

# Feeling the Beat

Sasha Latypova and Mikael Totterman at iCardiac look at de-risking drug candidates in early clinical development

**BACKGROUND: AN INDUSTRY SHIFT**

In 2005, the US and European regulators introduced a new set of guidelines (E14 guidance) that require a robust characterisation of cardiac safety for non-cardiac drugs. Specifically, drug developers are now required to demonstrate that their compounds do not have a significant effect on QT interval – a surrogate marker for arrhythmia liability that is measured from the surface electrocardiogram (ECG). These new guidelines were developed in response to the post-market withdrawal of nine non-cardiac drugs for cardiac safety reasons, of which five were withdrawn specifically for contributing to drug-induced arrhythmias. The studies performed to evaluate the effect of novel drugs on the QT interval have become known as thorough QT (TQT) studies.

Immediately after the introduction of the E14 guidelines, many drug developers elected to conduct the TQT studies early in the clinical development process, as had been envisioned by the regulators. However, having gained experience in these types of studies over the past three years, pharmaceutical sponsors have realised that this investment frequently leads to suboptimal returns. Specifically, the cost of a TQT study can range from \$1.5 to \$5 million, but the study only answers a single regulatory question (characterisation of the drug effect on the QT interval) and, for example, in drugs that have normal autonomic mediated QT changes, does not answer this question very well.

Given the significant limitations of conventional TQTs, pharmaceutical companies have been increasingly delaying investment in TQT studies until the ‘last responsible moment’ – often in parallel to Phase III studies. As a result, there has been a perceptible drop in the total number of TQTs conducted in any given year. While alleviating the upstream issue of the high cost of TQTs, delaying the investment decision for a market-enabling study, which can have serious labelling implications for the drug, leads to a host of even greater risks downstream in the development process. It

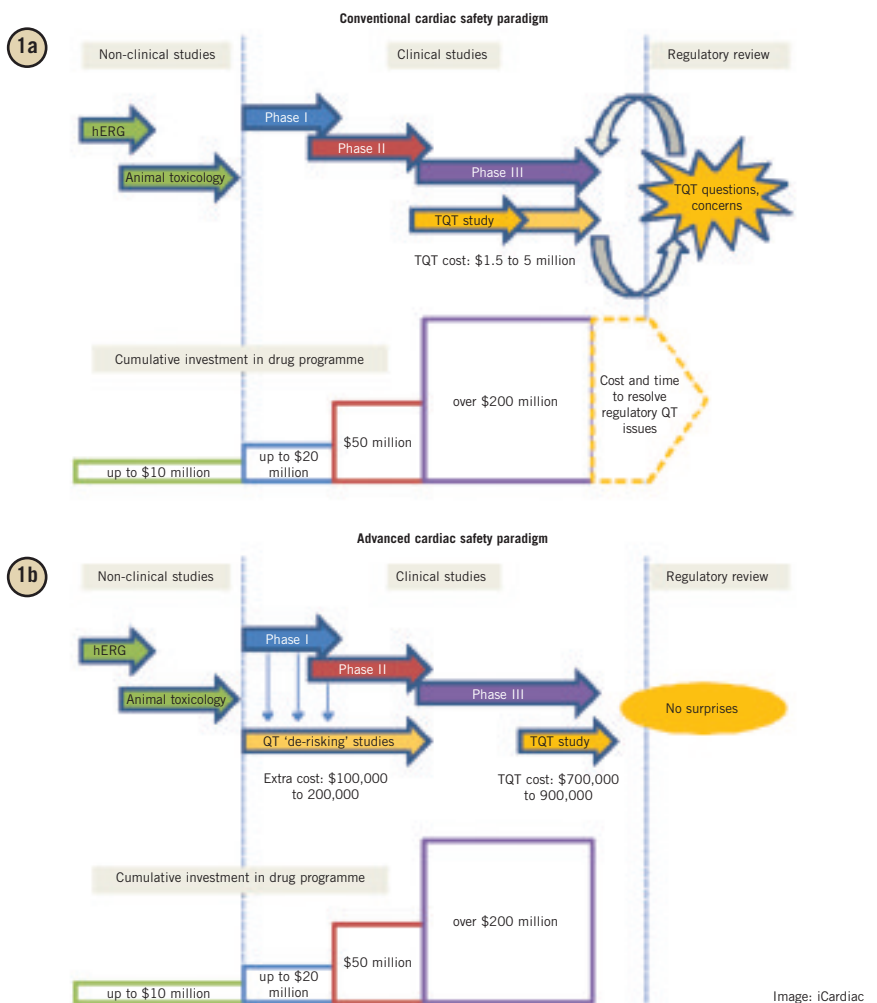
has become clear that, without implementing more intelligent and cost-effective solutions to TQT studies, this problem will continue to lead to an increase in the total cost and further reduction in the success rate of drug development.

**PROBLEMS WITH LATE CHARACTERISATION OF CARDIAC SAFETY**

As a result of the late characterisation of QT prolongation, pharmaceutical developers may run into a variety of unintended consequences. For example, if the drug’s effects on the heart rate and autonomic nervous system have not been well characterised in earlier clinical studies, the sponsor is at risk of getting unexpected effects in the TQT study. This could come in the form of uninterpretable

heart rate corrected QT or QTc changes such as inconsistent QTc-concentration relationships, effects in some groups of subjects that are not seen in others or unexpected effects at supra-therapeutic doses. Furthermore, as conventional Phase I studies provide even less stringent QT assessment, drug developers may be surprised to find QT prolongation even in non-hERG blocking agents. At this point, significant amounts of funding and time have been invested in a development programme and the sponsor is likely to spend months re-examining preclinical data, experiencing regulatory delays, and in some cases poor decision making, which all add costs for the entire programme. It is estimated that the delayed characterisation of cardiac safety can come to a total of up to \$260

Figure 1: Conventional versus advanced cardiac safety paradigm



million in aggregate cost to each drug development programme due to false positives or over-estimated QT effects for inherently safe products that get terminated or delayed in development.

Conventional QTc analyses in Phase I (if these data are gathered at all) have several important limitations. Firstly, Phase I studies generally have more noise because they are not designed solely for ECG data assessment. Since QTc measurements in these studies are generally performed at fixed timepoints, the results are highly variable. Thus, QTc analyses in Phase I studies are more prone to errors leading to poor decisions. In addition, many sponsors who do collect QT data in Phase I studies have been relying on ECG machine-computed QT data for cost saving reasons. Unfortunately, intermittent ECG machine-computed QT measurements alone are not sufficiently sensitive to detect small to moderate amounts of QT prolongation in few subjects. Clearly, it is critical for a sponsor to be able to answer QT questions reliably and early in the development process, but conventional QTc assessment approaches provide marginal results at best.

**Table 1: Benefits of the advanced cardiac safety paradigm**

Drug development issue	Conventional TQT paradigm	Advanced cardiac safety paradigm
Cost of QT effect characterisation per drug	\$1.5 million to \$5 million	Less than \$1 million
Time to regulatory-ready results	12 to 24 months	Less than 12 months
Robust QT-effect analysis for all studied doses (PK-QT characterisation)	No	Yes
Robust characterisation of the autonomic nervous system effects (if any)	No	Yes
Ability to avoid false-positives or un-interpretable QT data	No	Yes
Highly significant QT results	Late (TQT at Phase II/III)	Early (FIH, Phase I)

### OPPORTUNITY: ADVANCED CARDIAC SAFETY PARADIGM

Fortunately, the combination of two key strategies can be used to address the problems presented by late characterisation of cardiac safety, while reducing out-of-pocket cost, as well as risks and opportunity costs associated with cardiac safety assessment. Specifically, the total cost of cardiac safety assessment can be reduced by automating QT evaluation in late-stage TQT studies, while at the same time including advanced telemetry or Holter-based ECG analytics into single or multiple ascending dose studies to achieve accurate and precise early QT characterisation.

### WHAT ARE THE BENEFITS?

The total conventional TQT study cost is comparatively high in relation to the size of the study population, because of the necessity for both intensive monitoring in Phase I units, as well as the cost of using cardiologists to interpret visually the 8,000 to 25,000 ECGs that are collected in such studies.

The total cost of TQT studies, which are conducted late in development, can be reduced by recently validated FDA-accepted automated approaches to QT interval assessment. The FDA, jointly with the University of Rochester, has recently

completed a long-term project to validate software for automated QT measurements using data from eight TQT studies archived in the FDA ECG warehouse. The university-developed software tested in this validation programme, called COMPAS, has been shown to be equivalent to manual or semi-automated results previously submitted in these studies to the FDA. The increase in the number of cardiac cycles that can be analysed in highly automated studies results in significant cost savings, as well as reduced variability in the QT measurement precision. These advantages have caught the attention of both regulators and sponsors, highlighted by their inclusion in a broad set of validation programmes conducted by regulators, academia and sponsors. These approaches have now also supported the successful submission of data from TQT studies to the regulators. Furthermore, by using automated approaches, false positives that would otherwise be caused by heart rate changes can now be avoided. Specifically, QT-heart rate (QT-RR) changes can be fully characterised to separate the benign effect of heart rate changes on QT from dangerous repolarisation duration prolongation by analysing continuous ECG recordings (24-hour Holters or telemetry data) beat-to-beat.

Advanced Holter-based beat-to-beat analyses allow very cost-effective answers to key cardiac safety questions early in the development process. By including 24-hour Holter recordings and using automated techniques to analyse the full continuous

data sets (instead of only a few extracted replicates), the QT effects of the drug can be robustly characterised, despite the small sample sizes of these studies. This gives a solid foundation for understanding what results can be expected from TQT studies and gives development teams the confidence to move forward.

Additionally, in interpreting the results and planning for future QT studies, it is important to understand thoroughly how a compound may affect the heart rate and autonomic nervous system. As a result of the extensive experience of drug developers and the FDA over the past decade, it has now become clear that even minor changes in heart rate can lead to hard-to-interpret TQT study results, or even erroneous conclusions regarding QT effect. This is due to very well-known limitations of correction formulae frequently used in TQT studies. Correction formulae – Bazett, Fridericia or individual – have been demonstrated to over- or under-correct QT at increased or decreased heart rates, and these methods cannot distinguish between benign QT effect due to changes in underlying autonomic state and potentially dangerous QT effect due to repolarisation delay. By using Holter-based analyses in early development, a rigorous understanding of heart rate changes can be obtained, which allows the development team to understand if the QT prolongation is real and caused by repolarisation delay, or if it is simply caused by the effect that heart rate changes have on traditional corrected QT formulae.

Understanding these cardiac safety effects in early development is invaluable as it will help define appropriate TQT study design in downstream development and avoid any risky surprises. Finally, since the Holter-based data is collected continuously, it can be used to define and model dose response relationships at any extraction period necessary to characterise impact on QT interval. This will lead to better assessment of cardiac risk at various dose levels, and help to inform stage gating of development programmes.

## CONCLUSION

In order to address the concerns of both sponsors and regulators, a new cardiac safety paradigm can be adopted. The total cost of later stage TQT studies can be reduced by using FDA-accepted automated methods. In addition, critical safety questions can be answered earlier by incorporating Holter/telemetry-based ECG data collection and analysis into Phase I studies. The early characterisation of cardiac safety provides a number of benefits, including the ability to confidently move forward with a development programme, an understanding of any heart rate changes that may result in false positive QT using traditional methods, as well as a robust understanding of the best way to conduct the important downstream TQT study.

## About the authors



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## References

1. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, [www.fda.gov/cber/gdlns/iche14qtc.htm](http://www.fda.gov/cber/gdlns/iche14qtc.htm)
2. Latypova A, Intelligent ECG, *European Pharmaceutical Contractor*: pp88-89, March 2009
3. Handzel R, Garnett C *et al*, Comparison between highly-automatic versus FDA-submitted QT measurements for the detection of moxifloxacin induced prolongation of the QTc interval, *IEEE Computers in Cardiology* 35: pp693-696, 2008
4. Fossa AA, Wisialowski T, Magnano A, Wolfgang E, Winslow R, Gorczyca W, Crimin K and Raunig DL, Dynamic beat-to-beat modeling of the QT-RR interval relationship: analysis of QT prolongation during alterations of autonomic state versus human ether a-go-go-related gene inhibition, *J Pharmacol Exp Ther* 312: pp1-11, 2005