

Intelligent ECG

Three years after the E14 guidance, Alexandra Latypova at iCardiac Technologies, Inc investigates new cardiac safety assessment challenges and potential solutions

SOME PROBLEMS SOLVED, NEW CHALLENGES INTRODUCED

Beginning in the late 1980s, a number of non-cardiac drugs have been linked to an increased risk of adverse cardiac events. Since late 2005, regulators require that all new drugs go through ECG-based cardiac safety testing (1). Prolongation of the QT interval on surface ECG is currently used as a surrogate marker of risk for the potentially lethal drug-induced arrhythmia, *torsades de pointes*. The studies performed according to this guidance have been termed ‘Thorough QT’ (TQT) studies. A ‘positive TQT’ study means that the drug was found to prolong the QT interval in excess of the threshold for regulatory concern (upper 95 per cent confidence bound exceeding 10 msec).

Looking at the cardiac safety environment three years after the E14 guidance, it has become clear that, while some issues have been addressed, a new set of challenges has emerged. Greater focus from regulators and sponsors on cardiac safety is, undoubtedly, a good thing. The guidance has led to the standardisation of ECG data collection and assessment in clinical trials, as well as to greater use of digital technologies. The FDA ECG warehouse now contains millions of ECGs collected from clinical development programmes, and it has become a foundation for ongoing FDA-academia-industry collaboration around advanced ECG analysis technology development and validation. Some breakthrough technologies have emerged from these efforts and are discussed in this article.

While E14 guidance has been adopted by the industry, it would be premature to declare the problem of cardiac safety fully solved. QT/QTc interval as a surrogate marker of drug-induced arrhythmia liability has significant limitations which all too frequently lead to costly mistakes and further reduce productivity.

Specifically, due to the high precision imposed by E14 guidance, TQT studies conducted today rely on over-reading of every beat in every ECG by cardiologists. As a result, these studies are very expensive, costing sponsors \$2 to \$5 million per tested drug, depending on the study design.

Furthermore, even after a multi-million dollar study which measures the QT interval with very high precision, the sponsor can frequently end up with insufficient or misleading results (over- or under-estimation of effect on repolarisation, or puzzling QT effects in some groups of patients not explainable by gender or other differences). This typically happens when the study drug has an effect on the autonomic nervous system. It is now evident that drugs that change the heart rate even by as little as four beats per minute (BPM) may not be evaluated properly by the conventional E14 analyses. This is due to known limitations of the heart rate correction methods which are commonly used in the TQT studies – the correction methods over- or under-estimate the QT changes when the heart rate deviates significantly from 60 BPM. Since drug related increases in heart rate are more common than decreases, this in turn leads to a disproportionately high number of false-positive or overestimated QT findings that result in unnecessary delays or even late stage terminations for inherently safe products.

REAL COSTS OF AN IMPERFECT SAFETY MARKER

In order to properly evaluate the real cost of an imperfect safety marker, it is important to understand the categories of costs involved. For the purpose of making a direct comparison, we will look at these costs on the basis of each approved new drug and attempt to estimate the cost of new drugs before and after TQT studies became a requirement. Certainly, the direct costs

of conducting TQT studies added post E14 guidance are significant. Today, the market for conducting TQT studies and routine ECG studies is estimated at approximately \$800 million annually (2). The new drug approval rate has been hovering around 20 per year for the past several years. One may conclude, therefore, that QT studies add about \$40 million in R&D costs per every new drug. While not cheap, this cost is a rounding error to the average of \$1.7 billion total costs to develop and launch each new drug prior to E14 guidance introduction (3). One can also argue that it is a reasonable price to pay for much safer medicines on the market, although only time will tell if society will realise a significant improvement in drug safety as a result of the E14 guidance.

Unfortunately, the direct costs associated with the conduct of TQT studies represent only a minor portion of the total. In addition to the direct cost of any new biomarker test, one should consider the rate of false-positives and false-negatives, and the costs associated with these ‘biomarker failures’.

There are two types of statistical errors in biology: false-positives or false detection of a biological signal that is not real, and false-negatives or failure to detect a real biological signal. For example, to avoid failure to detect a biomarker signal with perceived serious consequences (such as sudden cardiac death), one might increase the sensitivity of detection by defining a very small threshold for a change in the biomarker (such as >10 msec QTc prolongation), thus minimising false-negatives. This action would inevitably lead to an increase in the false-positive rate (reduced specificity) for the same biomarker. On the surface of the cardiac safety problem, this trade-off may seem justified as drug-induced sudden cardiac death, quite reasonably, is treated as an outcome that should be avoided at all cost. What is this cost in reality?

As already noted, TQT studies are very expensive for each tested drug. It is well known that the higher the cost of a development programme, the greater the risk to the pharmaceutical developer associated with the programme's failure, especially in the late stages of development. Should a very expensive programme fail late in development, the company will have to absorb the expense and quickly find a replacement for the future revenues it was expecting from the failed drug. The significant role that the TQT studies play in increasing late-stage attrition is only now beginning to be understood by the pharmaceutical developers, and especially by those who have already experienced a well-conducted TQT study that still failed.

While the actual number is hard to confirm, based on our current experience in pharmaceutical cardiac safety testing, we estimate that large pharmaceutical companies each unnecessarily terminate between one and three drugs per year in clinical development due to a false-positive QTc signal. This can happen, for example, due to benign autonomic-mediated heart rate effect on QT. It is important to note that the majority of these terminations occur before the formal TQT study is conducted, in part because the TQT study represents a major investment, and in part because the sponsors seek to ensure a 'QT clean' drug. Based on Bain & Co's research into the top 10 pharmaceutical companies' pipelines prior to 2003, only one in 13 drugs entering the clinical phase reached market, or approximately an eight per cent cumulative success rate. The low rate of success made the total cost of approving a new drug reach \$1.7 billion at that time. Even if we take a very conservative view and assume that each top 10 pharmaceutical company terminates one drug per year

unnecessarily due to a benign QT signal, and we also imagine that the entire industry consists only of the 10 top pharma companies, this means that the overall rate of success post-E14 guidance has declined to one in 15 – approximately 6.6 per cent cumulative probability of success for each drug entering clinical development. If all other costs remain the same, the total cost per each new approved drug is now \$1.96 billion, of which the indirect cost associated with false-positive TQT studies is \$260 million. Combining direct and indirect costs, we arrive at approximately \$300 million of additional costs for each new drug on the market attributable to the shortcomings of QTc as a safety marker. The costs of false-negative QT studies are also significant. Each drug removed from the market due to adverse cardiac events or deaths causes hundreds of millions in litigation costs, as well as potentially billions in forgone revenue. However, because the false-negative rate of QTc is relatively low, we are not addressing them in this article.

With the current push towards 'zero risk' associated with drugs on the market, one might conclude that we should not only accept the skyrocketing costs of drug development and healthcare in general, but to expect further acceleration of this trend. After all, it would be an unsound strategy to argue for relaxing regulatory safety standards just because they cost too much. Fortunately, we do not have to make this trade-off. Thanks to the technological innovations of the past few years, these challenges are already being addressed by advanced ECG analysis technologies that not only reduce the direct costs associated with TQT studies, but also have the potential to reduce the false-positive and false-negative rates of these studies.

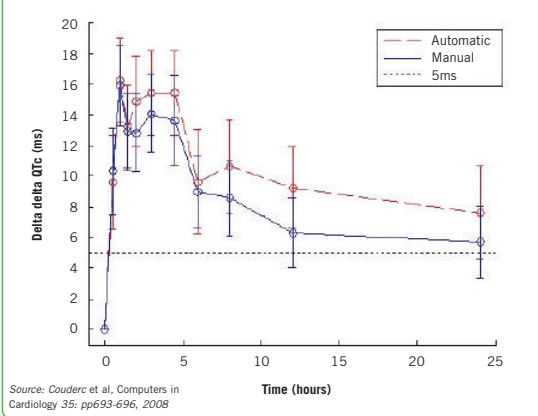
DOES A TQT STUDY HAVE TO BE SO EXPENSIVE?

One of the main drivers of the direct TQT study costs is the technical difficulty of measuring the QT interval against the precision standards imposed by the E14 guidance. The QT interval, which represents the length of a heartbeat, is highly variable from beat-to-beat within an individual, and across individuals. This high variability, in part, drives the need for a relatively large sample of subjects in a study (currently, approximately 50 subjects per arm, for a three- to four-arm crossover study), and thus high clinical costs associated with the study conduct. In addition to these costs, the ECG data analysis costs are also very high. The QT measurements generated by ECG recording equipment are not precise enough and thus cannot produce the 'assay sensitivity' required by the regulators – that is, up to five msec QT prolongation in the positive control arm of the study, as well as the expected positive control profile. In order to overcome this limitation, the industry, until recently, has relied on the 'over-reading' of all ECGs in a TQT study by cardiologists.

The industry has been searching for a reliable automation solution which would reduce the cost and increase the speed of ECG data analysis. Recently, the scientific collaboration between the FDA and University of Rochester, New York, around novel ECG analysis technologies and markers has reported encouraging results. The group announced the completion of the validation of the first highly automated QT analysis technology suitable for TQT studies. The validation project consisted of analysis of the ECG data from the positive control (moxifloxacin) and placebo arms of several TQT studies from the FDA ECG warehouse. The analysis has demonstrated that the highly automated

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Figure 1: Moxifloxacin-induced QTc prolongation profile: comparison of highly-automatic analysis versus FDA-submitted results in 8,911 ECGs from 66 healthy volunteers



Source: Couderc et al., Computers in Cardiology 35: pp693-696, 2008

technology developed by Rochester group is equivalent to the manual ‘over-reading’ approach (see Figure 1) (4).

The highly automated QT analysis technology relies on sophisticated signal processing algorithms that measure QT and identify the subset of ‘problem’ ECGs in the entire TQT dataset that require manual over-reading. Based on recent experience using this analysis tool in the TQT studies, the sponsors can realise up to 50 per cent cost savings, as well as dramatically reduce the analysis time from the several weeks required by manual analyses, to just a few days for the highly automated approach.

CAN WE REDUCE THE RATE OF FALSE-POSITIVE TQT STUDIES?

Drugs that affect the autonomic nervous system are more likely to have over-estimated or false-positive QTc findings because of inherent limitations of the heart rate correction methods (5-8). This can be problematic when trying to distinguish the changes in QT interval by drug-induced delayed repolarisation from autonomic-mediated physiological responses (9). In general, any compound that reduces blood pressure leading to reflex tachycardia is a candidate for a false-positive effect in a TQT study. Likewise, any compound causing increases in blood pressure can lead to false negative QTc results or under-

estimation of the pro-arrhythmia potential of the drug.

Advanced ECG analysis techniques have the potential to overcome this challenge. Dynamic assessment of the QT interval from continuous ECG or Holter data beat-to-beat (QTtbtb) allows for measurement of changes under varying conditions of heart rate and autonomic tone. Instead of linear correction for heart rate, the QTtbtb method utilises

statistical techniques to determine the upper (or lower) 97.5 per cent confidence boundary of QT in the normal 24-hour data (from baseline day of the study), and then compares the data on-drug against this boundary.

The physiologic model for the QT-RR interval relationship underlying the QTtbtb method is depicted in Figure 2 (8,9). This highly dynamic state that occurs from beat-to-beat allows humans to live within their own unique QT-RR boundary influenced by many different conditions of autonomic-mediated change, such as eating, sleeping and exercise or disease states that alter QT-RR heterogeneity. Holter acquired data plotted from long-term monitoring produces large QT-RR data ‘clouds’ that can span over 1,000ms in the RR interval range, and 70ms in QT magnitude in any given individual. However, conventional QTc methodology, adopted for drug safety evaluation by the E14 guidance assumes the RR relationship in a normal individual can be represented by a line. This assumption, while simplifying computation, may grossly misrepresent the underlying physiologic phenomena. The actual QT interval often is misrepresented because delayed cardiac repolarisation cannot be differentiated – using the linear formula – from autonomic-mediated responses, such as reflex tachycardia (RT) and reflex bradycardia

(RB) (see shaded areas in Figure 2 above and below Fridericia curve). In the QTtbtb method the normal (unstressed) autonomic-mediated QT-RR boundary is first established as the upper confidence bounds before drug administration. The area below this boundary represents a safe cardiac physiological limit for QT change. QT prolongation beyond this limit may represent drug-induced delayed repolarisation associated with some degree of as yet undefined arrhythmogenic risk.

QTtbtb provides a means to differentiate QT interval prolongation effects incurred through inhibition of the repolarisation process from changes in the QT interval incurred through physiologic autonomic-mediated reflexes. It avoids errors associated with the use of standard correction factors such as Bazett and Fridericia. Much of the cause for discrepancy in correction factors is because no single mathematical transformation can describe the rapidly changing nonlinear dynamics of the QT-RR interval relationship.

This advanced ECG analysis method is currently accepted by regulators as a secondary analysis in TQT studies of drugs that affect the autonomic nervous system. In addition, this method has much greater precision than E-14 type QTc analysis because it looks at the entire 24-hour Holter recording or 90,000 cardiac beats per subject, as opposed to sampling just a few beats at 10 to

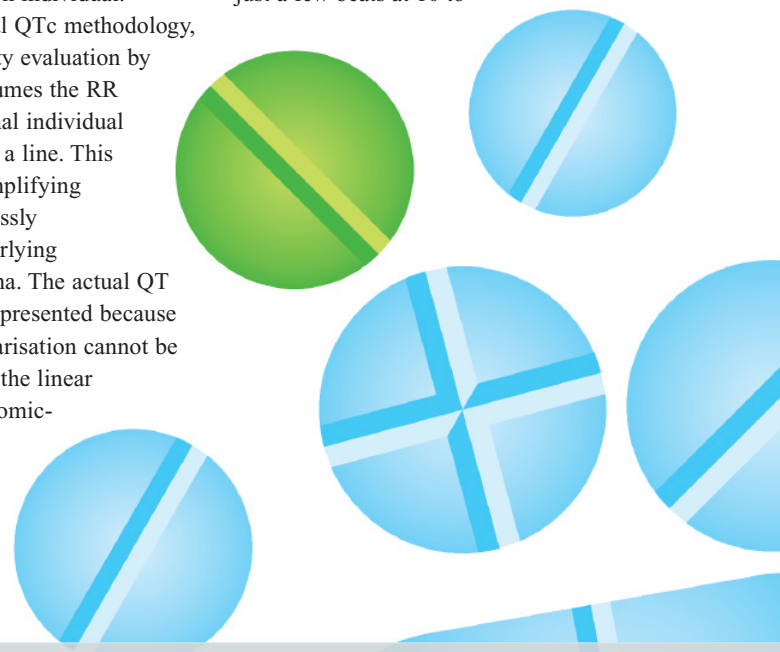
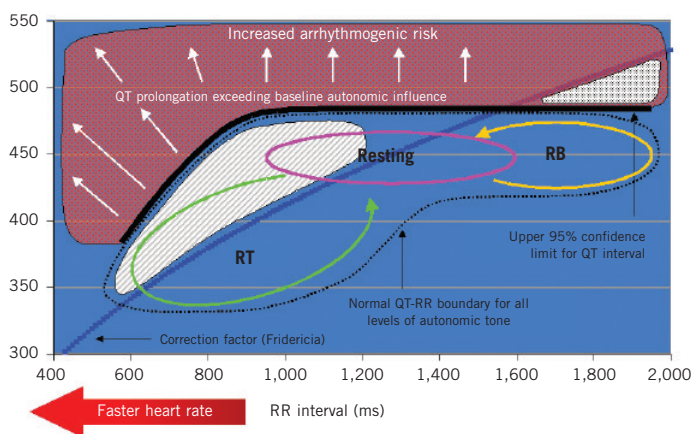


Figure 2: Model of QT-RR relationship in humans incorporating hysteresis due to normal autonomic nervous system reflexes



12 timepoints in the same subject. Because of the amount of data analysed, QTbtb can generate reliable results in a study containing a very small number of subjects – for example, first-in-human or other Phase I studies – making it an extremely valuable early development tool for go/no-go decision making. Using this advanced technology, pharmaceutical developers can answer crucial safety questions in early development programmes, before committing to major investments in later phases.

FUTURE OUTLOOK

Today, cardiac safety testing is taking a one-size-fits-all approach, setting the single marker (QTc) to a single threshold of concern (>10 msec prolongation) for all new drugs in development. We believe this approach leads to a lot of unnecessary terminations of inherently safe drugs in development and significantly contributes to the skyrocketing costs of drug development by reducing productivity of pharmaceutical R&D.

The number of new drugs reaching the market has been in steady decline for years, recently hovering around 20 a year, while the costs of R&D have exceeded \$40 billion per year in the US.

With a more intelligent use of advanced ECG technologies in cardiac safety TQT

studies, the sponsors can dramatically lower the cost and increase the speed of cardiac safety assessment. Most importantly, many more promising new drugs can be put forward in the development process, enriching the drug development pipelines and bringing new medicines to patients.

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