ISHNE Guidelines for Electrocardiographic Evaluation of Drug-related QT Prolongation and Other Alterations in Ventricular Repolarization: Task Force Summary

*A Report of the Task Force of the International Society for Holter and Noninvasive Electrocardiology (ISHNE), Committee on Ventricular Repolarization**

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1. INTRODUCTION

Quinidine has been used since the beginning of the twentieth century for the conversion of atrial fibrillation to sinus rhythm and for the control of ventricular arrhythmias. Although effective as an antiarrhythmic agent, quinidine is known to prolong the electrocardiographic QT interval and is associated with unexplained syncope and sudden cardiac death. This drug is the prototype of drug-induced QT prolongation.

During the past decade, mutations in several ion channel genes (KVLQT1, HERG, SCN5A, KCNE1, and KCNE2) have been identified that cause QT prolongation and the hereditary Long QT Syndrome (LQTS).[1-5] LQTS gene mutations cause alterations in the ion channel proteins with altered potassium or sodium currents that prolong ventricular repolarization. The increased repolarization interval is associated with an increased probability of episodic polymorphic ventricular tachycardia (torsades de pointes [TdP]) that is manifest as syncope and arrhythmic sudden death. This new knowledge about ionic channel dysfunction occurred almost simultaneously with the clinical recognition of the occurrence of sudden death in otherwise healthy individuals who were taking a new antihistamine, terfenadine, together with an azole antifungal drug.[6] Investigations revealed that terfenadine, at high blood concentrations, blocks the HERG potassium repolarization channel with resultant secondary QT prolongation and a propensity to malignant ventricular tachyarrhythmias.

During the past 5 years, a number of approved and marketed drugs, both cardiovascular and noncardiovascular agents, have been associated with QT interval prolongation, TdP, and sudden cardiac death.[7] Almost all of the noncardiovascular drugs associated with QT prolongation adversely affect the HERG channel. Several of these drugs have been removed from the market or have had restrictive labeling. This drug-induced QT prolongation problem is of considerable concern to drug regulatory agencies at the national and international

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level, pharmaceutical companies, physicians, and patients. The association between the magnitude of drug-induced QT prolongation and the risk of malignant ventricular arrhythmias is complex. In general, the longer the QT interval, the greater the likelihood that a life-threatening arrhythmia may develop. Drug-induced QTc intervals greater than 500 ms are of concern. However, there is no well-established threshold duration below which QT prolongation is known to be benign. An average increase in the QTc interval of 5-10 ms during drug testing in a small group of subjects may constitute a repolarization signal for drug-induced arrhythmias when the agent is widely prescribed. Although the risk of ventricular arrhythmias is small for any given drug-related QT-prolongation, the induced arrhythmia may be fatal.

Drug regulatory agencies such as the Food and Drug Administration (FDA) in the United States and the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products now scrutinize the potential QT prolonging effects of all new drugs undergoing regulatory approval as well as marketed drugs with QT prolongation observed during postmarketing surveillance. The CPMP has published a document, "Points to Consider: The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products,"[8] that is already influencing the way electrocardiographic data are collected and analyzed during clinical trials related to regulatory approval. While generally helpful, some aspects of the "Points to Consider" document have been superseded by new research findings that became available since its publication. It is the understanding of this Task Force that a new version of the "Points to Consider" document is being presently prepared. Similar standardization activity is now underway on the North American continent under the collaborative umbrella of the Canadian agency and the FDA.

There are three clinical phases in the regulatory assessment of a drug. This article focuses on drug-induced effects on ventricular repolarization that are part of the overall regulatory process. Phase I studies involve the first human administration of a drug with open-label administration of the drug to a small number of volunteers; screening repolarization analysis during drug administration is performed. Early Phase II studies evaluate drug efficacy in small numbers of selected patients with dose-ranging and safety-toxicity evaluations in placebo-controlled trials. The repolarization-related safety issue involves a search for a signal indicating altered ventricular repolarization during active drug administration. Late Phase II studies involve a larger number of more representative study subjects in placebo-controlled trials with efficacy and safety evaluations during higher doses of the drug with additional data on drug metabolism, drug elimination, and ventricular repolarization. Phase III studies involve large randomized, double-blind, placebo-controlled trials with representative subjects, full drug dosing, detailed efficacy and safety data, and further evaluation of the effects of the drug on ventricular repolarization in the clinical setting. Drug approval requires adequate documentation of drug safety and efficacy for specific indications with an appropriate risk/benefit ratio.

Within this context, a Committee on Ventricular Repolarization was appointed by the Board of Trustees of the International Society for Holter and Noninvasive Electrocardiology (ISHNE) to develop guidelines for electrocardiographic (ECG) evaluation of drug-induced QT prolongation and other alterations of ventricular repolarization for use in the regulatory drug-approval process. It is recognized that as new knowledge continues to accumulate about the mechanisms of drug-induced QT prolongation[9] and the ways to measure it, the current guidelines will require periodic updating.

Before presenting the recommended ventricular repolarization guidelines, background information is provided about quantification of ventricular repolarization in terms of currently available ECG recording instruments and the repolarization parameters the Committee considers potentially important. The methods for measuring each of the repolarization parameters selected for inclusion in the guidelines are provided in the references. In addition, suggestions are made for the appropriate timing for ECG evaluation during drug testing and for analysis of the repolarization data.

2. QUANTIFICATION OF THE VENTRICULAR REPOLARIZATION SIGNAL FROM THE ECG

A. Recorders

Standard 12-lead ECG: The 12-lead ECG is recorded for a short duration, usually less than 30

seconds, and is the most frequently used technique for obtaining the surface electrocardiographic signal for evaluation of ventricular repolarization. The current generation of 12-lead recorders acquires the ECG signal in digital format at 250-500 Hz with paper readout and capability for storing the electronic signal on disk. The paper tracing is usually printed at 25 mm/s at a gain setting of 10 mm/mV and can be displayed in a variety of selected formats. Most of the current recorders provide a computerized printout on the paper copy of standard parameters including measurements of heart rate (beats/min, PR interval (ms), QRS duration (ms), QT interval (ms), QTc interval (ms), QRS axis (degrees), and T axis (degrees), as well as overall interpretation, although the accuracy of the automatic measurements and the clinical interpretation is questionable in many cases. The electronically stored signal can be analyzed at a later time by software programs developed for quantitative interval, amplitude, and morphologic measurements.

Ambulatory 24-hour (Holter) ECG: The Holter recorder can acquire 1, 3, or 12 leads of surface electrocardiographic signal. The available Holter recorders can acquire the ECG signal in real time on tape (reel-to-reel or cassette) or electronically in digital format with storage in solid-state circuits or on disk. With digital technology, the ECG signal can be programmed to record at various frequencies ranging from 100 Hz to 1,000 Hz. The digital 12-lead Holter recorders can either be continuous or obtain standard 12-lead ECGs at specific time intervals throughout the 24 hours. The tape and digital ECG signals can be analyzed by computer using commercial or research-developed software programs with paper print out of specific or selected portions of the recording. Tape-recorded ECGs can also be digitized for analysis by computer-based software programs. These multi-lead Holter systems reliably reproduce the resolution characteristics required for ventricular repolarization analysis.

Exercise ECG: Exercise testing with a standard activity protocol can be used for evaluation of ventricular repolarization during exercise and recovery periods. Monitoring during the exercise testing may involve intermittent 12-lead ECGs or continuous multichannel ECG recordings. However, since the adaptation of QT interval duration to heart rate is not instantaneous,[10] substantial errors may be introduced if nonstationary episodes are analyzed.

Other ECG Recording Techniques: Other available ECG recording methods include patient-activated event recorders and implantable loop recorders. To date, these approaches have not been utilized in the evaluation of ventricular repolarization and are not recommended for evaluation of drug-related alterations in QT-related parameters.

Ventricular Repolarization Parameters

The quantification and interpretation of acquired ECG data should be carried out by an experienced Core ECG Laboratory having cardiovascular expertise, with ECG reading systems that are validated and quality assured.[11] Currently, the manual measurement approach is most widely utilized. Manual reading should involve trained technicians using a magnified digipad system or an on-screen caliper system. The R-R and subsequent QT interval measurement should be made on at least three sequential beats in a specific lead (usually lead II or V5), or in a prespecified alternate lead if characteristics of the repolarization amplitude in the primary lead are unsatisfactory. It should be recognized that substantial errors and bias can be introduced when comparing QT intervals measured in one lead with measurements in another lead. Software-driven computer analysis of digital ECG signals is now available and is sometimes used in repolarization analyses. Because various artifacts and low amplitude ECG signals can compromise electronic data analysis,[12] all automated computer measurement and analysis of ECG data should have operator overview/interaction to ensure quality analysis. Automated computer analysis of repolarization intervals will require full validation in a spectrum of populations before it can be reliably used in the quantitative measurement of ventricular repolarization.

Repolarization Duration: Several approaches for quantitative ECG analysis of the duration of ventricular repolarization have been reported.[11,13,14] The repolarization duration measurements may be recorded in seconds (s) or milliseconds (ms), with the latter the preferred unit.

(a) standard duration measurements: if the starting point for the time interval measurements is the onset of the QRS complex, then the measured duration includes ventricular depolarization plus por-

tions of, or the entire, ventricular repolarization interval. Three standard QT measurements include:

QTp: interval from onset of Q wave to the peak of the T wave
QT: interval from onset of Q wave to the end of the T wave
QTU: interval from onset of Q wave to the end of the U wave

If the starting point for the duration measurement is the peak of the R wave, as is frequently the case with computer analysis of digital signals, then the respective intervals are RTp, RT, and RTU, with corresponding definitions.

The peak of the T wave is defined as the point at the apex of the T wave or its first component if there are two T-wave peaks. The end of the T wave has been defined in several different ways. The most commonly accepted method identifies the end of the T wave when its descending limb returns to the TP baseline. Another method for identifying the end of the T wave is the intersection point of the tangent of the descending limb of the T wave with the isoelectric baseline. When a U wave interrupts the T wave before it returns to baseline, the QT interval is measured as the nadir between T and U waves. The end of the U wave is defined as the intersection point of the descending limb of the U wave and the isoelectric baseline. Different algorithmic approaches for measurement of the QT interval or its components are available. At present, no algorithm exists that can provide fully automatic and accurate measurements; all automatic readings require manual verification and over-read by trained personnel.

(b) area-based duration measurement: an area-based method for quantifying total repolarization requires computer processed, digital-signal analysis of electronically stored ECG data.[14] This approach permits quantification of repolarization duration in terms of the time needed to accumulate various percentage of the repolarization T-wave area. The presence of biphasic T wave, U wave, and notched T waves does not affect the accuracy of area-based repolarization measurement, and these time-dependent area parameter may be more robust than the standard QT interval measurements. One repolarization parameter based on T-wave area is the time interval (ms) from the offset of the QRS to the time to reach 90% of the total T-wave area (T_{A90}). At present, only limited normative data exist for this parameter.

(c) adjustment for heart rate: the time-duration intervals are influenced by heart rate (R-R cycle length), so heart rate correction is required in the analysis of repolarization duration. Various heart rate correction formulae are available,[15] including exponential square root, exponential cube root, logarithmic, and linear approaches. The exponential Bazett correction ($QTc = QT/RR^{1/2}$) and the exponential Fridericia correction ($QTc = QT/RR^{1/3}$) are the most widely used heart rate correction formulae. The Bazett correction may give erroneous results at both slow and fast heart rates, and the Fridericia correction may give erroneous results at fast heart rates. The linear Framingham correction[16] ($QTc = QT + 0.154[1-RR]$) and the regression-derived QT index of Rautaharju[17] ($QTindex = QT[HR + 100]/656$ ms) have been reported to have more uniform rate correction over a wide range of heart rates, but there is not general agreement on this issue. Thus, different heart rate-correction formulae can be applied to each repolarization-duration parameter, including those with proposed age and sex adjustments.

Concern has been raised regarding the use of the published heart rate correction formulae for assessment of drug-induced QT interval prolongation, especially when the drug itself induces changes in heart rate.[18,19] Significant intersubject variation in the QT/RR relationship exists, and this subject variability can compromise the accuracy of standard group-based correction formulae. Subject-specific regression analysis of the QT/RR relationship may be required to reduce QT correction errors in subjects undergoing drug testing.[18]

Repolarization Morphology: Although the morphology or configuration of repolarization can be described from visual inspection of the T wave and placed into pre-specified categories, quantitative analysis of the T-wave shape and pattern requires computer analysis of electronically stored ECG data.

(a) graphic presentation: the precordial or limb leads can be superimposed on each other using the R wave as the synchronization reference point.[20] Visualized heterogeneity in the repolarization morphology is easily identified in this type of graphic presentation.

(b) quantitative assessment: principal component analysis (PCA) can be applied to the repolarization segment on digitized 12-lead signals to quantify

three-dimensional features of the repolarization T-wave loop.[21] The principal components of the length of the T loop (λ1) and its width (λ2) can be computed. The roundness of the T loop in its preferential plane (λ2/λ1) has been considered as an index of an increased complexity of the T-wave morphology[21] and is easily calculated. More detailed and focused approaches to the quantitative assessment of 12-lead T-wave morphology have recently been proposed.[22, 23]

Repolarization Dynamicity: The duration of ventricular repolarization is dynamically influenced by the duration of the preceding cycle length (R-R interval), and the relationship between these two time-duration phenomena is referred to as repolarization dynamicity. This QT (or RT) dynamicity can be expressed in two different ways.

(a) QR/RR slope: paired QT (or RTp) and RR intervals are determined, the QT (or RTp)/RR slope, its 95% confidence interval, and the r correlation are calculated, and the scattergram of the raw QT (or RTm) versus R-R relationship can be graphically displayed.[24] The slope of the regression line is a measure of QT dynamicity, and the significance of the change in the slope before and after drug intervention can be determined. However, the hysteresis in QT/RR adaptation compromises the slope assessment if nonstationary data are used.

(b) QT by RR interval bins:[25] a change in the QT (or RTp) interval with a drug that affects the heart rate can be evaluated by grouping the QT (or RTp) intervals into selected RR interval ranges, e.g., 50 ms R-R interval bins, thus avoiding the need to correct for heart rate. The raw QT (or RTp) and its standard deviation in each R-R interval bin before and after drug intervention can be compared for statistically significant changes. However, the R-R "bin" approach is appropriate only when stationary data are analyzed because QT/RR adaptation hysteresis can confound the interpretation.

Repolarization Variability: Repolarization variability may be detected as differences in interlead repolarization parameters, so-called static variability, or as differences in beat-to-beat repolarization parameters during a series of sequential beats, so-called repolarization heterogeneity.

(a) Interlead variability:

(i) interlead QT dispersion:[26] – the QT interval is identified in all available ECG leads of a given tracing using the approach described in the Repolarization Duration section of this article. The differences in QT time duration are computed as a range value ($QT_{max-min}$: difference between maximum and minimum QT values across all leads) and as the standard deviation of the QT intervals values in the analyzed set of leads (QT_{std}). A minimum of 9 leads should be analyzed per 12-lead tracing for computation of QT dispersion. Although easy to measure, the conceptual and technical limitations that underlie QT dispersion have raised serious questions about its usefulness in evaluating drug-induced effects on ventricular repolarization.[27]

(ii) interlead T-wave area variability: using the area-based method for computing the time to accumulate the T-wave area (see Repolarization Duration section) in a minimum of 9 leads of a 12-lead ECG, the standard deviation of the time to accumulate 50% (T_{A50}_sd) or 90% (T_{A90}_sd) of the T-wave area can be computed for the analyzed leads.

(iii) interlead morphological variability: this variability analysis can be performed utilizing different algorithms including the wavelet transformation of the repolarization segment[28] and the projection of the principal T-wave loop into separate ECG leads.[22, 29] Wavelets are used for highlighting morphological changes of the repolarization between leads. The loop projection expresses the differences between morphological composition of separate leads of the 12-lead ECG. With both methods, an index of morphological differences is computed, and it corresponds to a measure of difference in repolarization amplitude distribution between leads.

(b) Heterogeneity in a series of sequential beats

(i) T-wave alternans (TWA) by correlation method: the correlation method is a time-domain approach that quantifies beat-to-beat changes in microvolt-level repolarization amplitude and morphology in resting 12-lead or Holter ECGs.[30] The alternans correlation index is computed from morphological changes of each of the consecutive T waves in comparison with the median T wave, representative for a series of beats. This technique is able to quantify both amplitude and duration of TWA.

(ii) T-wave alternans (TWA) by spectral method: the presence or absence of microvolt TWA can be evaluated during exercise-induced augmentation of the heart rate to >110 beats/min.[31] The spectral method identifies beat-to-beat changes occurring at 0.5 cycle/beat frequency, discriminating alternans-type repolarization changes from other nonalternating fluctuation of the repolarization. Beat-to-beat changes are represented as power spectra by calculating the squared magnitude of the Fou-

rier transformation of the beat-to-beat amplitude fluctuation of each sample point of 128 consecutive QRST complexes time-aligned by the R-waves. The resulting parameter is called the T-wave alternans ratio and it is defined as the ratio of alternans peak minus mean noise level divided by the standard deviation of the noise estimated from a predefined noise window.

3. TIMING OF ECG RECORDINGS FOR EVALUATION OF DRUG-INDUCED ALTERATIONS IN VENTRICULAR REPOLARIZATION

ECG recordings to evaluate possible drug-induced changes in ventricular repolarization should be carried out at baseline before drug administration, at peak blood concentration of the drug and its active metabolites, and at trough drug and metabolite levels. If a standard 12-lead ECG is used, frequent ECG recordings will be required during baseline and drug administration periods to be sure that appropriate time intervals are sampled. If 12-lead digital Holter recorders are used, multiple (sequential) recording samples can be obtained during the baseline period and during on-drug periods when levels of the drug and its metabolite change throughout the day. However, as Holter recordings may be obtained during nonstationary states, special care should be taken to exclude ECG samples that are preceded by heart rate trends in view of the QT/RR hysteresis effect.

4. DESIGN AND STATISTICAL ISSUES

A drug trial should utilize a randomized, double-blind, placebo-controlled approach, involving either a cross-over or parallel-group design depending on the question being asked. Multiple ECG recordings should be made during the baseline period (before drug administration) in order to have an adequate reference sample for comparison. The frequency and timing of ECG recordings after drug administration are related to the phase of the trial and the questions being raised.

Large amounts of repolarization data (QTc values and other parameters) are collected during each phase of a clinical trial. Data reduction of ventricular repolarization intervals, e.g., QTc, within each period of the trial, i.e., baseline and during drug administration, should be expressed as mean ± standard deviation (SD), range, and 95% confidence interval for the test drug and placebo/active comparator treatment.

Because no agreement presently exists on what constitutes an abnormal repolarization signal, the repolarization data should be presented in several different ways to provide full disclosure. Subjects with outlier QTc values during drug therapy may indicate a repolarization signal. Within each time period for test drug and placebo/active comparator, the percentage of subjects with QTc values (QT corrected for heart rate by at least two standard heart rate correction formulae) greater than three graded upper-range values (e.g, 450 ms, 480 ms, and 500 ms for Bazett-corrected QTc) should be provided. The change in QTc between baseline/placebo and active drug, i.e., the delta QTc (ΔQTc), should be presented as mean ± SD, range, and 95% confidence interval. The percentage of subjects with ΔQTc changes greater than 10%, 15%, and 20% above the baseline/placebo value and/or the percentage of subjects with ΔQTc values in the 30-60 ms and > 60 ms ranges should also be provided. The statistical significance of the difference in QTc or other repolarization parameters between baseline/placebo and active drug should be provided for the total population and for relevant subsets (gender, age groups, etc.) as data permit.

5. FORMAT FOR RECORDING AND MEASUREMENT RECOMMENDATIONS

The recommendations for electrocardiographic recordings and measurements of ventricular repolarization are expressed in the standard American College of Cardiology/American Heart Association format:

Class I: Ventricular repolarization recording and measurement for which there is general agreement that a specific electrocardiographic approach is useful and effective.

Class II: Ventricular repolarization recording and measurement for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a specific electrocardiographic approach.

Class IIa: Weight of evidence/opinion is in favor of usefulness of the approach

Class IIb: Usefulness/efficacy is less well established by evidence or opinion

Class III: Ventricular repolarization recording and measurement for which there is evidence and/or general agreement that an electrocardiographic approach is not useful/effective and in some cases may be misleading.

6. SPECIFIC ECG RECORDING AND REPOLARIZATION MEASUREMENT RECOMMENDATIONS

A. Phase I Studies

Phase I studies involve screening for drug-related repolarization changes in a small number of normal volunteers. The drug is usually administered for a short period of time. The standard 12-lead ECG should suffice, but a 3-lead or 12-lead 24-hour Holter ECG may provide additional information about changes in drug-induced ventricular repolarization. Repolarization measurements should be related to blood levels of the drug.

Phase I Studies, Class I Recommendation:
(1) Digital 12-lead ECG with manual measurement of paper copy and/or on-screen QT and RR intervals at baseline and at peak and trough blood levels of active drug and metabolite. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula.

Phase I Studies, Class IIa Recommendation:
(1) 24-hour Holter ECG (3-lead or 12-lead tape or digital recording) recorded before (baseline) and during drug administration. QT and RR intervals should be measured during representative periods at baseline and during time intervals approximating peak and trough blood levels of active drug and metabolite. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula that may include the formula shown to abolish the relationship between QTc and RR intervals in the actual study data (e.g., correlation QTc vs RR = 0).

Phase I Studies, Class IIb Recommendations:
(1) Correct the QT interval for heart rate using subject-specific regression analysis; (2) 24-hour Holter ECG (12-lead digital recording) recorded before (baseline) and during drug administration with computerized measurement of RTp/RR slope, its 95% confidence interval, the r correlation, and a graphical display of the QT/RR relationship.

Phase I Studies, Class III Recommendation:
(1) Interlead variability by 12-lead ECG or Holter.

B. Phase II Studies

Phase II studies involve drug safety and efficacy evaluation in randomized, double-blind, placebo-controlled trials of a small to moderate number of representative subjects. ECG monitoring is used to detect evidence of drug-induced alteration in ventricular repolarization in this population during steady-state drug exposure that may extend over periods from weeks to months. Repolarization measurements should be related to blood levels of the drug.

Phase II Studies, Class I Recommendation:
(1) Digital 12-lead ECG with manual measurement of paper copy and/or on-screen QT and RR intervals at baseline and at steady-state peak and trough blood levels of active drug and metabolite. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula.

Phase II Studies, Class IIa Recommendation:
(1) 24-hour Holter ECG (3-lead or 12-lead tape or digital recording) recorded before (baseline) and during steady-state drug administration. QT and RR intervals should be measured at baseline and during time intervals approximating peak and trough blood levels of active drug and metabolite. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula that may include formula shown to abolish the relationship between QTc and RR intervals in the actual study data (e.g., correlation QTc vs. RR = 0).

Phase II Studies, Class IIb Recommendations:
(1) Correct the QT interval for heart rate using subject-specific regression analysis; (2) 24-hour Holter ECG (12-lead digital recording) recorded during time intervals that include peak and trough blood levels of active drug and metabolite, with automated measurement (with over-read) of one or more of the following repolarization parameters:
(a) RTp/RR slope, its 95% confidence interval, the r correlation, and a graphical display of the QT/RR relationship
(b) Time interval (ms) to accumulate 90% of the total T-wave area (T_{A90})
(c) Principal component analysis of the length ($\lambda 1$), width ($\lambda 2$), and roundness ($\lambda 2/\lambda 1$) of the T-wave loop

Phase II Studies, Class III Recommendation:
(1) Interlead variability by 12-lead ECG or Holter.

ECG Repolarization Recordings and Measurements in Phase III Studies

Phase III studies are large randomized, double-blind, placebo-controlled trials involving clinically representative subjects. ECG monitoring is used to detect evidence of an infrequent or subtle signal of drug-induced alteration in ventricular repolarization in this population with drug exposure extending for months to years. Depending on the number of subjects being studied, recordings may be obtained only on a random representative sample of the drug-exposed study population.

Phase III Studies, Class I Recommendation:

(1) Digital 12-lead ECG recorded during a representative day and time on drug with manual measurement of paper copy and/or on-screen QT and RR intervals. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula.

Phase III Studies, Class IIa Recommendations:

(1) 24-hour Holter ECG (3-lead or 12-lead tape or digital recording) during steady-state drug administration with:

(a) Manual on-screen or computerized (with over-read) measurement of QT and RR intervals during time intervals approximating peak and trough blood levels of active drug and metabolite. QTc values should be calculated by Bazett and at least one other standard heart rate correction formula that may include formula shown to abolish the relationship between QTc and RR intervals in the actual study data (e.g., correlation QTc vs RR = 0).

(b) Automated measurement RTp/RR slope, its 95% confidence interval, the r correlation, and a graphical display of the QT/RR relationship.

Phase III Studies, Class IIb Recommendations:

(1) Correct the QT interval for heart rate using subject-specific regression analysis; (2) 24-hour Holter ECG (12-lead digital recording) with automated measurement (with over-read) during steady state drug administration at prespecified periods for one or more of the following:

(a) Time interval (ms) to accumulate 90% of the total T-wave area (T_{A90}).

(b) Principal component analysis of length ($\lambda 1$), width ($\lambda 2$), and roundness ($\lambda 2/\lambda 1$) of the T-wave loop.

Phase III Studies, Class III Recording Recommendation: (1) Interlead variability by 12-lead ECG or Holter.

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