VivaQuant™
Quantifying vital signs. Accurately.

Dynamic QTbtb and Restitution Analysis Services

Does your NCE prolong QTc? VivaQuant™ can provide turn-key dynamic btb and restitution analysis services. This technique has been used successfully in the past to establish a safety profile acceptable to FDA, even when the NCE prolongs QTc[1].

Dynamic QT beat-to-beat (QTbtb) analysis can circumvent many of the limitations of QTc as a biomarker of arrhythmia vulnerability. QTbtb has been shown to differentiate changes in QT interval due to heart rate or autonomic state from impaired repolarization. Dynamic QTbtb analysis compares QT intervals to individual cardiac cycles from all normal autonomic states at similar RR intervals, thereby eliminating potential sources of error from the use of QT correction functions. Since QTbtb compares all treatment related beats to similar beats under all baseline autonomic conditions, it can identify when abnormal autonomic states or impaired repolarization exist that may lead to increased arrhythmia vulnerability. Under these same conditions, QTc breaks down as a cardiac risk biomarker and can produce either a false positive or false negative indication of cardiac risk. FDA recognizes this limitation of QTc and has initiated an effort with the Cardiovascular Safety Research Consortium to identify alternative techniques that circumvent these limitations.

Restitution is a second beat-to-beat analysis tool that can be applied to the same dataset for quantifying the cardiac stress leading to arrhythmia vulnerability. Restitution assesses the ability of the heart to recover from one beat to the next. The methodology measures changes in QT interval (working phase of heart) in response to each preceding TQ interval (resting phase of heart) at every heart rate (RR interval) to quantify the stress on the heart and identify conditions where the likelihood of a re-entry arrhythmia is increased.

QT Beat-to-beat Analysis

Features

- Assesses QT interval changes without correction factors by comparing beats at similar heart rates under all normal autonomic conditions and hysteresis.
- Differentiates normal from impaired repolarization at any heart rate; not possible with QTc.
- Generates beat-to-beat QT-RR interval plots or "clouds" that allow visual validation and easy interpretation of findings.
- Clinically validated outcomes and used in FDA regulatory facing studies.
- More than 15 years of clinical and preclinical supporting data.

Benefits

- Data meet ICH E14 thorough QT assessment and S7B requirements for regulatory filing.
- Fully translational methodology from preclinical (dog or monkey) to clinical data.
- Assesses changes in QT interval during varying autonomic states where QTc often fails.
- Data are more accurate for PK/PD modeling since not affected by varying autonomic states.
- Provides mechanistic information underlying changes in QT-RR interval relationship.

Beat-to-beat Restitution Analysis

Features

- Restitution assesses the ability of the heart to recover from one beat to the next.
- Quantifies changes in QT interval (working phase of heart) in response to each preceding TQ interval (resting phase of heart).
- Quantifies stress on the heart at any heart rate.
- Considers abnormal hysteresis and changes in autonomic states.
- Quantifies extreme beats that represent heterogeneity and increased cardiac stress.
- Generates beat-to-beat QT/TQ vs RR interval plots or "clouds" for visual validation and interpretation.

Benefits

- Differentiates changes in QT or QTc interval from changes that pose no risk or may increase arrhythmia liability to alter therapeutic index.
- Identifies QTc effects that are antiarrhythmic.
- Identifies mechanisms related to changes in cardiac stress and arrhythmia liability.
- Allows for easy decision making related to safety of drugs that alter QTc and heart rate, blood pressure or contractility (provided the latter two are measured or known).

How does it work?

Step 1: Continuous ECG recordings are collected (Holter or telemetry) over at least 20 hours prior to and during study periods from any preclinical (canine or primate) or clinical study.

Step 2: Digital recordings are processed by VivaQuant's proprietary Multi-Domain signal Processing (MDSP™) and results are tabulated for beat-to-beat analyses by assessing specific parameters related to each QT and preceding RR and TQ interval.

Step 3: Baseline relationship of all QT, RR and TQ intervals along with 95% reference bounds created from predose dataset.

Step 4: All treatment ECG data are then compared to this relationship on a beat-to-beat basis at the same heart rate to determine magnitude and heterogeneity of dynamic measures.

What is calculated and what does it mean?

- Median TQ interval: As relative refractory period approaches zero, arrhythmia vulnerability may increase due to reentry.
- Lower 5% TQ quantile: Least amount of rest the most extreme beats are getting. Good indicator of temporal heterogeneity.
- Median QT/TQ ratio: A general indicator if restitution is moving toward impairment or stability. The lower the ratio the better.
- % of beats with QT/TQ ratio > 1: If higher % of beats is > 1, heart is working more than resting and under more stress and prone to arrhythmia.
- Upper 98% quantile of QT/TQ ratio: The most extreme beats of the heart. The higher this ratio the greater likelihood of triggering an arrhythmia. Good indicator of temporal heterogeneity.

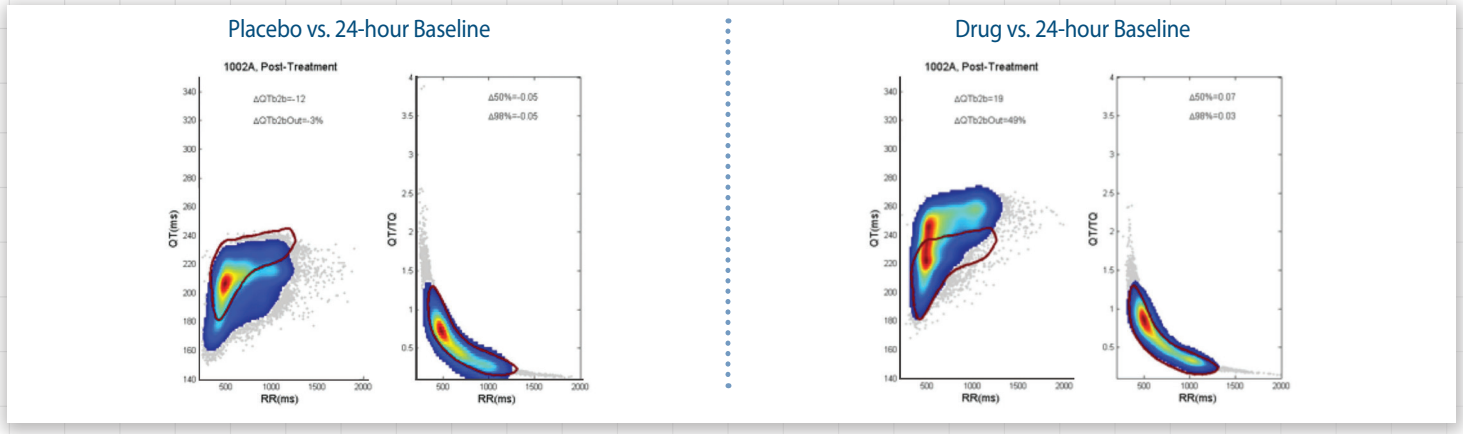

Figure 1: QTbtb (left side) and ECG restitution (right side) analyses in the same dog from a cross-over study. QT prolongation with no change in restitution (i.e. no increased risk of arrhythmia).

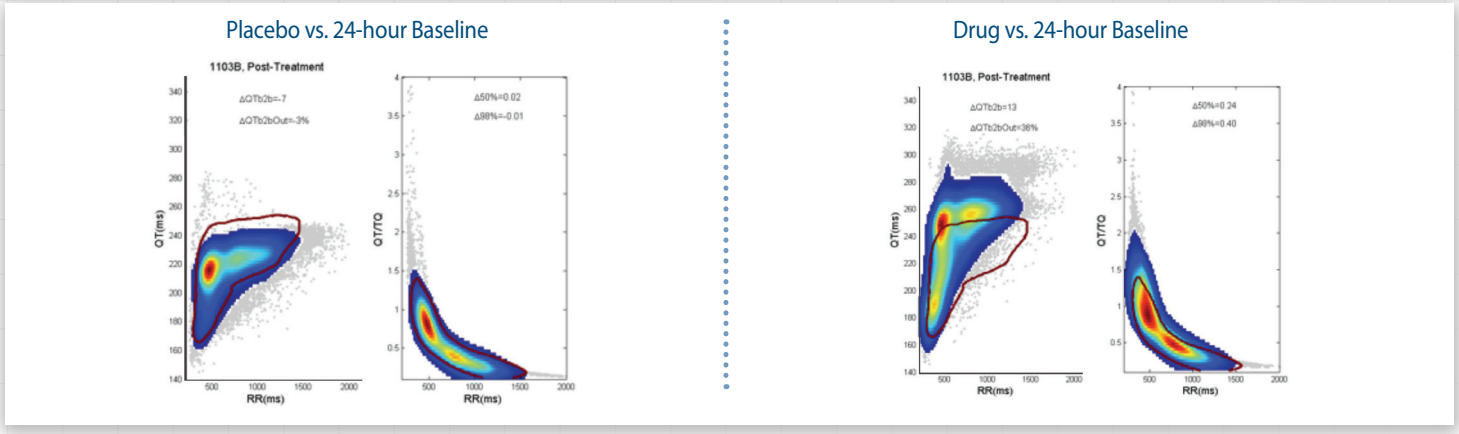

Figure 2: QTbtb and ECG restitution analysis in the same dog from a cross-over study. QT prolongation with impaired restitution (i.e. increased risk of arrhythmia).

1. Fossa, A, et. al. "Use of ECG restitution (beat-to-beat QT-TQ interval analysis) to assess arrhythmogenic risk of QTc prolongation with guanfacine" Ann Noninvasive Electrocardiol, 2014 Nov;19(6):582-94.
2. Fossa, A, Wisialowski, T, and Magnano, A et. al. "Dynamic beat-to-beat modeling of the QT-RR interval relationship . . ." J. Pharm. Exp. Ther. 2005; 312: pp 1-11.
3. Garnett CE, et. al ."Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic states" Am Heart J 2012; 163:912-930.

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651 217 2176 | www.vivaquant.com | Contact us at: Info@VivaQuant.com
4339 Nancy Place, Suite 100, St. Paul, MN 55126