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

As most of our readers probably know the ECG recording and analysis in clinical studies represent several million traces handled every year globally. Large companies, such ERT, handle almost 10 millions each year alone, and it is clear that the quality of the traces plays a huge role in the time and cost of each study. As it appears the current industry-standard ECG data error rates is still in the neighbourhood of 80-90%. That is a scary number, but reportedly the typical error rate is due to grossly antiquated methods of hand transcribing heart data to paper or an electronic system. To solve even minor mistakes is very expensive, running probably between $10 to $35 per error. Not to mention the time people have to spend to correct the problem via several emails, phone calls or even a personal visit to a clinical site. You do not need to multiply the numbers; I am sure you have already realized that even in the most optimistic scenario there is potential for huge savings.

In this issue we welcome a very interesting contribution on the subject of ECG quality from Dr Corina-Dana Dota, M.D. who has over a decade of clinical research and management experience in the field of safety biomarkers of pro-arrhythmia, digital ECGs and use of computerised systems in dECG analysis at AstraZeneca in Sweden. Currently she provides scientific expertise and leadership for the AstraZeneca ECG Centre in Molndal, Sweden and is co-chair of AstraZeneca´s QT/Arrhythmia Review Group, and therefore in an excellent position to appreciate the issue and provide and illuminating point of view. As usual: enjoy!

A Noteworthy Contribution:

ECG Data Quality- a shared task for a shared benefit.

By Corina-Dana Dota, M.D., AZ ECG Centre Director, AstraZeneca R&D, Mölndal, Sweden.

Less than six years have passed since the sign off of the ICH Harmonised Tripartite Guideline E14: "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" [1] but the changes triggered by this guideline in the field of ECG recording and analysis are unprecedented if we consider the venerable age of electrocardiography.

The progress and achievements are in multiple areas:

- The collection of exclusively digital electrocardiograms in clinical studies where a drug effect on ECG parameters is to be detected and measured, an achievement which seemed unthinkable no later than the end of the past millennium;
- The manufacturing of more and more sophisticated digital ECG equipment (12-lead ECG machines delivering various lengths of recordings, from the standard 10-seconds to hours; 12-lead Holter and telemetry devices), with features and technical performance fulfilling the requirements of clinical research within drug discovery and development;
- The standardization of digital files into one format, the XML.HL7;
- The development and validation of a plethora of software covering (almost) all steps of the digital ECG process, from set-up of the dECG acquisition at the clinical study site to the file validation and upload into the ECG Warehouse. Such tools enable: source data recording (as integral part of the digital ECG device), meta data check, metadata correction and validation, the transfer of digital files from the study to the analysis site; extraction of snapshots at stable heart rates from continuous files, and last but not least, the automated or semi-automated ECG measurements, analysis and interpretation.
- The refinement of the algorithms of ECG analysis softwares and the addition of signal quality checks

and metrics into some systems made the "highly" automated dream become reality;

- There is increased interest in ECG metrics from pharmaceutical companies and ECG Corelabs, and the imminent release of version 2 of such metrics by the MCC (Metrics Champions Consortium) reflects this.
- There is a continuously increasing number of digital ECG files stored in the FDA ECG Warehouse and in other repositories which provide a rich basis for defining (and redefining?) the reference values of durations and amplitudes of ECG waves and intervals and of signal quality metrics.

None of these would have happened so fast without the ICH E14 and without the creation of the FDA ECG Warehouse. And as we know, the digital ECG journey does not end here, the new frontier is the FDA Holter Warehouse and refined analysis methods and interpretation of all data from continuous recordings for better understanding of the QT adaptation and of QT/RR dynamics, just to mention two major goals.

This is the future, and we have learnt, it comes fast!

In the meantime we shall ask the question: what can we do to make the ECG evaluations even more reliable, less expensive and of even better quality?
Develop and refine our tools and softwares? Of course, innovation and creativity are key, as well as access to large datasets to validate these tools and algorithms.

Another important measure, is to emphasize again and again the role played by high quality input data to an accurate and precise measurement, and this is applicable to manual, semi-automated and automated (in all its incarnations as highly, fully, etc.) analysis. No automation or sophisticated tool can or should save ECG data of insufficient quality. But automated tools and sound quality control processes at the ECG Corelab should ensure strategies and algorithms to select these "bad" data from the data "fit for purpose" and by this to expand the use of highly automated analyses beyond the well controlled environment of Thorough QT Studies.

Noise levels in terms of high and low frequency noise, should be categorized and the data placed in "clusters" either for reader review, or for non inclusion in the measurements at all. One solution was already been described earlier in the AMPS magazine [2].

Disconnected (failed leads), impedance problems by insufficient skin preparation, incorrectly placed leads, etc. are problems that can be prevented by thorough training of the staff at the study site but once they happened, it is important that they are detected early and preferably automatically. An important step in right direction would be to have the faulty or noisy data identified by the ECG equipment (or a tool placed at the study site) at the recording time, to ensure timely remediation and further loss of data.

One study performed in our unit [3] showed that the inconsistent placement of leads impacts on the QT interval measurement and induces increased variability, false QT prolongations and T wave morphology "changes". Unfortunately, this is a data quality issue difficult to detect in a fully automated manner. Adequate site training is key.

The sooner in the ECG analysis process the quality issues are detected, the less impacted the study.

Developing and maintaining quality metrics, preferably based on a collaboration among multiple companies (sponsors, ECG corelabs, CROs) will allow a more objective and solid definition of "bad" and "good" data and will ensure the ability to compare data across sites.

I would like to end by saying that it is very important for us all, sponsors, ECG Corelabs, CROs, professionals working in the ECG field, to collaborate to find best solutions for the improvement and effectiveness of quality and advancement of the good, old ECG and for the advancement of science !

References:

[1] E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs: Guidance to Industry. In: ICH, ed. Federal Registry2005:61134-61135.

[2] William Wheeler, MD, FACC and Joy Olbertz, PharmD, PhD; Celerion, Lincoln, NE.- The Highly Automated Hybrid Phase I/ECG Core Laboratory

[3] Malena Asgeirsson, MSc, AZ ECG Centre- Presentation DIA QT conference, BERLIN, December, 2006.

Products News

Latest Releases

In February version 3.2.0 of CalECG has been released. This new version is compatible with the new Window 7 Operating System.

Looking forward

In Q2 AMPS is planning to release:

- an updated version of CalECG v.3 with enhancements to the automatic algorithm.
- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- an update version of FAT-QT with new scoring metrics, synchronized with FDAEcg Suite v.2.

AMPS Notebook

Fabio Badilini will be co-chairman of the 36th **ISCE conference** that will be held in San Jose, CA from April 13 to April 17.

He will chair the Pre-conference Tutorial focused on Heart Rate Variability, where he will be presenting the "*Frequency Domain HRV Approaches: modeling-based versus FFT-methods*" tutorial.

He will also present the paper entitled "*Frequency domain assessment of the QT-RR coupling strength during graded head-up tilt*" on April 15th.

AMPS People

We continue our round of staff introductions with Martino Vaglio.

Martino started his Engineering studies in Italy at the Polytechnic University of Milan where he obtained his Master Thesis degree in 2003.

He then moved to Zurich, Switzerland to work in the Automatic Department of the Zurich Technical University.

In 2004 he joined the University of Rochester, Rochester, NY, USA where he worked on ECG signal processing and analysis, focusing mainly on the repolarization signal.

Martino, who joined AMPS in 2006, works on Technical Support as well as in Research and Development, focusing on the high-level design and requirements of new AMPS products.

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