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Analysis of Respiratory Fluoroquinolones and the Risk of Sudden Cardiac Death Among Patients Receiving Hemodialysis

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IMPORTANCE Respiratory fluoroquinolone antibiotics are some of the most common medications with QT interval–prolonging potential prescribed to patients with hemodialysis-dependent kidney failure—individuals who have a very high risk of sudden cardiac death (SCD). To date, there have been no large-scale, population-specific studies evaluating the cardiac safety of respiratory fluoroquinolones in the hemodialysis population.

OBJECTIVE To investigate the cardiac safety of respiratory fluoroquinolones among individuals with hemodialysis-dependent kidney failure.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study examining safety using an active comparator new-user design was conducted using administrative claims data from a US-wide kidney failure registry from January 1, 2007, to December 31, 2016, including 264 968 Medicare beneficiaries receiving in-center maintenance hemodialysis. Data analysis was performed from January 4 to August 16, 2021.

EXPOSURES Respiratory fluoroquinolone (levofloxacin or moxifloxacin) vs amoxicillin-based (amoxicillin or amoxicillin with clavulanic acid) antibiotic treatment.

MAIN OUTCOMES AND MEASURES Sudden cardiac death within 5 days of outpatient initiation of a study antibiotic. Inverse probability of treatment-weighted survival models to estimate hazard ratios (HRs), risk differences (RDs), and corresponding 95% CIs. Death due to a cause other than SCD was treated as a competing event. Fracture was considered as a negative control outcome.

RESULTS The study cohort included 264 968 unique in-center hemodialysis patients and 626 322 study antibiotic treatment episodes: 251 726 respiratory fluoroquinolone treatment episodes (40.2%) and 374 596 amoxicillin-based treatment episodes (59.8%). Of the 264 968 patients, 135 236 (51.0%) were men, and the mean (SD) age was 61 (15) years. Respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was associated with a higher relative and absolute 5-day risk of SCD (weighted HR, 1.95; 95% CI, 1.57-2.41; and weighted RD per 100 000 treatment episodes, 44.0; 95% CI, 31.0-59.2). Respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was not associated with the 5-day risk of fracture.

CONCLUSIONS AND RELEVANCE In this study, compared with amoxicillin-based antibiotic treatment, respiratory fluoroquinolone treatment was associated with a higher short-term risk of SCD among patients with hemodialysis-dependent kidney failure. This finding suggests that decisions between the use of respiratory fluoroquinolones and amoxicillin-based antibiotics should be individualized, with prescribers considering both the clinical benefits and potential cardiac risks.

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Supplemental content

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Fluoroquinolone antibiotics, such as levofloxacin and moxifloxacin, are prescribed widely,[1] have advantageous pharmacokinetic properties (eg, high oral bioavailability, long half-lives, and good tissue penetration) and provide excellent coverage for most respiratory pathogens.[2-4] Although levofloxacin and moxifloxacin are generally well tolerated, they can delay ventricular repolarization, which manifests as QT interval prolongation and is associated with the life-threatening ventricular tachyarrhythmia torsade de pointes (TdP).[5,6] Meta-analyses of studies evaluating the cardiac safety of respiratory fluoroquinolones in the general population have reported associations between these medications and a heightened risk of serious arrhythmias and cardiovascular death.[7,8] However, findings across studies are inconsistent, and variable degrees of risk have been reported. These inconsistencies may relate, in part, to differences in the underlying cardiac risk of the populations studied.

Respiratory fluoroquinolones are some of the most common medications with QT interval-prolonging potential prescribed to individuals receiving hemodialysis,[9] patients with a very high risk of sudden cardiac death (SCD). Sudden cardiac death is the leading cause of death among individuals receiving hemodialysis, accounting for 1 in every 3 deaths.[10] The rate of SCD in the hemodialysis population exceeds that of the general population by more than 20-fold.[11] Risk factors known to enhance the QT interval-prolonging effects of respiratory fluoroquinolones, such as structural heart disease, electrolyte derangements, and use of multiple medications with QT interval-prolonging potential, are highly prevalent among patients receiving hemodialysis, rendering them susceptible to drug-induced cardiac complications. More than 80% of patients undergoing hemodialysis have a least 1 demographic or clinical risk factor for drug-induced QT interval prolongation.[9] However, evidence linking respiratory fluoroquinolones to adverse cardiac outcomes in dialysis-dependent kidney failure is limited to case reports of TdP with levofloxacin and moxifloxacin.[12,13] We undertook this study to investigate the cardiac safety of respiratory fluoroquinolones among individuals receiving in-center maintenance hemodialysis.

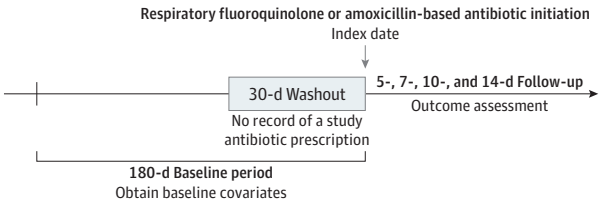
Key Points

Question Compared with amoxicillin-based antibiotics, are respiratory fluoroquinolones associated with a higher risk of sudden cardiac death among patients receiving hemodialysis?

Findings In this cohort study, among 264 968 patients receiving in-center hemodialysis, respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was associated with higher relative and absolute 5-day sudden cardiac death risks.

Meaning The findings of this study suggest that, among patients receiving hemodialysis, treatment with a respiratory fluoroquinolone may be associated with an increased risk of sudden cardiac death more than treatment with an amoxicillin-based antibiotic.

Figure 1. Study Design



Antibiotic treatment episodes for an oral respiratory fluoroquinolone (levofloxacin or moxifloxacin) and an oral amoxicillin-based antibiotic (amoxicillin or amoxicillin with clavulanic acid) were identified based on initiation of one of these medications after a 30-day washout period free of documented prescription fills for either medication class. The index date was defined as the date of study antibiotic initiation. Baseline covariates were identified in the 180-day period before the index date and study follow-up began on the index date.

Methods

Data Source

We used data from the US Renal Data System, a government-funded national surveillance system that collects information on almost all individuals with kidney failure in the US.[14] The US Renal Data System database includes the End Stage Renal Disease Medical Evidence Report, the Death Notification form, and Medicare standard analytic files, including enrollment information and final action administrative fee-for-service hospital (Medicare Part A), physician/supplier (Medicare Part B), and prescription drug (Medicare Part D) claims.[14] This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board with a waiver of informed consent owing to the study's large size, data anonymity, and retrospective nature. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study Design and Population

We conducted a retrospective cohort study using an active comparator new-user design[15] (**Figure 1**) to investigate the association between oral respiratory fluoroquinolone (levofloxacin or moxifloxacin) vs oral amoxicillin-based antibiotic (amoxicillin or amoxicillin with clavulanic acid) treatment and the short-term risk of SCD among patients receiving in-center hemodialysis. We selected amoxicillin-based antibiotics as the comparator because they are also used to treat respiratory infections and are not associated with QT interval prolongation, according to a source that categorizes the QT interval-prolongation-related risk of medications based on published literature, medication package inserts, data from the US Food and Drug Administration's Adverse Event Reporting System, and other sources.[16] We selected a primary follow-up period of 5 days because this is the minimum recommended duration of levofloxacin and moxifloxacin therapy for respiratory infections.[3,17-19] Recognizing that patients may receive longer treatment, we also considered 7-, 10-, and 14-day follow-up periods.[3,17-20]

All outpatient study antibiotic fills between January 1, 2007, and December 30, 2016, among patients receiving

in-center hemodialysis were evaluated for inclusion. Individual patients could contribute multiple respiratory fluoroquinolone and/or amoxicillin-based antibiotic treatment episodes to the analysis. Each treatment episode consisted of a 180-day baseline period, 30-day washout period, and 14-day follow-up period (Figure 1). To assemble the study cohort, we identified outpatient antibiotic treatment episodes in which an oral respiratory fluoroquinolone or an oral amoxicillin-based antibiotic was newly initiated after a 30-day washout period free of documented prescription fills for either medication class among adults (age ≥18 years) receiving in-center maintenance hemodialysis. We then applied the following patient-based exclusion criteria to the treatment episodes: (1) missing information on patient sex; (2) 90 days or less on hemodialysis at the start of the baseline period; (3) lack of continuous Medicare Part A, B, and D coverage during the baseline period; (4) receipt of hospice care during the baseline period; and (5) presence of an implantable cardioverter-defibrillator. Within individual patients, we also evaluated treatment episodes for overlap, excluding episodes in which the associated washout period overlapped a preceding, already included treatment episode. Because an outpatient antibiotic fill immediately following hospital discharge may represent continuation of inpatient antibiotic therapy, we excluded treatment episodes of patients hospitalized during the last 7 days of the washout period.

Exposure, Outcomes, and Covariates

We used Medicare Part D prescription drug claims to identify outpatient oral respiratory fluoroquinolone and oral amoxicillin-based antibiotic treatment episodes. For each antibiotic treatment episode, we defined the index date as the date of the first respiratory fluoroquinolone or amoxicillin-based antibiotic prescription after a 30-day washout period.

We used the End Stage Renal Disease Death Notification form for death date and cause. The primary outcome was SCD, defined using the established US Renal Data System definition of death due to cardiac arrhythmia or cardiac arrest listed as the primary cause.[14,21,22] We considered 3 broader outcomes in secondary analyses: (1) a composite of SCD or hospitalized ventricular arrhythmia, (2) cardiovascular mortality, and (3) all-cause mortality (eTable 1 in the Supplement). We studied hospitalization for fracture as a negative control outcome.

Baseline covariates included potential confounders and variables known to be strong risk factors for the study outcome.[23] For each antibiotic treatment episode, we identified covariates in the 180 days before the index date using Medicare Part A, B, and D claims. Covariates included patient demographics, comorbid conditions, prescription medication use, and metrics of health care use (eTable 2 and eTable 3 in the Supplement). We obtained patient demographic characteristics, including race and ethnicity, from the US Renal Data System Medical Evidence Report form. Missing data were minimal and limited to demographic covariates. Treatment episodes with missing race (n = 448) were classified as having other race and treatment episodes with missing Hispanic ethnicity (n = 2349) were classified as non-Hispanic.

Statistical Analysis

Data analysis was conducted from January 4 to August 16, 2021. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). We describe baseline characteristics across respiratory fluoroquinolone and amoxicillin-based antibiotic treatment episodes as count (percentage) for categorical variables and as mean (SD) for continuous variables. We compared baseline covariate distributions between groups using absolute standardized differences. A standardized difference greater than 0.10 represents an imbalance between exposure groups.[24]

We used an intention-to-treat approach to evaluate the association between respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment and the 5-day risk of SCD. Longer follow-up periods were considered in separate analyses. An intention-to-treat analytic approach in observational studies of medication therapies is analogous to an intention-to-treat analysis in clinical trials: the initial therapy is used as the exposure whether or not a patient changes therapies during follow-up.[25] In our study, patients were analyzed according to their initially prescribed antibiotic in each treatment episode regardless of treatment changes during the corresponding follow-up period. For each study antibiotic treatment episode, individuals were followed up forward in historical time from the index date to the first occurrence of an outcome, censoring, or competing event. Censoring events included (1) dialysis modality change; (2) kidney transplantation; (3) kidney function recovery; (4) loss of Medicare Part A, B, or D coverage; (5) loss to follow-up; (6) end of the designated follow-up period; and (7) study end (December 31, 2016). Death due to a cause other than SCD was treated as a competing event.

In primary analyses, all eligible antibiotic treatment episodes were considered. We estimated both relative and absolute effect measures to assess the study antibiotic and SCD association. We estimated hazard ratios (HRs) and their 95% CIs using Fine and Gray proportional subdistribution hazards models.[26] To account for within-person correlation of repeated measures, SEs were obtained using robust variance estimation.[27] The null value for HRs is 1.00. We used the Aalen-Johansen nonparametric estimator to estimate the cumulative incidence of SCD in each treatment group and computed risk differences (RDs) by subtracting the cumulative incidence of SCD in the amoxicillin-based antibiotic group from the cumulative incidence of SCD in the respiratory fluoroquinolone group. We obtained 95% CIs for RDs using a cluster-based bootstrap procedure with 500 resamples to account for within-person correlation of repeated measures.[28]

We used inverse probability of treatment (IPT) weighting for confounding control. Briefly, we calculated the predicted probability (ie, propensity score) of initiating a respiratory fluoroquinolone vs an amoxicillin-based antibiotic as a function of baseline covariates using logistic regression. We generated IPT weights from propensity scores using standard methods.[29] We estimated weighted HRs by applying IPT weights in our regression models and weighted RDs by applying IPT weights to the Aalen-Johansen estimator.

We used analogous methods to conduct secondary analyses considering exposure and outcome variations. The US Food

and Drug Administration–approved product labeling for both levofloxacin and moxifloxacin recommends avoiding use of these drugs with other QT interval–prolonging medications.[17,18] Therefore, we evaluated the association between respiratory fluoroquinolone and amoxicillin-based antibiotic treatment in patients taking and not taking other QT interval–prolonging medications with known TdP risk (eTable 3 in the Supplement). In addition, electrocardiogram studies indicate that moxifloxacin may prolong the QT interval to a greater extent than levofloxacin (mean, 3-7 milliseconds for levofloxacin vs 7-14 milliseconds for moxifloxacin).[30-34] Thus, we compared moxifloxacin and levofloxacin, separately, with amoxicillin-based antibiotics. Given that 3 different treatments were considered, we estimated propensity scores and generated IPT weights using standard methods for multicategorical exposures.[29,35] In addition, we considered 3 broader outcomes, as detailed above. In analyses evaluating cardiovascular mortality, noncardiovascular death was treated as a competing event.

We conducted sensitivity analyses to assess the robustness of our main findings. These analyses included restricting the cohort to patients' first eligible study antibiotic treatment episode and, separately, to patients who were not hospitalized during the 30-day washout period. We also compared respiratory fluoroquinolone treatment vs amoxicillin with clavulanic acid treatment and evaluated a negative control outcome not expected to be influenced by the study antibiotics: hospitalization associated with fracture. In fracture analyses, all-cause death was treated as a competing event.

Results

eFigure 1 in the Supplement depicts the study cohort flow diagram. A total of 626 322 antibiotic treatment episodes among 264 968 unique adults receiving in-center hemodialysis were included: 251 726 respiratory fluoroquinolone treatment episodes (40.2%) (148 417 patients) and 374 596 amoxicillin-based antibiotic treatment episodes (59.8%) (180 887 patients). Individual patients contributed a median of 2 (IQR, 1-3) treatment episodes to the analysis, and among the 138 801 patients with multiple treatment episodes, the median time between study antibiotic prescription fills was 209 (IQR, 106-430) days. Overall, among the 264 968 unique patients, the mean (SD) age was 61 (15) years, 129 732 (49.0%) were women, and the most common cause of kidney failure was diabetes (47.9%). The propensity score distributions of the study antibiotic groups exhibited substantial overlap (eFigure 2 in the Supplement), indicating that the groups were comparable. Baseline characteristics of the primary cohort stratified by study medication are presented in **Table 1** and eTable 4 in the Supplement. Individuals treated with a respiratory fluoroquinolone vs an amoxicillin-based antibiotic were older (mean age, 61.9 vs 58.5 years) and had a higher prevalence of cardiovascular comorbid conditions (eg, heart failure, 45.1% vs 35.9%) and health care use, among other factors. After IPT weighting, all baseline covariates were well balanced between groups.

Sudden Cardiac Death

In the 5-day follow-up period, a total of 416 SCDs occurred: 266 during respiratory fluoroquinolone treatment and 150 during amoxicillin-based antibiotic treatment. The corresponding incidence of events was 105.7 SCDs per 100 000 treatment episodes in the respiratory fluoroquinolone group compared with 40.0 SCDs per 100 000 treatment episodes in the amoxicillin-based antibiotic group. **Figure 2** and eTable 5 in the Supplement display the association between respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment and SCD. Compared with amoxicillin-based antibiotic treatment, respiratory fluoroquinolone treatment was associated with a higher 5-day risk of SCD (weighted HR, 1.95; 95% CI, 1.57 to 2.41; weighted RD per 100 000 treatment episodes, 44.0; 95% CI, 31.0-59.2). The number needed to harm, obtained by inverting the weighted RD, suggests that 1 additional SCD would occur during a 5-day follow-up period for every 2273 respiratory fluoroquinolone treatment episodes. Consistent associations were seen when follow-up was extended to 7, 10, and 14 days.

In analyses evaluating the association between respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment and SCD in patients taking and not taking other medications with known TdP risk, the HRs were higher in patients taking another medication with known TdP risk (eTable 6 in the Supplement): 5-day weighted HR, 2.50 (95% CI, 1.61-3.88) vs 1.79 (95% CI, 1.40-2.29) and weighted RD per 100 000 treatment episodes, 98.3 (95% CI, 54.1-143.7) vs 34.0 (95% CI, 20.2-49.6).

Of the 251 726 respiratory fluoroquinolone treatment episodes, 225 559 (89.6%) were levofloxacin treatment episodes (135 865 patients), and 26 167 (10.4%) were moxifloxacin treatment episodes (20 187 patients). Analyses comparing levofloxacin and moxifloxacin with amoxicillin-based antibiotics are presented in **Figure 3** and eTable 7 in the Supplement. Both levofloxacin and moxifloxacin treatment vs amoxicillin-based antibiotic treatment were associated with a higher risk of SCD. When comparing levofloxacin with moxifloxacin, the risk of SCD was similar.

In analyses considering alternative outcomes, we found that, compared with amoxicillin-based antibiotic treatment, respiratory fluoroquinolone treatment was associated with an increased risk of the composite outcome, SCD or hospitalized ventricular arrhythmia, cardiovascular mortality, and all-cause death at all time points (**Table 2** and eTable 5 in the Supplement).

Sensitivity Analyses

Sensitivity analyses restricting the cohort to patients' first eligible antibiotic treatment episode and, separately, to patients not hospitalized during the 30-day washout period were consistent with our primary analyses (eTable 8 in the Supplement). The comparison of respiratory fluoroquinolone treatment vs amoxicillin with clavulanic acid treatment also produced findings consistent with our primary analyses (eTable 8 in the Supplement).

In the 5-day follow-up period, a total of 493 hospitalized fractures occurred, 249 during respiratory fluoroquinolone

Table 1. Select Baseline Patient Characteristics of Respiratory Fluoroquinolone and Amoxicillin-based Antibiotic Treatment Episodes[a]

Characteristic	Unweighted			Weighted		
	Respiratory fluoroquinolone (n = 251 726)	Amoxicillin-based (n = 374 596)	Standardized difference[b]	Respiratory fluoroquinolone (n = 250 736)	Amoxicillin-based (n = 375 886)	Standardized difference[b]
Age, mean (SD), y	61.9 (14.7)	58.5 (14.7)	0.23	59.9 (14.8)	59.9 (14.8)	<0.01
Women	135 754 (53.9)	183 987 (49.1)	0.10	128 140 (51.1)	192 210 (51.1)	<0.01
Men	115 972 (46.1)	190 609 (50.9)	0.10	122 596 (48.9)	183 676 (48.9)	<0.01
Race[c]						
Black	82 791 (32.9)	148 606 (39.7)	0.14	91 979 (36.7)	138 121 (36.7)	<0.01
White	155 493 (61.8)	204 375 (54.6)	0.15	144 761 (57.7)	216 767 (57.7)	<0.01
Other	13 442 (5.3)	21 615 (5.8)	0.02	13 995 (5.6)	20 997 (5.6)	<0.01
Hispanic ethnicity	48 407 (19.2)	64 240 (17.1)	0.05	45 425 (18.1)	67 873 (18.1)	<0.01
Medicare Part D low-income subsidy	198 325 (78.8)	290 742 (77.6)	0.03	195 332 (77.9)	293 334 (78.0)	<0.01
Time on maintenance dialysis, y						
<1.0	33 663 (13.4)	44 964 (12.0)	0.04	31 518 (12.6)	47 303 (12.6)	<0.01
1.0-1.9	40 909 (16.3)	56 363 (15.0)	0.03	38 864 (15.5)	58 373 (15.5)	<0.01
2.0-2.9	35 581 (14.1)	50 295 (13.4)	0.02	34 481 (13.8)	51 648 (13.7)	<0.01
≥3.0	141 573 (56.2)	222 974 (59.5)	0.07	145 873 (58.2)	218 562 (58.1)	<0.01
Cause of ESKD						
Diabetes	123 447 (49.0)	167 773 (44.8)	0.09	116 988 (46.7)	175 344 (46.6)	<0.01
Hypertension	65 266 (25.9)	103 153 (27.5)	0.04	66 913 (26.7)	100 668 (26.8)	<0.01
Glomerular disease	27 399 (10.9)	49 059 (13.1)	0.07	30 520 (12.2)	45 663 (12.1)	<0.01
Other	35 614 (14.1)	54 611 (14.6)	0.01	36 315 (14.5)	54 210 (14.4)	<0.01
Arrhythmia	73 015 (29.0)	92 023 (24.6)	0.10	66 613 (26.6)	99 805 (26.6)	<0.01
Conduction disorder	20 200 (8.0)	25 232 (6.7)	0.05	18 339 (7.3)	27 447 (7.3)	<0.01
Heart failure	113 616 (45.1)	134 539 (35.9)	0.19	100 321 (40.0)	150 189 (40.0)	<0.01
Hypertension	223 494 (88.8)	319 069 (85.2)	0.11	217 595 (86.8)	326 019 (86.7)	<0.01
Ischemic heart disease	118 737 (47.2)	148 959 (39.8)	0.15	108 031 (43.1)	161 715 (43.0)	<0.01
Stroke	56 145 (22.3)	64 934 (17.3)	0.12	48 792 (19.5)	73 271 (19.5)	<0.01
Asthma or COPD	91 288 (36.3)	97 937 (26.1)	0.22	76 656 (30.6)	114 886 (30.6)	<0.01
History of nonadherence	16 825 (6.7)	22 606 (6.0)	0.03	15 971 (6.4)	23 844 (6.3)	<0.01
Use of ≥1 medication with known TdP risk[d]	45 101 (17.9)	53 449 (14.3)	0.10	39 739 (15.8)	59 711 (15.9)	<0.01
Use of ≥1 medication with any risk of TdP[d]	159 622 (63.4)	217 813 (58.1)	0.11	151 461 (60.4)	227 087 (60.4)	<0.01
Use of antibiotics in last 30 d of baseline						
Oral antibiotic use	60 431 (24.0)	64 636 (17.3)	0.17	51 307 (20.5)	76 828 (20.4)	<0.01
Intravenous antibiotic use	42 207 (16.8)	33 086 (8.8)	0.24	30 669 (12.2)	46 300 (12.3)	<0.01
Infection in the last 60 d of baseline						
Pneumonia	55 995 (22.2)	46 086 (12.3)	0.27	41 410 (16.5)	62 381 (16.6)	<0.01
Acute respiratory	51 737 (20.6)	64 723 (17.3)	0.08	47 131 (18.8)	70 572 (18.8)	<0.01
Chronic respiratory	32 494 (12.9)	32 743 (8.7)	0.13	26 472 (10.6)	39 796 (10.6)	<0.01
No. of baseline hospital admissions						
0	135 648 (53.9)	234 707 (62.7)	0.18	146 907 (58.6)	220 620 (58.7)	<0.01
1	57 586 (22.9)	76 840 (20.5)	0.06	54 262 (21.6)	81 062 (21.6)	<0.01
≥2	58 492 (23.2)	63 049 (16.8)	0.16	49 567 (19.8)	74 204 (19.7)	<0.01
ECG during the last 30 d of baseline	56 968 (22.6)	59 880 (16.0)	0.17	47 011 (18.7)	70 639 (18.8)	<0.01

Abbreviations: COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ESKD, end-stage kidney disease; TdP, torsade de pointes.

[a] All covariates were measured during the 180-day baseline period. The weighted cohort is the pseudopopulation generated by inverse probability of treatment weighting. eTable 4 in the Supplement displays the full list of baseline characteristics considered. All of these variables were used to estimate propensity scores and inverse probability of treatment weights.

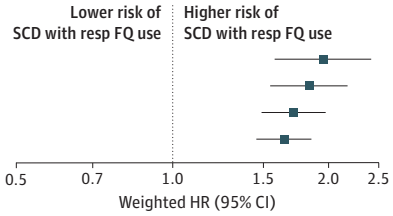
[b] Values greater than 0.10 represent meaningful imbalance between groups.

[c] Information on race was obtained from the US Renal Data System Medical Evidence Report form; categories included Black, White, and Other (individuals not considered Black or White, eg, Asian, Hawaiian/Pacific Islander).

[d] Drugs were classified as having a known, possible, or conditional TdP risk using a clinical resource with up-to-date information about medications that can cause QT interval prolongation and/or TdP.[16] Medications classified as having any level of TdP risk are those falling into any of the 3 categories. Medications in each category are given in eTable 3 in the Supplement.

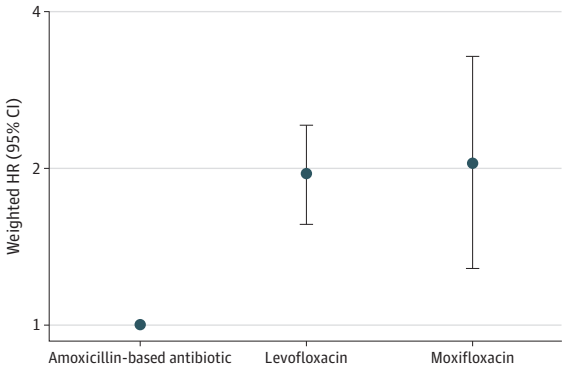
Figure 2. Respiratory Fluoroquinolone (Resp FQ) vs Amoxicillin (AMOX)–Based Antibiotic Treatment and Sudden Cardiac Death (SCD)

Variable	Weighted HR (95% CI)
5-d Follow-up, resp FQ vs AMOX-based antibiotics	1.95 (1.57-2.41)
7-d Follow-up, resp FQ vs AMOX-based antibiotics	1.83 (1.54-2.17)
10-d Follow-up, resp FQ vs AMOX-based antibiotics	1.71 (1.48-1.97)
14-d Follow-up, resp FQ vs AMOX-based antibiotics	1.64 (1.45-1.85)



Associations between resp FQ vs AMOX-based antibiotic treatment and SCD at 5, 7, 10, and 14 days of follow-up are displayed. An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate hazard ratios (HRs) and 95% CIs. Inverse probability of treatment weighting was used for confounding control. Weighted (ie, adjusted) HRs are presented. Corresponding weighted risk differences (95% CI) per 100 000 treatment episodes are listed in Table 2.

Figure 3. Individual Respiratory Fluoroquinolone Treatment vs Amoxicillin-Based Antibiotic Treatment and 5-day Sudden Cardiac Death



Associations between levofloxacin and moxifloxacin treatment vs amoxicillin-based antibiotic treatment (considered separately) and sudden cardiac death at 5 days of follow-up. An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate hazard ratios (HRs) and 95% CIs. Inverse probability of treatment weighting was used for confounding control. Weighted (ie, adjusted) HRs are presented. Corresponding weighted risk differences (95% CI) per 100 000 treatment episodes are listed in eTable 7 in the Supplement.

treatment and 244 during amoxicillin-based antibiotic treatment. The corresponding incidence of events was 98.9 fractures per 100 000 treatment episodes in the respiratory fluoroquinolone group compared with 65.1 fractures per 100 000 treatment episodes in the amoxicillin-based antibiotic group. Analyses evaluating the study antibiotic-negative control outcome association found that respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was not associated with the 5-day risk of hospitalized fracture (weighted HR, 1.09; 95% CI, 0.90 to 1.31; weighted RD per 100 000 treatment episodes, 6.7; 95% CI, -7.6 to 21.3) (eTable 9 in the Supplement).

Discussion

In this retrospective cohort study on cardiac safety, we found that patients receiving in-center hemodialysis treated with a respiratory fluoroquinolone vs an amoxicillin-based antibiotic had a higher short-term risk of SCD, with the most pronounced risk at 5 days. This risk was heightened among individuals taking other medications with known TdP risk, and the observed association was consistent across several sensitivity analyses.

Our findings are consistent with meta-analyses of large pharmacoepidemiologic studies of the general population reporting that respiratory fluoroquinolone use is associated with a heightened risk of cardiac complications compared with β-lactam antibiotic use and antibiotic nonuse.[7,8] The QT interval-prolonging potential of fluoroquinolones has been well described,[5,6] and some agents, such as grepafloxacin and sparfloxacin, have been removed from the US and other international markets due, in part, to cardiac safety concerns.[36] The levofloxacin and moxifloxacin package inserts warn prescribers of potential QT interval prolongation and TdP, particularly in the setting of electrolyte abnormalities and when other QT interval-prolonging medications are used.[17,18] Levofloxacin and moxifloxacin block myocardial potassium channels encoded by the human ether-a-go-go-related gene (*hERG*).[37,38] This blockade reduces the delayed rectifier potassium current, delaying ventricular repolarization and creating an electrophysiologic environment conducive to TdP.[39]

Individuals receiving maintenance hemodialysis may be particularly susceptible to the QT interval-prolonging effects of respiratory fluoroquinolones. For example, structural heart disease is highly prevalent in the hemodialysis population, and conditions such as left ventricular hypertrophy and heart failure can lead to cardiac remodeling and associated downregulation of *hERG* and other myocardial ion channels.[40,41] The resultant diminished repolarization reserve renders the heart susceptible to proarrhythmic triggers, such as QT interval-prolonging medications.[40,42] In addition, reductions in extracellular potassium levels can enhance drug-induced inhibition of the cardiac repolarizing ionic potassium current.[42] Patients receiving hemodialysis are recurrently exposed to dialysis treatment-related electrolyte shifts, potentially enhancing the proarrhythmic risk of QT interval-prolonging medications. Also, it is well established that using multiple drugs that can prolong the QT interval may result in more profound QT interval prolongation, increasing cardiac risk.[39] Patients receiving hemodialysis are exposed to 2 or more QT interval-prolonging medications with known TdP risk at a rate 7 times

Table 2. Respiratory Fluoroquinolone vs Amoxicillin-based Antibiotic Treatment and Outcomes[a]

Outcome by follow-up, d	No. of events	Respiratory fluoroquinolones vs amoxicillin-based antibiotics	
		Weighted HR (95% CI)	Weighted RD per 100 000 treatment episodes (95% CI)
Sudden cardiac death			
5	416	1.95 (1.57-2.41)	44.0 (31.0-59.2)
7	615	1.83 (1.54-2.17)	58.3 (41.9-75.0)
10	880	1.71 (1.48-1.97)	73.9 (53.5-93.5)
14	1235	1.64 (1.45-1.85)	97.3 (71.9-120.3)
Sudden cardiac death or hospitalization due to ventricular arrhythmia			
5	465	1.92 (1.57-2.34)	48.0 (34.6-64.3)
7	681	1.79 (1.52-2.11)	62.8 (45.4-79.3)
10	961	1.69 (1.47-1.94)	80.1 (59.2-101.2)
14	1339	1.61 (1.43-1.80)	101.5 (75.6-125.5)
Cardiovascular death			
5	548	1.89 (1.57-2.27)	55.0 (39.2-71.4)
7	793	1.75 (1.50-2.04)	69.9 (51.7-88.1)
10	1172	1.66 (1.47-1.88)	93.3 (71.4-115.6)
14	1682	1.62 (1.46-1.79)	128.6 (99.7-154.7)
All-cause death			
5	1005	2.17 (1.88-2.50)	121.1 (101.8-145.3)
7	1475	1.98 (1.76-2.22)	156.9 (131.4-186.4)
10	2255	1.83 (1.67-2.00)	213.8 (185.7-248.0)
14	3335	1.75 (1.63-1.89)	296.7 (262.0-340.3)

Abbreviations: HR, hazard ratio; RD, risk difference.

[a] An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate HRs, and the Aalen-Johansen estimator was used to estimate RDs. Inverse probability of treatment weighting was used for confounding control.

that of similarly aged individuals without dialysis-dependent kidney failure.[9]

Our study provides population-specific safety data suggesting that respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment elevates the already high underlying SCD risk among individuals receiving in-center hemodialysis. Even though the QT interval–prolonging potential of individual respiratory fluoroquinolones differs, we found that the risk of SCD during levofloxacin and moxifloxacin vs amoxicillin-based antibiotic treatment was similar. These findings are consistent with randomized clinical trial data demonstrating that levofloxacin and moxifloxacin have comparable cardiac safety profiles in older patients with pneumonia.[43] We also found that patients taking other medications with known TdP risk had higher risks of SCD during respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment compared with those not receiving such medications. Despite prescribing guidance against it,[17,18] concomitant use of respiratory fluoroquinolones with other medications with known TdP risk was common in our study (nearly 20% of respiratory fluoroquinolone treatment episodes). Our results emphasize the importance of performing a thorough medication review and considering pharmacodynamic drug interactions before prescribing new drug therapies for any condition.

Strategies that prevent SCD in the general population, such as implantable cardioverter-defibrillators,[44] appear to be ineffective in the hemodialysis population. As such, any practice that potentially lowers the SCD risk in patients receiving hemodialysis may be of clinical importance. Our data suggest that curtailing respiratory fluoroquinolone prescribing may be one actionable strategy to mitigate SCD risk in the hemodialysis population. However, the associated absolute risk reduction would be relatively small; we found that 1 additional SCD event would occur during a 5-day follow-up period for every 2273 respiratory fluoroquinolone treatment episodes. Given that pathogen-directed treatment of respiratory infections is paramount, the risks associated with undertreatment of an infection with an amoxicillin-based antibiotic likely far outweigh the potential cardiac risks from treatment with a respiratory fluoroquinolone. Respiratory fluoroquinolones should still be prescribed to patients receiving hemodialysis when an amoxicillin-based antibiotic would be suboptimal. When prescribing respiratory fluoroquinolones, clinicians should consider electrocardiographic monitoring before and during therapy, especially among high-risk individuals.[39]

Strengths and Limitations

Strengths of our study include using US Renal Data System Medicare claims data to conduct a large-scale cardiac safety assessment of respiratory fluoroquinolones applying a new-user design to mitigate selection and immortal time biases and performing a head-to-head comparison of respiratory fluoroquinolones and amoxicillin-based antibiotics to minimize the effects of confounding by indication. In addition, this comparison reflects a meaningful treatment decision encountered by clinicians when treating respiratory infections.[3,17-20]

The study has limitations. First, because this study was observational, residual confounding may remain, including potential indication bias from prescribing respiratory fluoroquinolones vs amoxicillin-based antibiotics to patients with more

severe infections or a greater overall comorbid condition burden. Sensitivity analyses comparing respiratory fluoroquinolones with a more tailored treatment alternative—amoxicillin with clavulanic acid—yielded results similar to our primary analyses. In addition, we did not observe an association between study antibiotics and fracture, which was the negative control outcome. However, we noted that respiratory fluoroquinolone vs amoxicillin-based antibiotic treatment was associated with all-cause mortality. Despite accounting for numerous clinical and health care use metrics to minimize confounding from difficult-to-measure factors, it is possible that indication bias may remain, and our results should be interpreted within the context of these limitations. Second, although we ascertained electrocardiogram performance in the month before study medication initiation, we were unable to determine whether electrocardiogram findings were used to inform prescribing decisions. Third, although we defined SCD as reported by physicians on the Death Notification form, contemporary information on the sensitivity and specificity of this definition is limited.[20,21] Outcome misclassification may have occurred, but it is likely that such misclassification would be nondifferential (ie, not differ between exposure categories). Analyses considering broader cardiac outcomes yielded consistent results. Fourth, Medicare Part D prescription claims data lack information on medication administration instructions; thus, we were unable to evaluate whether failing to properly adjust levofloxacin dosing in patients with kidney failure affects SCD risk. Fifth, our findings may not generalize to other fluoroquinolones, other comparator antibiotics (eg, macrolides), or to patients excluded from this study, such as those with recent hospitalizations, without Medicare coverage, and without non-dialysis-dependent kidney disease.

Conclusions

In this study, respiratory fluoroquinolone treatment compared with amoxicillin-based antibiotic treatment was associated with a higher short-term risk of SCD. However, in many cases, the antimicrobial benefits of prescribing a respiratory fluoroquinolone may outweigh the potential cardiac risks of these drugs.

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Concept and design: Assimon, Pun, Al-Khatib, Weber, Winkelmayer, Flythe.
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