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

In this issue of AMPS-QT, we proudly introduce Dr. Carlos Iribarren MD, MPH, PhD. Carlos has been a Research Scientist at the Kaiser Permanente Northern California Division of Research since 1997, and an adjunct assistant professor at the Department of Epidemiology and Biostatistics, University of California, San Francisco since 1998. Dr. Iribarren is a clinical epidemiologist and his current research interests include the genetic basis of coronary disease, biomarkers of atherosclerosis and psychosocial factors in coronary disease.

Dr. Iribarren's ECG research studies are an excellent illustration of how AMPS technology can be used effectively beyond the pharmaceutical borders. Indeed, Dr. Iribarren is an active clinical epidemiologist with primary interests in characterizing electrocardiographic features such as the QT interval in very large populations, a context where AMPS software solutions can be very handy and useful.

In one of his recently published contributions, Dr. Iribarren and his colleagues focused on the drug-induced alterations of QT interval in 59,467 subjects undertaking a comprehensive list (n=90) of selected drugs used as part of routine clinical practice and using the AMPS resting ECG tool CalECG to validate their methodology [1,2].

We have asked Dr. Iribarren to give us an overview of his findings which, we are sure, all our readers will greatly enjoy.

[1] Iribarren C, Round AD, Peng JA, Lu M, Zaroff JG, Holve TJ, Prasad A, Stang P. **Validation of a population-based method to assess drug-induced alterations in the QT interval: a self-controlled crossover study.** Pharmacoepidemiol Drug Saf. 2013 Nov; 22(11): 1222-32.

[2] Iribarren C, Round AD, Peng JA, Lu M, Klatsky AL, Zaroff JG, Holve TJ, Prasad A, Stang P. **Short QT in a Cohort of 1.7 Million Persons: Prevalence, Correlates, and Prognosis.** Ann Noninvasive Electrocardiol 2014 Sep; 19(5): 490-500.

A Noteworthy Contribution:

Validation of a Population-based Method to Assess Drug-induced Alterations in the QT Interval.

Carlos Iribarren, MD, PhD, MPH; Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA.

Prior studies examining effects of drugs on the QT interval have generally focused on single drugs or therapeutic classes, and tended to be case reports of critically ill patients, where polypharmacy is common [1]. The intent of this study was to demonstrate the ability of a linked ECG database to identify QT alterations known to occur in selected drugs and to introduce to the scientific, regulatory and drug development communities a potential resource reflecting a large, diverse and generally representative patient population.

Population and Study Design

For this study, we took advantage of a recently created database containing all the 12-lead surface ECGs that were performed on Kaiser Permanente of Northern California health plan members as part of routine outpatient or inpatient medical care. This database contains the waveforms and associated ECG output including the automatically-generated QT and RR measurements, plus associated diagnostic interpretations. The database contains 6,547,785 12-lead surface ECGs performed on 1,731,452 KPNC members as part of routine outpatient or inpatient care between January 1, 1995 and June 30, 2008. To the best of our knowledge, this is the largest ECG database in the world.

QT Measurement, Adjustment for Heart Rate and Automatic ECG Diagnostic Statements

All ECGs were obtained using cardiographs manufactured by Philips Medical Systems (Andover, Massachusetts). For this study, we extracted the raw QT interval and RR measurements that were generated from each 12-lead waveform by proprietary Philips algorithms, which are described elsewhere [2, 3]. Because of its limitations [4] and to follow current recommendations [5], we did not use the Bazett heart rate correction in our primary analyses. Instead we performed log-linear regression of raw QT on RR and then fitted correction equations within 98 strata of gender (2 groups), age (7 groups) and race/ethnicity (7 groups) to generate gender-, age- and race/ethnicity-specific heart rate-corrected QT values (denoted by QTcreg) [6]. The Pearson correlation between the Bazett-corrected QT and QTcreg was 0.93. Besides the automatic measurement of QT, we also captured in our database all the automatic ECG diagnostic statements generated by the cardiograph, as approved and edited by the attending physician at the point of care. ECG tracings with evidence of pacemakers (n=105,067), with heart rate out of physiological range (< 40 or > 180 bpm; n=51,680) and with implausible QTcreg values (< 200 or > 800 ms; n=3,968) were sequentially excluded, resulting in 6,387,070 ECGs.

A subset database was then created with person as the level of analyses (the index ECG cohort) by selecting the available ECGs among persons with only one ECG and one ECG at random among persons with more than one ECG. To implement the study design, a self-controlled cross-over study [7], we excluded subjects having only one ECG (n=627,109) and those with no ECGs prior to the index ECG (n=239,206) resulting in 906,847 subjects. We then ascertained active prescriptions as of the date of the index ECG for drugs listed in the Arizona Center for Education & Research on Therapeutics (CERT) website (www.azcert.org) as having QT liability [8] and also searched prescriptions for 6 additional drugs not listed in the Arizona CERT website: carbamazepine, primidone, phenytoin, digoxin, lidocaine and aripripazole [9]. Our final list of drugs included 94 compounds. A total of 90,523 subjects (about 10 percent) had 1 or more active prescriptions for the drugs under consideration whose prescription time window coincided with the index ECG (which we denote hereinafter "post-ECG") and had at least 1 prior ECG (which we denote hereinafter "pre-ECG"). For those with more than one prior ECGs, we selected the closest in time to the post-ECG. For each person, the pre-ECG was the first encountered ECG going back in time from the beginning of the prescription dispensing period, so the change in QTcreg between the pre- and post-ECG can be attributed to within-person exposure to the drug under consideration. If a person had more than one active prescription at the time of the index ECG, the baseline ECG was chosen using the longest prescription window. Further exclusions prior to statistical analyses included heart rate over 120 bpm (n=2,423), left or right bundle branch blocks (n=1,122), long QTcreg at the pre-ECG (n=7,072), and time between pre- and post-ECG longer than 3 years (n=20,439), resulting in a cohort of 59,476 subjects for analyses. Because of problems with stability of estimates and convergence of the models, 4 drugs with 15 users or less (solifenacin, dofetilide, isradipine, nicardipine) were excluded for further analysis, resulting in 90 drugs examined. Because medications are covered by the health plan and there is therefore little incentive for patients to go outside the plan [10], we feel that we have captured most if not all medication use.

Statistical analysis

We used mixed models for repeated measures analysis of covariance (ANCOVA) to estimate the within-person change in QTcreg between pre- and post-ECG's associated with each individual medication adjusting for age, gender, race/ethnicity, comorbidities, number of ECGs before the pre-ECG and time between pre- and post-ECGs [11]. We also estimated the proportion of

exposed subjects to each drug that developed incident long QTcreg (long QTcreg defined as > 440 ms in men or > 460 ms in women) and the proportion of patients with a QTcreg prolongation greater than 20 ms. To assess the background noise/variability in QTcreg we assembled a large control cohort of subjects (n=220,440) with at least 3 ECGs (the index ECG, one prior and one after, the prior and after ECGs within a 3-year window each way) who were not exposed to any of the drugs under consideration at any point in time between first and last ECGs. Additional analyses were performed for the drugs prolonging QTcreg more than 15 ms limiting drug exposures to single agents (in other words, those receiving concomitant prescriptions for any of the drugs under consideration were excluded).

Results

The mean age of the cohort was 56 years (SD=17 years); 66% was female, 64% white, and the largest minority was Latino (12%). The time between pre- and post-ECGs was 0.8 years, and in 77% of subjects this time was shorter than 1 year. The mean pre- and post-ECGs QTcreg were 411 ms and 423 ms, respectively. Hypertension was the most common comorbidity (61%), followed by obesity and hyperlipemia (both about 40%).

The ten most commonly prescribed medications were atenolol (n=18,322), fluoxetine (n=8,537), albuterol (n=5,433), paroxetine (n=4,531), amitriptyline (n=2,655), nortriptyline (n=2,591), ofloxacin (n=2,568), ciprofloxacin (n=1,844), sertraline (n=1,834) and digoxin (n=1,371). Only 2 drugs (levalbuterol and nicardipine) evidenced shortening of the QTcreg (less than 3 ms), but none of these shortening effects were statistically significant. There were 10 drugs associated with non-statistically significant QTcreg lengthening effect (gatifloxacin, chloralhydrate, terbutaline, isradipine, mexiletine, solifenacin, voriconazole, protryptyline, procainamide and galantamine). Statistically significant mean QTcreg prolongation ranged from 7.6 ms for aripiprazole to 25.2 ms for amiodarone. Overall, there were 3 drugs with a mean QTcreg prolonging effect greater than 20 ms (amiodarone, terfenadine and quinidine), and 11 drugs with QTcreg prolongation 15 ms of greater but less than 20 ms. In order of strength these were: trimipramine, clomipramine, disopyramide, chlorpromazine, sotalol, itraconazole, phenylpropanolamine, fenfluramine, midodrine, digoxin and procainamide.

The proportion of subjects who developed long QTcreg after drug exposure ranged from 0% among users of trimipramine, pimozide, clozapine, protriptyline, voriconazole, solifenacin, chloralhydrate, levalbuterol and nicardipine to 41% among user of amiodarone. The drugs in second, third and fourth place in regards to long QTcreg development were quinidine (40%), sotalol (27%) and procainamide (23%). The proportion of users whose QTcreg increased by 20 ms or more was highest in the case of terfenadine (86%), followed by itraconazole (68%), quinidine (66%) and trimipramine (64%). In the sensitivity analyses where we used the Bazett correction for heart rate instead of our internal regression correction, we observed similar results although prolonging effects tended to be (with a few exceptions such as clomipramine, itraconazole, midodrine among the top 15 prolongers) slightly smaller compared with the results using QTcreg.

Conclusions

We examined drug-induced QTcreg alterations of 90 compounds among more than 59 thousand patients with at least 2 ECGs followed for more than 13 years and establishes a firm basis to create a real-time, prospective active surveillance system for drug-induced QT shortening/prolongation. Because this is an initial analysis intended to inform the possibility of using this system for surveillance, further research should be undertaken to address the cardiovascular safety of these products in light of the limitations noted above.

References

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Products News

Latest Releases

In Q3 2015 we have finally released:

- The first version of ABILE algorithm for beat detection and arrhythmia assessment for Continuous ECG Recordings.
- A new version of CER-S, with the new ABILE algorithm, including the following platforms:
  - Continuous ECG beat detection and classification
  - ECG beat editor
  - Arrhythmia detection and Arrhythmia editor

Looking forward

In Q4 of 2015 AMPS is planning to release:

- A new version of our 12-leads measuring algorithm, BRAVO, taking advantage of the benchmark study we have performed between Q4 2014 and Q2 2015.
- A new version of CalECG, Fat-QT and TrialPerfect with the latest version of BRAVO algorithm.

AMPS Notebook

Fabio attended **Computing in Cardiology** Confernece and **STAFF** meeting, held in Nice, France in early September 2015.

In Nice, Fabio, together with other industry players, was involved in an open round table to discuss the future of the PDF-ECG format, covered in AMPS-QT Issue 23 with the editorial of Dr. Sassi from the University of Milan.

AMPS is one of the pioneer promoters and will continue to support this initiative; we will soon start to support PDF-ECG within our product line. Look for more news and updates on the next issues of AMPS-QT.

Fabio Badilini will be attending the **American Heart Association**, Scientific Session, that will be held from November 7th to 11th in Orlando, FL.

He will also be attending **CSRC Annual Meeting** that will be held in Washington DC on December 2nd and 3rd.