



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

Most probably our readers already familiar with the Cardiac Safety Research Consortium (very likely the majority) were already wondering how come we had not, in one form or another, given the CSRC more space in these pages. We hope that the contribution from Mitchell W. Krucoff, M.D., F.A.C.C., F.C.C.P. Co-director of CSRC in this 16th issue of AMPS-QT will provide you a good overview of the Consortium and its important role in our world. If you take the time and visit the CSRC web site (www.cardiac-safety.org) you will find out that the most relevant companies are already members (and for a very good reason), and if yours is not in the list maybe this article will provide you the opportunity to talk your managers into joining the club. Mitch Krucoff you surely know already, giving his impressive contributions to the cardiac safety world. Besides being Professor of Medicine/Cardiology and an Interventional Cardiologist at Duke University Medical Center he is internationally recognized for his pioneering research in several areas. Author of more than 100 publications in the cardiology literature and book chapters in medical texts, Mitchell is Senior Editor of the Journal of Alternative & Complementary Medicine. For a full overview of his achievements please see: www.healingmoves.com/mitchell/. From the AMPS Team please accept our best wishes for a successful 2013!

A Noteworthy Contribution:

Update From the Cardiac Safety Research Consortium

Mitchell W. Krucoff MD, FACC, FAHA, FSCAI; Duke University Medical Center Durham, North Carolina, USA
Co-Director, CSRC.

On December 10, 2012, the Cardiac Safety Research Consortium conducted its sixth annual meeting at FDA Headquarters in White Oak, Maryland, USA.

In 2004 the U.S. FDA launched the Critical Path program (<http://www.fda.gov/oc/initiatives/criticalpath>) to address concerns about the rising cost of research and development and dropping numbers of new therapies emerging in the USA. Rare but catastrophic cardiac safety concerns represent the most significant barrier to innovation in phase II and III development. In 2006 a Memo Of Understanding (MOU) was signed between Duke University and the U.S. FDA establishing the CSRC and focus exclusively on advancing regulatory science associated with cardiac safety concerns. Operationally CSRC uses the university setting as a “neutral ground” in which to convene a transparent, public-private partnership (PPP) between industry manufacturers, academics and regulatory authorities and other federal agencies. The PPP uses the CSRC committee structure to develop a collaborative, pre-competitive focus on key areas of cardiac safety through thinktanks, white papers and pragmatic research projects. As summarized in its Five Year Report in 2011, since its inception CSRC has conducted more than two dozen thinktanks and published white papers on optimal measurement of QTc, QT in oncology compounds, pediatric cardiac safety, translational issues and cardiac safety, diabetes, blood pressure effects of non-cardiac drugs, atrial fibrillation ablation safety and obligatory drug-device safety interactions such as dual anti-platelet therapy and drug eluting stent thrombosis and arteriotomy bleeding safety with anti-thrombotic drugs. In addition to a growing membership with more than 26 industry manufacturers, CSRC has been joined by federal agencies and international regulatory authorities including the National Institutes of Health, the Agency for Healthcare Research and Quality, Health Canada and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA). In addition CSRC has also partnered with a wide variety of professional societies and organizations such as the Drug Information Agency, the American College of Cardiology, the American Heart Association,

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the Health and Environmental Sciences Institute, and the International Cardio-Oncology Society.

While the growth in both membership and breadth of activities of the CSRC has been remarkable over its six years of activity, the pre-competitive, collaborative approach to cardiac safety was first crystallized around the ability to move digital ECG waveforms from the FDA's proprietary ECG Warehouse into public domain use for ECG instruments and technology development. Leveraging the ECG Warehouse infrastructure developed through a Cooperative Research And Development Agreement (CRADA) between FDA and Mortara Instrument in Milwaukee, Wisconsin, more than 50,000 ECGs from over a dozen thorough QT studies are now fully annotated and available in the CSRC ECG Warehouse. AMPS founder Fabio Badilini serves on the CSRC ECG Warehouse Committee, and has contributed to the development research projects using this resource.

At this year's annual meeting four very exciting areas of advancement in 2012 were highlighted. First amongst these was the completed uploading of the Genetic Long QT ECG Warehouse, donated to the CSRC by Dr. Pierre Maison-Blanche of Lariboisiere Hospital in Paris, currently Chief Medical Officer of Biomedical Systems in Missouri. Dr. Badilini and AMPS led the way in the digital conversion of upload of more than 500 ECGs from 312 human subjects and family members—the world's largest collection of ECGs from patients with congenital QT prolongations. The upload was completed by AMPS less than a month before the CSRC Annual meeting. Other programs of interest in 2012 included the development of a diabetes clinical data and cardiovascular outcomes warehouse, efforts to develop a public domain common format case report form for cardiovascular safety reporting, and the use of direct digital data capture from professional society registries for prospective randomized IDE and IND clinical trial efficiencies.

In closing the CSRC overview for this year's annual meeting, the Co-directors' cover letter from the 5 Year Report was quoted: "The fabric of CSRC and the key to past and future success is our membership—engaged, creative individuals with diverse professional backgrounds...our members bring experience and expertise from industry, academia, regulatory and other Federal agencies together as a brain-trust of unique breadth and depth. Over time our members have developed trust in each other and in the CSRC's public-private partnership processes—trust that we come together to listen to each other's perspectives, to exchange and discuss ideas, not to give speeches; trust that our pragmatic emphasis is

productive, with deliverables that have impact on the landscape of cardiac safety."

Mutations	Subjects	Females	ECGs
LQT1	194	118	307
LQT2	100	55	202
LQT3	16	8	25
Other	2	1	3
Overall	312	182	537

Table (*Editor's Note*): details of the LQTS Database described by Dr. Krucoff. The total number of subjects and ECG recordings and gender distribution is provided separately for the three main LQTS-type subgroups.

Products News

Looking forward

In Q1 2013, AMPS is going to release:

- o CalECG v. 3.5.0, with updated BRAVO algorithm;
- o Fat-QT v. 1.2.0, with updated BRAVO algorithm;
- o TrialPerfect v. 2.9.0, with new CalECG and Fat-QT and improved usability

And last, but not least: beat-to-beat news for 2013...Our experience with beat-to-beat QT/RR analysis dates back to 1992 (1). Although we never released a specific product tailored for the pharmaceutical industry, we continued through the years to support this method, mainly in the academic research arena. While still supporting our historical and philosophical Holter-bin approach, in 2013 we plan to deliver a couple of new Holter-based tools. One of these will be our beat-to-beat module which will be upgraded to incorporate our signal processing library BRAVO and for which a completely redesigned report, inclusive of hysteresis effect compensation, will be developed. More news on the next issue of AMPS-QT.

[1] Merri M, Moss AJ, Benhorin J, Locati E, Alberti M, Badilini F. **Relation Between Ventricular and Cardiac Cycle Length During 24-Hour Holter Recordings**, *Circulation* 1992; 85(5):1816-1821.

AMPS Notebook

Fabio Badilini has recently attended the **American Heart Association**, Scientific Session held from November 3rd to 7th in Los Angeles, California.

At the beginning of December, Fabio Badilini took part in the **CSRC Annual Meeting**, held at the FDA White Oak facility in the Washington DC area.

AMPS Recommends

In this issue we recommend an extremely interesting article published on the November issue of the Journal of Electrocardiology. The first author of the manuscript is Licia Iacoviello, the head of The Moli-Sani Project (www.moli-sani.org), a unique longitudinal population cohort from Molise, a region from central Italy, that has already recruited more than 24,000 subjects, aged 35 or higher. The goal of this huge repository is to evaluate the risk factors linked to chronic-degenerative disease with particular regard to CVD and cancer and intermediate metabolic phenotypes such as hypertension, dyslipidemia, diabetes, obesity, and metabolic syndrome. In addition to all the biological data samples, all the recruited members of Moli-Sani undertook 10-seconds digital ECGs which are currently being analyzed and we are proud to collaborate with Licia and her team on some of the ECG-related projects. We believe that in addition to serve as a tremendous support for epidemiological research, the Moli-Sani database could also constitute a valuable benchmark to assess the accuracy of ECG measuring algorithms in large and heterogeneous populations.

Iacoviello L et al. (2012) The Moli-sani project: computerized ECG database in a population-based cohort study. J Electrocardiol 45(2012), 684-689.

The paper can be downloaded from the AMPS website.

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AMPS People

Last, but far from least: Alessandra Betalli.



Alessandra received an Italian degree in Foreign Languages in 1986; after that she spent over 10 years abroad between the US, namely Rochester, NY and Paris, France, where she obtained recognition degrees in both languages. Alessandra is the head of AMPS Accounting Department. Her e-mail address is: betallia@amps-llc.com.

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