QT-Prolonging Antibiotics, Serum-to-Dialysate Potassium Gradient, and Risk of Sudden Cardiac Death Among Patients Receiving Maintenance Hemodialysis

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Rationale & Objective: Treatment with certain QT interval-prolonging antibiotics is associated with a higher risk of sudden cardiac death among individuals with hemodialysis-dependent kidney failure. Concurrent exposure to large serum-to-dialysate potassium gradients, which promote large potassium shifts, may augment the proarrhythmic effects of these medications. The primary objective of this study was to examine whether the serum-to-dialysate gradient modifies the cardiac safety of azithromycin, and separately, levofloxacin/moxifloxacin.

Study Design: Retrospective observational cohort study using a new-user study design.

Setting & Population: Adult in-center hemodialysis patients with Medicare coverage in the US Renal Data System (2007-2017).

Exposure: Initiation of azithromycin (or levofloxacin/moxifloxacin) as compared to amoxicillin-based antibiotics (*exposure*). Serum-to-dialysate potassium gradient (*effect modifier*). Individual patients could contribute multiple study antibiotic treatment episodes to the analyses.

Outcomes: Sudden cardiac death (14 days).

Analytical Approach: Inverse probability of treatment-weighted survival models to estimate HRs and robust 95% CIs.

Results: The azithromycin versus amoxicillin-based antibiotic cohort included 89,379 unique patients with 113,516 azithromycin and 103,493 amoxicillin-based treatment episodes. Azithromycin versus amoxicillin-based antibiotic treatment was associated with a higher risk of sudden cardiac death overall, HR, 1.68; 95% CI, 1.31-2.16. The risk was numerically higher when the baseline serum-to-dialysate potassium gradient was ≥3 mEq/L compared with <3 mEq/L (HR, 2.22; 95% CI, 1.46-3.40 vs HR, 1.43; 95% CI. 1.04-1.96, $P_{interaction}$ = 0.07). Analogous analyses in a respiratory fluoroquinolone (levofloxacin/ moxifloxacin) versus amoxicillin-based antibiotic cohort with 79,449 unique patients and 65,959 respiratory fluoroquinolone and 103,776 amoxicillin-based treatment episodes yielded similar results.

Limitations: Residual confounding.

Conclusions: Although treatment with azithromycin and, separately, respiratory fluoroquinolones were each associated with a heightened risk of sudden cardiac death, this risk was augmented in the setting of larger serum-to-dialysate potassium gradients. Minimizing the potassium gradient may be an approach to reduce the cardiac risk of these antibiotics.

Patients with hemodialysis-dependent kidney failure have high risks of cardiac arrhythmias and sudden cardiac death (SCD), which account for 35%[1] of all deaths and occur at an annual incidence rate that is 20 times greater than the rate in the general population.[2] A signif-

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icant risk factor for cardiac arrhythmias in these patients is disordered potassium homeostasis. Although hemodialysis treatments remove potassium to counteract potassium accumulation, excessive removal can result in large fluctuations in intradialytic and post-dialytic potassium levels. The amount of intradialytic potassium removal is driven by the magnitude of the serum-to-dialysate gradient; a larger difference between serum potassium and prescribed dialysate potassium concentration results in a larger gradient and greater intradialytic potassium removal.[3-5] Exposure to large potassium gradients has been linked to electrocardiographic

risk markers for cardiac arrest, including QT interval prolongation[6-10] and QT dispersion,[6,11-13] and is associated with higher risks of hospitalization and mortality.[14,15]

Another common proarrhythmic trigger among patients treated with maintenance hemodialysis is the use of medications that can prolong the QT interval. QT-prolonging medication utilization rates among hemodialysis patients are upwards of 2.5 times higher than the utilization rates among individuals without dialysis-dependent kidney failure, with azithromycin and respiratory fluoroquinolones being some of the most common QT-prolonging medications prescribed.[16] Recent studies among patients treated with hemodialysis have reported associations between these antibiotics and higher risks of SCD,[17,18] but the potential for intradialytic potassium shifts to augment the proarrhythmic risk of these medications has not been explored.

We conducted this study to examine whether the serum-to-dialysate potassium gradient modifies the cardiac risk of QT-prolonging antibiotics. We hypothesized that

PLAIN LANGUAGE SUMMARY

Certain antibiotics cause QT interval prolongation, which increases the risk of sudden death. Hemodialysis patients already have a high risk of sudden death, and a larger serum-to-dialysate potassium gradient (difference between blood and dialysate potassium concentrations) during hemodialysis further heightens the risk of sudden death. In this retrospective cohort study of QT-prolonging antibiotics in hemodialysis patients, we found that azithromycin (a QT-prolonging antibiotic) had a higher risk of sudden death compared with amoxicillin-based antibiotics (non–QT-prolonging antibiotics). The risk was the highest among patients who were also exposed to a larger serum-to-dialysate potassium gradient. Findings were similar for levofloxacin and moxifloxacin (other QT-prolonging antibiotics). Minimizing the serum-to-dialysate potassium gradient during hemodialysis may reduce the risk of sudden death associated with QT-prolonging antibiotics.

exposure to larger serum-to-dialysate potassium gradients would increase the risk of SCD associated with azithromycin and respiratory fluoroquinolone treatment among patients receiving maintenance hemodialysis.

METHODS

This study was approved by the University of North Carolina Institutional Review Board (#18-0297). A waiver of consent was granted because of the study's large size, data anonymity, and retrospective nature.

Data Sources

We used data from the US Renal Data System (USRDS) linked at the patient level with data from the electronic health record of a large US dialysis provider (DaVita Incorporated). The USRDS database includes: the End Stage Renal Disease Medical Evidence Report, a registration form completed at the outset of maintenance dialysis to establish Medicare eligibility for individuals less than 65 years of age and to reclassify previously eligible Medicare beneficiaries as having end-stage kidney disease; the End Stage Renal Disease Death Notification form, a form submitted to the Centers for Medicare & Medicaid Services to notify them of patient deaths and the presumed cause; and Medicare standard analytic files, including enrollment information and final action institutional (Part A), physician/supplier (Part B), and prescription drug (Part D) insurance claims.[19] The dialysis organization owns and operates more than 2,500 outpatient dialysis clinics throughout the United States, and its electronic health record captures detailed demographic, clinical, laboratory, and dialysis treatment data. In general, laboratory tests are performed biweekly or monthly and analyzed at a central laboratory,

and hemodialysis treatment parameters are recorded at every treatment.

Study Design and Populations

We conducted a retrospective cohort study using an active comparator, new-user design[20] (Fig 1) to evaluate if the comparative risk of SCD associated with azithromycin versus amoxicillin-based antibiotic treatment among patients in which hemodialysis-dependent kidney failure is modified by the serum-to-dialysate potassium gradient. To evaluate whether the potassium gradient also modifies the SCD risk when patients are treated with other QT-prolonging antibiotics, we conducted an additional analogous study considering respiratory fluoroquinolones as the antibiotic class of interest. We generated separate new-user cohorts for each antibiotic contrast.

All outpatient study of antibiotic prescription fills between January 1, 2007 and December 31, 2017 were evaluated for inclusion in the 2 cohorts. In both cohorts, study antibiotic treatment episodes consisted of a 180-day baseline period, a 30-day washout period, and a 14-day follow-up period. Individual patients could contribute multiple antibiotic treatment episodes to the analyses. To assemble each cohort, we identified all outpatient antibiotic treatment episodes where a relevant oral antibiotic of interest was newly initiated by adults (greater than or equal to 18 years of age) receiving in-center hemodialysis. We then applied the following patient-based exclusion criteria: receipt of maintenance dialysis for ≤90 days at the start of the baseline period; lack of continuous Medicare Part A, B, and D coverage during the baseline period; receipt of hospice care during the baseline; and presence of an implantable cardioverter–defibrillator. Within individual patients, we evaluated antibiotic treatment episodes for overlap, excluding episodes in which the associated washout period overlapped a preceding, already included treatment episode. Because an outpatient antibiotic
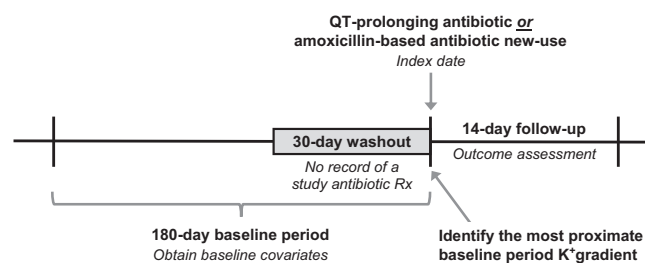

Figure 1. Study design. The figure depicts how a single antibiotic treatment episode was identified. Two separate new-user cohorts were created to evaluate the modifying effect of the serum-to-potassium gradient during: (1) azithromycin versus amoxicillin-based antibiotic treatment and (2) respiratory fluoroquinolone versus amoxicillin-based antibiotic treatment. Abbreviations: K⁺ gradient, serum-to-dialysate potassium gradient; Rx, prescription.

prescription fill after a hospitalization or skilled nursing facility stay may represent a continuation of therapy, we excluded treatment episodes of patients who were hospitalized or residing in a skilled nursing facility during the 30-day washout period. Finally, we excluded treatment episodes of patients who received <3 hemodialysis treatments at the dialysis organization during the last 30 days of baseline, with missing serum and/or dialysate potassium values, and with missing covariate information.

Study Exposures and Effect Modifier

We used Medicare Part D prescription drug claims to identify relevant outpatient study antibiotic treatment episodes for oral azithromycin, an oral respiratory fluoroquinolone (levofloxacin, moxifloxacin), or an oral amoxicillin-based antibiotic (amoxicillin, amoxicillin/clavulanic acid). In each new-user cohort, we defined the index date as the date of the first study antibiotic prescription fill after a 30-day washout period free of prescription fills for the cohort's relevant study antibiotics. We studied azithromycin and respiratory fluoroquinolones as the antibiotics of interest because these medications have known QT-prolonging potential[21] and are commonly prescribed to patients receiving maintenance hemodialysis for the treatment of respiratory infections.[22-24] We selected amoxicillin-based antibiotics as the comparator medication class for both cohorts because amoxicillin-based antibiotics are also used to treat respiratory infections[22-24] and do not have known QT-prolonging potential.[21]

The effect modifier of interest was the baseline serum-to-dialysate potassium gradient, calculated from the baseline serum and dialysate potassium values closest to, but preceding or on, the index date. For each antibiotic treatment episode, we computed the baseline potassium gradient as pre-dialysis serum potassium minus dialysate potassium, all measured in mEq/L. In our primary effect modification analysis, the potassium gradient was parameterized as a dichotomous variable (≥3 mEq/L and <3 mEq/L), based on published data demonstrating that exposure to larger potassium gradients associates with higher risks of death and hospitalization.[14]

Study Outcomes

We obtained dates and causes of death from the End Stage Renal Disease Death Notification form. The primary outcome of interest was SCD within 14 days of the index date. We defined SCD using the established USRDS definition, death due to cardiac arrhythmia, or cardiac arrest listed as the primary cause of death.[19] In secondary analyses, we considered 2 broader cardiac outcomes: a composite of SCD or hospitalized ventricular arrhythmia and, separately, cardiovascular mortality (Table S1). We selected a 14-day follow-up period because the treatment of respiratory infections with antibiotic therapy often lasts up to 14 days.[22-24]

Study Covariates

Covariates included potential confounders and variables known to be risk factors for the study outcome.[25] In each cohort, we identified baseline covariates in the 180 days before the index date for every study antibiotic treatment episode using Medicare Parts A, B, and D claims or relevant information from the dialysis provider electronic health record. Covariates of interest included patient demographics, comorbid conditions, laboratory values, dialysis treatment parameters, and metrics of health care utilization (Tables S2-S4).

Statistical Analysis

We used analogous analytic approaches in both new-user cohorts. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc). We described baseline characteristics across relevant study antibiotic treatment episodes in each cohort as count (%) for categorical variables and as mean ± standard deviation or median [interquartile range] for continuous variables and compared baseline covariate distributions between groups using absolute standardized differences. A standardized difference >0.10 indicates a potentially problematic imbalance between groups.[26]

We used an intention-to-treat analytic approach. During each antibiotic treatment episode, individuals were followed forward in historical time from the index date to the first occurrence of a study outcome, censoring, or competing event. Censoring events included: (1) change in dialysis modality, (2) kidney transplantation, (3) recovery of kidney function, (4) loss of Medicare Part A, B, or D coverage, (5) loss to follow-up, (6) completion of 14 days of follow-up, and (7) study end (December 31, 2017).

In primary analyses, we used Fine and Gray proportional subdistribution hazards models[27] to estimate hazard ratios (HRs) for SCD, comparing treatment with a study QT-prolonging antibiotic (azithromycin or respiratory fluoroquinolones) versus amoxicillin-based antibiotic treatment. We assessed whether the dichotomous baseline serum-to-potassium gradient (≥3 mEq/L and <3 mEq/L) was an effect modifier by including a multiplicative interaction term between the study exposure (new-use of a relevant study antibiotic) and the baseline potassium gradient in the regression models. We used inverse probability of treatment weighting, a propensity score method, for confounding control and estimated weighted (ie, adjusted) HRs by applying stabilized inverse probability of treatment weights in the regression models. We used robust variance estimation to obtain standard errors, which were then used to estimate 95% confidence intervals (CIs).[28] Death due to a cause other than SCD (ie, non-SCD) was treated as a competing event.

In secondary analyses, we used analogous methods to consider the 2 broader cardiac outcomes. In analyses evaluating cardiovascular mortality, non-cardiovascular

death was treated as a competing event. In separate analyses assessing the incremental modifying effect of the potassium gradient, we considered the serum-to-dialysis potassium gradient as a 3-level categorical variable (<2 mEq/L, 2 mEq/L to <3 mEq/L, and ≥3 mEq/L).

RESULTS

Azithromycin Versus Amoxicillin-based Antibiotics
Overall, 217,009 study antibiotic treatment episodes among 89,379 patients were included: 113,516 (52.3%) azithromycin treatment episodes and 103,493 (47.7%) amoxicillin-based treatment episodes (Fig 2). Individual patients contributed a median [interquartile range] of 2

[1, 3] treatment episodes to the analysis, and among the 46,434 patients with multiple treatment episodes, the median [interquartile range] time between prescription fills was 205 [101, 419] days. In total, 83,980 (38.7%) study antibiotic treatment episodes had a baseline serum-to-dialysate potassium gradient of ≥3 mEq/L and 133,029 (61.3%) treatment episodes had a baseline potassium gradient <3 mEq/L. The mean ± standard deviation serum potassium concentration was 5.4 ± 0.5 mEq/L among treatment episodes with baseline gradients ≥3 mEq/L compared to 4.4 ± 0.4 mEq/L among treatment episodes with baseline gradients <3 mEq/L. The use of dialysate potassium concentrations <2 mEq/L was more common among treatment episodes with baseline
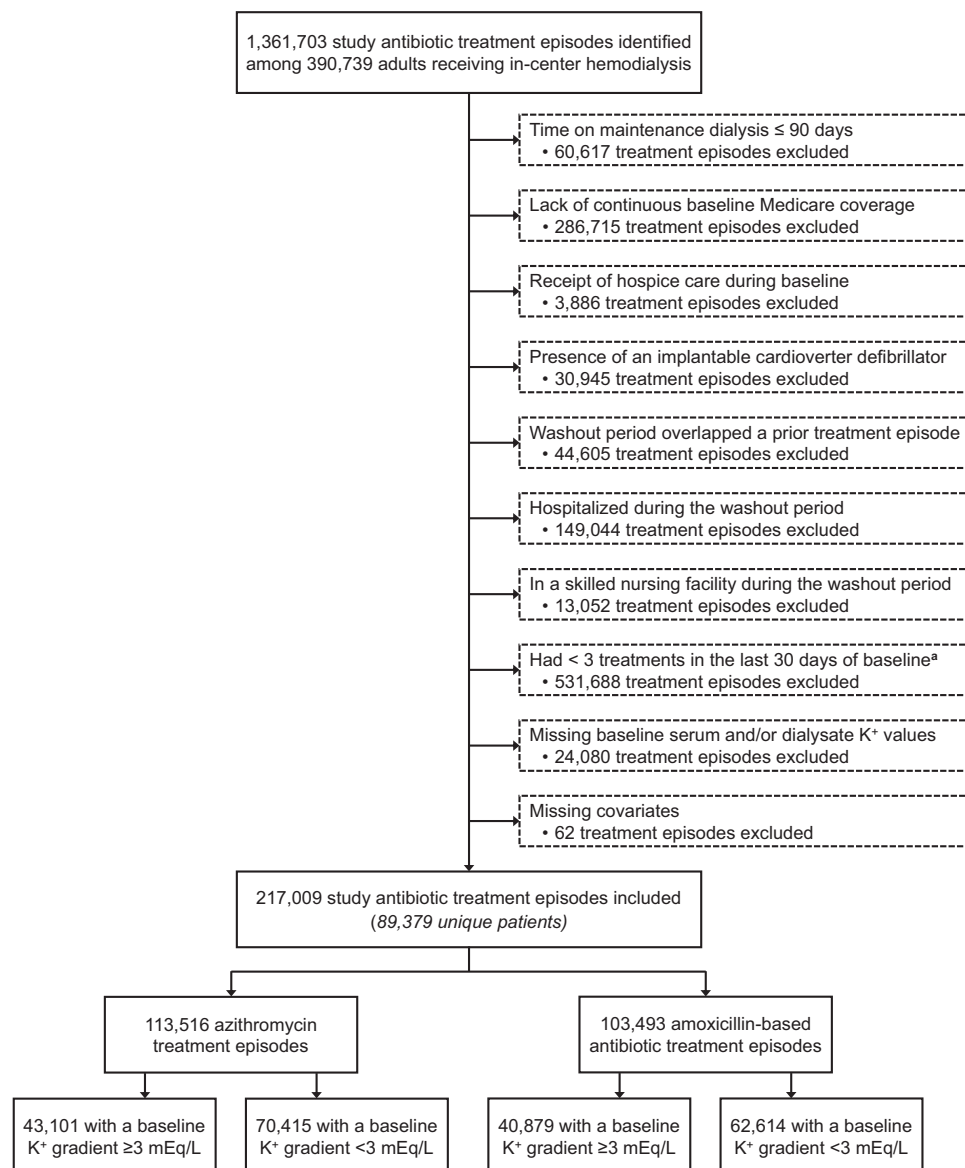

Figure 2. Flow diagram depicting assembly of the azithromycin versus amoxicillin-based antibiotic cohort. [a] This exclusion criteria resulted in the exclusion of patients who were receiving their maintenance dialysis treatments at non-DaVita dialysis provider organizations and DaVita-treated patients who received <3 treatments at an outpatient DaVita dialysis clinic during the last month of the baseline period. Abbreviations: K+ gradient, serum-to-dialysate potassium gradient.

Table 1. Select Baseline Characteristics of Azithromycin Versus Amoxicillin-based Antibiotic Cohort Before the Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

Characteristic	Baseline K⁺ gradient ≥3 mEq/L			Baseline K⁺ gradient <3 mEq/L		
	Azithromycin n=43,101	Amoxicillin-based n=40,879	Std diff	Azithromycin n=70,415	Amoxicillin-based n=62,614	Std diff
Age (y)	57.1 ± 14.5	57.2 ± 14.3	<0.01	59.9 ± 14.9	59.6 ± 14.7	0.02
Female	23,278 (54.0%)	19,602 (48.0%)	0.12	38,500 (54.7%)	30,366 (48.5%)	0.12
Race						
Black	14,799 (34.3%)	13,386 (32.7%)	0.03	32,609 (46.3%)	28,033 (44.8%)	0.03
White	25,670 (59.6%)	24,785 (60.6%)	0.02	34,239 (48.6%)	31,266 (49.9%)	0.03
Other	2,632 (6.1%)	2,708 (6.6%)	0.02	3,567 (5.1%)	3,315 (5.3%)	0.01
Hispanic	10,111 (23.5%)	9,630 (23.6%)	<0.01	10,842 (15.4%)	9,095 (14.5%)	0.02
Cause of end-stage kidney disease						
Diabetes	18,732 (43.5%)	18,897 (46.2%)	0.06	30,035 (42.7%)	27,506 (43.9%)	0.03
Hypertension	11,058 (25.7%)	10,060 (24.6%)	0.02	21,451 (30.5%)	18,518 (29.6%)	0.02
Glomerular disease	6,402 (14.9%)	5,583 (13.7%)	0.03	8,598 (12.2%)	7,206 (11.5%)	0.02
Other	6,909 (16.0%)	6,339 (15.5%)	0.01	10,331 (14.7%)	9,384 (15.0%)	<0.01
Dialysis vintage						
<1.0 y	3,167 (7.3%)	3,182 (7.8%)	0.02	8,896 (12.6%)	8,321 (13.3%)	0.02
1.0–1.9 y	5,070 (11.8%)	4,885 (11.9%)	<0.01	10,964 (15.6%)	10,036 (16.0%)	0.01
2.0–2.9 y	5,341 (12.4%)	5,142 (12.6%)	<0.01	9,477 (13.5%)	8,568 (13.7%)	<0.01
≥3.0 y	29,523 (68.5%)	27,670 (67.7%)	0.02	41,078 (58.3%)	35,689 (57.0%)	0.03
Vascular access						
Catheter	4,294 (10.0%)	4,084 (10.0%)	<0.01	6,511 (9.2%)	5,709 (9.1%)	<0.01
Fistula	28,392 (65.9%)	27,361 (66.9%)	0.02	45,469 (64.6%)	41,141 (65.7%)	0.02
Graft	10,415 (24.2%)	9,434 (23.1%)	0.03	18,435 (26.2%)	15,764 (25.2%)	0.02
History of a prior kidney transplant	4,403 (10.2%)	4,337 (10.6%)	0.01	4,945 (7.0%)	4,571 (7.3%)	0.01
Medicare Part D low-income subsidy	35,542 (82.5%)	32,445 (79.4%)	0.08	55,393 (78.7%)	47,583 (76.0%)	0.06
Body mass index						
<18.5 kg/m²	1,225 (2.8%)	1,190 (2.9%)	<0.01	2,067 (2.9%)	1,808 (2.9%)	<0.01
18.5-24.9 kg/m²	13,740 (31.9%)	13,351 (32.7%)	0.02	20,665 (29.3%)	18,689 (29.8%)	0.01
25.0-29.9 kg/m²	12,013 (27.9%)	11,471 (28.1%)	<0.01	19,479 (27.7%)	17,655 (28.2%)	0.01
≥30.0 kg/m²	16,123 (37.4%)	14,867 (36.4%)	0.02	28,204 (40.1%)	24,462 (39.1%)	0.02
Arrhythmia	8,974 (20.8%)	9,021 (22.1%)	0.03	15,482 (22.0%)	14,628 (23.4%)	0.03
Conduction disorder	2,675 (6.2%)	2,674 (6.5%)	0.01	4,192 (6.0%)	3,872 (6.2%)	<0.01
Dyslipidemia	20,080 (46.6%)	19,912 (48.7%)	0.04	33,850 (48.1%)	31,179 (49.8%)	0.03
Heart failure	15,161 (35.2%)	13,948 (34.1%)	0.02	25,078 (35.6%)	21,180 (33.8%)	0.04
Hypertension	35,800 (83.1%)	34,394 (84.1%)	0.03	58,413 (83.0%)	52,392 (83.7%)	0.02
Ischemic heart disease	15,810 (36.7%)	15,420 (37.7%)	0.02	26,373 (37.5%)	23,794 (38.0%)	0.01
Peripheral arterial disease	11,439 (26.5%)	12,197 (29.8%)	0.07	18,661 (26.5%)	18,375 (29.3%)	0.06
Stroke	6,372 (14.8%)	6,334 (15.5%)	0.02	11,043 (15.7%)	10,536 (16.8%)	0.03
History of non-compliance	2,773 (6.4%)	2,477 (6.1%)	0.02	3,396 (4.8%)	2,957 (4.7%)	<0.01
Infections in the last 60 days of baseline						
Pneumonia	2,070 (4.8%)	1,359 (3.3%)	0.07	3,302 (4.7%)	2,016 (3.2%)	0.08
Acute respiratory infection	3,836 (8.9%)	2,352 (5.8%)	0.12	6,501 (9.2%)	4,079 (6.5%)	0.10
Chronic respiratory infection	1,765 (4.1%)	1,398 (3.4%)	0.04	2,909 (4.1%)	2,168 (3.5%)	0.04
Calcium						
<8.5 mg/dL	7,853 (18.2%)	7,164 (17.5%)	0.02	10,944 (15.5%)	9,448 (15.1%)	0.01
8.5-10.2 mg/dL	33,792 (78.4%)	32,320 (79.1%)	0.02	57,271 (81.3%)	51,229 (81.8%)	0.01
>10.2 mg/dL	1,456 (3.4%)	1,395 (3.4%)	<0.01	2,200 (3.1%)	1,937 (3.1%)	<0.01
Hemoglobin						
< 9.5 mg/dL	2,739 (6.4%)	2,424 (5.9%)	0.02	5,013 (7.1%)	4,175 (6.7%)	0.02
9.5-12.0 mg/dL	30,451 (70.7%)	28,420 (69.5%)	0.02	51,391 (73.0%)	45,058 (72.0%)	0.02

(Continued)

Table 1 (Cont'd). Select Baseline Characteristics of Azithromycin Versus Amoxicillin-based Antibiotic Cohort Before the Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

Characteristic	Baseline K⁺ gradient ≥3 mEq/L			Baseline K⁺ gradient <3 mEq/L		
	Azithromycin n=43,101	Amoxicillin-based n=40,879	Std diff	Azithromycin n=70,415	Amoxicillin-based n=62,614	Std diff
>12.0 mg/dL	9,911 (23.0%)	10,035 (24.5%)	0.04	14,011 (19.9%)	13,381 (21.4%)	0.04
Pre-dialysis systolic BP						
<130 mm Hg	5,592 (13.0%)	6,060 (14.8%)	0.05	11,417 (16.2%)	11,807 (18.9%)	0.07
130-149 mm Hg	13,383 (31.1%)	13,411 (32.8%)	0.04	23,279 (33.1%)	21,684 (34.6%)	0.03
150-169 mm Hg	15,626 (36.3%)	14,047 (34.4%)	0.04	23,875 (33.9%)	19,884 (31.8%)	0.05
≥170 mm Hg	8,500 (19.7%)	7,361 (18.0%)	0.04	11,844 (16.8%)	9,239 (14.8%)	0.06
Dialysis treatment time <240 min	31,542 (73.2%)	29,102 (71.2%)	0.04	50,450 (71.6%)	43,696 (69.8%)	0.04
Number of baseline hospital admissions						
0 admissions	28,330 (65.7%)	26,838 (65.7%)	<0.01	48,439 (68.8%)	43,118 (68.9%)	<0.01
1 admission	8,808 (20.4%)	8,331 (20.4%)	<0.01	13,690 (19.4%)	12,092 (19.3%)	<0.01
≥2 admissions	5,963 (13.8%)	5,710 (14.0%)	<0.01	8,286 (11.8%)	7,404 (11.8%)	<0.01
Use of ≥1 med with any level of TdP risk[a]	24,475 (56.8%)	23,556 (57.6%)	0.02	40,436 (57.4%)	36,124 (57.7%)	<0.01
Use of ≥1 med with known TdP risk	5,405 (12.5%)	5,659 (13.8%)	0.04	9,115 (12.9%)	8,793 (14.0%)	0.03
Use of other antibiotics in the last 30 days of baseline						
IV antibiotics	11,949 (27.7%)	11,797 (28.9%)	0.03	19,215 (27.3%)	17,871 (28.5%)	0.03
Oral antibiotics	3,727 (8.6%)	4,485 (11.0%)	0.08	6,358 (9.0%)	7,308 (11.7%)	0.09

Values are given as number (%) for categorical variables and as mean ± standard deviation for continuous variables. All covariates were measured during the 180-day baseline period. Supplemental Tables S8 and S9 display the full list of baseline covariates considered in our analyses for both the unweighted and inverse probability of treatment-weighted cohorts. After the inverse probability of treatment weighting, all baseline covariates were well balanced between the treatment groups within potassium gradient strata (standardized differences ≤0.10).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure, COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ED, emergency department; EKG, electrocardiogram; IV, intravenous; med, medication; SNF, skilled nursing facility; std diff, standardized difference; TdP, Torsade de Pointes.

[a]QT-prolonging medications of interest included drugs classified as having a known, conditional, or possible risk of risk of torsade de pointes according to the CredibleMeds website (https://crediblemeds.org/). Medications classified as having any level of TdP risk are those falling into any of the 3 CredibleMeds categories.

potassium gradients ≥3 mEq/L (18.3% vs <1.0%). The distribution of baseline dialysate and serum potassium concentrations for both the cohorts are provided in Tables S5-S6. The propensity score distributions of the azithromycin and amoxicillin-based antibiotic treatment episodes are displayed in Fig S1, and the distribution of stabilized inverse probability of treatment weights is shown in Table S7. The baseline characteristics of the cohort according to the antibiotic group stratified by serum-to-dialysate potassium gradient are presented in Table 1 and Tables S8-S9.

During the 14-day follow-up period, 274 SCDs occurred. The rate of SCD was higher during azithromycin versus amoxicillin-based antibiotic treatment (15.5 vs 9.5 events per 10,000 treatment episodes). Table 2 displays the results from analyses evaluating the association between azithromycin versus amoxicillin-based antibiotic treatment and SCD, overall and stratified by baseline serum-to-potassium gradient. Treatment with azithromycin versus amoxicillin-based antibiotics was associated with a higher risk of SCD overall (weighted HR, 1.68; 95% CI, 1.31-2.16). However, the risk was numerically higher when with baseline potassium gradient was ≥3 mEq/L compared to <3 mEq/L (weighted HR,

2.22; 95% CI, 1.46-3.40 vs 1.43; 95% CI, 1.04-1.96). Formal testing for effect modification approached but did not reach the threshold for statistical significance ($P_{interaction} = 0.07$). Analyses evaluating secondary cardiac outcomes generated similar results (Table 2). Finally, Fig 3A shows the 14-day risk of SCD associated with azithromycin versus amoxicillin-based antibiotic treatment within 3 strata of the baseline serum-to-dialysate potassium gradient. The risk of SCD comparing azithromycin to amoxicillin-based antibiotics increased incrementally as the size of the potassium gradient increased.

Respiratory Fluoroquinolones Versus Amoxicillin-based Antibiotics

To evaluate whether the serum-to-dialysate potassium gradient also modifies SCD risk when patients are treated with other QT-prolonging antibiotics, we assembled a separate new-user cohort to compare respiratory fluoroquinolones versus amoxicillin-based antibiotics (Fig S2). Overall, 169,735 study antibiotic treatment episodes among 79,449 patients receiving hemodialysis were included: 65,959 respiratory fluoroquinolone treatment episodes (38.9%) and 103,776 amoxicillin-based treatment episodes (61.1%). Individual patients contributed a

Table 2. Azithromycin *vs.* amoxicillin-based antibiotics and the 14-day risk of cardiac outcomes stratified by baseline serum-to-dialysate potassium gradient

Sudden cardiac death—primary outcome

K⁺ gradient and antibiotic	No. events	Unweighted HR (95% CI)	Weighted HR (95% CI)
Overall			
Amoxicillin-based	98	1.00 (ref.)	1.00 (ref.)
Azithromycin	176	1.64 (1.28-2.10)	1.68 (1.31-2.16)
K⁺ gradient ≥3 mEq/L			
Amoxicillin-based	32	1.00 (ref.)	1.00 (ref.)
Azithromycin	71	2.11 (1.39-3.20)	2.22 (1.46-3.40)
K⁺ gradient <3 mEq/L			
Amoxicillin-based	66	1.00 (ref.)	1.00 (ref.)
Azithromycin	105	1.42 (1.04-1.93)	1.43 (1.04-1.96)

Sudden cardiac death or hospitalized ventricular arrhythmia—secondary outcome

K⁺ gradient and antibiotic	No. events	Unweighted HR (95% CI)	Weighted HR (95% CI)
Overall			
Amoxicillin-based	107	1.00 (ref.)	1.00 (ref.)
Azithromycin	185	1.58 (1.24-2.00)	1.62 (1.27-2.07)
K⁺ gradient ≥3 mEq/L			
Amoxicillin-based	35	1.00 (ref.)	1.00 (ref.)
Azithromycin	77	2.09 (1.40-3.11)	2.21 (1.47-3.31)
K⁺ gradient <3 mEq/L			
Amoxicillin-based	72	1.00 (ref.)	1.00 (ref.)
Azithromycin	108	1.33 (0.99-1.80)	1.35 (1.00-1.83)

Cardiovascular death—secondary outcome

K⁺ gradient and antibiotic	No. events	Unweighted HR (95% CI)	Weighted HR (95% CI)
Overall	133		
Amoxicillin-based	222	1.00 (ref.)	1.00 (ref.)
Azithromycin		1.52 (1.23-1.88)	1.54 (1.23-1.91)
K⁺ gradient ≥3 mEq/L			
Amoxicillin-based	40	1.00 (ref.)	1.00 (ref.)
Azithromycin	86	2.04 (1.40-2.97)	2.11 (1.44-3.09)
K⁺ gradient <3 mEq/L			
Amoxicillin-based	93	1.00 (ref.)	1.00 (ref.)
Azithromycin	136	1.30 (1.001.69)	1.30 (0.99-1.70)

Fine and Gray proportional subdistribution hazards models were used to estimate HRs and corresponding 95% CIs, and the inverse probability of treatment weighting was used for confounding control.
Abbreviations: CI, confidence interval; HR, hazard ratio; K⁺ gradient, serum-to-dialysate potassium gradient; No., number; ref., referent.

median [interquartile range] of 2 [1, 3] treatment episodes to the analysis, and among the 37,226 patients with multiple treatment episodes, the median [interquartile range] time between prescription fills was 213 [102, 456] days. In total, 63,242 (37.3%) treatment episodes had baseline serum-to-dialysate potassium gradients ≥3 mEq/L, and 106,493 (62.7%) treatment episodes had baseline potassium gradients <3 mEq/L. The mean ± standard deviation serum potassium concentration was 5.4 ± 0.5 mEq/L among treatment episodes with baseline potassium gradients ≥3 mEq/L compared to 4.4 ± 0.4 mEq/L among those with gradients <3 mEq/L. The use of dialysate potassium concentrations <2 mEq/L was more common in antibiotic treatment episodes with baseline potassium gradients ≥3 mEq/L (19.3% vs <1.0%). The propensity score distributions of the respiratory fluoroquinolone and

amoxicillin-based antibiotic groups are displayed in Fig S1, and the baseline characteristics of the cohort according to the antibiotic group stratified by serum-to-dialysate potassium gradient level are presented in Tables S10-S11.

During the 14-day follow-up period, 233 SCDs occurred. Similar to the azithromycin analyses, the rate of SCD was higher during respiratory fluoroquinolone versus amoxicillin-based antibiotic treatment (20.3 vs 9.5 events per 10,000 treatment episodes). Table 3 displays the findings from analyses assessing the associations between respiratory fluoroquinolone versus amoxicillin-based antibiotic treatment and SCD, overall and stratified by baseline serum-to-potassium gradient. Although overall the risk of SCD comparing respiratory fluoroquinolones to amoxicillin-based antibiotics was elevated (weighted HR, 1.72; 95% CI, 1.30-2.27), the risk was numerically highest
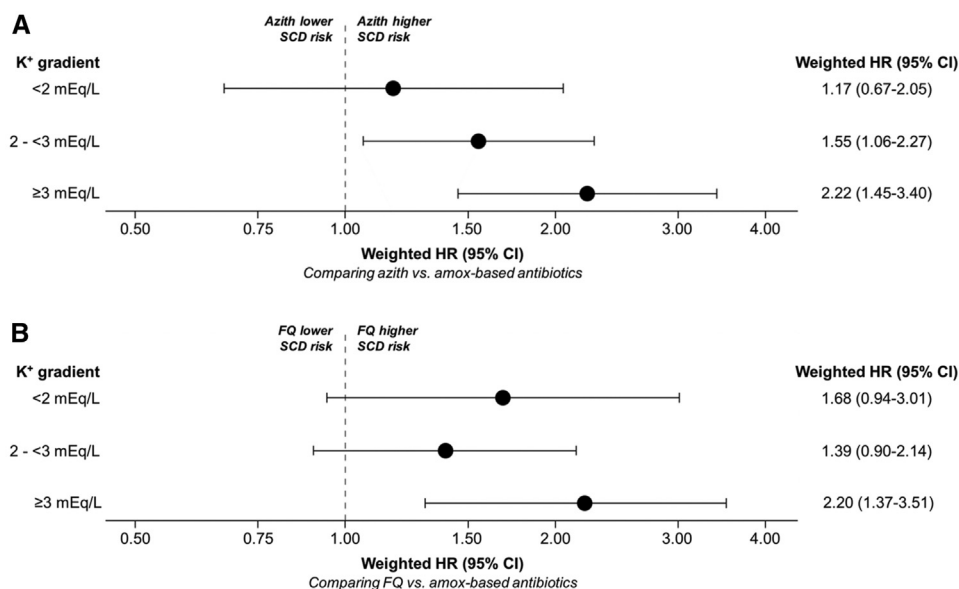
Figure 3. Azithromycin and respiratory fluoroquinolones versus amoxicillin-based antibiotics and 14-day sudden cardiac death risk by strata of the serum-to-dialysate potassium gradient. Fine and Gray proportional subdistribution hazards models were used to estimate HRs and corresponding 95% CIs, and the inverse probability of treatment weighting was used for confounding control. HRs for sudden cardiac death comparing azithromycin versus amoxicillin-based antibiotics (*Panel A*) and respiratory fluoroquinolones *vs.* amoxicillin-based antibiotics (*Panel B*) for 3 strata of the serum-to-dialysate potassium gradient are presented. Abbreviations: amox-based, amoxicillin-based; Azith, azithromycin; CI, confidence interval; FQ, fluoroquinolone; HR, hazard ratio; K+ gradient, serum-to-dialysate potassium gradient.

when baseline potassium gradients were ≥3 mEq/L compared to <3 mEq/L (weighted HR, 2.19; 95% CI, 1.37-3.50 vs 1.50; 95% CI, 1.06-2.11). Formal testing for effect modification did not reach the threshold for statistical significance ($P_{interaction} = 0.71$). Analyses evaluating secondary cardiac outcomes generated analogous results (Table 3). Finally, Fig 3B shows the 14-day risk of SCD associated with respiratory fluoroquinolones versus amoxicillin-based antibiotics within 3 strata of the serum-to-dialysate potassium gradient. No incremental trend in risk was observed.

DISCUSSION

In this study evaluating the SCD risk associated with commonly prescribed QT-prolonging antibiotics and the modifying effect of the serum-to-dialysate potassium gradient, there were 2 principal findings. First, we found that both azithromycin treatment and respiratory fluoroquinolone treatment was associated with a higher risk of SCD compared with amoxicillin-based antibiotic treatment. Second, we found that the risk associated with these QT-prolonging antibiotics was increased in the setting of higher serum-to-dialysate potassium gradients.

The overall cardiac safety of QT-prolonging antibiotics such as azithromycin and respiratory fluoroquinolones has been investigated in prior studies. We recently reported that the cardiac risks associated with azithromycin and respiratory fluoroquinolones in the general population[29-32]

extend to the hemodialysis population.[17,18] Even though the azithromycin and respiratory fluoroquinolone package inserts warn that these medications have QT-prolonging potential and can trigger potential fatal arrhythmias, especially in the setting of hypokalemia, these warnings do not specifically identify hemodialysis patients as a high-risk population.[33-35] Because of the nature of kidney failure and the hemodialysis treatment, hemodialysis patients carry unique risks as they are especially prone to electrolyte abnormalities. However, whether the serum-to-dialysate potassium gradient modifies the risk profile of these medications has not been previously explored.

Because the maintenance of normal serum potassium levels is critical to cardiac conduction, removal of accumulated potassium is one of the fundamental goals of hemodialysis treatment. The amount and rapidity of potassium removal are determined by the magnitude of the serum-to-dialysate potassium gradient. Larger potassium gradients result in larger and more rapid reductions in serum potassium levels, but this comes with the potential risk of provoking intradialytic and post-dialytic hypokalemia. Both lower dialysate potassium concentrations (ie, <2 mEq/L) and higher serum potassium levels can contribute to higher serum-to-dialysate potassium gradient levels. Exposure to lower dialysate potassium has been associated with higher risks of hospitalization[14] and sudden death.[36] These observations have contributed to less frequent use of low potassium dialysate concentrations over time, although use is still prevalent in many regions

Table 3. Respiratory fluoroquinolones *vs.* amoxicillin-based antibiotics and the 14-day risk of cardiac outcomes stratified by baseline serum-to-dialysate potassium gradient

Sudden cardiac death—primary outcome			
K+ gradient and antibiotic	**No. events**	**Unweighted HR (95% CI)**	**Weighted HR (95% CI)**
Overall			
Amoxicillin-based	99	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	134	2.28 (1.76-2.96)	1.72 (1.30-2.27)
K+ gradient ≥3 mEq/L			
Amoxicillin-based	34	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	52	2.69 (1.74-4.14)	2.19 (1.37-3.50)
K+ gradient <3 mEq/L			
Amoxicillin-based	65	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	82	2.07 (1.50-2.87)	1.50 (1.06-2.11)
Sudden cardiac death or hospitalized ventricular arrhythmia—secondary outcome			
K+ gradient and antibiotic	**No. events**	**Unweighted HR (95% CI)**	**Weighted HR (95% CI)**
Overall			
Amoxicillin-based	107	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	145	2.28 (1.78-2.93)	1.74 (1.33-2.27)
K+ gradient ≥3 mEq/L			
Amoxicillin-based	37	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	55	2.61 (1.72-3.96)	2.16 (1.38-3.39)
K+ gradient <3 mEq/L			
Amoxicillin-based	70	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	90	2.11 (1.55-2.89)	1.53 (1.10-2.13)
Cardiovascular death—secondary outcome			
K+ gradient and antibiotic	**No. events**	**Unweighted HR (95% CI)**	**Weighted HR (95% CI)**
Overall			
Amoxicillin-based	135	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	193	2.40 (1.93-3.00)	1.77 (1.40-2.24)
K+ gradient ≥3 mEq/L			
Amoxicillin-based	42	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	73	3.05 (2.09-4.46)	2.53 (1.68-3.80)
K+ gradient <3 mEq/L			
Amoxicillin-based	93	1.00 (ref.)	1.00 (ref.)
Resp fluoroquinolone	120	2.12 (1.62-2.78)	1.46 (1.10-1.95)

Fine and Gray proportional subdistribution hazards models were used to estimate HRs and corresponding 95% CIs, and the inverse probability of treatment weighting was used for confounding control.
Abbreviations: CI, confidence interval; HR, hazard ratio; K+ gradient, serum-to-dialysate potassium gradient; No., number; ref., referent; Resp, respiratory.

worldwide.[37] The contributions of hyperkalemia to excess sudden death among hemodialysis patients have also been well documented.[38,39]

When prescribing QT-prolonging antibiotics to individuals treated with maintenance hemodialysis, our study suggests that clinicians should consider implementing strategies to minimize the serum-to-dialysate potassium gradient to reduce the potential cardiac risk associated with QT-prolonging antibiotic treatment. Whether the detrimental association of the serum-to-dialysate gradient with the comparative cardiac safety of the studied antibiotics is more closely related to exposure to lower potassium dialysate concentrations or to higher serum potassium levels could not be determined in our analysis because of sample size limitations. However, lower dialysate potassium concentrations drove larger serum-to-dialysate potassium gradients in most cases. Specifically, a dialysate potassium concentration <2 mEq/L was used in ∼20% of study antibiotic treatment episodes with a serum-to-dialysate potassium gradient ≥3 mEq/L, whereas a dialysate potassium concentration <2 mEq/L was used in <1% of study antibiotic treatment episodes with a gradient <3 mEq/L. Avoiding the use of potassium dialysate <2 mEq/L is a general approach to mitigating SCD already supported by the literature,[36,38] and the current findings underscore the importance of avoiding potassium dialysate <2 mEq/L while patients are being treated with QT-prolonging antibiotics.

Attention to lowering serum potassium levels to reduce serum-to-dialysate gradients should also be considered; however, this requires knowledge of potassium levels throughout the course of QT-prolonging antibiotic

treatment. In practice, this can be difficult because serum potassium levels are not routinely ordered with high frequency, and most outpatient dialysis clinics do not have the capacity to perform point-of-care serum potassium testing to assess treatment-to-treatment potassium levels. Nevertheless, more frequent monitoring of serum potassium levels could be considered during QT-prolonging antibiotic treatment. When hyperkalemia is present, potassium-binding agents could be given to reduce the need for a lower dialysate potassium concentration, which further widens the serum-to-dialysate potassium gradient.[40,41]

The opportunity to reduce the risk of medication-related SCD through modification of the serum-to-dialysate potassium gradient is dependent on the dialysis clinicians' awareness of QT-prolonging antibiotic use in the first place. Individuals receiving dialysis are at a particularly high risk for drug-related complications due to polypharmacy,[42,43] and on average, dialysis patients are treated by 5 or more clinicians from different specialties.[44] Patients with complex conditions who receive prescriptions from multiple providers have been shown to be at an increased risk of experiencing drug toxicities.[45] Because our study incorporated all Medicare Part D prescription claims and was not limited to medications prescribed by dialysis providers, it is likely that many prescriptions for QT-prolonging medications originated from providers and care locations outside the dialysis clinic (eg, emergency departments, hospitals, ambulatory clinics). The potential for adverse drug effects, drug-drug interactions, and drug-dialysis treatment interactions is increased when multiple prescribers are involved. Frequent medication reconciliation is an effective strategy to reduce medication-related errors and harm,[43,46] but further research on the origins of QT-prolonging medication prescriptions and the potential for dialysis clinic-based medication reconciliation programs to effectively capture these medications is needed.

Our study has limitations. First, there were relatively few SCD events during the 14-day follow-up period in each cohort, limiting the statistical power to detect differences among potassium gradient subgroups. This was particularly notable in the respiratory fluoroquinolone versus amoxicillin-based antibiotic analyses and might explain the more extensively overlapping CIs when comparing gradient subgroups. Second, even though we defined SCD using the established USRDS definition, it is possible that outcome misclassification occurred. However, analyses considering a composite of SCD or hospitalized ventricular arrhythmia yielded consistent results. Third, because post-dialysis serum potassium levels were not available in our dataset, and are not typically measured in clinical practice, we were unable to determine if the magnitude of serum potassium decline during hemodialysis and/or the occurrence of post-dialysis hypokalemia contributed to the observed higher risk of SCD associated with QT-prolonging antibiotics among patients with

higher serum-to-dialysate potassium gradients. Future mechanistic studies are needed. Fourth, serum potassium levels may vary within the weekly dialytic interval. Analyses did not consider the day of the week that the baseline serum potassium was measured, possibly resulting in bias from unaccounted differences between the study groups. Fifth, although we were able to determine and control for electrocardiogram performance in the month prior to study antibiotic initiation, we were unable to determine if electrocardiogram findings were used to inform antibiotic prescribing decisions. Finally, given the observational nature of our study, residual confounding may have influenced the results, and we were unable to identify a suitable negative control outcome to detect potential residual confounding. Thus, it is possible that residual confounding remains, even though the propensity score models included an extensive list of covariates.

In conclusion, azithromycin treatment and, separately, respiratory fluoroquinolone treatment were each associated with a higher risk of SCD compared with amoxicillin-based antibiotic treatment, and the risks were augmented when baseline serum-to-dialysate potassium gradients were ≥3 mEq/L. Selecting antibiotics that do not prolong the QT interval when appropriate and minimizing the potassium gradient during the course of QT-prolonging antibiotic therapy may be an important steps to reducing the already high risk of SCD borne by patients receiving maintenance hemodialysis.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Propensity score distributions

Figure S2: Flow diagram depicting the assembly of the respiratory fluoroquinolone versus amoxicillin-based antibiotic cohort

Table S1: Outcome Definitions

Table S2: ICD-9/ICD-10 Diagnosis and Procedure Codes Were Used to Identify Comorbid Conditions and Other Covariates

Table S3: Definitions of Laboratory and Dialysis Treatment Covariates

Table S4: Lists of Relevant Medications

Table S5: Distribution of the Stabilized Inverse Probability of Treatment Weights

Table S6: Description of Dialysate Potassium Levels in Both the Cohorts

Table S7: Description of Serum Potassium Levels in Both the Cohorts

Table S8: Baseline Characteristics of the Azithromycin Versus Amoxicillin-based Antibiotic Cohort Before the Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

Table S9: Baseline Characteristics of the Azithromycin Versus Amoxicillin-based Antibiotic Cohort After Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

Table S10: Baseline Characteristics of the Respiratory Fluoroquinolone Versus Amoxicillin-based Antibiotic Cohort Before the

Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

Table S11: Baseline Characteristics of the Respiratory Fluoroquinolone Versus Amoxicillin-based Antibiotic Cohort After the Inverse Probability of Treatment Weighing Stratified by the Baseline Serum-to-Dialysate Potassium Gradient

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Is the serum-dialysate potassium gradient associated with sudden cardiac death risk in patients receiving QT-prolonging antibiotics?

Kidney Medicine

- Retrospective, observational cohort
- USRDS 2007 - 2017 adult Medicare patients
- Azithromycin or Fluoroquinolone vs Amoxicillin exposure
- **K** 19 Potassium — Serum-to-dialysate potassium gradient

Risk of Sudden Cardiac Death (SCD)

Azithromycin 113,516 episodes **versus** **Amoxicillin** 103,493 episodes

in 89,379 unique hemodialysis patients
HR 1.68 (CI 1.31 - 2.16)

If serum-to-dialysate potassium ≥ 3 mEq/L — **HR 2.22** (CI 1.46 - 3.40)

If serum-to-dialysate potassium < 3 mEq/L — **HR 1.43** (CI 1.04 - 1.96)

Conclusion: Treatment with either azithromycin or fluoroquinolones was associated with a heightened risk of SCD, and this risk was greater in the setting of larger serum-to-dialysate potassium gradients. Minimizing the potassium gradient may be an approach to reduce the cardiac risk of antibiotics.

Reference: Pun P, Assimon M, Wang L, et al. QT-prolonging antibiotics, the serum-to-dialysate gradient, and the risk of sudden cardiac death among patients receiving chronic maintenance dialysis. *Kidney Medicine*, 2023.

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