p = 0.01). In a subgroup analysis, patients who underwent transfemoral TAVR had the lowest in-hospital mortality, post-procedure length of stay, need for blood transfusion, and cost of hospitalization, compared with transapical TAVR and SAVR.

Over the 11-month period in the NRD, a total of 446 patients with ESRD had undergone an aortic valve replacement; 118 had TAVR (73 transfemoral and 26 transapical), and 347 had SAVR. Of these, 104 (23.32%) patients had a readmission within a 30-day period after discharge. No differences between the 30-day readmission rates were observed after TAVR and SAVR. The median times to readmission, length of stay, and in-hospital mortality during the 30-day readmission were also similar for the patient cohorts.

Our findings suggested that the patients with ESRD are at higher risk of mortality (13.21%) and complications after aortic valve replacement procedures. Almost 1 of 4 patients were readmitted within 30 days. Despite selecting older ESRD patients, TAVR resulted in similar mortality and 30-day readmission rates when compared to SAVR, but had a shorter length of stay and lower hospitalization costs. The likelihood of discharge to home was higher after TAVR. Transfemoral TAVR appeared to be the safest and the most effective treatment for these patients, sustaining the least mortality.

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Combination Therapy With Ceftriaxone and Lansoprazole, Acquired Long QT Syndrome, and Torsades de Pointes Risk

We read with great interest the paper by Lorberbaum et al. (1) recently published in the *Journal*, in which evidence was provided that ceftriaxone plus lansoprazole combination therapy (CFX+LSZ) was unexpectedly associated with an increased risk of acquired long QT syndrome (aLQTS); thus, it is also theoretically associated with Torsades de Pointes (TdP) and sudden cardiac death. We report on 2 clinical observations that possibly further support these findings.

First, we recently observed a patient affected with pneumonia who specifically developed aLQTS after CFX+LSZ administration.

On admission, the patient's electrocardiogram (ECG) showed a normal corrected QT interval (QTc; 422 ms). Ceftriaxone administration was started (2 g/day), and a second ECG performed 3 days later did not reveal any significant change in the QTc (417 ms). On day 8, the patient reported epigastralgia, and lansoprazole (30 mg/day) was added to therapy. After 2 days of the combined treatment, QTc prolongation developed (475 ms), despite no changes in electrolytes, echocardiography findings, or further drug use. Lansoprazole was stopped and replaced with pantoprazole, whereas ceftriaxone was continued. Two days later, QTc normalized with restoration of baseline values (424 ms).

Second, in a cohort of unselected TdP patients, we observed that CFX+LSZ was assumed by a non-negligible percentage of subjects.

Since 2008, we have prospectively recruited patients who experienced TdP, independent of ongoing therapies and concomitant diseases. To date, 40 consecutive patients have been recruited. As expected (2), a high prevalence of recognized QT-prolonging factors of acquired origin were present (on average >4), including mainly cardiac diseases (82%), electrolyte imbalances (70%),

QT-prolonging medications (57%, globally considered), and anti-Ro/Sjogren's syndrome-related antigen A antibodies (52%) (3).

In this cohort, we found that 2 patients (5%) were receiving CFX+LSZ when TdP developed. Notably, this percentage was identical to that observed with levofloxacin, clarithromycin, or promazine (5% each) and was higher than that seen with ciprofloxacin, sotalol, or haloperidol (2%), which all represent well-recognized QT-prolonging medications (4). Only amiodarone (27%) and citalopram, fluconazole, or sertraline (7%) were more frequently administered.

Although follow-up studies are required to confirm the findings of Lorberbaum et al. (1), our observations seem to be in agreement with the view that CFX+LSZ may represent a currently overlooked contributing factor that increases the TdP risk, via specific (not class-related) QT-prolonging effects exerted by these 2 molecules when combined.

The potential harmfulness of this association should be carefully kept in mind, particularly in the presence of other recognized QT-prolonging factors. Both drugs are used worldwide, but they are presently considered as having neutral effects on ventricular repolarization.

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REPLY: Combination Therapy With Ceftriaxone and Lansoprazole, Acquired Long QT Syndrome and Torsades de Pointes Risk

We thank Dr. Lazzerini and colleagues for sharing their clinical observations supporting the drug–drug interaction (DDI) findings in our recent paper (1). In isolation, their observations could be dismissed as idiosyncratic by skeptics, but data science—the application of rigorous analytical methods to large datasets—provides the context needed to explain these effects across large patient populations. The integration of adverse event report mining, electronic health record corroboration, electrophysiology experiments, and now these case studies paints a clear picture of a DDI that could not have been identified using traditional surveillance approaches (2).

We have further capitalized on the promise of health data science by participating in Observational Health Data Sciences and Informatics (OHDSI), an international network of >140 researchers in >20 countries performing large-scale analyses on distributed databases that in total comprise >600 million patients (3). Each participating site converts their patient data to a common data model that enables analyses created at one location to be replicated across the entire network while maintaining patient privacy. This open and international collaboration has developed open source software tools for data exploration and evidence generation, conducted multivariate analyses to predict drug side effects, and improved definition of the heterogeneity in treatment pathways (4,5). The latter study was performed on an underlying population of >250 million patients from 11 data sources in 4 countries and took 20 days from conception to results from 7 sources, highlighting the efficiency with which these analyses can be performed at scale.

In the case of ceftriaxone and lansoprazole, we used a combination of public and private clinical data to identify the interaction. Through collaborations like OHDSI, these data are available to all researchers with interests in large-scale retrospective studies. We hope that the current study motivates others to participate in these new data science initiatives.

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