTc interval in target patient populations should be studied further, with optimal designs including exposure to a range of NME doses with confirmed serum drug concentrations mapped against QT prolongation. Based on current ICH E14 guidelines, this positive- and placebo-controlled "thorough QT/QTc study" (TQT) designed to detect a 5 to 10 milliseconds (msec) alteration in the QT/QTc interval is required before new drugs are approved and has stimulated much debate over the best way to measure efficacy of novel drugs while still protecting the public and actual populations of use from potentially harmful treatments.

Defining the safety profile of NMEs in actual patient populations has many challenges compared to the controlled conditions of TQT studies, particularly in populations in which the disease can affect the QT interval. Patients suffering from ST elevation myocardial infarction (STEMI) are one such group. More than 300,000 (21%) of the 1.57 million annual US hospital admissions are due to acute coronary syndromes. [1] Mortality rates in STEMI have been reduced to less than 5% through advances in reperfusion therapies such as thrombolytics and percutaneous coronary intervention (PCI). [2-3] Although therapies for STEMI are effective in restoring perfusion at the epicardial level, ongoing cellular injury "downstream," which can result in heart failure and arrhythmic events, remains an area of active drug research. [4-5]

Establishing if a new treatment administered during the acute phase of a STEMI creates a proarrhythmic safety risk, such as QT/QTc prolongation, requires the development of a reference standard quantifying the natural history of the QT behaviour from the disease itself. Such a standard would need to define boundary conditions of expected QT/QTc changes related to key aspects of the STEMI, such as amplitude, infarct location, and potential interaction with descriptors such as age, sex and diabetes. Such a reference standard provided in the public domain would be a first-in-kind and could significantly promote cardiac safety assessment in these vulnerable and complex patients.

To this end, we performed a retrospective analysis using data randomly selected from a large, existing warehouse of continuously recorded, 12-lead electrocardiograms (ECGs) collected during STEMI and reperfusion available at the ECG Core Laboratory at the Duke Clinical Research Institute (DCRI) to determine the feasibility of creating a public domain reference standard that defines the expected range of dynamic QT/QTc change during STEMI and reperfusion. QT measurements were performed using specialized core laboratory software at time points related to varying degrees of ST elevation and recovery to develop a disease-related boundary for QT/QTc interval behaviour in STEMI before, during, and after reperfusion. If successful, the results of the proposed study could be used to design a larger retrospective study to establish an accurate model for safety evaluation of drugs used as adjuncts to STEMI care and potentially establish a population-of-use standard in the public domain for short term QT exposure for evaluation of the proarrhythmic safety of NMEs in the actual STEMI setting.

2. Subject and Methods

A retrospective analysis using 44 subjects randomly selected from an existing larger database of three primary PCI clinical trials previously analyzed for ST-segment changes were used to investigate temporal fluctuations of the QT/QTc interval during STEMI and following reperfusion. [6] Continuous ECG data were collected using a 12-lead, digital, 24-hour, high-

fidelity NEMON (Northeast Monitoring, Maynard, MA, USA) Holter monitor which acquires and stores a standard 12-lead median beat ECG every 60 seconds for 24 hours. ECG data were analysed at an independent ECG core laboratory (Duke Clinical Research Institute, Durham, NC, USA) blinded to treatment and clinical outcomes.

The QT interval was defined as the duration in milliseconds (msec) from the initial deflection of the Q-wave through the end of the T-wave upon return to isoelectricity using a global superimposed median beat. The end of the T-wave was defined as the intersection of a tangent to the steepest slope of the last limb of the T-wave and the baseline in lead II or lead V5. The global QT measure is not an average, but rather a measure obtained from superimposing all 12 leads onto the joint isoelectric line. This is a standard method used by core laboratories for FDA submissions and is more consistent and reproducible than a lead-specific approach. Four readers were used to confirm reliability and reproducibility of results, while inter- and intra-observer reliability statistics were used to determine agreement among readers based on already existing ECG core laboratory standards. Neither the QT intervals nor ST deviation were measured during conduction abnormalities, such as U-waves or bundle branch block.

Continuous QT interval measurements were made at time points previously labelled for ST-segment deviation during periods of ischemia and subsequent reperfusion. These time points included monitor initiation (ECG prior to PCI), the start and end of each ischemic event, peak ST deviation, first 50% reperfusion, first and last contrast injection, 30 minutes post-PCI, stable reperfusion (reperfusion lasting > 4 hours), and baseline (most normal ECG). Each subject had at least two measurements (monitor initiation and baseline), while most subjects had more than 7 measurements, depending on the number of ischemic episodes and peak ST location. The Fridericia formula (QTcF) was used to obtain a QT measure corrected for heart rate.

A repeated measures linear mixed-effects model was used to estimate the least squares mean QT/QTc effect and QT/QTc variation with associated 95% confidence intervals. Confidence intervals were constructed for the QT/QTc mean estimate using the residual error of the ANCOVA regression model at varying degrees of ST-segment deviation. A p-value < 0.05 was considered statistically significant, and SAS version 9.2 was used all statistical analyses.

3. Results

Four cardiologists each measured QT and RR intervals in 44 randomly selected subjects at seven pre-specified time points previously labelled during ST-segment analyses, giving us 1,413 ECGs for this feasibility exercise. Using repeated measures analysis, QTcF mean estimates with confidence intervals were computed for each time point demonstrating the range, accuracy, and variation across time points that can be obtained from just a small number of the ECGs in our database across different periods of ST elevation and reperfusion. Mean QTcF estimates by decreasing ST deviation ranged from 416±5.2 to 431±5.2 msec, demonstrating a significant negative correlation between ST-segment deviation and QTcF (p=0.02).

Intra-observer correlation statistics were computed across all 4 readers and among each possible pair of readers using Shrout-Fleiss methodology. [7] The QT reliability ranged from 0.87 to 0.94 when a single QT measure was considered, while reliability ranged from 0.90 to 0.97 when the average of at least 2 readers was considered demonstrating the stability and consistency of the measures. RR reliability ranged from 0.90 to 0.99.

4. Discussion

Our goal is to create a public domain reference standard that defines the expected range of QT/QTc changes in the setting of dynamic ST-segment changes associated with STEMI and reperfusion. This model would be used to develop a disease-related boundary for QT/QTc

interval behaviour across a range of ST amplitudes and vector locations using a sufficient number of patients to show variability across other descriptors such as age, sex, and diabetes. We propose to establish boundaries for STEMI subjects by defining the expected QT/QTc ranges and boundary conditions within 2-3 standard deviations around the mean effect on QT/QTc for risk related to NMEs given during an acute STEMI. These proposed boundary conditions would enable outliers to be characterized as safety concerns for proarrhythmic risk.

We have previously described ST-elevation and recovery patterns in STEMI patients from more than 12 clinical trials, all using continuous 12-lead ECG monitors. [8] Using this larger dataset, we propose to retrospectively validate our feasibility study findings and quantify QT/QTc at varying degrees of ST deviation. Establishing boundaries in actual STEMI patients will significantly enhance cardiac safety evaluation for novel therapies in these vulnerable patients.

5. Conclusions

We have demonstrated the range, accuracy and variation of QT/QTc estimates across time points related to ST deviation that can be obtained from a small number of the ECGs. The QT-ST negative correlation implies that a relationship exists, and validation of these results in a larger study could provide a global first-in-kind reference standard for actual STEMI patients to complement the existing standards utilized for thorough QT studies in normal volunteers.

References

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