AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

The people in the audience of the July 23, 2013 CSRC/ HESI Thinktank meeting in Silver Spring must have realized that the TQT studies era is reaching its sunset, probably faster than they had imagined. According to meeting material, the target date to abandon the ICH E14 FDA Policy reads: "July 2015"… 2 years, or, in other words, tomorrow, for an industry like ours, where major turns like this one takes years to implement.

If you were not amongst the attendees, whom were able to ask questions during the lively and spirited discussion that ensued, you will be interested in reading the article written by Dr Fabio Badilini FACC in this AMPS-QT issue. What is going to change, how does this tie-in with the new FDA Holter warehouse development, but mainly, how is this likely going to affect your operations and what tools will you need to stay ahead in the market? In order to answer these and many more questions as a follow-up AMPS is organizing, in cooperation with Mortara Instrument, a one-day seminar to take place in the DC area on December 11, contiguous with the next CSRC meeting. We are happy to confirm the participation of Dr Norman Stockbridge of the FDA at the seminar, and you will find the first announcement with more details in the last page of this issue of AMPS-QT. Hope to see many of you in Washington DC next December!

As TQT studies have not yet been sunset, in this issue of AMPS-QT we offer you a contribution from Dr Snehal Kothari, MD, FACC, Senior Medical Director at Quintiles. Dr. Kothari and his colleagues have been rather active in the last years and have published several journal and conference papers, covering many aspects of repolarization and specifically the implications of the QT measuring method to assess drug-induced changes. In his article, the author illustrates their measuring approaches and latest findings.

A Noteworthy Contribution:

Different methods of QT measurement and their impact on the outcomes of a TQT study

Snehal Kothari, MD, FACC; Senior Medical Director, Cardiac Safety Services, Quintiles.

Ten years after the FDA's Digital ECG Initiative, the conduct of cardiac safety trials has significantly changed to include the process of reviewing annotated digital ECG waveforms (1). The availability of digital ECGs has also enabled the use of different QT measurement methods in serial ECG evaluations. Some of the methods we have studied to measure the QT interval in TQT studies include the single lead threshold method, single lead tangent method, measurement in the lead with the longest QT interval, and the superimposed and global median beat (see Figure below) (2, 3). They are briefly described below.

1. Using Raw waveforms

A. Single lead threshold method

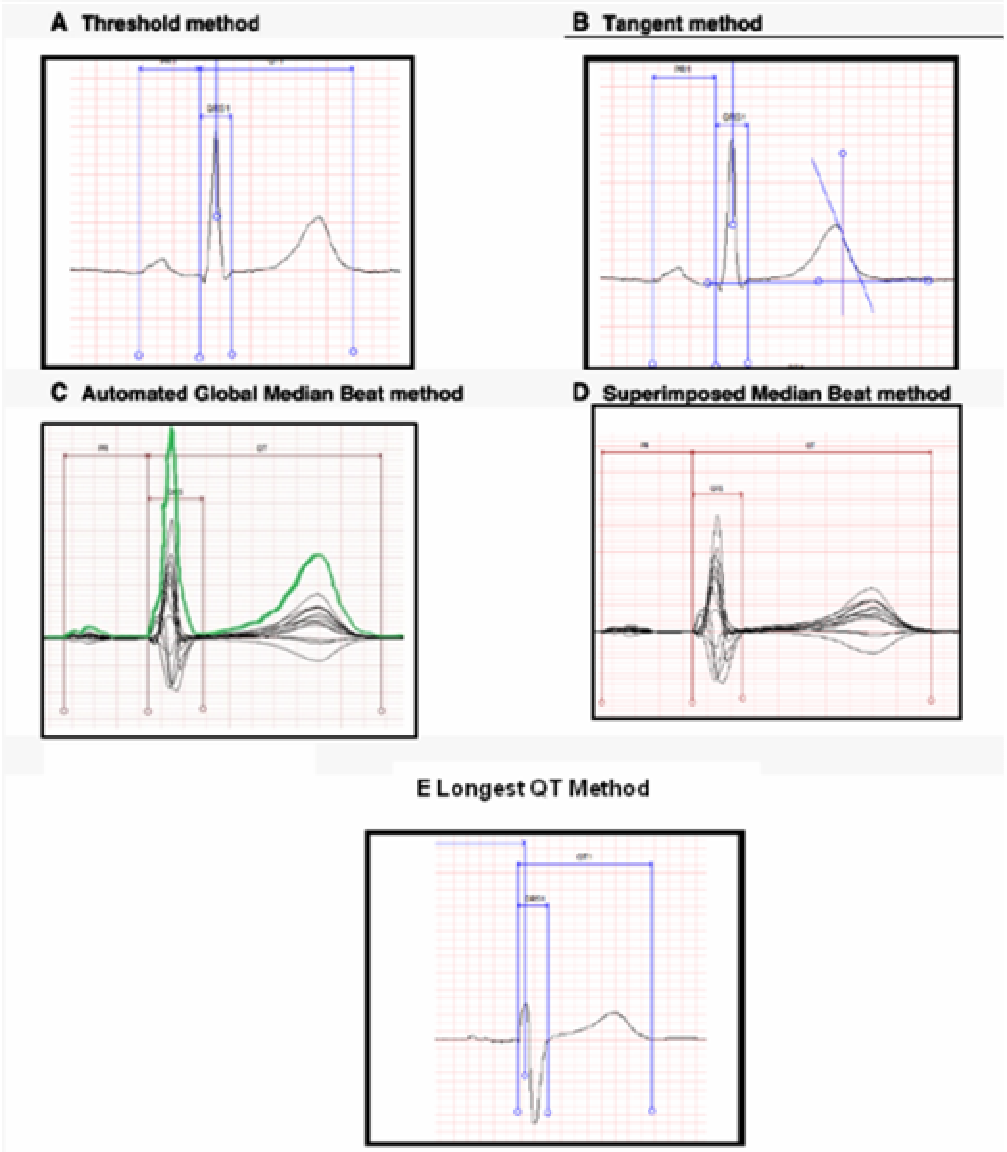
In the threshold method, the reader visually identifies the end of the T-wave as the point at which the T-wave reaches the isoelectric baseline (2). QT interval is manually measured on 3-5 consecutive complexes in a single lead, typically lead II.

B. Single lead tangent method

The manual tangent method involves the drawing of a tangent line which is determined from the peak of the T-wave to the steepest point of the terminal limb of the T-wave. In the tangent method, the end of the T-wave is defined as the point where the tangent intersects the isoelectric baseline, which can be obtained by a line joining the midpoints of the TP segment of the complex in which

QT interval is measured and the preceding complex (2). As in the threshold method, QT interval is measured on 3-5 consecutive complexes in a single lead, typically lead II.

Figure 1: Different methods of QT measurement using CalECG in a TQT study.



C. Longest QT method

In the longest QT method, QT intervals are measured in all 12 leads of an ECG. As in the threshold method, the end of the QT interval is defined as the intersection of the terminal part of the T-wave and the isoelectric line.

The QT interval values from the lead with longest QT interval are retained for serial ECG comparison (2).

2. Using Median Beats

D. Global median beat

The global median beat (GMB) method for QT measurement is a fully automated QT measurement method, in which the automated algorithm constructs a single Global beat from the 12 median beats, which is then used by the algorithm for QT measurement (2).

E. Superimposed median beat method

In the superimposed median beat (SMB) method, all dominant normally conducted complexes in the 10-second ECG recording are used to create a single median beat for each of the 12 leads. These beats are then superimposed on-screen such that they are temporally aligned and the earliest onset of the Q wave and the latest T offset are identified for QT measurement (2).

An ECG measurement tool like CalECG allows for the vertical separation (ungrouping) of the SM beats which enables the identification of earliest Q onset and latest T offset with greater distinction as compared to the conventional SMB visualization where the median beats are grouped together (4).

Remarks on the different methods of QT measurement

Any of these methods can be used in TQT studies, if a tool like CalECG is part of the ECG analysis workflow. The threshold method in a single lead remains the commonly used method for QT measurement in TQT studies, with lesser number of studies employing the tangent and longest QT method. In recent years, the number of studies using the SMB method has increased.

An evaluation of these 5 methods on a TQT study demonstrated their ability in detecting moxifloxacin-induced QTcF prolongation (2). However, the lower

bound of 90% 2-sided confidence interval of QTcF prolongation did not exceed 5 ms with the longest QT method, thus not meeting the recommended criteria for assay sensitivity. This may have been due to the greater intra-individual variability in QT interval resulting from the fact that it may be measured in different leads at different time points. This makes the longest QT method unsuitable for routine use in TQT studies. This study concluded that the threshold, tangent, global median and SMB methods were comparable in detecting the moxifloxacin effect and may be suitable for use in TQT studies. The proportion of categorical outliers was similar with the threshold, GMB, and SMB methods. However, longest QT and tangent methods resulted in more outliers. These points must be considered when interpreting findings of individual TQT studies.

[1] Salvi V, Karnad DR, Panicker GK, Kothari S. **Update on the evaluation of a new drug for effects on cardiac repolarization in humans: issues in early drug development**, *Br J Pharmacol* 2010; 159: 34.

[2] Salvi V, Karnad DR, Panicker GK, Natekar M, et al. **Comparison of 5 methods of QT interval measurements on electrocardiograms from a thorough QT/QTc study: effect on assay sensitivity and categorical outliers**, *J Electrocardiol.* 2011; 44: 96-104.

[3] Lepeschkin E, Surawicz B. **The measurement of the QT interval of the electrocardiogram**, *Circulation* 1952; 6: 378.

[4] Hingorani P, Karnad DR, Ramasamy A, Panicker GK, et al. **Semiautomated QT interval measurement in electrocardiograms from a thorough QT study: comparison of the grouped and ungrouped superimposed median beat methods**, *J Electrocardiol.* 2012; 45:225-30.

Products News

Latest Releases

In Q3 2013 we have released:

- CalECG v. 3.6.0, with the latest BRAVO algorithm (v. 4.2.7).

Looking forward

In Q4 of 2013 AMPS is planning to release:

- The first version of our beat-to-beat continuous-ECG solution, as anticipated on issue 16 of this newsletter, which is in the same class of solutions as WinAtrec, the AMPS software package including the Holter-bin approach.

  Our beat-to-beat Holter solution provides a set of interactive graphical display tools to edit and review individual-beat annotations, including QT and RR time trends and QT/RR clouds.

  For each individual beat, noise level and preceding heart-rate stability are also computed, so that beat-to-beat measurements can be filtered based on the ECG beat quality and preceding heart rate.

In Q1/Q2 of 2014 AMPS is planning to release:

- The first version of our beat-detection Editor.
  This tool will allow the manual editing on the automated detection/classification performed by the beat-detection tool just mentioned.
- The first version of AMPS viewer for annotated ECG of continuous ECG data.

AMPS Notebook

As anticipated in the Editorial, AMPS will be organizing together with Mortara Instrument a full-day seminar on the new Holter aECG format and Holter submission to the FDA Warehouse. The Seminar will be held on December 11th in the Washington DC area.

Fabio Badilini will be attending the **American Heart Association**, Scientific Session held from November 16th to 20th in Dallas, Texas.

He will also be attending **CSRC Annual Meeting**, held in Washington DC on December 12th and 13th.

Toward a more intensive usage of continuous ECG data

Fabio Badilini, PhD, FACC; Chief Scientist, AMPS LLC.

The CSRC-HESI meeting held on FDA's White Oak Campus on July 23rd has raised a number of important questions. We will most probably soon move toward a new paradigm that will utilize preclinical data with the implementation of in-vitro testing of several ion channels, in silico models to reconstruct the action potentials and stem cells based proarrhythmia assessment, and we may thus see the end of the QT analysis according to the ICH-E14 and S7A/B guidelines. Indeed, the meeting has highlighted the costly risk in current paradigm to detect false positives, justified by a significant decrease in post-marketing reports of Torsade de Pointes, and the consequent concern that "not all QT prolonging drugs will necessarily carry proarrhythmic risk".

From our perspective, these changes will translate to a different usage of the ECG signal and the current implementation of the TQT study, based on the assessment of the signal (placebo-corrected changes versus baseline) at specific and protocol-designed timepoints with a most intensive usage of continuous data. In fact a CSRC driven initiative, the IQ-CRSC group, has been working since December 2011 on the use of continuous ECG data from early Phase 1 and PK/PD modeling to replace the TQT protocol. In the meantime, the FDA has extended the warehouse used to review submitted digital ECGs to be capable of hosting continuous data.
We don't know yet which continuous ECG analysis tools will be primarily used in the mid- or long-term (1), but certainly we need to be prepared to manage this type of data and, most importantly, to submit it to regulatory bodies.

The December 11th workshop, co-organized with Mortara Instruments, will specifically focus on all the nuts and bolts of continuous ECG data and its implementation in the FDA warehouse.
The workshop will cover all the technical aspects and caveats, describing the HL7 and XML implications of the extension to continuous data, but will also provide practical examples on how currently known methods can be implemented. Special emphasis will be given to the concept of annotations in the context of a continuous ECG and, most importantly, what should be precisely provided from a regulatory perspective.

[1] Garnett CE, Hao Z, Malik M, Fossa AA, et al. **Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects**, *Am Heart J*. 2012; 163 Vol.6:912-930.

To conclude this issue, a picture taken during AMPS summer BBQ in Montichiari where two special guests and old time good friends had a chance to join us.
On the left Dr. William Wheeler (proudly wearing his 2007 AMPS shirt), who collaborated with AMPS while he was Chief Medical Officer at Spacelabs and later on at MDS/Celerion. On the right Giuseppe Corbelli, a former AMPS software engineer, whose work to build a reliable IT/software infrastructure proved extremely helpful in the company's early days.
Dr. Wheeler and Dr. Corbelli worked closely in 2006 and the AMPS BBQ reunion was a great opportunity to spend a lovely Italian summer evening all together.

Advertisement

First Workshop Announcement:

Regulatory Review of Continuous ECGs

Washington D.C. December 11th, 2013

Mortara Instrument initiated the expansion and upgrade of tools for submitting continuous ECG data to the ECG Warehouse in 2010. As part of this initiative, the FDA held a public meeting on March 12, 2012 to discuss changes in how continuous digital ECG data is gathered and submitted to the ECG Warehouse and new tools for visualizing the continuous, annotated ECG recordings. An extension of the Health Level-7 Annotated ECG standard data format was proposed for this purpose. The new data format is intended to facilitate electronic submission and sharing of ECG data from continuous recordings.

Now that the ECG Warehouse stands ready to receive data in the proposed format, sponsors and ECG core laboratories are moving forward quickly to implement compliant solutions. As expected, through these implementation activities, several questions regarding the proper utilization of the continuous aECG Waveform Standard have surfaced.

In order to provide answers to such implementation questions and other related issues, AMPS, LLC and Mortara Instrument, Inc. are organizing a workshop designed for representatives from sponsor organizations and ECG core laboratories who are responsible for compliance with the new Regulatory Review of Continuous ECGs.

This one day workshop will feature presentations about:

- Why the FDA wants to review continuous ECG data
- What is continuous ECG data, and how is it collected, analyzed, and managed
- Clarify missions of various organizations, the data they collect, and the tools they use
- A review of the HL7 aECG v1 Standard
- Present changes in v2 to support continuous ECGs
- ECG Warehouse v2: the new tools
- Beyond ICH using aECG v2: examples from the CSRC white paper
- Case Studies from industry leaders

The presenters will include:

- Dr. Norman Stockbridge, Director of the Division of Cardiovascular and Renal Products in FDA's Center for Drug Evaluation and Research
- Dr. Fabio Badilini, Chief Scientist of AMPS
- Barry Brown, Product Integration Manager at Mortara Instrument.

Attendance will be strictly limited to encourage open exchange and discussion between presenters and participants.

Early bird registration fee (until Oct 31st) is of $2,000 per attendee, $2,500 afterward. Additional attendees from the same companies will enjoy a reduced fee of $500 per person. To reserve space and receive an invitation with complete workshop agenda, please contact:

Aimee.Kops@Mortara.com

We look forward to a productive workshop in December.