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

Most if not all of our readers, are surely aware that cardiac safety considerations do not end with the approval of a drug. As the Institute of Medicine has noted, "The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug: preapproval clinical trials do not obviate continuing formal evaluation after approval." In this issue of AMPS-QT we host a contribution by Dr. Rick Turner, DSc, FASH, FACC, FESC, Chief Scientific Advisor at QuintilesIMS Cardiac Safety Center of Excellence, who strongly believes that embedding the discipline of cardiac safety into mainstream medical education is now essential. His article is a Call to Action for the international cardiac safety community to make this into a reality.

Before joining Quintiles, Dr. Turner served as the chairman of the Department of Clinical Research at Campbell University School of Pharmacy. Prior to this, he was a Principal Clinical Submissions Scientist at GlaxoSmithKline, where he received awards for his work on the GlaxoSmithKline Clinical Trial Registry and for his contribution to new product development. Dr. Turner is keenly interested in the integration of behavioral medicine and biopharmaceutical medicine approaches for the continued enhancement of patient health and well-being. His work has been published extensively in several peer-reviewed and professional journals. He has also authored six books addressing statistical and methodological aspects of randomized concurrently-controlled clinical trials.

We believe that Dr. Turner's commendable work would invoke our readers' interest and will be thought-provoking. By means of this article and Dr. Turner's future contributions, AMPS aims to keep AMPS-QT readers updated on his efforts.

A Noteworthy Contribution:

Cardiac Safety Education: A Call to Action

By J. Rick Turner, PhD, DSc, FASH, FACC, FESC, Chief Scientific Advisor at QuintilesIMS Cardiac Safety Center of Excellence, Durham, NC, USA.

It's a pleasure to write this article for *AMPS-QT*, and I'm grateful to Dr Badilini for the opportunity to do so. I will share some thoughts on one of my personal passions and goals: providing dedicated cardiac safety education to the next generation of physicians, pharmacists, and nurses. Before doing so, I will summarize some of the recent advances in the field of cardiac safety that would comprise parts of an educational curriculum. Important considerations in clinical practice will also be addressed.

It is an unfortunate but immutable fact that no biologically active drug is free from the possibility of causing adverse reactions, including cardiac and vascular reactions, in certain individuals who are genetically and/or environmentally susceptible.[1] Indeed, as Link and colleagues observed, "One of the most feared complications in medicine is sudden death caused by drug-induced proarrhythmia. Accordingly, concerted efforts have been made to define a drug's proarrhythmic potential before

regulatory approval."[2] Many readers of *AMPS-QT*, authors who have published here, and organizations discussed in the AMPS articles have played instrumental roles in these cardiac safety efforts.

Cardiac safety considerations do not stop upon a drug's approval. As the Institute of Medicine has noted, "The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug: preapproval clinical trials do not obviate continuing formal evaluation after approval."[3] It is vital to remain alert to unexpected cardiac adverse drug reactions during a drug's entire time on the market. Pharmacovigilance strategies (both passive and active) have been employed for many years in this regard. Attention is now turning to complementary approaches, one of which is social listening, the act of monitoring public conversations on the internet to inform our understanding of medical product safety in a better manner.[4]

Having reviewed these topics, attention then turns to the main focus of this paper: a Call to Action to develop and implement comprehensive cardiac safety education for healthcare providers with regard to the judicious use of drugs that have a known potential to be unsuitable for patients with certain clinical characteristics.[5] (Patient education is also extremely important, but that is a topic for another discussion.)

Preapproval Cardiac Safety Investigations: New Approaches

The ICH S7B- and E14-driven preapproval regulatory landscape which centers around the biomarkers of reductions in the cardiac repolarizing ionic current I_{Kr} and prolongation of the QT interval as seen on the surface electrocardiogram (ECG) has been successful in that no drug with unanticipated potential for *Torsades de Pointes* has entered the market since their adoption. However, the paradigm's Thorough QT/QT study is highly sensitive but not very specific for predicting QT prolongation, and many pharmaceutical companies may have unnecessarily terminated the development of potentially useful drug molecules.[6, 7]

Collaboration between the Cardiac Research Safety Consortium (CSRC) and the International Consortium for Innovation and Quality in Pharmaceutical Development led to a study providing support for the alternate approach of employing QTc exposure-response modeling, and hence a move towards intensive ECG evaluation in early-phase drug development.[8-10] The third revision of the ICH E14 "Questions & Answers" document,[11] released in December 2015, provided widespread acknowledgment of the benefits of this methodology and offered an alternative primary methodology for the evaluation of a drug's clinical QTc prolongation liability (see also Bloomfield[12]). Regulatory agencies have found this approach acceptable.[13, 14]

The Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative comprises an integrated set of investigations that may lead to modifications in the preapproval nonclinical cardiac safety landscape. The first major presentation and discussion of this initiative occurred at a July 2013 Think Tank co-sponsored by CSRC, HESI, and the US FDA,[15] and multiple related reports have followed.[16-26] In December 2015, the ICH Assembly endorsed the establishment of the E14/S7B Discussion Group, which includes nonclinical and clinical experts brought together to discuss advances in science and methods related to the clinical assessment of QT prolongation and to continue discussion of CiPA. The Group's Work Plan lists "Preliminary recommendation to ICH Assembly regarding whether to re-open ICH E14 and S7B for complete revision" as an Anticipated Milestone for December 2017.[27]

Postapproval Cardiac Safety Investigations: New Frontiers

An illustrative example of new lines of investigation in this realm is discussed in an upcoming paper by Seifert and colleagues that captures discussions at a Think Tank entitled "Enabling Social Listening for Cardiac Safety," held in June 2016 and jointly sponsored by the CSRC and the Drug Information Association.[28] The meeting's goals were to explore current methods of collecting and evaluating social listening data and to consider their applicability to cardiac safety surveillance. Regulators from the US

FDA and the United Kingdom's Medicines and Healthcare Products Regulatory Agency participated along with representatives from industry, academia, and patient groups. While social media represents a novel, global, and publicly accessible source of data, and therefore holds tremendous potential in this regard, its ability to provide reliable post-marketing safety data requires further clarification and verification. One anecdotal example of challenges in this field concerns colloquial speech: if, following a visit to a car dealership, an individual reports on the lines that "The price of the car I wanted gave me a heart attack," it is unlikely that the person actually had a myocardial infarction.[28]

Clinical Practice: How Well do Prescribing Physicians Do?

All the preapproval cardiac safety investigations performed for a drug influence the drug's prescribing information (label). If a drug is approved owing to compelling evidence of efficacy and general safety at the public health level, but regulators also wish to convey information concerning potential QT prolongation liability (as we know, an imperfect predictor of *Torsades*, but nonetheless the current one of importance), such information is placed in the drug's label. Everything to this point is very important, but then the rubber hits the road: prescribers should decide if the drug has a favorable benefit–risk balance for their patients on a case-by-case basis by taking into account multiple clinical considerations. A key question of interest therefore becomes: How well do they do in this regard? Studies reported in the literature provide a disconcerting answer:[29-31] See Dhanani and colleagues[32] for commentary.

Fortunately (if that is the right word), the occurrence of drug-induced *Torsades* itself (rather than just QT/QTc prolongation) typically requires multiple contributing factors to be present at the same time. Clinical risk factors include female sex, structural heart disease, metabolic and electrolyte abnormalities (particularly hypokalemia and hypomagnesemia), bradycardia and conduction disease, increased drug bioavailability, and inherited long QT syndrome.[33] Taking concomitant medications that prolong the QT interval may also be a risk factor. Hence, an injudicious prescribing decision may not have serious consequences. Nonetheless, avoiding such decisions via more thorough cardiac safety education is a worthy goal (see also Trinkley and colleagues[34] and Li and Ramos[35]).

Cardiac Safety Education

Embedding the discipline of cardiac safety into mainstream medical education—where 'medical' covers physicians, pharmacists, nurses, and allied health professionals—is now essential, and this article represents a Call to Action to the international cardiac safety community to do so. Admittedly, getting this topic into multiple professional school curricula is not likely to be an easy task since most schools seem to regard their curricula as already full to overflowing.[5] Nonetheless, it is incumbent upon those of us in the field of cardiac safety to work diligently in this regard: it is imperative to enable healthcare professionals to do everything possible to eliminate adverse cardiac drug reactions while also providing optimal therapeutic benefit to their patients.[32]

Drugs prescribed by physicians are dispensed by pharmacists. Given their expert knowledge of pharmacology, additional education and hence awareness of the multiple aspects of cardiac safety would enable clinical pharmacists to be influential arbiters of safer prescribing decisions.[32] Before joining my present company I was a professor in a school of pharmacy, and, for several years, Chairman of its Department of Clinical Research. I am also a member of pharmacy and clinical pharmacology organizations. Accordingly, with regard to my Call to Action, I will be focusing initial attention on pharmacy schools, and hoping that success there will pave an easier path into other professional schools.

What I am proposing could be as simple as creating a relatively small set of PowerPoint slides and lecture notes (ideally endorsed by multiple relevant academic societies and organizations), and sending these at no cost to all medical, pharmacy, and nursing schools in a given country in the appropriate language. The most appropriate professor in each school could deliver these lectures. If there are

concerns about impinging upon existing and already-overflowing curricula, the schools could be asked at least to post the lectures on their web site, allowing self-selecting students to access them outside regular classroom time. Other possibilities include creating videos and making these available on the web sites of professional societies interested in cardiac safety, cardiac safety experts offering to go into local professional schools to give a lecture or two at no cost to the schools, and a whole host of things that I hope colleagues will suggest.

As already noted, widespread implementation of cardiac safety education in appropriate professional schools may not be easily accomplished. That said, if we harness and dedicate the intellectual and decision-influencing horsepower of our collective group of colleagues and organizations, I believe we can succeed. I am in initial discussions with several interested individuals, and, with Fabio's permission, I'll keep *AMPS-QT* readers updated. To borrow and adapt the sentiments expressed in John Lennon's song "Imagine," you may say I'm a dreamer, but, if we can get things up and running, I hope someday you'll join us, and the 'cardiac safety education world' will be as one.

References

[1] Turner JR, Karnad DR, Kothari S. Cardiovascular safety in drug development and therapeutic use: new methodologies and evolving regulatory landscapes. Switzerland: Springer International Publishing; 2017.

[2] Link MG, Yan G-X, Kowey PR. Evaluation of toxicity for heart failure therapeutics: studying effects on the QT Interval. Circ Heart Fail. 2010;3:547-555.

[3] Institute of Medicine of the National Academies. The future of drug safety: promoting and protecting the health of the public. Washington, DC: National Academies Press, 2007.

[4] Powell GE, Seifert HA, Reblin T, et al. Social media listening for routine post-marketing safety surveillance. Drug Saf. 2016;39:443-445.

[5] Turner JR. Integrated cardiovascular safety: multifaceted considerations in drug development and therapeutic use. Expert Opin Drug Saf. 2017;16:481-492.

[6] de Ponti F, Pharmacological and regulatory aspects of QT prolongation. In JR Vaz, T Klabunde (Eds), Antitargets: prediction and prevention of drug side effects. Weinheim, Germany: Wiley-VCH; 2008, pp 55–88.

[7] Zhang J, Chen H, Tsong Y, Stockbridge N. Lessons learned from hundreds of Thorough QT studies. Ther Innov Regul Sci. 2015;49:392–397.

[8] Darpo B, Garnett C, Benson CT, et al. Cardiac safety research consortium: can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward. Am Heart J. 2014;168:262–272.

[9] Darpo B, Benson C, Dota C, et al. Results from the IQ-CSRC prospective study support replacement of the Thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. 2015;97:326–335.

[10] Darpo B, Garnett C, Keirns J, Stockbridge N. Implications of the IQ-CSRC prospective study: time to revise ICH E14. Drug Saf. 2015;38:773-780.

[11] ICH. E14 Q&A(R3) - 5.1: Use of concentration response modeling of QTc Data. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_QAs_R3_presentation_Aug2016.pdf (Accessed 12 September 2017)

[12] Bloomfield DM. Incorporating exposure-response modeling into the assessment of QTc interval: a potential alternative to the Thorough QT study. Clin Pharmacol Ther. 2015;97:444–446.

[13] Nelson CH, Wang L, Fang L, et al. A quantitative framework to evaluate proarrhythmic risk in a first-in-human study to support waiver of a Thorough QT study. Clin Pharmacol Ther. 2015;98:630-638.

[14] Murphy PJ, Yasuda S, Nakai K, et al. Concentration-response modeling of ECG data from early-phase clinical studies as an alternative clinical and regulatory approach to assessing QT risk: experience from the development program of lemborexant. J Clin Pharmacol. 2017;57:96-104.

[15] Sager PT, Gintant G, Turner JR, Pettit S, Stockbridge N. Rechanneling the cardiac proarrhythmia safety paradigm: a meeting report from the Cardiac Safety Research Consortium. Am Heart J. 2014;167:292-300.

[16] Colatsky T, Fermini B, Gintant G, et al. The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative - update on progress. J Pharmacol Toxicol Methods. 2016;81:15-20.

[17] Fermini B, Hancox JC, Abi-Gerges N, et al. A new perspective in the field of cardiac safety testing

through the Comprehensive in vitro Proarrhythmia Assay paradigm. J Biomol Screen. 2016;21:1–11.
[18] Gintant G, Sager PT, Stockbridge N. Evolution of strategies to improve preclinical cardiac safety testing. Nat Rev Drug Discov. 2016;15:457-471.
[19] Johannesen L, Vicente J, Hosseini M, Strauss DG. Automated algorithm for J-Tpeak and Tpeak-Tend assessment of drug-induced proarrhythmia risk. PLoS One. 2016;11:e0166925.
[20] Johannesen L, Vicente J, Mason JW, et al. Late sodium current block for drug-induced long QT syndrome: results from a prospective clinical trial. Clin Pharmacol Ther. 2016;99:214-23.
[21] Vicente J, Stockbridge N, Strauss DG. Evolving regulatory paradigm for proarrhythmic risk assessment for new drugs. J Electrocardiol. 2016;49:837-842.
[22] Dutta S, Chang KC, Beattie KA, et al. Optimization of an in silico cardiac cell model for proarrhythmia risk assessment. Front Physiol. 2017;8:616.
[23] Gintant G, Fermini B, Stockbridge N, Strauss D. The evolving roles of human iPSC-derived cardiomyocytes in drug safety and discovery. Cell Stem Cell. 2017;21:14-17.
[24] Huang H, Pugsley MK, Fermini B, et al. Cardiac voltage-gated ion channels in safety pharmacology: review of the landscape leading to the CiPA initiative. J Pharmacol Toxicol Methods. 2017;87:11-23.
[25] Li Z, Dutta S, Sheng J, et al. Improving the in silico assessment of proarrhythmia risk by combining hERG (human ether-à-go-go-related gene) channel-drug binding kinetics and multichannel pharmacology. Circ Arrhythm Electrophysiol. 2017;10:e004628.
[26] Pugsley MK, de Korte T, Authier S, et al. Safety pharmacology methods and models in an evolving regulatory environment. J Pharmacol Toxicol Methods. 2017;87:1-6.
[27] ICH. ICH E14/S7B IWG/DG Work Plan, 26 August 2016. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_S7B_WG_Work_plan_26Aug2016.pdf (Accessed 12 September 2017)
[28] Seifert HA, Malik RE, Bhattacharya M, et al. Enabling social listening for cardiac safety monitoring: proceedings from a DIA-CSRC co-sponsored Think Tank. Am Heart J, in press.
[29] Tisdale JE, Wroblewski HA, Overholser BR, et al. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US. Drug Saf. 2012;35:459-470
[30] Franchi C, Ardojno I, Rossio R, et al: REPOSI Investigators. Prevalence and risk factors associated with use of QT prolonging drugs in hospitalized older people. Drugs Aging. 2016;33:53-61.
[31] Michels G Kochanek M, Pfister R. Life-threatening cardiac arrhythmias due to drug-induced QT prolongation: a retrospective study over 6 years from a medical intensive care unit. Med Klin Intensivmed Notfmed. 2016;111:302-309.
[32] Dhanani TC, Mantovani EH, Turner JR. Clinical pharmacists' opportunities to reduce inappropriate prescription of QT-prolonging medications: calls to action. Int J Pharm Pract. 2017;25:176-179.
[33] Vlachos K et al. An update on risk factors for drug-induced arrhythmias. Expert Rev Clin Pharmacol. 2016;9:117-127.
[34] Trinkley KE et al. QT interval prolongation and the risk of torsades de pointes: essentials for clinicians. Curr Med Res Opin. 2013;29:1719-1726.
[35] Li M, Ramos LG. Drug-induced QT prolongation and Torsades de Pointes. P T. 2017;42:473-477.

Products News

Looking forward

In Q4 2017 AMPS is planning to release:

- A new version of CER-S (v. 3.1.0.), including the following optimized platforms:
  - Continuous ECG beat detection and classification, including refined algorithm
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia

AMPS Notebook

Fabio will be attending the **CSRC Meeting** and **CSRC Think Tank** that will be held in at the FDA facility in Silver Spring, MD on October 24th and 25th.

AMPS People

Marco Denti joined AMPS in June 2016. He has a Master's degree in Industrial Engineering and has over 10 years' experience in projects development and management. He started off as an Industrial Engineer

in a manufacturing company and then progressed as a consultant in an aerospace company (Accenture for AgustaWestland). He then moved to the renewable energy sector joining Turboden, a company that designs and develops turbogenerators for biomass and geothermal applications. There he entered as a Project Manager and through the years became the Project Management Office head, coordinating a team of 7 Project Managers with a portfolio of more than 40 projects worth roughly 100 Million €. At AMPS Marco took over the role of Project Director, coordinating the software development team to ensure on-time delivery and optimization of resources allocation. Marco is passionate about Project Management and Product Development across different business sectors, where he effectively implements models and best practices assimilated through the years. When not busy managing projects, he really enjoys sports: tennis, kitesurfing and skiing are his favorites.

AMPS congratulates Marco and Simona for their very recent wedding!