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

There are industries and markets where change happens at a lightning speed, where, as an old joke goes, there are 3 categories of people, the ones that make changes happen, the ones that carefully watch changes as they happen, and the ones that go: "*what happened?!?*". Our industry is something very different, where, as Dan Goodman, the author of this issue's contribution and one of the people that do make change happen, very rightly states: "*Real change comes slowly*". In case you need any proof it's enough to look at what happened to the few "highly innovative" labs proposing, e.g. new revolutionary 3D methods to analyze heart electrical signals or claimed to have 'invented' new heart biomarkers only few years ago: they either completely disappeared, after wasting a good amount of VC funds, or changed path quickly in favor of more traditional methods in order to survive and eventually were mostly bought out by more traditional players. But as Dan Goodman concludes: "*While change comes slowly, with dedicated efforts to reach better outcomes, real progress is inevitable*".

At AMPS we are 100% behind this paradigm, as we continuously strive to bring to our customers the best state-of-the-art technology possible and empower them to achieve better outcomes and thus "inevitable progress". For the few of our readers not familiar with him, Daniel B. Goodman, MD, is Vice President and Medical Director, at BioTelemetry Research, where he directs all aspects of protocol planning and development for Sponsors, and for analysis of cardiac safety results. After graduating from Yale University and Cornell University Medical School he founded Cardiology for Clinical Trials in the early 1990, one of the world's first cardiac core labs, then went on to direct medical affairs for Covance Cardiac Safety Services from 1994 until 2007. After this post, Dr. Goodman worked closely with the medical team at BioTelemetry as a consultant before joining full-time in 2012 as a senior scientific consultant for several years. Dr. Goodman is an international thought leader in cardiac safety testing, developing protocols, producing scientific reports, conferring with regulators and publishing extensively. We are sure you will find his contribution compelling. Please accept from the whole AMPS team our best wishes for a peaceful and productive 2018!

A Noteworthy Contribution:

Is all QTc prolongation the same?

By Daniel B. Goodman, MD, Vice-president and Medical Director BioTelemetry Research, Rockville, MD, USA

Introduction

Real change comes slowly. Over the past 25 years the use of the ECG in pharmaceutical drug development has evolved from a clinical tool, with implications mainly for the safety of individual subjects, to a highly precise surrogate for the potential for development of serious arrhythmia. The driving force for this change of emphasis was the international regulatory activities that culminated in the ICH E14 guidance, formally accepted in 2005 [1]. In the years since its adoption, E14 has been amended significantly only once in 2015

[2], with the adoption of exposure-response (E-R) modelling, also called concentration-QT (C-QT) modelling, as an alternate primary endpoint method for determining significant repolarization prolongation. E-R modeling greatly increases the statistical power of studies by assessing the change of QTc as a function of drug concentration combining all doses and timepoints, rather than by assessment of change of QTc at each dose and at each observation timepoint. An important result of having greater statistical power is the ability to definitively assess QTc in early human trials, using current single ascending dose (SAD) and/or multiple ascending dose (MAD) designs, rather than the more complex and expensive design for the thorough QT/QTc (TQT) study, as originally prescribed in E14.

While successful in avoiding approval of QTc prolongers, there have been concerns that drug development programs may have been discontinued because of ambiguous or false-positive preclinical signals, or may have been abandoned based on QTc prolongation in clinical studies without the ability to fully know the proarrhythmic implications. Efforts to improve the preclinical assessment of compounds are proceeding under the Comprehensive in-vitro Proarrhythmia Assay (CiPA) initiative. On the clinical side, scientists, led by researchers at the FDA, have added a significant new tool for the characterization of the arrhythmia potential of drugs with demonstrated QTc prolongation.

It is well established that certain QTc prolongers have a low risk of arrhythmia. The new approach is based on the determination of sub-intervals of the QT, defined as: 1) the time from the J point (end of QRS) to the peak of the T wave (JTp); and 2) the time from the peak of the T wave to the end of the T wave (TpTe).

This article reviews the current state of knowledge of QT sub-interval analysis and presents what the author believes is the first instance of its use in actual drug development. The intent of the following is to emphasize the availability of assessment of sub-intervals by core ECG laboratories, and to demonstrate the practicality of planning for its optimal use in early human studies.

Background

In most cases, QTc prolongation is the result of late potassium blockade (hERG or IKr). Some QTc prolonging drugs have low potential for ventricular arrhythmia. It is understood that the QTc prolongation in some of these cases is due to a combination of blockade of hERG and of late sodium and/or calcium inward currents. Multi-ion channel blockade is thought to reduce the risk of arrhythmia by decreasing dispersion of repolarization across the myocardium, and by reducing after depolarization. Two examples are ranolazine, which is believed to block not only the hERG potassium channel but also the late sodium current, and verapamil, which blocks hERG and the L-type calcium channel [3, 4].

In 2014, the FDA researchers and their co-authors published methods and the results of measurements of the sub-intervals of the QT for four drugs known to prolong the QTc and chosen to represent various patterns of ion channel blockade [5]. The compounds tested were: ranolazine and verapamil, mixed ion channel blockers with low proarrhythmic risk; dofetilide, a pure hERG prolonger clearly associated with arrhythmia; and quinidine, a pure hERG blocker at low concentrations, but mixed blocker at higher concentrations. For quinidine, most arrhythmic events occur at lower concentrations. A total of 22 subjects, equally divided by sex, participated in a 5-arm crossover study to receive each of the four drugs and placebo, with a 7-day washout between treatments.

Data were collected using 12-lead Holter monitoring. From the continuous recordings, three replicate 10-second ECGs were extracted at 16 predefined timepoints coincident with concentration determinations. For each ECG, after transformation to a vectorcardiogram and extraction of a vector magnitude lead, manual measurements were made of: QT corrected for heart rate by the Fridericia method (QTcF); JTp corrected for heart rate by a similar exponential formula but with exponent 0.58 (JTpc); and TpTe. The concentration relationships for the three parameters were then assessed using the E-R approach.

Study results showed that the QTcF and sub-interval relationships to concentration were able to differentiate pure hERG blockade from mixed blockade. For dofetilide, QTcF increased linearly with concentration with JTpc and TpTe both increasing linearly with concentration. Ranolazine had QTcF prolongation but the TpTe contributed to all the increase, with JTpc decreasing slightly with concentration. Verapamil showed slight but non-significant QTcF prolongation with increasing concentration, with JTpc and TpTe having little change with concentration. Quinidine showed preferential prolongation of TpTe especially at higher concentrations. Another review of the data confirmed the earlier results [6]. The left half of Figure 1 presents the results of the 2014 analysis by the FDA team.

Confirmation and Generalizability

The FDA research group analyzed the same dataset in an exploratory assessment of 8 ECG biomarkers using the same Holter data [7]. They found that JTpc "is the only biomarker that improves detection of the presence of late sodium current block compared to using QTc alone." They also published data showing that automated analysis of the same sub-intervals was found to have similar diagnostic power [8].

Multiple independent commercial teams, using the same Holter data, have demonstrated the ability to measure the sub-intervals using fully automated analysis to confirm the original findings. Brockway, et al (Rhythm Express, VivaQuant, St. Paul, MN, USA) were able to decrease the variability of the outcome findings and adequacy of the linear model fit compared to the Johannesen 2014 results [9], see Figure 1.

Badilini, et al confirmed the results (BRAVO, AMPS-LLC, NY, USA), based on either the vectorcardiogram or RMS leads [10], and further confirmations were published by groups using analysis platforms from Mortara Instruments (VERITAS, Milwaukee, WI USA) [11] and Phillips Healthcare (Philips DXL, Andover, MA, USA) [12]. Reviews by academic experts supported the use of this new tool as well as implementation using fully automated analysis [13, 14], as did a recent update from the FDA researchers [15].

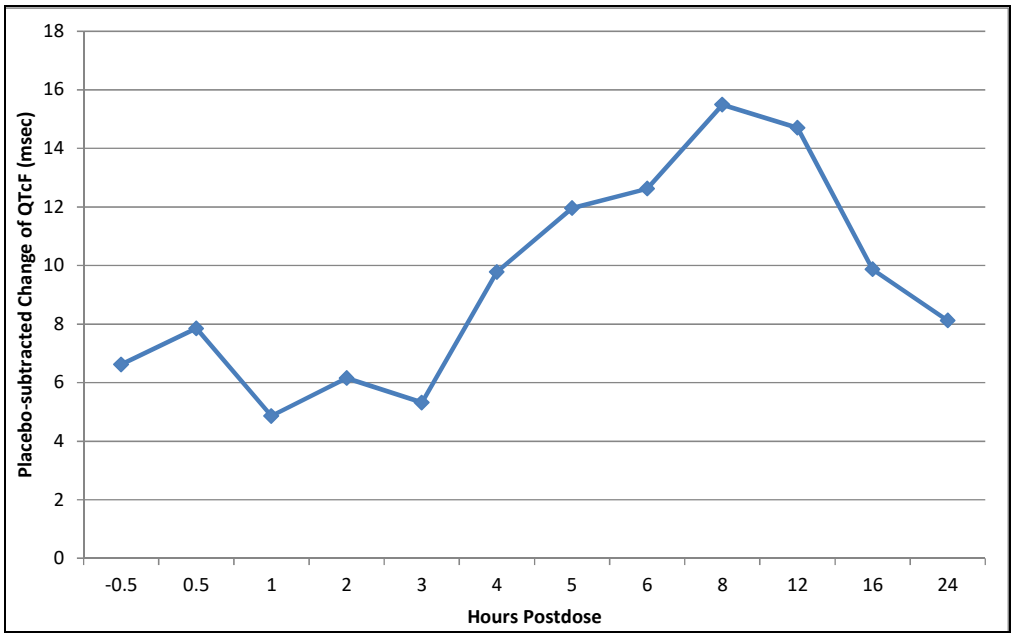

Figure 2: Placebo-subtracted Change of QTcF (msec) on Last Day of Treatment.

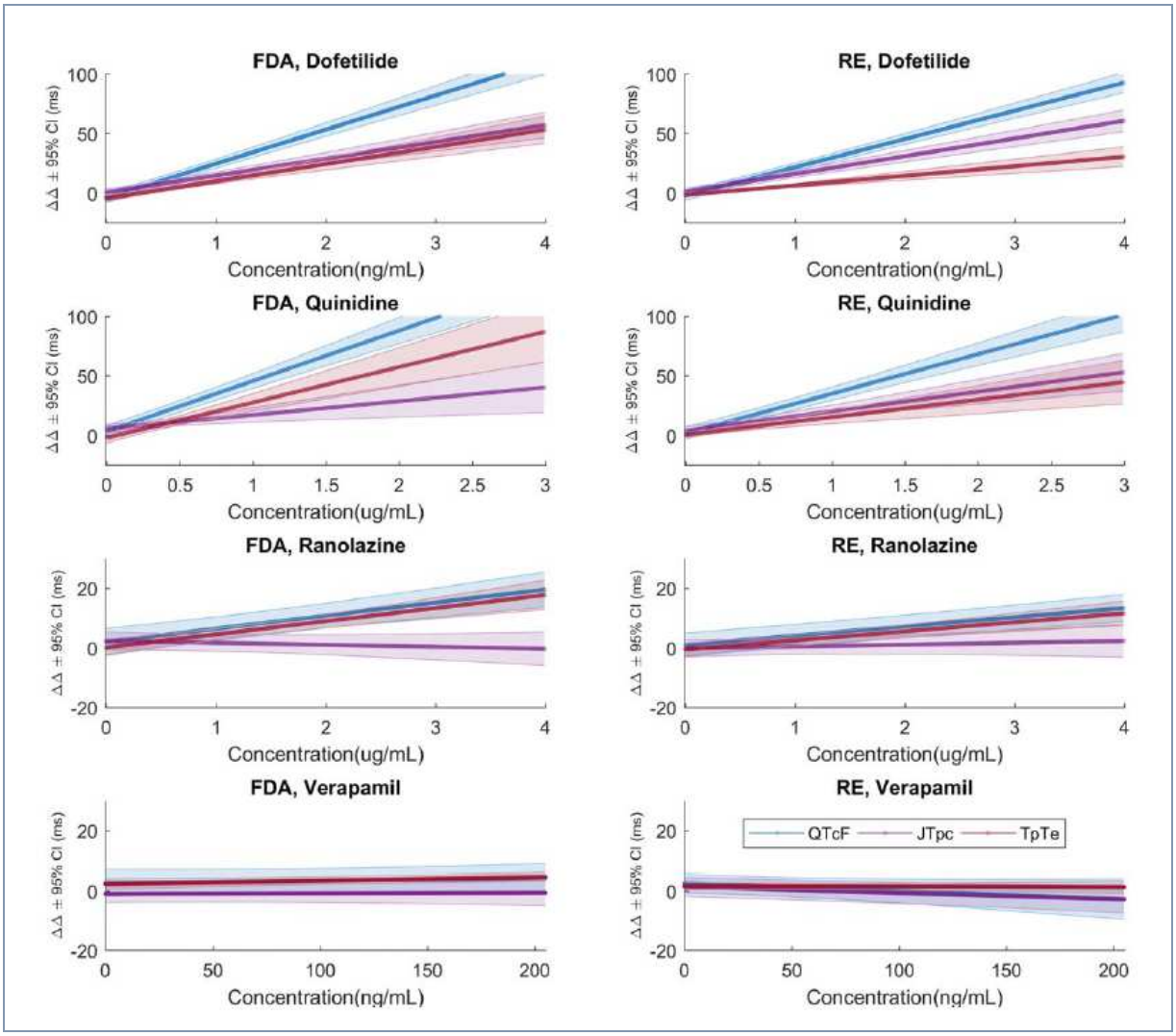

Figure 1: Exposure-Response Regression Modelling – FDA [16] vs Rhythm Express Examples [17].

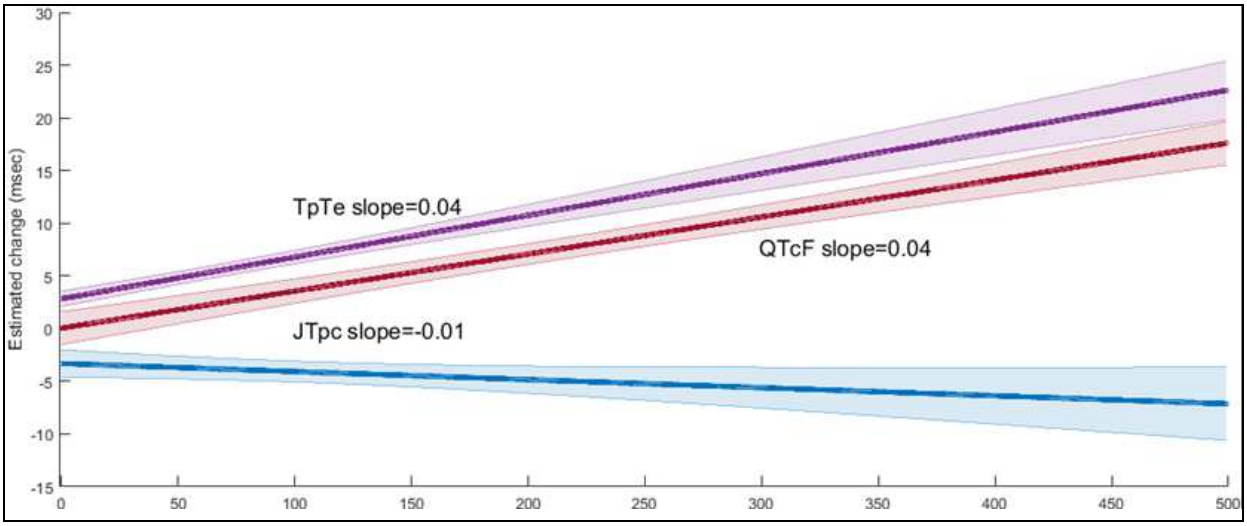

Figure 3: Estimated Change from Baseline with Placebo-adjustment of QTcF, JTpc and TpTe (msec) vs concentration - Linear Slope and 95% Slope Confidence Intervals.

First Report of Use in Drug Development

The author's company was approached to conduct QT sub-interval assessment after a definitive QTc study in Phase I found moderate QTcF prolongation, see Figure 2. This is thought to be the first use of sub-intervals in actual drug development.

Based on the same 12-lead Holter data used for the conventional ECG extractions, fully automated QT and sub-interval assessments using the Rhythm Express algorithm were performed by VivaQuant. Individual beat values of QT, JTp and TpTe were averaged over each of three 10-second recordings from each 5-minute period immediately preceding the PK assessments. Fredericia correction was applied to the mean of the 10-second tracing QT (QTcF). The mean of the 10-second tracing JTp was corrected with the exponent set to 0.58 (JTpc). The resulting mean values for the three 10-second recordings were averaged to provide a single measurement of QTcF, JTpc and TpTe. The results were combined with the concentration values and E-R modelling performed for QTcF, JTpc and TpTe.

The findings showed prolongation of both the QTcF and TpTe with increasing concentration, but slight shortening of JTpc, as seen in Figure 3.

The pattern of these results was nearly identical to those for ranolazine from the validation study. This suggested that the compound has mixed hERG and late sodium channel blocker effects and may not be associated with proarrhythmic risk.

Practical Use in Drug Development

A comprehensive approach during early human-phase development could be implemented in stages: 1) collect 12-lead Holter data for all or most cohorts of SAD and/or MAD studies; 2) extract ECGs and analyze for QTc only when appropriate for the drug development program, and only in the appropriate cohorts; and 3) analyze the sub-intervals if needed.

This is an optimal approach to accomplish the goal of definitive determination of QTc effects in early human-phase studies. This approach ensures maximum availability of data without incurring the cost of detailed analysis of ECGs when not necessary or for conducting a new study for analysis of QT sub-intervals. It is fully compatible with suggestions for integrating findings from the preclinical assessments, planned in the CiPA initiative, with clinical ECG results.

If CiPA data indicates a low risk of arrhythmia, unexpected QTc prolongation would be followed by analysis of QT sub-intervals; or, if there is a prediction of intermediate risk, sub-interval analysis would be used to confirm the presence of mixed ion channel blockade. This is outlined in the schematic in Figure 4.

Conclusion

Assessment of sub-intervals of the QT is an important new development in the evolution of the use of the ECG in drug development. It can characterize QTc prolongation as likely or unlikely to be associated with arrhythmia, and is intended to reduce unnecessary discontinuation of drug development programs. A staged approach is proposed to make available in early human studies assessment of repolarization effects with attention to minimizing costs and in full compliance with the latest regulatory suggestions. The data is optimally collected with 12-lead Holter monitoring in SAD and/or MAD studies, as already standard in early human-phase testing. The continuous data can be used when progress in the drug development program justifies definitive determination of QTc effects. QT sub-interval analysis is also available from the same data using fully automated systems. Several ECG collection and signal processing platforms currently have been shown to adequately perform these measurements. While change comes slowly, with dedicated efforts to reach better outcomes, real progress is inevitable.

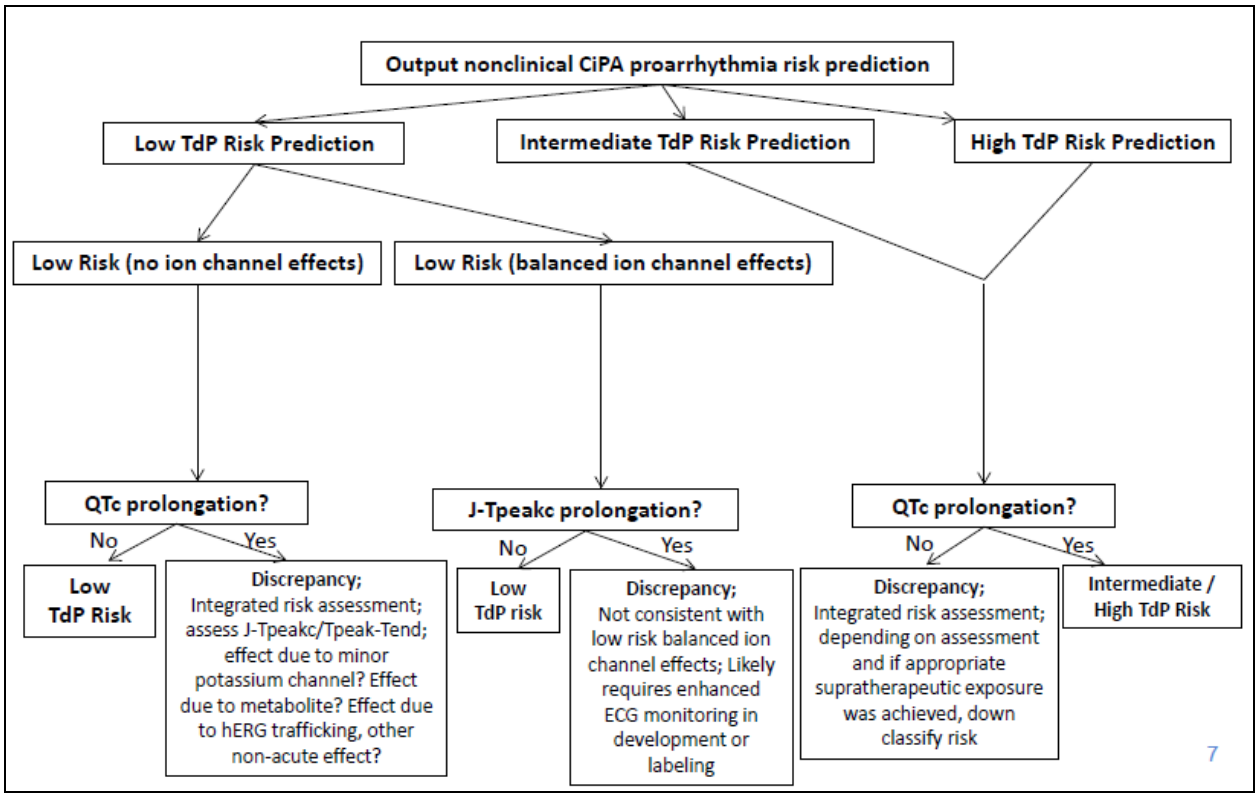

Figure 4: Phase 1 ECG Assessment [18].

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Products News

Looking forward

In Q1 we shall release a new version of CER-S (v.3.1.0), including the following revised platforms:

- Continuous ECG beat detection and classification
- ECG beat editor
- Arrhythmia detection and Arrhythmia editor
- ECG Beat Measure, for measuring both on beat-to-beat basis and averaged time-templates.

AMPS People

Tomaso Contessi (pictured) joined AMPS in September 2016, as expert C++ developer. His first task is to manage the Beat Detection algorithm in ABILE algorithm, which is a key component of our CER-S application.

Graduated in Physics at Milan University, he has mostly worked in the fields of telecommunications and scientific satellites, alternating research and industrial projects.

After a couple years in Olivetti, in 1986 he joined a research group at Milan University, led by Prof. Piero Mussio, developing tools for designing 3D virtual scenes illuminated by virtual car headlights. Alfa Romeo funded this project to test their headlights without going in the streets.

In 1989 he moved to Siemens Telecomunicazioni to develop software for networks management. It was the years when the GSM networks were being developed, so there was a lot of exciting work to do and many expert people to learn from. For Siemens he wrote compilers, low level libraries, communication protocols, user interfaces, and various tools for networks design and maintenance.

In 1995 he joined the ground segment team of the INTEGRAL satellite, an orbital gamma ray observatory developed by the European Space Agency. He was part of the team working at the Geneva Observatory, led by Prof. Thierry Couvoisier, and developed the software handling the housekeeping and scientific data from the satellite and its instruments.

Back to Siemens in 2001 he returned to science in 2008 joining the Agile satellite team, at the Italian National Astrophysics Institute (INAF). Agile is another gamma ray satellite, developed by the Italian Space Agency, for which he wrote the software for analyzing the gamma ray detections and locating the sources in the sky. At AMPS Tomaso's focus is helping the R&D team to improve the speed and reliability of the AMPS algorithms.

At the end of an intense working day he likes to relax at the pool table, and at the end of the week he loves to go for a walk and spend time with family and friends in open air.