Comparison of Six Commonly Used QT Correction Formulae And Three Parameter Estimation Methods

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Background: QT interval on an electrocardiogram (ECG) trace has become an important and widely used surrogate parameter in the assessment of drug safety during drug development. The QT interval changes inversely with heart rate and is often corrected to a heart rate independent value known as the corrected QT interval (QTc). Although various parametric QT correction formulae exist, there is a lack of assessment of sensitivity of formula parameter estimates and QTc variability on parameter estimating methods.

Methods: Six commonly used QT correction formulae (linear, hyperbolic [QTc=QT-α(1/RR-1)], parabolic [QTc=QT/RR²], logarithmic, shifted logarithmic, and exponential models) and three available parameter estimation methods (golden section [finding the minimum/maximum of a unimodal function by narrowing the range of values inside which the minimum exists], regression, and mixed model) using five indices for QTc validation (correlation coefficient between QTc and RR, regression slope of QTc on RR, RMSE, standard deviation and range of QTc) were compared. These methods were applied to four off-drug ECG datasets, one on-drug ECG dataset and a simulated dataset.

Results: The golden section approach always found the correction factor which makes QTc values totally independent of RR interval for all 6 formulae in terms of correlation coefficient and regression slope. The resulting parabolic model from the golden approach method generated QTc values with the smallest variation in terms of standard deviation and range. Correction formulae derived from regression and mixed model approaches often failed to make QTc intervals independent of RR.

Conclusion: Parabolic correction formula (QTc=QT/RR²) with its correction factor (α) being estimated using the golden section approach is recommended to correct QT for heart rate in clinical studies. In contrast, regression approach should be avoided for deriving correction factors for any correction formula.