Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors among Individuals Receiving Maintenance Hemodialysis

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ABSTRACT

Background Individuals receiving maintenance hemodialysis may be particularly susceptible to the lethal cardiac consequences of drug-induced QT prolongation because they have a substantial cardiovascular disease burden and high level of polypharmacy, as well as recurrent exposure to electrolyte shifts during dialysis. Electrophysiologic data indicate that among the selective serotonin reuptake inhibitors (SSRIs), citalopram and escitalopram prolong the QT interval to the greatest extent. However, the relative cardiac safety of SSRIs in the hemodialysis population is unknown.

Methods In this retrospective cohort study, we used data from a cohort of Medicare beneficiaries receiving hemodialysis included in the US Renal Data System registry (2007–2014). We used a new-user design to compare the 1-year risk of sudden cardiac death among hemodialysis patients initiating SSRIs with a higher potential for prolonging the QT interval (citalopram, escitalopram) versus the risk among those initiating SSRIs with lower QT-prolonging potential (fluoxetine, fluvoxamine, paroxetine, sertraline). We estimated adjusted hazard ratios using inverse probability of treatment weighted survival models. Nonsudden cardiac death was treated as a competing event.

Results The study included 30,932 (47.1%) hemodialysis patients who initiated SSRIs with higher QT-prolonging potential and 34,722 (52.9%) who initiated SSRIs with lower QT-prolonging potential. Initiation of an SSRI with higher versus lower QT-prolonging potential was associated with higher risk of sudden cardiac death (adjusted hazard ratio, 1.18; 95% confidence interval, 1.05 to 1.31). This association was more pronounced among elderly individuals, females, patients with conduction disorders, and those treated with other non-SSRI QT-prolonging medications.

Conclusions The heterogeneous QT-prolonging potential of SSRIs may differentially affect cardiac outcomes in the hemodialysis population.

Depression affects 25%–40% of the hemodialysis population¹ and associates with a range of adverse health outcomes, including treatment nonadherence, lower quality of life, higher hospitalization rates, and increased mortality.² With the inclusion of the Clinical Depression Screening and Follow-Up Reporting Measure in the 2018 ESRD Quality Incentive Program,³ the diagnosis and treatment of depression among United States hemodialysis patients became a quality-of-care target.

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patients may increase in the coming years. Selective serotonin reuptake inhibitors (SSRIs) are recommended as frontline agents for the pharmacologic management of depressive disorders, and in 2015, >20% of United States hemodialysis patients filled a prescription for an SSRI. Even though clinical trials have demonstrated that SSRIs are efficacious antidepressants in the hemodialysis population, their small sample sizes and limited follow-up time precluded adequate safety assessments.

Electrophysiologic data indicate that all six SSRIs have QT-prolonging capabilities. However, citalopram and escitalopram prolong the QT interval to the greatest extent at therapeutic doses, and currently carry pharmacologic regulatory agency–issued warnings related to their proarrhythmic potential. Although these cardiac safety warnings highlight patient populations at increased risk for QT prolongation and subsequent torsades de pointes (e.g., individuals with hypokalemia or hypomagnesemia), there is no specific mention of hemodialysis patients. Individuals receiving maintenance hemodialysis may be particularly susceptible to the lethal cardiac consequences of citalopram- and escitalopram-induced QT prolongation due to their substantial cardiovascular disease burden, recurrent exposure to electrolyte shifts during dialysis treatments, and extensive use of medications that can enhance the proarrhythmic effects of citalopram and escitalopram via pharmacokinetic and/or pharmacodynamic drug interactions.

In the proarrhythmic ESRD environment, the differential QT-prolonging nature of SSRIs may render certain SSRIs safer than others. We undertook this study to investigate the comparative cardiac safety of SSRIs in a cohort of >65,000 United States hemodialysis patients. We hypothesized that individuals initiating higher (citalopram or escitalopram) versus lower (fluoxetine, fluvoxamine, paroxetine or sertraline) QT-prolonging–potential SSRIs would have a higher risk of sudden cardiac death.

METHODS

This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (#17–0011). A waiver of consent was granted due to the study’s large size, data anonymity, and retrospective nature.

Data Source

The data source for this study was the US Renal Data System (USRDS) database. The USRDS is a national ESRD surveillance system that collects, analyzes, and distributes information on individuals with ESRD in the United States. The USRDS database includes the Medical Evidence and ESRD Death Notification Forms as well as Medicare standard analytic files, including the Medicare enrollment database and final action administrative claims (Medicare Parts A, B, and D).

Study Design and Population

We conducted a retrospective cohort study using an active comparator new-user design to investigate the association between the initiation of higher (citalopram or escitalopram) versus lower (fluoxetine, fluvoxamine, paroxetine, or sertraline) QT-prolonging–potential SSRIs and the 1-year risk of sudden cardiac death among individuals receiving maintenance hemodialysis. First, we identified hemodialysis patients with Medicare coverage (Parts A, B, and D) who newly initiated SSRI therapy from January 1, 2007 to December 30, 2014 after a 180-day washout period free of documented SSRI use. To be included in the study, SSRI new-users had to receive in-center hemodialysis during the 180 days before SSRI initiation (i.e., baseline period) and also have continuous Medicare Part A, B, and D coverage during this period. We then applied the following exclusion criteria: (1) age<18 years at the start of the baseline period, (2) dialysis vintage ≤90 days at the start of the baseline period, (3) presence of an implantable automatic cardiac defibrillator, (4) receipt of hospice care during the baseline period, and (5) missing demographic data. Thus, the study cohort consisted of prevalent, center-based hemodialysis patients who were SSRI new-users.

Study Exposure, Outcomes, and Baseline Covariates

We used Medicare Part D prescription claims to identify SSRI new-users. The index date was the date of the first SSRI prescription after the 180-day washout period. We used published QT Drug Lists from the CredibleMeds website to identify the QT-prolonging potential of SSRIs marketed in the United States during the study period. Funded by the US Food and Drug Administration (FDA), research grants, and charitable donations, CredibleMeds is a reliable and up-to-date clinical resource that contains information about medications that can cause QT prolongation and/or torsades de pointes. On the basis of published medical literature, medication package inserts, and the FDA’s Adverse Event Reporting System, CredibleMeds classifies medications

Significance Statement

Patients on hemodialysis may be particularly susceptible to the lethal cardiac consequences of drug-induced QT prolongation because they generally have a substantial cardiovascular disease burden and high level of polypharmacy, and are recurrently exposed to electrolyte shifts during dialysis. Electrophysiologic data indicate that among selective serotonin reuptake inhibitors (SSRIs), citalopram and escitalopram prolong the QT interval to the greatest extent. In a cohort of 65,654 hemodialysis patients, individuals receiving SSRIs with higher (citalopram, escitalopram) versus lower (fluoxetine, fluvoxamine, paroxetine, sertraline) potential to prolong the QT interval had a higher risk of sudden cardiac death. This risk was more pronounced among elderly individuals, females, those with conduction disorders, and those taking other non-SSRI QT-prolonging medications. When prescribing SSRIs to patients on hemodialysis, clinicians should consider the QT-prolonging potential of these agents.
as having a known, conditional, or possible risk of torsades de pointes (corresponding definitions are provided in Table 1). Citalopram and escitalopram are classified as having a known risk of torsades de pointes. Fluoxetine, fluvoxamine, paroxetine, and sertraline are classified as having a conditional risk of torsades de pointes. Thus, we considered (1) citalopram and escitalopram new-users as initiators of a higher QT-prolonging-potential SSRI, and (2) fluoxetine, fluvoxamine, paroxetine, and sertraline new-users as initiators of a lower QT-prolonging-potential SSRI.

The primary outcome of interest was 1-year sudden cardiac death. We defined sudden cardiac death using the established USRDS definition, death due to cardiac arrhythmia or cardiac arrest listed as the primary cause (Supplemental Table 1). We obtained dates and causes of death from the ESRD Death Notification Form. We used a 1-year follow-up period to mirror clinical practice guidelines which recommend that patients starting an initial course of antidepressant pharmacotherapy are treated for a minimum of 6–12 weeks to achieve initial depressive symptom remission, followed by an additional 4–9 months of continued antidepressant treatment to prevent relapse (i.e., approximately 1 year of total pharmacotherapy).

Baseline covariates included potential confounders and variables known to be strong risk factors for the study outcome. We identified covariates in the 180 days before the index date using Medicare Part A, B, and D claims. Covariates of interest included patient demographics, comorbid conditions, prescription medication use, and metrics of health care utilization. Comorbid conditions were considered present if an applicable International Classification of Diseases, Ninth Revision discharge code (located in any position) was associated with ≥1 institutional or physician/supplier claim during the 180-day baseline period (Supplemental Table 2). Medication utilization on the last day of the baseline period was determined using Medicare Part D claims and Healthcare Common Procedure Coding System codes (for medications not covered by Medicare Part D, such as intravenous drugs). Non-SSRI QT-prolonging medications of interest included drugs classified as having a known, conditional, and possible risk of torsades de pointes according to CredibleMeds (Supplemental Tables 3 and 4). Cytochrome P450 inhibitors of interest included medications that can reduce the hepatic metabolism of SSRIs (Supplemental Table 5). Use of a 180-day baseline period enabled us to: (1) maximize cohort generalizability and (2) capture patient characteristics occurring close to study medication initiation that may have influenced SSRI-prescribing decisions and were highly predictive of the study outcome.

<table>
<thead>
<tr>
<th>CredibleMeds Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known risk of torsades de pointes</td>
<td>Drugs that prolong the QT interval and are clearly associated with a known risk of torsades de pointes, even when taken as recommended.</td>
</tr>
<tr>
<td>Conditional risk of torsades de pointes</td>
<td>Drugs that are associated with torsades de pointes only under certain conditions (e.g., excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or drugs that create conditions that facilitate or induce torsades de pointes (e.g., cause an electrolyte disturbance that induces torsades de pointes).</td>
</tr>
<tr>
<td>Probable risk of torsades de pointes</td>
<td>Drugs that can cause QT prolongation but currently lack evidence for a risk of torsades de pointes when taken as recommended.</td>
</tr>
</tbody>
</table>
All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). We described baseline characteristics across individuals who initiated higher and lower QT-prolonging–potential SSRIs as count (percentage) for categoric variables and as mean±SD for continuous variables. We compared baseline covariate distributions using absolute standardized differences. A standardized difference >10% represents an imbalance between exposure groups.33

We used an on-treatment (i.e., per-protocol) analytic approach to evaluate the association between the initiation of a higher versus lower QT-prolonging–potential SSRI and the 1-year risk of sudden cardiac death. Individuals were followed forward in historical time from the index date to the first occurrence of the study outcome, censoring event, or competing event. Censoring events included: (1) change of dialysis modality to home hemodialysis or peritoneal dialysis; (2) kidney transplantation; (3) recovery of kidney function; (4) loss of Medicare Part A, B, or D coverage; (5) discontinuation of index SSRI therapy; (6) switch to a nonindex SSRI; (7) completion of 1-year of follow-up; and (8) study end (December 31, 2014). We defined the SSRI discontinuation date as the date when the index SSRI was exhausted for >7 days (i.e., grace period) without a subsequent dispensing of the same SSRI (Supplemental Figure 1). We defined the index SSRI switching date as the date of the first prescription fill for a nonindex SSRI during follow-up. Patients were at risk for a switching event only during times of continuous index medication use (Supplemental Figure 1).

In primary analyses, we assessed the SSRI QT-prolonging potential–sudden cardiac death association in the full study cohort using Fine and Gray proportional subdistribution hazard models, treating nonsudden cardiac death as a competing risk.34 In prespecified, exploratory secondary analyses, we evaluated the SSRI QT-prolonging potential–sudden cardiac death association within clinically relevant subgroups using the same analytic approach. Subgroups of interest included individuals with and without known risk factors for drug-induced QT prolongation: advanced age, female sex, cardiac conduction disorder, heart failure, liver disease, and use of other non-SSRI QT-prolonging medications.35,36 Across all analyses, we used inverse probability of treatment (IPT) weighting to control for confounding. Briefly, we calculated the predicted probability (i.e., propensity score) of receiving an SSRI with higher versus lower QT-prolonging potential as a function of baseline covariates using multivariable logistic regression. We generated IPT weights from propensity scores using standard methods and estimated adjusted hazard ratios (HRs) by applying IPT weights in regression models.37,38

We conducted several sensitivity analyses to evaluate the robustness of our primary study findings. First, we evaluated two alternative study outcomes including: (1) a composite outcome of sudden cardiac death or hospitalized ventricular arrhythmia and (2) cardiovascular mortality (Supplemental Table 1). In analyses evaluating cardiovascular mortality, noncardiovascular death was treated as a competing risk. Second, we compared citalopram and escitalopram initiators (separately) to initiators of an SSRI with lower QT-prolonging potential using methods analogous to the primary analyses. Third, because exact dates of medication discontinuation are not available in administrative claims data, we repeated primary analyses using longer grace periods of 14 and 30 days to define index SSRI discontinuation. Fourth, because long-term antidepressant therapy may be required in some patients (i.e., those with histories of multiple major depressive episodes or residual depressive symptoms), we repeated primary analyses using all available follow-up time.4 Fifth, we used an intention-to-treat analytic approach (i.e., first-exposure–carried-forward analysis) to evaluate the SSRI QT-prolonging potential–sudden cardiac death association. In these analyses, we did not consider SSRI discontinuation and switching as censoring events. Sixth, to test the specificity of our findings we evaluated the association between the initiation of a higher versus lower QT-prolonging–potential SSRI and nonsudden cardiac death, a negative control outcome that we did not expect to be influenced by SSRI type.39 In these analyses, sudden cardiac death was treated as a competing risk.

RESULTS

Study Cohort Characteristics

Figure 2 displays a flow diagram of study cohort selection. A total of 65,654 individuals receiving maintenance hemodialysis were included in the study: 30,932 (47.1%) initiators of higher QT-prolonging–potential SSRIs and 34,722 (52.9%) initiators of lower QT-prolonging–potential SSRIs. There were 16,288 (32.3%) citalopram, 14,644 (22.3%) escitalopram, 6468 (9.9%) fluoxetine, 44 (0.1%) fluvoxamine, 7011 (10.7%) paroxetine, and 21,199 (32.3%) sertraline initiators in the study cohort. Overall, study patients had an average age of 67.0±17.2 years, 52.8% were women, 35.5% were black, 19.2% were Hispanic, and the most common cause of ESRD was diabetes (50.2%). Depression (33.2%) and anxiety (17.7%) were the most prevalent mental health conditions.

The propensity score distribution of initiators of higher and lower QT-prolonging–potential SSRIs exhibited substantial overlap (Supplemental Figure 2), indicating that study groups were highly comparable. Table 2 and Supplemental Table 6 show patient baseline characteristics stratified by SSRI QT-prolonging potential (higher versus lower). Before IPT weighting, baseline covariates were generally well balanced between treatment groups (standardized differences ≤10%), with some exceptions (e.g., race other than black or white, year of index SSRI fill, depression, and history of stroke). After IPT weighting, all baseline covariates were well balanced between treatment groups.
Under the on-treatment analytic paradigm, the study cohort was followed for a total of 16,633 person-years (7858 person-years for initiators of a higher QT-prolonging potential SSRI and 8775 person-years for initiators of a lower QT-prolonging potential SSRI). A total of 51,005 individuals discontinued index SSRI therapy, and 2017 individuals switched to nonindex SSRI during follow-up. The median (interquartile range) duration of follow-up was 37 (65) days among patients initiating an SSRI of higher QT-prolonging potential, and 37 (63) days among patients initiating an SSRI with lower QT-prolonging potential. Exposure to non-SSRI QT-prolonging medications during follow-up was similar among initiators of higher and lower QT-prolonging potential SSRIs.

During the 1-year follow-up period, 1303 sudden cardiac deaths occurred at an incidence rate of 78.3 events per 1000 person-years (702 sudden death events occurred at an incidence rate of 89.3 events per 1000 person-years among initiators of higher QT-prolonging potential SSRIs, and 601 sudden death events occurred at a rate of 68.5 events per 1000 person-years among initiators of lower QT-prolonging potential SSRIs). Figure 3 and Supplemental Table 7 display the SSRI QT-prolonging potential–sudden cardiac death association. Compared with individuals initiating lower QT-prolonging potential SSRIs, individuals initiating higher QT-prolonging potential SSRIs had a higher 1-year risk of sudden cardiac death (adjusted HR, 1.18; 95% confidence interval, 1.05 to 1.31).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unweighted</th>
<th>Weighted</th>
<th>Std Diff(a) (%)</th>
<th>Unweighted</th>
<th>Weighted</th>
<th>Std Diff(a) (%)</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>67.6 ± 17.2</td>
<td>66.5 ± 17.2</td>
<td>6.2</td>
<td>67.0 ± 17.2</td>
<td>67.0 ± 17.2</td>
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<td>Female</td>
<td>16,512 (53.4%)</td>
<td>18,121 (52.2%)</td>
<td>2.3</td>
<td>16,316 (52.8%)</td>
<td>18,324 (52.8%)</td>
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</tr>
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<td>Race</td>
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<td></td>
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<td>Black</td>
<td>11,339 (36.7%)</td>
<td>11,959 (34.4%)</td>
<td>6.3</td>
<td>10,967 (35.5%)</td>
<td>12,320 (35.5%)</td>
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<tr>
<td>White</td>
<td>18,434 (59.6%)</td>
<td>21,005 (60.5%)</td>
<td>1.5</td>
<td>18,589 (60.1%)</td>
<td>20,870 (60.1%)</td>
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<tr>
<td>Other</td>
<td>1159 (3.7%)</td>
<td>1758 (5.1%)</td>
<td>33.5</td>
<td>1371 (4.4%)</td>
<td>1540 (4.4%)</td>
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<td>Hispanic</td>
<td>5233 (16.9%)</td>
<td>7346 (21.2%)</td>
<td>22.7</td>
<td>5933 (19.2%)</td>
<td>6654 (19.2%)</td>
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</tr>
<tr>
<td>Year index SSRI was filled</td>
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<td>2007</td>
<td>3961 (12.8%)</td>
<td>4751 (13.7%)</td>
<td>6.9</td>
<td>4086 (13.2%)</td>
<td>4594 (13.2%)</td>
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<td>2008</td>
<td>4095 (13.2%)</td>
<td>4388 (12.6%)</td>
<td>4.8</td>
<td>3977 (12.9%)</td>
<td>4468 (12.9%)</td>
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<td>2009</td>
<td>4061 (13.1%)</td>
<td>4343 (12.5%)</td>
<td>5.0</td>
<td>3948 (12.8%)</td>
<td>4435 (12.8%)</td>
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<td>2010</td>
<td>4139 (13.4%)</td>
<td>4161 (12.0%)</td>
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<td>3907 (12.6%)</td>
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<td>2011</td>
<td>4034 (13.0%)</td>
<td>4061 (11.7%)</td>
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<td>3814 (12.3%)</td>
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<td>2012</td>
<td>3611 (11.7%)</td>
<td>4152 (12.0%)</td>
<td>2.5</td>
<td>3670 (11.9%)</td>
<td>4118 (11.9%)</td>
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<td>2013</td>
<td>3507 (11.3%)</td>
<td>4398 (12.7%)</td>
<td>11.5</td>
<td>3738 (12.1%)</td>
<td>4194 (12.1%)</td>
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<td>2014</td>
<td>3524 (11.4%)</td>
<td>4468 (12.9%)</td>
<td>12.7</td>
<td>3787 (12.2%)</td>
<td>4246 (12.2%)</td>
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<td>Low-dose index SSRI(b)</td>
<td>27,935 (90.3%)</td>
<td>31,560 (90.9%)</td>
<td>0.6</td>
<td>28,011 (90.6%)</td>
<td>31,456 (90.6%)</td>
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<td>Cause of ESRD</td>
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<td>Diabetes</td>
<td>15,563 (50.3%)</td>
<td>17,416 (50.2%)</td>
<td>0.3</td>
<td>15,542 (50.3%)</td>
<td>17,458 (50.3%)</td>
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<td>Hypertension</td>
<td>7941 (25.7%)</td>
<td>8760 (25.2%)</td>
<td>1.8</td>
<td>7848 (25.4%)</td>
<td>8813 (25.4%)</td>
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<td>Glomerular disease</td>
<td>3359 (10.9%)</td>
<td>3934 (11.3%)</td>
<td>4.4</td>
<td>3442 (11.1%)</td>
<td>3864 (11.1%)</td>
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<td>Other</td>
<td>4069 (13.2%)</td>
<td>4612 (13.3%)</td>
<td>1.0</td>
<td>4095 (13.2%)</td>
<td>4596 (13.2%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Dialysis vintage, yr</td>
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<tr>
<td>0.7–0.9</td>
<td>5467 (17.7%)</td>
<td>5903 (17.0%)</td>
<td>4.0</td>
<td>5364 (17.3%)</td>
<td>6023 (17.3%)</td>
<td>0.0</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>5965 (19.3%)</td>
<td>6622 (19.1%)</td>
<td>1.1</td>
<td>5939 (19.2%)</td>
<td>6661 (19.2%)</td>
<td>0.0</td>
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<tr>
<td>2.0–2.9</td>
<td>4631 (15.0%)</td>
<td>5136 (14.8%)</td>
<td>1.3</td>
<td>4594 (14.9%)</td>
<td>5162 (14.9%)</td>
<td>0.1</td>
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<tr>
<td>≥3</td>
<td>14,869 (48.1%)</td>
<td>17,061 (49.1%)</td>
<td>2.2</td>
<td>15,035 (48.6%)</td>
<td>16,883 (48.6%)</td>
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<td>Depression</td>
<td>10,960 (35.4%)</td>
<td>10,851 (31.3%)</td>
<td>12.7</td>
<td>10,298 (33.3%)</td>
<td>11,567 (33.3%)</td>
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<td>Anxiety</td>
<td>5590 (18.1%)</td>
<td>6046 (17.4%)</td>
<td>3.8</td>
<td>5492 (17.8%)</td>
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<td>Arrhythmia</td>
<td>9616 (31.1%)</td>
<td>10,135 (29.2%)</td>
<td>6.4</td>
<td>9327 (30.2%)</td>
<td>10,471 (30.1%)</td>
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<tr>
<td>Conduction disorder</td>
<td>2434 (7.9%)</td>
<td>2659 (7.7%)</td>
<td>2.9</td>
<td>2403 (7.8%)</td>
<td>2699 (7.8%)</td>
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<td>Dyslipidemia</td>
<td>15,756 (50.9%)</td>
<td>17,566 (50.6%)</td>
<td>0.7</td>
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<td>17,652 (50.8%)</td>
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<td>Heart failure</td>
<td>14,937 (48.3%)</td>
<td>15,884 (45.7%)</td>
<td>5.5</td>
<td>14,536 (47.0%)</td>
<td>16,321 (47.0%)</td>
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<td>Hypertension</td>
<td>28,289 (91.5%)</td>
<td>31,297 (90.1%)</td>
<td>1.5</td>
<td>28,073 (90.8%)</td>
<td>31,522 (90.8%)</td>
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<td>Ischemic heart disease</td>
<td>15,171 (49.0%)</td>
<td>16,216 (46.7%)</td>
<td>4.9</td>
<td>14,810 (47.9%)</td>
<td>16,624 (47.9%)</td>
<td>0.0</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>11,332 (36.6%)</td>
<td>11,737 (33.8%)</td>
<td>8.2</td>
<td>10,878 (35.2%)</td>
<td>12,216 (35.2%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>8225 (26.6%)</td>
<td>8033 (23.1%)</td>
<td>14.2</td>
<td>7668 (24.8%)</td>
<td>8615 (24.8%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2112 (6.8%)</td>
<td>2165 (6.2%)</td>
<td>9.8</td>
<td>2023 (6.5%)</td>
<td>2273 (6.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1385 (4.5%)</td>
<td>1577 (4.5%)</td>
<td>1.6</td>
<td>1400 (4.5%)</td>
<td>1570 (4.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Unweighted</td>
<td>SSRI with Lower QT-Prolonging Potential, n=34,722</td>
<td>Std Diffa (%)</td>
<td>Weighted</td>
<td>SSRI with Lower QT-Prolonging Potential, n=34,730</td>
<td>Std Diffa (%)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>------------</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21,520 (69.6%)</td>
<td>23,690 (68.2%)</td>
<td>2.0</td>
<td>21,305 (68.9%)</td>
<td>23,927 (68.9%)</td>
<td>0.0</td>
</tr>
<tr>
<td>History of noncompliance</td>
<td>3501 (11.3%)</td>
<td>4072 (11.7%)</td>
<td>3.7</td>
<td>3575 (11.6%)</td>
<td>4013 (11.6%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Had a cardiac pacemaker</td>
<td>1431 (4.6%)</td>
<td>1463 (4.2%)</td>
<td>10.6</td>
<td>1361 (4.4%)</td>
<td>1529 (4.4%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Had an ECG during the last 30 d of baseline</td>
<td>588 (1.9%)</td>
<td>614 (1.8%)</td>
<td>10.7</td>
<td>565 (1.8%)</td>
<td>635 (1.8%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Had a cardiac surgery during the last 30 d of baseline</td>
<td>9908 (32.0%)</td>
<td>10,796 (31.1%)</td>
<td>3.0</td>
<td>9777 (31.6%)</td>
<td>10,974 (31.6%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Had an ECG during the last 30 d of baseline</td>
<td>5749 (18.6%)</td>
<td>6542 (18.8%)</td>
<td>1.4</td>
<td>5801 (18.8%)</td>
<td>6509 (18.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>3018 (9.8%)</td>
<td>3530 (10.2%)</td>
<td>4.3</td>
<td>3082 (10.0%)</td>
<td>3462 (10.0%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>8768 (28.3%)</td>
<td>10,385 (29.9%)</td>
<td>5.5</td>
<td>9031 (29.2%)</td>
<td>10,141 (29.2%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Central α agonist</td>
<td>3906 (12.6%)</td>
<td>4413 (12.7%)</td>
<td>0.7</td>
<td>3913 (12.7%)</td>
<td>4394 (12.7%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2903 (9.4%)</td>
<td>3565 (10.3%)</td>
<td>9.5</td>
<td>3048 (9.9%)</td>
<td>3420 (9.8%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of ≥1 medication with a known risk of TdP</td>
<td>11,442 (37.0%)</td>
<td>13,114 (37.8%)</td>
<td>2.1</td>
<td>11,562 (37.4%)</td>
<td>12,981 (37.4%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Use of ≥1 medication with a conditional risk of TdP</td>
<td>12,634 (40.8%)</td>
<td>14,238 (40.2%)</td>
<td>0.4</td>
<td>12,675 (41.0%)</td>
<td>14,231 (41.0%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Use of ≥1 medication with a possible risk of TdP</td>
<td>3228 (10.4%)</td>
<td>3123 (9.0%)</td>
<td>15.6</td>
<td>3001 (9.7%)</td>
<td>3375 (9.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of ≥1 CYP 1A2 inhibitor</td>
<td>1154 (3.7%)</td>
<td>1290 (3.7%)</td>
<td>0.5</td>
<td>1155 (3.7%)</td>
<td>1296 (3.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of ≥1 CYP 3A4 inhibitor</td>
<td>2419 (7.8%)</td>
<td>2770 (8.0%)</td>
<td>2.1</td>
<td>2450 (7.9%)</td>
<td>2746 (7.9%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Use of ≥1 CYP 2C9 inhibitor</td>
<td>2074 (6.7%)</td>
<td>2385 (6.9%)</td>
<td>2.6</td>
<td>2104 (6.8%)</td>
<td>2360 (6.8%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Use of ≥1 CYP 2C19 inhibitor</td>
<td>8119 (26.2%)</td>
<td>9022 (26.0%)</td>
<td>1.0</td>
<td>8095 (26.2%)</td>
<td>9087 (26.2%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Use of ≥1 CYP 2D6 inhibitor</td>
<td>8777 (28.4%)</td>
<td>9999 (28.8%)</td>
<td>1.5</td>
<td>8845 (28.6%)</td>
<td>9931 (28.6%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Hospitalized during the last 30 d of the baseline period</td>
<td>8701 (28.1%)</td>
<td>8749 (25.2%)</td>
<td>11.2</td>
<td>8248 (26.7%)</td>
<td>9264 (26.7%)</td>
<td>0.0</td>
</tr>
<tr>
<td>Had ≥1 psychotherapy visit during the baseline period</td>
<td>3314 (10.7%)</td>
<td>2738 (7.9%)</td>
<td>31.8</td>
<td>2859 (9.2%)</td>
<td>3211 (9.2%)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Values are given as number (percentage) for categoric variables and as mean ± SD for continuous variables. Higher QT-prolonging-potential SSRIs included citalopram and escitalopram. Lower QT-prolonging-potential SSRIs included fluoxetine, fluvoxamine, paroxetine, and sertraline. All covariates were measured during the 180-d baseline period before SSRI initiation. The weighted cohort is the pseudo-population generated by the IPT weighting. Std diff, standardized differences; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TdP, torsades de pointes; CYP, cytochrome P450.

aA std diff >10.0% represents meaningful imbalance between groups.

The definition of low-dose was on the basis of the dosing recommendations found in each SSRI’s package insert. Low doses: citalopram ≥20 mg/d; escitalopram ≥10 mg/d; fluoxetine ≥20 mg/d; immediate release fluvoxamine ≥50 mg/d; controlled release fluvoxamine ≥100 mg/d; immediate release paroxetine ≥20 mg/d; controlled release paroxetine ≥25 mg/d; and sertraline 50 mg/d.

cLists of medications with known, conditional, and possible risks of TdP are presented in Supplemental Table 3.

dLists of medications that are relevant CYP 1A2, 3A4, 2C9, 2C19, and 2D6 inhibitors are provided in Supplemental Table 4.
initiation of a higher versus lower QT-prolonging–potential SSRI was not associated with the 1-year risk of nonsudden cardiac death (adjusted HR, 1.01; 95% confidence interval, 0.95 to 1.09; Supplemental Table 13).

**DISCUSSION**

This observational study evaluated the comparative cardiac safety of SSRIs in the hemodialysis population. We found that individuals initiating higher (citalopram, escitalopram) versus lower (fluoxetine, fluvoxamine, paroxetine, sertraline) QT-prolonging–potential SSRIs had a higher 1-year risk of sudden cardiac death. This association was robust across multiple sensitivity analyses. Furthermore, our exploratory sub-group analyses suggest that the observed SSRI QT-prolonging potential–sudden cardiac death association may be more pronounced among elderly individuals, females, patients with conduction disorders, and those treated with other non-SSRI QT-prolonging medications.

An undesirable property of SSRIs is their ability to delay ventricular repolarization, an effect that manifests as QT interval prolongation on an electrocardiogram (ECG).16–18 All six SSRIs can prolong the QT interval via their antagonistic effects on myocardial human ether-a-go-go (hERG) potassium channels.40–45 However, despite their common off-target effects on myocardial potassium channels, individual agents within the SSRI class have differential QT-prolonging abilities.16–18 Citalopram and escitalopram (the S-enantiomer of the citalopram racemate) prolong the QT interval more than other SSRIs.16–18 In fact, randomized, placebo-controlled trials conducted in healthy volunteers have demonstrated that citalopram and escitalopram can prolong the QT interval beyond the threshold of regulatory concern, an increase of 5 milliseconds from baseline,46,47 at therapeutic doses.19–21

To date, data characterizing the QT-prolonging effects and cardiac safety profiles of SSRIs in the hemodialysis population are limited. QT prolongation and ventricular arrhythmias, such as torsades de pointes, were not reported in clinical trials evaluating the antidepressant efficacy of SSRI therapy in dialysis patients.6–15,48 However, it is likely that cardiac safety signals could not be detected in these trials due to their small sample sizes (7–62 participants) and limited follow-up (4 weeks to 6 months).6–15,48 To our knowledge, published evidence linking SSRIs to adverse cardiac outcomes in ESRD is limited to a few case reports of citalopram- and escitalopram-induced QT prolongation and torsades de pointes.49–51 Given the paucity of population-specific data, international experts have called for high-quality safety studies to inform antidepressant prescribing in patients receiving dialysis.52

To begin to address this evidence gap, we conducted a pharmacoepidemiologic study to assess the association between the initiation of higher versus lower QT-prolonging–potential SSRIs and sudden cardiac death in the hemodialysis population.
Our findings provide initial evidence that the heterogeneous QT-prolonging potential of SSRIs may differentially affect cardiac outcomes in hemodialysis-dependent ESRD. In addition, results from our exploratory subgroup analyses suggest that patients with risk factors for drug-induced QT prolongation (e.g., advanced age, female sex, cardiac conduction disorders, and use of non-SSRI QT-prolonging medications) may have heightened susceptibility to the proarrhythmic effects of higher QT-prolonging–potential SSRIs. Although our subgroup analyses should be considered preliminary in nature, our findings do align with published postmarketing surveillance data. Cases of citalopram- and escitalopram-induced QT prolongation and torsades de pointes reported to pharmaceutical regulatory agencies primarily involved individuals with risk factors for drug-induced QT prolongation (e.g., female sex, preexisting QT prolongation, or known cardiac disease).

Relative to the general population, individuals receiving maintenance hemodialysis may have an increased susceptibility to the QT-prolonging effects of citalopram and escitalopram for several reasons. First, cardiovascular comorbid conditions that result in structural heart damage are common in ESRD. Cardiovascular remodeling due to coronary artery disease, left ventricular hypertrophy, and heart failure can lead to a progressive downregulation of myocardial ion channels,

Figure 4. Initiation of a higher versus lower QT-prolonging–potential SSRI associates with a higher 1-year risk of sudden cardiac death within clinically relevant subgroups. An on-treatment analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate the association between the initiation of higher versus lower QT-prolonging–potential SSRIs and the 1-year risk of sudden cardiac death within clinically relevant subgroups. Higher QT-prolonging–potential SSRIs included citalopram and escitalopram. Lower QT-prolonging–potential SSRIs included fluoxetine, fluvoxamine, paroxetine, and sertraline. Adjusted analyses controlled for baseline covariates listed in Supplemental Table 6 using IPT weighting. The square sizes of HR point estimates are proportional to the size of the subgroup. The larger the square size the larger the subgroup. Within each respective subgroup, the interaction $P$ value was $\geq0.05$. 95% CI, 95% confidence interval; med, medication.
diminishing cardiac repolarization reserve,53–55 ultimately leaving the heart vulnerable to proarrhythmic triggers such as QT-prolonging drugs. Second, patients on hemodialysis are exposed to electrolyte shifts during dialysis treatments. It is plausible that rapid dialytic removal of electrolytes, such as potassium, and the use of proarrhythmic medications have additive QT-prolonging effects. Exposure to wider versus narrower blood-to-dialyse electrolyte gradients results in more extensive dialysis-induced QT prolongation.36 Furthermore, in vitro models have demonstrated that reductions in extracellular potassium enhance the degree of drug-induced inhibition of the cardiac repolarizing ionic current IKr.57 Finally, patients receiving hemodialysis have high medication burdens, increasing the likelihood that they are exposed to interacting medications. Concurrent use of two or more QT-prolonging medications and the use of a QT-prolonging medication in combination with a metabolic inhibitor may result in QT interval lengthening.35,36

Future studies are needed to fully elucidate the cardiac safety profiles of SSRIs in the hemodialysis population, including the frequency and magnitude of SSRIs induced QT prolongation measured via serial ECG monitoring or implantable loop recorders. However, in the interim, our results suggest that SSRIs therapy selection should be individualized and clinicians should consider the differential QT-prolonging properties of SSRIs, among other factors, in their prescribing choices. In particular, prescribers should be mindful of the demographic, comorbid, and medication-related risk factors for drug-induced QT prolongation, taking into account patient medical history, laboratory results, ECG findings, and concomitant medication use when selecting an SSRI. A lower QT-prolonging–potential SSRI may be a better option for patients at high risk for drug-induced QT prolongation, such as women, the elderly, individuals with cardiac conduction abnormalities, and those treated with other non-SSRI QT-prolonging medications.35,36 However, if citalopram or escitalopram therapy is unavoidable in a high-risk patient, clinicians should look to the drug safety warnings issued by pharmaceutic regulatory agencies for guidance on therapeutic monitoring.19–24 Regulatory agencies, including the FDA, recommend serial ECG monitoring throughout the course of therapy in high-risk patients.19,22–24 If the length of a patient’s corrected QT interval surpasses 500 milliseconds, treatment should be withdrawn gradually.19,22,23

Our study has several strengths. First, the use of Medicare claims data enabled us to conduct a large-scale safety study in a cohort of >65,000 hemodialysis patients initiating SSRI therapy. Second, we utilized a new-user study design to mitigate biases common to observational studies of prescription drugs such as selection and immortal time biases.25 Third, by performing a head-to-head comparison of SSRIs with higher versus lower QT-prolonging potential, we minimized the influence of bias due to confounding by indication because medications within the SSRI class have similar clinical indications and therapeutic roles.30,58 Furthermore, the comparison of SSRIs with a higher versus lower QT-prolonging potential reflects a clinically meaningful treatment decision encountered by prescribers in real-world practice.30,31 Finally, we performed multiple sensitivity analyses to test the robustness of our primary results.

Our findings should be considered within the context of study limitations. First, because our study was observational, residual confounding may remain. However, we adjusted for a wide-range of clinical and health care utilization metrics in our analyses to minimize confounding from difficult-to-measure factors such as ambient health status. In particular, the lack of an observed association between SSRI QT-prolonging potential and nonsudden cardiac death (the negative control outcome) suggests that the influence of unmeasured confounding in our study was minimal.39 Second, although we were able to determine whether an ECG was conducted in the month before SSRI initiation, we lacked accompanying clinical information to know whether ECG findings were used to inform SSRI-prescribing decisions. Third, although we defined our primary study outcome using the established USRDS sudden cardiac death definition, contemporary information on the validity of this outcome definition (e.g., sensitivity, specificity, positive predictive value, and negative predictive value) is limited.59,60 Because cause of death information was taken from the ESRD Death Notification Form, outcome misclassification may have occurred. However, such misclassification would likely be nondifferential (i.e., not dependent on exposure classification), biasing results toward the null.61 Reassuringly, sensitivity analyses considering broader cardiac outcomes produced consistent results. Fourth, information on missed or shortened hemodialysis treatments is not available in USRDS data. However, to minimize associated confounding, we adjusted our analyses for a history of noncompliance (International Classification of Diseases, Ninth Revision diagnosis codes V15.81 and V45.12). Fifth, information on laboratory parameters, including serum electrolytes, and patient-reported medication ineffectiveness or side effects were not available. We were unable to determine the clinical factor(s) that may have led to SSRI discontinuation or therapy switches during follow-up. Sixth, our subgroup analyses had limited power. Despite strong biologic plausibility, additional research is needed to confirm our findings. Finally, our study population was comprised of prevalent ESRD patients receiving in-center hemodialysis. Our results may not generalize to excluded populations such as incident hemodialysis, home hemodialysis, or peritoneal dialysis patients. Understanding the relative risk-benefit profiles of SSRIs in excluded patient populations is an area for future inquiry.

In conclusion, we observed that the initiation of a higher versus lower QT-prolonging–potential SSRI was associated with a higher 1-year risk of sudden cardiac death in a cohort of prevalent patients on hemodialysis. Data from our subgroup analyses suggest that the SSRI QT-prolonging potential–sudden cardiac death association may be more potent among individuals
with established risk factors for drug-induced QT prolongation. When prescribing SSRIs to hemodialysis patients, providers should consider the QT-prolonging potential of these agents.

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The data reported here have been provided by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the United States government.

Research idea and study design: M.M.A. and J.E.F.; data acquisition: M.M.A., M.A.B., and J.E.F.; statistical analysis: M.M.A.; data interpretation: M.M.A., M.A.B., and J.E.F.; and supervision: J.E.F. All authors approved the final version of the manuscript.

DISCLOSURES

M.M.A. and J.E.F. have received investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America. M.A.B. has received research support from Amgen and AstraZeneca; served as a scientific advisor for Merck, Amgen, Genentech, Fibrogen, AbbVie, and RxAnte; and owns equity in NoviSci, LLC, a data sciences company. In the last 2 years, J.E.F. has received speaking honoraria from American Renal Associates; the American Society of Nephrology; Dialysis Clinic, Inc.; the National Kidney Foundation; and multiple universities. J.E.F. is on the medical advisory board of NxStage Medical, Inc. and has received consulting fees from Fresenius Medical Care, North America.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018101032/-/DCSupplemental:

Supplemental Figure 1. Illustration of SSRI discontinuation and switching events.

Supplemental Figure 2. Propensity score distribution of patients treated with higher and lower QT-prolonging-potential SSRIs.

Supplemental Table 1. Outcome definitions.

Supplemental Table 2. ICD-9 diagnosis, ICD-9 procedure, and CPT procedure codes used to identify relevant baseline covariates.

Supplemental Table 3. List of non-SSRI QT-prolonging medications.

Supplemental Table 4. HCPCS codes used to identify QT-prolonging medications not billable to Medicare Part D.

Supplemental Table 5. List of cytochrome P450 inhibitors.

Supplemental Table 6. Full list of baseline characteristics among study patients initiating a higher and lower QT-prolonging-potential SSRI.

Supplemental Table 7. Association between the initiation of a higher versus lower QT-prolonging-potential SSRI and the 1-year risk of fatal cardiac outcomes.

Supplemental Table 8. Association between the initiation of a higher versus lower QT-prolonging-potential SSRI and the 1-year risk of sudden cardiac death within clinically relevant subgroups.

Supplemental Table 9. Association between the initiation of individual higher QT-prolonging-potential SSRIs versus lower QT-prolonging-potential SSRIs and the 1-year risk of sudden cardiac death.

Supplemental Table 10. Association between the initiation of a higher versus lower QT-prolonging-potential SSRI and the 1-year risk of sudden cardiac death when longer grace periods were used to define SSRI discontinuation.

Supplemental Table 11. Association between the initiation of a higher versus lower QT-prolonging-potential SSRI and the 1-year risk of sudden cardiac death considering all possible follow-up time.

Supplemental Table 12. Association between the initiation of a higher versus lower QT-prolonging-potential SSRI and the risk of sudden cardiac death using an intent-to-treat analytic approach.

Supplemental Table 13. Association between the initiation of an SSRI with higher versus lower QT-prolonging potential and the 1-year risk of the negative control outcome.

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