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Coupling Data Mining and Laboratory Experiments to Discover Drug Interactions Causing QT Prolongation

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ABSTRACT

BACKGROUND QT interval-prolonging drug-drug interactions (QT-DDIs) may increase the risk of life-threatening arrhythmia. Despite guidelines for testing from regulatory agencies, these interactions are usually discovered after drugs are marketed and may go undiscovered for years.

OBJECTIVES Using a combination of adverse event reports, electronic health records (EHR), and laboratory experiments, the goal of this study was to develop a data-driven pipeline for discovering QT-DDIs.

METHODS 1.8 million adverse event reports were mined for signals indicating a QT-DDI. Using 1.6 million electrocardiogram results from 380,000 patients in our institutional EHR, these putative interactions were either refuted or corroborated. In the laboratory, we used patch-clamp electrophysiology to measure the human ether-à-go-go-related gene (hERG) channel block (the primary mechanism by which drugs prolong the QT interval) to evaluate our top candidate.

RESULTS Both direct and indirect signals in the adverse event reports provided evidence that the combination of ceftriaxone (a cephalosporin antibiotic) and lansoprazole (a proton-pump inhibitor) will prolong the QT interval. In the EHR, we found that patients taking both ceftriaxone and lansoprazole had significantly longer QTc intervals (up to 12 ms in white men) and were 1.4 times more likely to have a QTc interval above 500 ms. In the laboratory, we found that, in combination and at clinically relevant concentrations, these drugs blocked the hERG channel. As a negative control, we evaluated the combination of lansoprazole and cefuroxime (another cephalosporin), which lacked evidence of an interaction in the adverse event reports. We found no significant effect of this pair in either the EHR or in the electrophysiology experiments. Class effect analyses suggested this interaction was specific to lansoprazole combined with ceftriaxone but not with other cephalosporins.

CONCLUSIONS Coupling data mining and laboratory experiments is an efficient method for identifying QT-DDIs. Combination therapy of ceftriaxone and lansoprazole is associated with increased risk of acquired long QT syndrome. (J Am Coll Cardiol 2016;68:1756–64) © 2016 by the American College of Cardiology Foundation.

Torsades de pointes is a ventricular tachycardia that can result in sudden death (1) and occurs as an adverse effect of more than 40 medications that prolong the QT interval, referred to as acquired long QT syndrome (LQTS) (2). The U.S. Food and Drug Administration (FDA) has established strict guidelines for evaluating the risk of acquired LQTS for new compounds when

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administered individually. Nonantiarrhythmic compounds that increase the QT/QTc interval by 20 ms or more are unlikely to be approved, and a compound associated with an increase of 10 ms or more would face many challenges (3). Even a 5 ms increase would prompt an evaluation of the risks and benefits of the new compound (3). Studies of both cardiac and noncardiac compounds found that a QTc interval above 500 ms is associated with significant risk of Torsades de pointes (4,5).

Acquired LQTS is of particular concern when it is not anticipated and occurs as the result of a QT interval-prolonging drug-drug interaction (QT-DDI) (2,6). QT-DDIs are not routinely evaluated preclinically and can go undiscovered for years. For example, quetiapine (an antipsychotic agent) was on the market for nearly 10 years before reports of a QT-DDI with methadone (an analgesic agent) prompted investigation into a possible mechanism (7). It took 3 more years before a label change was made to caution against the use of quetiapine in combination with other drugs known to prolong the QT interval.

SEE PAGE 1765

Large clinical databases, such as electronic health records (EHR), represent an opportunity to rapidly detect QT-DDIs and save lives (8,9). Drug safety algorithms could be applied to health record data in near real time, flagging potentially dangerous drug interactions before they become widespread. Furthermore, these analyses are in situ and therefore focus on the most important drug combinations: those that are actually used in clinical practice. Unfortunately, analysis of medical records is complex, due to issues of missing data, noise, and bias (10). This leads to high false positive rates and algorithms that often will mislead health care providers. Laboratory experiments, especially if they are high-throughput, can be used to screen data-mined hypotheses for plausibility. Following observational analysis with confirmatory prospective experiments can remove the spurious signals, enabling clinically useful discoveries (11).

We developed a data science pipeline to mine potential QT-DDIs from clinical databases. In this pipeline, we combine evidence of QT-DDIs from the FDA Adverse Event Reporting System (FAERS) and the EHR at New York-Presbyterian/Columbia University Medical Center (CUMC-EHR). We identified a putative interaction between lansoprazole (a proton-pump inhibitor [PPI]) and ceftriaxone (a cephalosporin antibiotic). Importantly, this is an interaction that would not have been suspected using current surveillance methods. We used patch-clamp electrophysiology of cells stably expressing human ether-à-go-go-related gene (hERG) channels to establish a physiological mechanism. We further confirmed the specificity of our pipeline by also investigating the combination of cefuroxime (another cephalosporin) and lansoprazole, a drug pair that did not have evidence of an interaction in FAERS. In the clinic, patients on the combination of ceftriaxone and lansoprazole had 12 ms (95% confidence interval [CI]: 7 to 15 ms) longer QTc intervals than patients exposed to either drug alone and were 1.4 times as likely to have a QTc interval above 500 ms. The negative control showed no significant effect. A QT-DDI between ceftriaxone and lansoprazole has the potential for significant morbidity and mortality.

ABBREVIATIONS AND ACRONYMS

APD70 = action potential duration at 70% of repolarization

DDI = drug-drug interaction

ECG = electrocardiogram

EHR = electronic health records

FAERS = Food and Drug Administration adverse event reporting system

hERG = human ether-à-go-go-related gene

LQTS = long QT syndrome

PPI = proton-pump inhibitor

QT-DDI = QT interval-prolonging drug-drug interaction

METHODS

DATA SOURCES. We used 2 independent databases to investigate possible QT-DDIs. The first database (Twosides) was a derivative of 1.8 million adverse event reports from FAERS mined for evidence of adverse drug-drug interactions that could not be explained by the individual effects of the drugs (12). The second database consisted of 1.6 million electrocardiograms (ECGs) from 382,221 patients treated at New York-Presbyterian/CUMC between 1996 and 2014. To obtain the heart rate-corrected QT (QTc) intervals, we wrote a parser to automatically extract the patient identifier, laboratory date, and QTc value from the ECG reports. QTc values were calculated using Bazett's formula. We manually checked 50 abnormal ECGs (defined as QTc >500 ms) to confirm we were extracting the correct values and found that the parser obtained 100% precision and recall. We implemented the pipeline using Python 2.7.9 (Python Foundation, Wilmington, Delaware) and R version 3.2.2. (R Foundation for Statistical Computing, Vienna, Austria).

IDENTIFICATION OF CANDIDATE QT-DDIs. We used the side effect reporting frequencies in Twosides to find drug pairs significantly over-reported with the 6 adverse events in the standardized MedDRA (Medical Dictionary for Regulatory Activities) query for "Torsade de Pointes/QT prolongation"; we call this the direct evidence model (12). However, most drug pairs are not directly reported with QT prolongation. In addition, we performed latent signal detection, a method we have previously validated (13,14), to

identify candidate QT-DDIs that lacked prior direct evidence. To perform latent signal detection, we used machine learning to define and validate a side effect profile of 13 side effects associated with known QT-prolonging compounds. Some of these latently identified side effects (such as arrhythmia and rhabdomyolysis) are positively correlated with QT interval prolongation, whereas others (such as hemorrhage and myocardial infarction) are negatively correlated (**Figure 1B**). We previously validated the method using drug pairs containing a known QT-prolonging drug (2) and demonstrated high specificity and sensitivity (Online Figure 1). We then scanned for novel drug interactions in the TWOSIDES database that matched the side effect profile; we refer to this as indirect evidence. We scored each drug pair for the amount of both direct and indirect evidence.

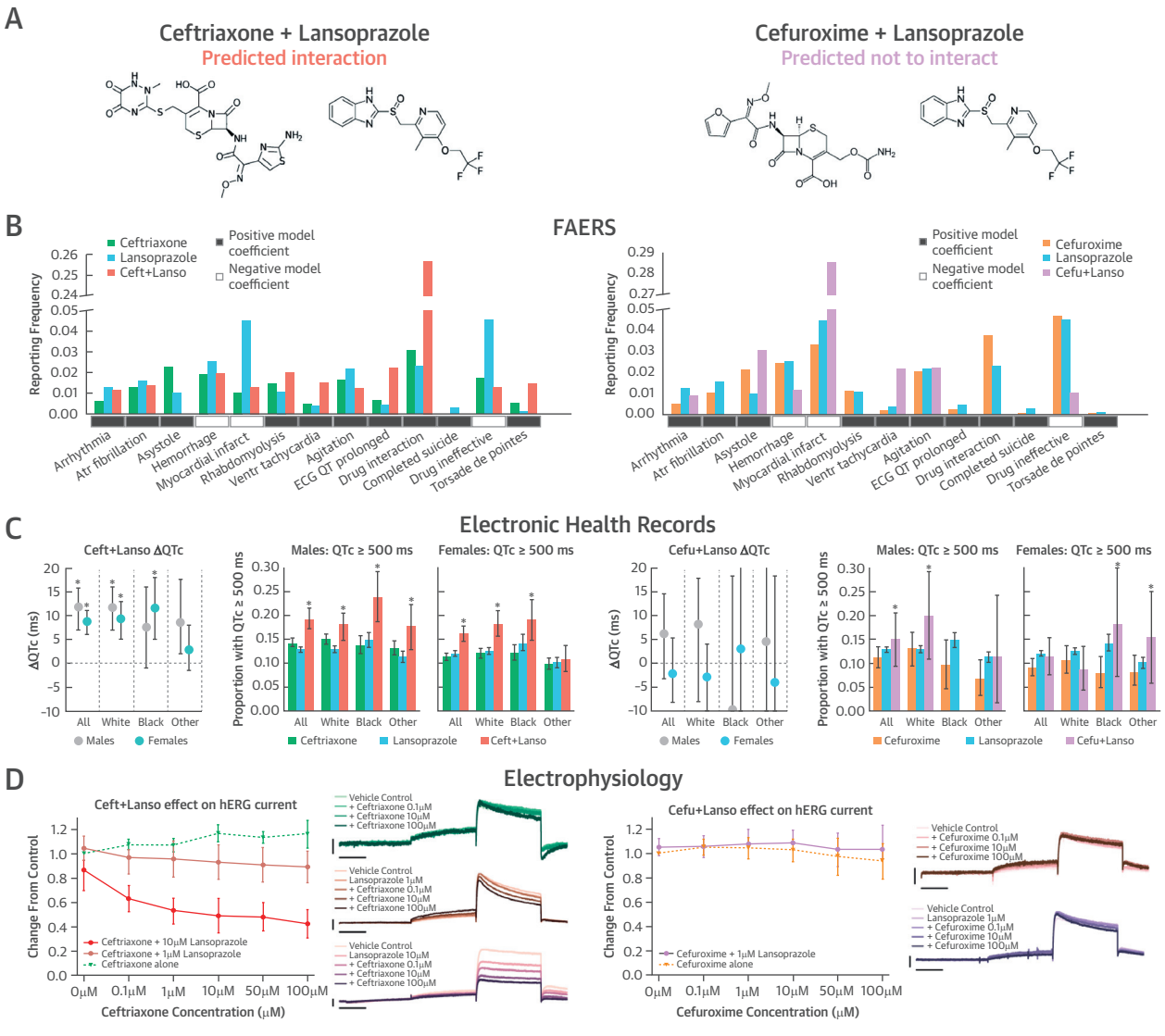
EVALUATION OF CANDIDATE QT-DDIs USING THE EHR. We attempted to corroborate (or refute) each of the candidate QT-DDI hypotheses using the heart rate-corrected QTc values from ECGs stored in the CUMC-EHR. For each candidate drug-drug interaction, we defined an exposed cohort and 2 control cohorts. Those patients included in the exposed cohort were administered both of the drugs within a 7-day window. Those in the control cohorts had evidence of exposure to only 1 of the 2 drugs ever in their records. Only patients who had at least 1 ECG in the following 36 days after drug exposure (either combination or single) were included. Corroboration required that we found significantly longer heart rate-corrected QTc intervals in patients on combination treatment compared with patients on either drug alone. The CUMC-EHR uses Bazett's formula by default; we also evaluated the change in QT interval using the Fridericia, Framingham, and Hodges correction formulae (15). Because the distributions of QTc intervals were non-normal, we assessed significance using a Mann-Whitney *U* test with a Bonferroni correction for multiple hypothesis testing. We further verified that this effect could not be explained by concomitant medications (analysis of covariance with concomitant medications modeled as categorical variables) (14). This analysis was stratified by sex because QT interval durations are known to differ between men and women (16). We evaluated the effects of each drug pair both on individual races and on all races combined (Mann-Whitney *U* test). We also performed a post hoc power analysis to estimate our ability to detect a change in QTc interval for the sample and effect sizes present in our EHR (17). Only those QT-DDIs corroborated by the EHR data (in either men, women, or both) were considered for laboratory analysis.

PATCH-CLAMP ELECTROPHYSIOLOGY. QT-prolonging drugs have in common the ability to block the hERG channel (which conducts I_{Kr}) in the heart. We evaluated the combination of ceftriaxone and lansoprazole by performing patch-clamp electrophysiology of cells stably expressing I_{Kr}. Using an automated patch-clamp system (PatchLiner, Nanion, Germany) in voltage clamp mode, we examined the concentration-dependent block of the I_{Kr} current by each drug individually, as well as in combination, using dimethyl sulfoxide as vehicle control (**Figure 1D**). We applied a voltage protocol with a step to +40 mV, followed by a return to −40 mV, to elicit the inward-rectifying tail current. This protocol was repeated every 20 s for the length of the experiment, and after 10 consecutive sweeps in each concentration, the concentration was increased. We then averaged the current at the end of each drug application and normalized it to the control to measure the block by each compound. We assessed significance by using a test of repeated measures on the log-normalized block percentages.

We performed patch-clamp electrophysiology experiments as described for ceftriaxone alone, lansoprazole alone, and ceftriaxone and lansoprazole combined, and similarly for the negative controls of cefuroxime alone and cefuroxime and lansoprazole combined. We evaluated the ability of ceftriaxone or cefuroxime to block the hERG channel at concentrations of 0.1, 1, 10, 50, and 100 μM. For lansoprazole, we evaluated at 0.1, 1, and 10 μM. We performed 3 combination experiments. For the combination of ceftriaxone and lansoprazole, we held lansoprazole constant at either 1 μM or 10 μM and increased the dose of ceftriaxone stepwise from 0.1 to 100 μM. To evaluate our negative control of cefuroxime and lansoprazole, we held lansoprazole constant at 1 μM and increased the dose of cefuroxime stepwise from 0.1 to 100 μM. The concentrations tested were chosen to include the range of plasma concentrations usually reached during routine clinical use of the drugs (1.9 to 3.9 μM for lansoprazole, 24 to 228 μM for ceftriaxone, and 35 to 428 μM for cefuroxime) (18–21).

COMPUTATIONAL MECHANISTIC MODEL. We used a computational model of the human ventricular myocyte (22) to simulate the action potential for the hERG block we observed for ceftriaxone, lansoprazole, and the combination from our laboratory experiments. We ran the model for a ventricular action potential paced at 1 Hz with baseline conditions and 10% or 55%

FIGURE 1 Data Science and Experimental Pipeline for Identifying and Validating QT-DDIs



(A) Chemical structures for ceftriaxone (cephalosporin) and lansoprazole (proton pump inhibitor), which we predicted would have a QT-DDI. We predicted cefuroxime (cephalosporin) and lansoprazole not to interact. **(B)** QT-DDI discovery in FAERS: data-driven side effect profile containing latent evidence of a QT-DDI (**solid boxes** = positive correlation with QT prolongation; **open boxes** = negative correlation). Each bar represents the reporting frequency of a given side effect in FAERS for ceftriaxone **(green)**, lansoprazole **(blue)**, cefuroxime **(orange)**, ceftriaxone + lansoprazole **(red)**, and cefuroxime + lansoprazole **(purple)**. **(C)** Retrospective corroboration in electronic health records. **(Left)** Differences in QTc interval (mean ± 95% CI) between cases (patients prescribed the drug pair) and controls (patients on only 1 drug). We stratified the analysis by sex (men = **gray**; women = **teal**) and evaluated all races combined, as well as whites, blacks, and "other, including Hispanic" separately. The **asterisk** indicates the change in QTc intervals is statistically significant (Mann-Whitney *U* test with Bonferroni correction). We obtained 95% CIs by bootstrapping case and control QTc distributions and calculating the change in median QTc for each iteration. **(Right)** Percentage of patients with a QTc interval ≥500 ms (mean ± 95% CI), stratified by sex and race. The **asterisk** indicates the combination had a significantly greater proportion of patients with a QTc interval ≥500 ms than either drug alone (independent samples Student *t*-test with Bonferroni correction, comparing means of single drug and combination therapy percentage$_{\geq 500}$ distributions generated using bootstrapping). **(D)** Experimental validation using patch-clamp electrophysiology. **(Left)** Change in hERG current from control (mean ± SD) for increasing concentrations of cephalosporin alone **(dashed line)**, and increasing concentrations of cephalosporin in the presence of a single concentration of lansoprazole **(solid lines)**. **(Right)** Representative traces from each patch-clamp electrophysiology experiment. **(Top to bottom)** hERG channel current in the presence of vehicle only (control), and then cephalosporin at 3 concentrations (0.1, 10, and 100 μM); hERG channel current in the presence of lansoprazole alone and then in combination with progressively increasing concentrations of cephalosporin. CI = confidence interval; other abbreviations as in Central Illustration.

TABLE 1 Demographic and Clinical Characteristics of Cohort

	Men	Women
Combination of ceftriaxone + lansoprazole		
n	934	1,414
Demographic		
Age, yrs	61.3 ± 16.9	66.5 ± 18.5
% Race distribution		
White	57.3	52.9
African American	18.9	20.2
Other/unknown	23.8	26.9
QTc, ms	458 (398-588)	457 (401-571.7)
% Patients with QTc ≥500 ms	19.27	16.34
Combination of cefuroxime + lansoprazole		
n	107	228
Demographic		
Age, yrs	66.1 ± 15.7	67.6 ± 17.9
% Race		
White	56.1	60.1
African American	13.1	14.9
Other/unknown	30.8	25.0
QTc, ms	450 (393.6-579.4)	443.5 (398.7-579.2)
% Patients with QTc ≥500 ms	14.95	11.40
Ceftriaxone only		
n	5,734	6,850
Demographic		
Age, yrs	59.5 ± 17.9	63.7 ± 19.8
% Race		
White	46.6	45.1
African American	19.0	18.4
Other/unknown	34.4	36.5
QTc, ms	446 (394-566)	448 (398-560)
% Patients with QTc ≥500 ms	14.21	11.43
Cefuroxime only		
n	636	957
Demographic		
Age, yrs	61.5 ± 17.6	66.0 ± 19.3
% Race		
White	54.1	50.3
African American	20.6	19.3
Other/unknown	25.3	30.4
QTc, ms	435 (391.9-552.1)	439 (397-551.1)
% Patients with QTc ≥500 ms	11.16	9.09
Lansoprazole only		
n	12,271	13,074
Demographic		
Age, yrs	60.0 ± 15.8	63.1 ± 17.7
% Race		
White	60.8	54.6
African American	13.9	16.7
Other/unknown	25.3	28.7
QTc, ms	443 (395-572)	445 (399-569)
% Patients with QTc ≥500 ms	12.84	12.07

Values are n, mean ± SD, or median (95% confidence interval).

block of hERG current (chosen using the current block observed in the electrophysiology experiments). We evaluated the action potential duration at 70% of repolarization (APD70).

RESULTS

CANDIDATE QT-DDI DISCOVERY VIA DATA SCIENCE. We detected 889 putative signals in FAERS, of which 34 (1.42× more than expected by chance, $p = 0.003$) were corroborated by the CUMC-EHR, after multiplicity correction. Twenty-six signals were eliminated by confounder analysis for concomitant medications. The remaining 8 combinations could not be explained by concomitant medications and were not previously associated with acquired LQTS (14). We prioritized the combination of ceftriaxone and lansoprazole for experimental validation, as lansoprazole is available over the counter and is one of the top 200 most-prescribed drugs (totaling over 2.6 million prescriptions in 2010) (23). An interaction with a PPI could therefore have a profound impact on patient safety. As a negative control, we chose to evaluate the combination of cefuroxime and lansoprazole as, according to our algorithm, it did not match the side-effect profile for QT prolongation in FAERS (**Figures 1A and 1B**).

CO-MEDICATION OF CEFTRIAXONE AND LANSOPRAZOLE IS ASSOCIATED WITH PROLONGED QT IN THE EHR. Overall, the QTc intervals (Bazett's correction) for male patients taking this combination were 12 ms (95% CI: 7 to 15 ms; $n = 934$) longer than those of patients taking either drug alone ($p < 0.001$); for female patients, QTc intervals for patients taking the combination were 9 ms (95% CI: 5.2 to 11.3 ms; $n = 1,414$) longer than those of patients taking either drug alone ($p < 0.001$) (**Figure 1C**). We evaluated QT interval prolongation post hoc using the Fridericia, Framingham, and Hodges correction formulae. In men, all 3 formulae were significant, with $p < 0.01$ (Online Table 1), and in women, Fridericia and Hodges formulae were significant, with $p < 0.01$. When stratifying by race in addition to sex, we observed the largest effects were in white men (12 ms increase; 95% CI: 6.5 to 17 ms; $p < 0.001$) and in black women (12 ms increase; 95% CI: 3.7 to 18.5 ms; $p < 0.001$). We performed a regression analysis which confirmed the increased sensitivity to the drug pair in white patients ($p = 0.049$) (Online Table 2). In 19% of men taking the combination, the QTc was ≥500 ms, an accepted threshold for clinical concern (3), compared with 14% ($p < 0.001$) of patients taking only 1 drug (**Table 1**).

Applying the same case-control analysis to cefuroxime and lansoprazole showed no significant differences in QTc intervals for either men (7 ms increase; 95% CI: −4.5 to 17 ms, $n = 107$; $p = 0.167$) or women (1.5 ms decrease; 95% CI: −9.3 to 4.3 ms;

n = 228; p = 0.155). We observed no significant changes in QTc interval when further stratifying by race. See Figure 1C for complete results.

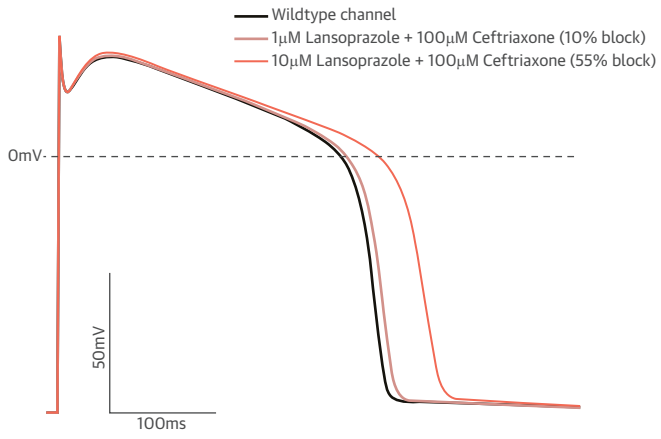
We performed sample-size and effect-size analyses, which demonstrated that, with 100 patients prescribed either combination, we would be able to detect a 10 ms QT interval prolongation with 80% power; with 1,000 patients, the same effect size could be detected with 100% power (Online Figure 2).

A total of 603 patients taking ceftriaxone and lansoprazole had ECGs both before and after they started combination treatment. To control for baseline confounders, we performed a paired analysis comparing each of these patient's highest QTc interval from ECGs performed up to 36 days before and after exposure to ceftriaxone and lansoprazole. We stratified the analysis by both sex and race. We observed a statistically significant increase in QTc interval for both white men (14.0 ± 4.0 ms increase; $p = 6.56 \times 10^{-4}$) and white women (12.9 ± 3.3 ms increase; $p = 1.03 \times 10^{-4}$). We observed no significant change in QTc interval for patients prescribed our negative control. See Online Table 3 for complete results.

IN COMBINATION, CEFTRIAXONE AND LANSOPRAZOLE BLOCK THE hERG CHANNEL. Using a test of repeated measures, we found no significant effect from ceftriaxone on the hERG channel (p = 0.096). We found a significant effect from lansoprazole alone ($p = 1.63 \times 10^{-4}$), causing a drop in current to 86.6 ± 16.7% at 10 μM (no effect at 1 or 0.1 μM). In the presence of 1 μM lansoprazole, ceftriaxone caused a dose-dependent drop in current (96.8 ± 13.2% of control at 0.1 μM; and 89.3 ± 13.2% at 100 μM; $p = 1.07 \times 10^{-4}$). In the presence of 10 μM lansoprazole, ceftriaxone caused a dose-dependent drop in current (63.1 ± 10.9% of control at 0.1 μM; and 42.4 ± 11.6% at 100 μM; $p < 3.45 \times 10^{-5}$) (Figure 1D, left). For our negative control, we saw a small block in cefuroxime alone (94.0 ± 14.8% of control at 100 μM cefuroxime; $p = 5.62 \times 10^{-5}$) but no dose-dependent response of cefuroxime combined with 1 μM lansoprazole (p = 0.083) (Figure 1D, right).

COMPUTATIONAL MODEL RECAPITULATES CLINICAL OBSERVATIONS. Using the hERG current blocks observed in the electrophysiology experiments as input to the computational model, the APD prolongation (measured as APD70) was 9 ms for the combination of 1 μM lansoprazole and 100 μM ceftriaxone and 50 ms for 10 μM lansoprazole and 100 μM ceftriaxone (Figure 2). For the combination of 1 μM lansoprazole and 100 μM cefuroxime, the APD70 was shortened by 2 ms.

FIGURE 2 Results of the Computational Model of Ventricular Epicardial Myocytes



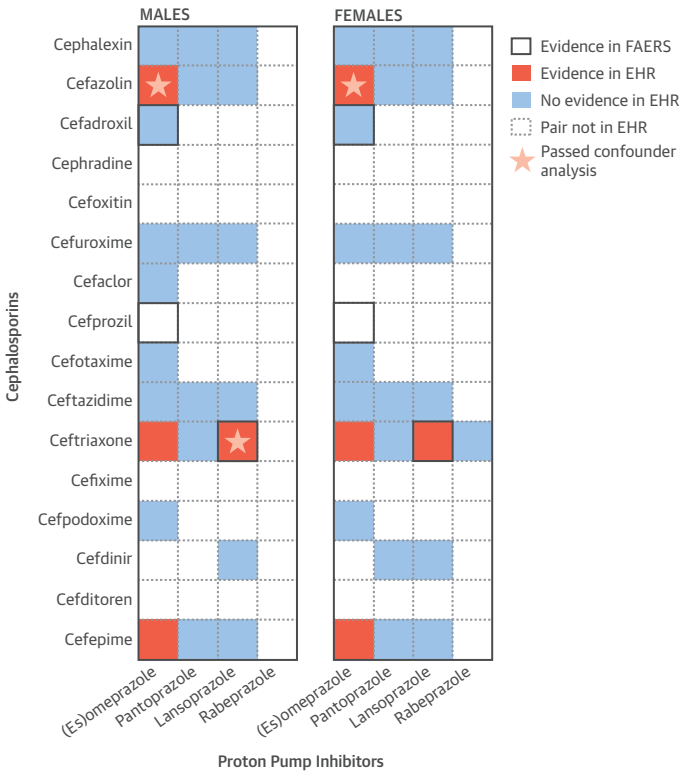
The APD prolongation (measured as APD70) for each case are 9 ms and 50 ms, simulating 1 μM lansoprazole + 100 μM ceftriaxone and 10 μM lansoprazole + 100 μM ceftriaxone, respectively. Briefly, the model was run for a ventricular action potential paced at 1 Hz with baseline conditions **(black)** and 10% or 55% block of peak hERG current (**brown and red** respectively). APD70 = action potential duration at 70% of repolarization; other abbreviations as in Central Illustration.

NO EVIDENCE OF CLASS EFFECTS BETWEEN CEPHALOSPORINS AND PPIs. Given our identification of a putative drug interaction between a cephalosporin antibiotic and a PPI, we systematically evaluated all combinations of cephalosporins and PPIs for evidence of a drug interaction in FAERS, EHR, or both (Figure 3). The combination of ceftriaxone and lansoprazole in men was the only drug pair that had evidence in both FAERS and the EHR that also passed our confounder analysis for concomitant medications.

DISCUSSION

NEW DATA SOURCES PRESENT NEW AVENUES FOR DISCOVERY. Data science and large clinical databases present new opportunities to discover adverse drug effects and drug-drug interactions. This is especially true in situations where traditional methods are impractical or unfeasible, as is often the case for DDIs. There are many advantages to taking a retrospective approach for detecting DDIs. The analyses are relatively rapid and inexpensive to perform, and because they are in situ, they focus on drug combinations that are actually used together in clinical practice. In particular, our use of latent signal detection to mine for DDIs using side-effect profile models allowed us to circumvent many of the limitations inherent in

FIGURE 3 Analysis of Class Effects Between Cephalosporins and PPIs



We analyzed each cephalosporin and PPI pair for evidence of an interaction in FAERS (**solid box** = drug pair matches side effect profile), EHR (**red** = patients on combination have significantly prolonged QT intervals compared with those on either drug alone; **blue** = no significant change between cases and controls; **open** = no patients on the drug pair in the EHR), and that the change seen in the EHR was not due to concomitant medications **(red star)**. We stratified the analysis between men and women. Only ceftriaxone and lansoprazole in men passed each of these criteria. Abbreviations as in Central Illustration.

conventional data mining approaches that rely solely on direct evidence between drug pairs and side effects (13,14). However, there are many disadvantages as well. Retrospective analysis, and data mining in particular, are notorious for their potential biases and high false discovery rates. There are simply too many potentially confounding variables to make strong statements about causal relationships.

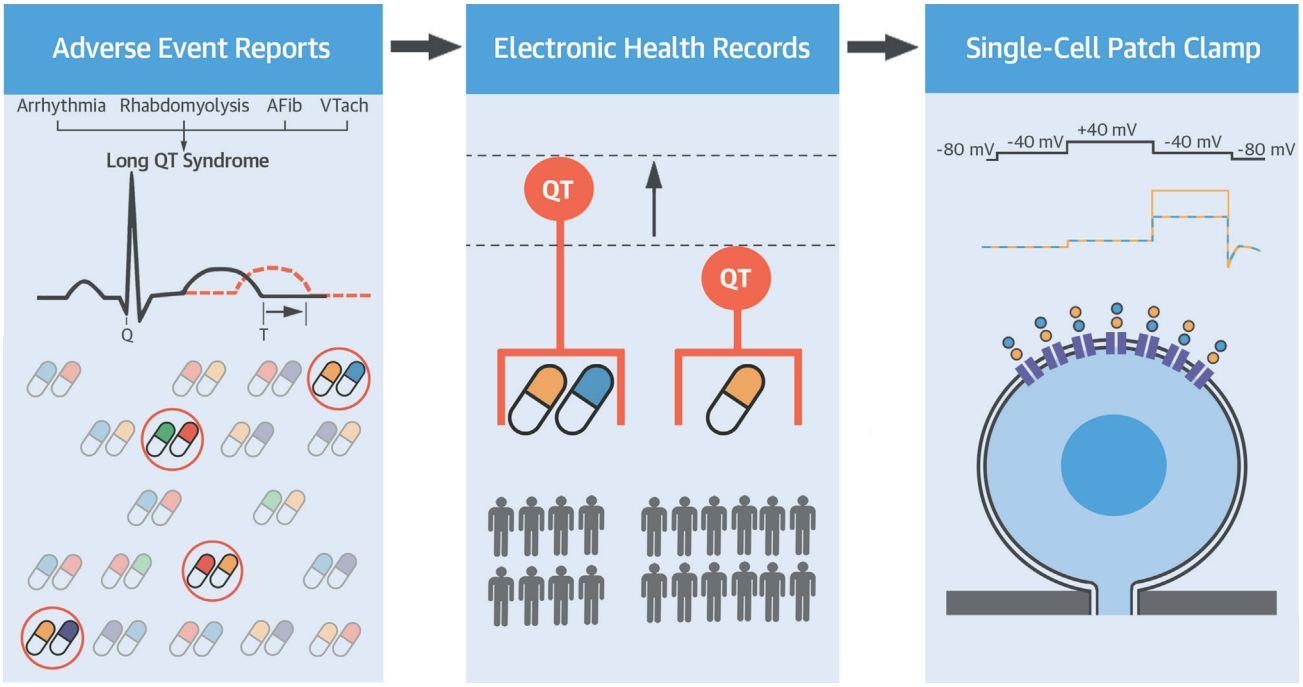
Here, we present a novel strategy that couples observational data mining with laboratory experiments to identify QT-DDIs (Central Illustration). Our observational analysis establishes the presence of a clinically significant association between co-medication and a prolonged QT interval. There are many hypotheses that may explain such an association. For example, a patient prescribed the putative interacting drugs may also be prescribed a known QT-prolonging agent. In fact, this is what we observed. Of 34 drug combinations that were associated with increased QT intervals, 26 could be dismissed as likely confounded by a known agent. Alternatively, it may be that there is a real drug interaction, in the pharmacological sense. The most common physiological explanation would be hERG block; therefore, we tested this hypothesis for our top prediction (ceftriaxone/lansoprazole) by using patch-clamp electrophysiology. This atypical path, going from the clinic into the laboratory, has great potential to increase the efficiency of DDI discovery.

CRITICAL EVALUATION OF DATA MINING USING LABORATORY EXPERIMENTS. We combined data from FAERS with our local EHR to find evidence of QT-prolonging drug interactions. Either data source alone provides only weak evidence of a potential DDI producing thousands of equivalent hypotheses. By integrating these data, we increased power and focused the analysis on only the strongest candidates. Most importantly, we followed up on these DDI hypotheses by using laboratory experiments to identify a possible mechanism.

AN INTERACTION BETWEEN CEFTRIAXONE AND LANSOPRAZOLE IS UNEXPECTED. Our top candidate, ceftriaxone and lansoprazole, would not have been suspected using current surveillance methods. In the clinical records, we found that co-medication of these 2 common drugs is associated with significantly prolonged QTc intervals. This increase was highest for white men and black women, in whom we observed an average increase of 12 ms. It is important to note that, if this effect size was observed for a single drug, it would be well above the threshold for regulatory concern during the approval stage (3). In the laboratory, we found that, in combination, lansoprazole and ceftriaxone block the hERG channel up to 57.6%, corresponding to an APD70 increase of 50 ms. At these higher lansoprazole concentrations, it is likely that, if treated as a single entity, the combination would not have received regulatory approval.

STUDY LIMITATIONS. We discovered that ceftriaxone and lansoprazole were significantly associated with prolonged QT intervals using clinical data. Our laboratory analysis suggests that this effect may be mediated through the hERG potassium channel, the most common mechanism by which drugs prolong the QT interval. However, the molecular explanation is not clear. Possibilities include a chemical interaction between the 2 compounds, cooperative binding to the channel, or an indirect mechanism through proteins that function with hERG. Furthermore, we

CENTRAL ILLUSTRATION **Ceftriaxone and Lansoprazole Are Associated With Acquired LQTS**



Lorberbaum, T. et al. J Am Coll Cardiol. 2016;68(16):1756–64.

We combined mining of adverse event reports, corroboration in electronic health records, and experimental validation using single-cell patch clamp to discover and validate a QT-DDI between ceftriaxone and lansoprazole. We used a data-driven profile of side effects that are predictive of LQTS to prioritize drug pairs in FAERS. We corroborated these findings in the electronic health records by comparing the QTc intervals of patients administered the prioritized drug pair to patients exposed to either drug alone. We then validated our top prediction (ceftriaxone/lansoprazole) by measuring the dose-dependent changes in hERG channel current using patch-clamp electrophysiology. AFib = atrial fibrillation; FAERS = FDA Adverse Event Reporting System; hERG = human Ether-à-go-go-Related Gene; LQTS = long QT syndrome; QT-DDI = QT-prolonging drug-drug interaction; VTach = ventricular tachycardia.

found significantly different effects when our analysis was stratified by race and ethnicity. White men and women appear to be sensitive to the interaction, whereas black men experience only an intermediate change, and women identifying as "other, including Hispanic" experience no detectable effect. This is consistent with the large amount of ethnic heterogeneity in cardiac potassium channels (24,25) and may guide a structural analysis of the interaction.

PRIOR EVIDENCE OF RELATED ADVERSE EVENTS. Lansoprazole is a commonly used PPI that is available over-the-counter. In retrospective analyses, PPIs were associated with a slightly increased risk of myocardial infarction (26). Additionally, there have been a large number of deaths reported to the FDA for patients taking this class of drugs, although this association is not statistically significant. Our discovery of a drug interaction with a PPI may explain these observations, although this requires follow-up study. Notably, evaluation of cefuroxime and lansoprazole, a pair predicted not to interact from the FAERS reporting frequencies, suggests that our pipeline is capable of distinguishing between safe and unsafe pairs, even within the same drug class.

CONCLUSIONS

We present evidence of a novel QT-DDI between lansoprazole and ceftriaxone. This interaction was discovered by using a combination of data mining and laboratory experiments. Our clinical data suggest that patients taking this pair of interacting drugs are more likely to have acquired LQTS, and the experimental study suggests that this effect may be mediated by blocking the hERG channel, the most common mechanism of acquired LQTS. This interaction appears to be

specific to ceftriaxone and does not extend to other cephalosporin antibiotics in combination with lansoprazole. Follow-up studies are required to confirm our findings and should include evaluation of the mechanism of the interaction at the hERG channel, the effect of ceftriaxone and lansoprazole on other ion channels, and investigation of these drugs in combination with other hERG blockers.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Data science methodologies may accelerate evaluation of the safety of drug combinations. Data from large numbers of patients and ECGs in electronic health records can corroborate clinical event reports of adverse drug interactions and, for those involving QT-interval prolongation, laboratory methods can then be used to elucidate the electrophysiological mechanisms involved.

TRANSLATIONAL OUTLOOK: Further work is needed to systematically extend this paradigm to evaluate the safety of commonly used drug combinations in other cardiovascular domains.

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KEY WORDS data mining, data science, drug-drug interaction, long QT syndrome

APPENDIX For supplemental tables and figures, please see the online version of this article.