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Objectives: Concentration-QT (c-QT) modeling of early phase ECG data is recognized as a viable alternative to thorough-QT (TQT) study for assessing QT/QTc-interval prolongation. However, multiple statistical characteristics have to be assessed before reliable modeling results can be produced. Herein, we develop a comprehensive set of statistical methods to assess modeling characteristics such as, model fitting, robustness of results to assumption violations, sensitivity and specificity of the modeling approach in detecting QT/QTc-interval prolongation. Statistical methods are also developed to address issues related to the lack of positive control arm.

Methods: ECG data quality is assessed using variance component and variability analysis. Variability statistics are compared to those in TQT studies. The sensitivity and specificity of c-QT modeling approach are confirmed by Monte Carlo simulation studies. Goodness-of-fitting is evaluated by AIC parameter and diagnostic plots. Model robustness is assessed through sensitivity analyses with alternative model structure and independent variable terms.

Results: through rigorous statistical testing, ECG data quality is confirmed to be comparable with TQT standard. Adequate model sensitivity and specificity assures ability of the method to detect true positive or negative QT prolongation. Consistent QT-RR relation validates selection of dependent variable. Goodness and robustness of model fitting ensures excellence of final model, providing a concrete foundation to conclude the c-QT relationship. This set of statistical methodology was successfully applied to c-QT of 3 different investigational compounds to monitor data quality and to ensure correctness of model fitting. One compound was granted TQT waivers from US FDA and EMA based on c-QT analysis [1]. Waiver submission for the other two compounds is ongoing.

Conclusions: With a thorough evaluation of model characteristics, reliable and robust results can be produced using c-QT modeling approach, as a viable alternative to TQT for QT/QTc prolongation assessment. Lack of positive control in early phase studies can be addressed by the proposed statistical analyses.

References: