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Editorial

The "Thorough QT study": A valid paradigm to test new algorithms for QT interval measurements?

In their article, Meyer and colleagues[1] report on a novel method, based on pattern recognition analysis of digital ECGs, which introduces a number of innovative features that seem to favor a machine-based continuous QT interval assessment.

The topic of more accurate QT measurements has been recently revitalized by the clinical pharmacology world, and more specifically by the mandate to assess the drug-induced effect on the QT interval in a large spectrum of non-antiarrhythmic compounds. Specific guidelines have been published and the "Thorough QT Study" (TQT), a study conducted under strictly controlled clinical environment has been established.[2] Following these guidelines, the industry revolving around the assessment of cardiac safety has rapidly evolved, moving away from rather poorly defined measuring protocols. Consider that only a few years ago QT interval assessment was based on the manual measurements from a few QT intervals from a specific lead, sometimes based on scanned ECG images. There are now more and more sophisticated methods, for example measuring a single QT interval from the so-called "representative beats" with the support of an underlying measuring algorithm.[3,4] In parallel efforts, existing commercial algorithms have been improved and new methods have been introduced.[5]

The spread of the TQT study paradigm and the implementation of the ECG warehouse under the umbrella of the Food and Drug Administration have provided many edited ECGs that can be used as a benchmark for comparison and assessment of new approaches, as that in the article of Meyer et al., and also other existing approaches.[6] Because of this, it is relevant to underline some of the specific features of this type of study.

First of all, subjects enrolled in a TQT study are by definition young and healthy; this is because this kind of studies are typically carried out in the early phase of the drug development cycle, before the new compound is administered to the so-called target population. A TQT Study is typically characterized by four periods (arms of the study) during which enrolled subjects are randomly and blindly administered a placebo, two separate dose levels of the target compound, and a single dose of a compound that is known to produce a moderate but benign prolongation of the QT interval (e.g. 400 mg of moxifloxacin). This dose that produces no morphologic distortion of the repolarization waveform is used to determine to so-called "assay sensitivity" of the system (e.g. its capability to detect a known level of QT prolongation). Consequently, the ECGs from TQT studies are relatively simple to analyze, and would be easily and properly measured by most algorithms. It thus appears that the TQT study benchmark can be on one side extremely useful, but on the other side it could embed the risk to provide a too simple validation model for new algorithms which may not be as effective against challenging ECG shapes, particularly when the target compound may not significantly affect the repolarization pattern. In the study of Meyer et al. this limitation is mitigated because the active compound (saquinavir), is actually a QT-prolonging drug that induces changes in T-wave morphology.[7]

There are, however, at least other two potential confounding factors associated with the use of TQT studies conducted by core laboratories as benchmarks. The first is that, in the absence of a gold standard that precisely defines the QT interval (or, better, the location of the T-wave end), different core laboratories may actually produce different QT measurements. One of the concerns of regulatory bodies, and in part the reason why the assay sensitivity test is systematically required, is that the absence of a gold standard causes potential biases in the methods used to assign the QT interval. It is accepted that if a systematic bias exists between methods of different laboratories, there should be at least an agreement on the amount of drug-induced changes (or better on the so-called baseline and placebo-corrected double delta effect) produced by a given compound. This is precisely the goal of the assay sensitivity component of a TQT study. Using a specific core laboratory TQT benchmark may thus hide potential biases in the absolute value of the QT interval. The second confounding factor is that the ECG lead used for measurement selected by core laboratories could limit the spectrum over which the comparison can be done. As pointed out in the limitations section of their manuscript, this also applies to the study of Meyer and colleagues, as the measurements from the core laboratory were based on lead II and those from the machine-based system were based on lead V_4.[1]

However, regardless and beyond these limitations, the work of Meyer et al. represents an interesting step forward.

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What is compared is a traditional return-to-baseline method applied individually to every cardiac beat, with a novel approach based on the pre-determination of subject-specific libraries of representative template waveforms which are then used in a conformational match fashion to characterize the markers of each cardiac beat.[1] This method would seem to reduce significantly the incidence of T-wave-end measurement errors, and to provide more reliable (smaller) intra-individual variability of the QT interval.

In another published article completely unrelated to clinical pharmacology, Baumer and colleagues[8] recently compared two similar template-based methods (one characterized by template stretching and the other by template time shifting) with a conventional derivative-based algorithm to assess the beat-to-beat variability of the QT interval. In this study, both simulated data and ECGs from continuous Holter recording selected from a commercial repository after administration of sotalol (a drug that is known to produce both an increase of the QT interval and distortions in repolarization morphology) were compared. The three methods exhibited significant differences in the presence of broadband noise, baseline wander and T-wave amplitude modulation. Similarly, and not surprisingly, in agreement with the study of Meyer et al., template-based algorithms provided an overall better performance, particularly in the presence of noise. Although it can also be concluded that conventional methods are far from being outscored and in certain conditions (specifically under baseline wander) are as good as the novel methods.

The TQT study paradigm can be used as a valid benchmark to test the performance of ECG measuring algorithms. Further testing should be conducted to gain insight into the performance of these methods in a more pathological, and less controlled, clinical environment.

Fabio Badilini, PhD, FACC
AMPS LLC, NY, USA
E-mail address: badilini@amps-llc.com

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