Journal of the American Heart Association

ORIGINAL RESEARCH

Use of QT Prolonging Medications by Hemodialysis Patients and Individuals Without End-Stage Kidney Disease

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BACKGROUND: The rate of sudden cardiac death in the hemodialysis population exceeds that of the general population by >20-fold. Hemodialysis patients may be particularly susceptible to sudden cardiac death provoked by drug-induced QT prolongation because of their substantial cardiovascular disease burden, exposure to electrolyte shifts during dialysis, and extensive polypharmacy. However, population-specific data regarding the frequency and patterns of QT prolonging medication use are limited.

METHODS AND RESULTS: We conducted a descriptive drug utilization study using 3 administrative databases, the United States Renal Data System, MarketScan, and Medicare claims. We characterized the extent and patterns of QT prolonging medication use by adult hemodialysis patients and individuals without end-stage kidney disease annually from 2012 to 2016. We also identified instances of high-risk QT prolonging medication use among hemodialysis patients. In total, 338 515 hemodialysis patients and 40.7 million individuals without end-stage kidney disease were studied. Annual utilization rates of QT prolonging medications with known torsades de pointes risk in hemodialysis patients were ~1.4 to ~2.5 times higher than utilization rates in individuals without end-stage kidney disease. Hemodialysis patients with demographic and clinical risk factors for drug-induced QT prolongation were exposed to medications with known torsades de pointes risk more often than patients without risk factors.

CONCLUSIONS: Hemodialysis patients use QT prolonging medications with known torsades de pointes risk more extensively than individuals without end-stage kidney disease. Given the widespread use and instances of high-risk prescribing, future studies evaluating the cardiac safety of these drugs in the hemodialysis population are needed.

Key Words: Hemodialysis ■ patterns of use ■ QT prolonging medications

Sudden cardiac death (SCD) is the leading cause of mortality among individuals receiving maintenance hemodialysis, accounting for ~30% of all deaths.[1] SCD typically occurs when a vulnerable myocardium is exposed to a pro-arrhythmic trigger.[2] Structural heart disease is highly prevalent in end-stage kidney disease (ESKD) and can alter cardiac conduction pathways,[3–5] making the heart more likely to produce fatal arrhythmias when it's exposed to pro-arrhythmic triggers (eg, medications that prolong the QT interval, electrolyte abnormalities). Unfortunately, traditional preventative therapies, such as prophylactic implantable cardioverter defibrillators, have limited efficacy in hemodialysis patients.[6] Therefore, it is of utmost importance to identify modifiable population-specific SCD risk factors.

Drug-induced SCD may be preventable. Many medications can induce QT interval prolongation, an electrocardiographic manifestation of delayed ventricular repolarization that increases the risk of rapidly

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.015969

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What is New?

- This descriptive drug utilization study shows that hemodialysis patients, a population with an extraordinarily high rate of cardiac arrhythmias and sudden cardiac death, use QT prolonging medications to a much greater extent than similarly aged individuals without end-stage kidney disease.
- Use of QT prolonging medications with known torsades de pointes risk was particularly high among hemodialysis patients at risk for drug-induced QT prolongation (eg. the elderly, women, and individuals with underlying heart disease), and frequent exposures to potential drug interactions occurred.

What are the Clinical Implications?

- Given the widespread use and frequent instances of high-risk prescribing, future studies evaluating the cardiac safety of QT prolonging drugs in the hemodialysis population are needed.

Nonstandard Abbreviations and Acronyms

ESKD	end-stage kidney disease
SCD	sudden cardiac death
TdP	torsades de pointes

fatal arrhythmias like torsades de pointes (TdP). More than 175 drugs on the United States market have documented QT prolonging effects, including antiarrhythmic and non-antiarrhythmic agents.[7] Data from the general population indicate that QT prolonging medication use associates with a higher risk of SCD,[8] especially among individuals with multiple pro-arrhythmic risk factors and/or existing QT prolongation.[9,10] Hemodialysis patients may be particularly susceptible to drug-induced arrhythmias and SCD because of their substantial cardiovascular disease burden, recurrent exposure to electrolyte shifts during thrice-weekly hemodialysis treatments, and extensive polypharmacy, among other factors.[11,12] However, despite studies indicating that 65% to 75% of hemodialysis patients have prolonged QT intervals,[13,14] we lack data on the frequency and patterns of QT prolonging medication use in this vulnerable population.

To address this evidence gap, we aimed to: characterize the (1) extent and (2) patterns of QT prolonging medication use in the hemodialysis population relative to individuals without ESKD; and (3) identify instances of high-risk QT prolonging medication use among hemodialysis patients.

METHODS

Because of contractual data use and licensing agreements, the authors cannot make the data and materials used in this study available to other investigators for the purposes of reproducing results. Interested parties can contact: the United States Renal Data System Coordinating Center to obtain United States Renal Data System data; the Centers for Medicare & Medicaid Services to obtain Medicare data; and Truven Health Analytics to obtain the MarketScan Commercial Claims and Encounters Database.

Study Design and Populations

The University of North Carolina at Chapel Hill Institutional Review Board approved this study (#18-3175). A waiver of consent was granted because of the study's large size, data anonymity, and retrospective nature.

When information on medication use in a given population is unknown, initial descriptive drug utilization studies help to identify areas requiring more in-depth evaluation in future investigations (eg, comparative safety and effectiveness studies).[15] Thus, we conducted a drug utilization study (Figure S1) to describe the magnitude of prescription QT prolonging medication use by the hemodialysis population on an annual basis from 2012 to 2016. Since medication use is dynamic, we tracked QT prolonging medication use starting from January 1 (the index date) until December 31 in each study year. We defined the baseline period as the 180 days before January 1. To contextualize the observed level of QT prolonging medication use in the hemodialysis population, we also described QT prolonging medication use in individuals without ESKD (ie, the non-ESKD population) during the same time period using the same study design and approach.

Annual Hemodialysis Cohorts

We used data from the United States Renal Data System, a national ESKD surveillance system, linked with Medicare claims to generate annual cohorts of adult hemodialysis patients from 2012 to 2016. In each study year, we identified individuals aged ≥18 years who received in-center hemodialysis on January 1 and during the 180-day baseline period. We excluded patients if they had a dialysis vintage (ie, total time on maintenance dialysis therapy) ≤90 days at the start of

baseline and those who lacked continuous insurance enrollment (Medicare Parts A, B, and D) or received hospice care during baseline. We also created annual sub-cohorts of younger (aged 18–64 years) and older (aged ≥66 years) hemodialysis patients for comparison with similarly aged individuals without ESKD, as further described below.

Annual Non-ESKD Comparator Cohorts

To facilitate consideration of non-ESKD comparator cohorts that spanned the adult age range, we used 2 distinct US administrative claims data sources, the MarketScan Commercial Claims and Encounters Database and a 20% random sample of Medicare fee-for-service beneficiaries. We generated annual cohorts (2012–2016) of younger and older adults without ESKD (i.e. individuals without a relevant ESKD diagnosis or procedure code during the 180-day baseline period, Table S1) using Marketscan and Medicare data, respectively. We identified adults without ESKD who met age specifications (18–64 years for Marketscan and ≥66 years for Medicare) on January 1 of each year. In both cohorts, we excluded individuals if they lacked continuous insurance enrollment (commercial medical and prescription coverage for MarketScan, and Medicare Parts A, B, and D for Medicare) or received hospice care during baseline.

Cohort Characterization

Covariates of interest were ascertained during the baseline period and included patient demographics, comorbid conditions, medication use, and metrics of healthcare utilization. Comorbid conditions were considered present if an applicable discharge diagnosis code (located in any billing position) was associated with ≥1 inpatient claim or ≥2 outpatient claims during the 180-day baseline period (Table S2). Medication use was determined on the last day of the baseline period and polypharmacy was defined as taking ≥5 medications.[16] We present the baseline characteristics of the most contemporary (2016) hemodialysis and non-ESKD cohorts.

QT Prolonging Medication Use

We compiled a comprehensive list of QT prolonging medications using the CredibleMeds website, a reliable online clinical resource with up-to-date information about medications that can cause QT prolongation and/or TdP.[7] Based upon published literature, medication package inserts, data from the US Food and Drug Administration's Adverse Event Reporting System, and other sources, CredibleMeds classifies QT prolonging medications as having a known, possible, or conditional TdP risk (Table 1 and Table S3).[7] In each study year, we used prescription claims data to longitudinally track the daily use of outpatient medications with a known, possible, or conditional TdP risk for each individual in the hemodialysis and non-ESKD populations.

To quantify the extent of prescription QT prolonging medication use in each population from 2012 to 2016, we determined the annual rate of exposure to ≥1 QT prolonging medication, overall and by CredibleMeds class (known, possible, or conditional TdP risk). We also conducted a supplemental extent of use analysis excluding QT prolonging thiazide/thiazide-like diuretics (eg, hydrochlorothiazide, indapamide, metolazone; Table S3) since these agents have limited efficacy in ESKD,[17] but are frequently used by individuals without ESKD.[18]

In addition, we characterized the patterns of QT prolonging medication use in the hemodialysis and non-ESKD populations by identifying the top 5 medications prescribed in each CredibleMeds class and determining the rate of concurrent (ie, simultaneous) use of medications with known TdP risk with other QT prolonging drugs. Given that QT prolonging medication use was stable across time, these analyses focused on the most contemporary study year, 2016.

Finally, we identified instances of high-risk QT prolonging medication use in the hemodialysis population, including the use of QT prolonging medications by patients with risk-factors for drug-induced QT prolongation and exposure to potential drug interactions. In these analyses, we focused on medications with known TdP risk since these drugs are associated with QT prolongation and TdP when taken as recommended (ie, at typical therapeutic doses).[7] Using the

Table 1. CredibleMeds Definitions for Medications With Known, Possible, and Conditional TdP Risk

CredibleMeds Classification[7]	Definition
Known TdP risk	Drugs that prolong the QT interval *and* are clearly associated with a known risk of TdP, even when taken as recommended.
Possible TdP risk	Drugs that can cause QT prolongation *but* currently lack evidence for a risk of TdP when taken as recommended.
Conditional TdP risk	Drugs that are associated with TdP only under certain conditions (eg, excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) *or* drugs that create conditions that facilitate or induce TdP (eg, cause an electrolyte disturbance that induces TdP).

CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Lists of medications falling into each CredibleMeds category are provided in Table S3. TdP indicates torsades de pointes.

2016 hemodialysis cohort, we determined the rate of exposure to ≥1 medication with known TdP risk among hemodialysis patients with and without demographic and clinical risk factors for drug-induced QT prolongation (advanced age, female sex, conduction disorder, ischemic heart disease, heart failure, and liver disease).[9,10] Additionally, since concurrent use of multiple QT prolonging medications can lead to more extensive QT prolongation (ie, a potential pharmacodynamic drug interaction),[9,10] we identified medications with known TdP risk that are frequently used together by computing the rate of concurrent use. Finally, concurrent use of a QT prolonging medication with a drug that inhibits its metabolism (ie, a potential pharmacokinetic drug interaction) can raise serum concentrations of the QT prolonging drug, enhancing its arrhythmogenicity.[9,10] Thus, we identified the most commonly prescribed medications with known TdP risk that are major substrates of cytochrome P450 isoenzymes and calculated the rate (95% CI) of concurrent use of these drugs and pertinent cytochrome inhibitors (Table S4).

Statistical Analysis

We described the baseline characteristics of the hemodialysis and non-ESKD cohorts as mean ± SD or median [quartile 1, quartile 3] for continuous variables and as count (%) for categorical variables. In each annual cohort, individuals were followed forward in historical time from January 1 until December 31 or the occurrence of a censoring event. Censoring events common to both populations included loss of insurance, hospice entry, and death. A change of dialysis modality to home hemodialysis or peritoneal dialysis, kidney transplantation, and recovery of kidney function were additional censoring events for the hemodialysis population, whereas the development of ESKD was an additional censoring event for the non-ESKD population.

Across all analyses, we calculated medication utilization rates in each annual hemodialysis and non-ESKD cohort as the: [total # of days exposed / total follow-up time] and estimated Wald 95% CIs. We expressed the resultant QT prolonging medication utilization rates as the number of days exposed per person year (a descriptor of medication use across time). To facilitate comparisons between the hemodialysis and non-ESKD populations, we age- and sex-standardized medication utilization rate estimates using standardized mortality ratio weighting.[19] In analyses of younger individuals, we standardized estimates to the age and sex distribution of the 2016 younger hemodialysis cohort (aged 18–64 years). In analyses of older individuals, we standardized estimates to the age and sex distribution of the 2016 older hemodialysis cohort (aged ≥66 years). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Overall, 338 515 hemodialysis patients and 40 663 741 individuals without ESKD were studied. Annual cohort sizes ranged from 96 447 to 102 786 for the younger hemodialysis population; 64 636 to 79 037 for the older hemodialysis population; 13 992 738 to 20 358 190 for the younger non-ESKD population; and 2 341 761 to 3 134 841 for the older non-ESKD population (Tables S5, S6 and Figures S2 through S4).

Table 2 displays baseline characteristics of the 2016 hemodialysis and non-ESKD cohorts. The adult hemodialysis population had a high prevalence of cardiovascular comorbidities, and 80.9% of patients had ≥1 demographic or clinical risk factor for drug-induced QT prolongation. Cardiac comorbidities, such as arrhythmias, conduction disorders, and heart failure, were more common in hemodialysis patients compared with similarly aged individuals without ESKD. In addition, >50% of the hemodialysis cohort was exposed to polypharmacy, and a higher proportion of these patients were using QT prolonging medications at baseline compared with the non-ESKD population. For example, 10.4% of younger hemodialysis patients were using ≥1 medication with known TdP risk versus 3.8% of similarly aged individuals without ESKD. Analogous patterns were observed among older individuals.

The extent and patterns of QT prolonging medication use differed between the hemodialysis and non-ESKD populations. In each study year (2012–2016), annual standardized rates of exposure to ≥1 QT prolonging medication in any CredibleMeds class as well as those with known and possible TdP risk (separately) were higher in younger and older hemodialysis patients compared with similarly aged individuals without ESKD Figure 1 and Tables S7 through S9). However, the magnitude of these population-specific differences in utilization rates varied across age groups. For example, in 2016, the standardized rate (95% CI) of exposure to ≥1 QT prolonging medication with known TdP risk in the younger hemodialysis population was 2.5 times higher than that of the younger non-ESKD population (38.6 [37.8–39.4] versus 15.4 [15.0–15.9] days exposed per person-year), and the rate in the older hemodialysis population was 1.4 times higher than that of the older non-ESKD population (58.3 [57.2–59.4] versus 42.0 [41.1–42.9] days exposed per person-year). The use of QT prolonging medications with conditional TdP risk in the hemodialysis population relative to the non-ESKD population varied by age group (Figure 1 and Tables S7 through S9). Annual standardized rates of exposure

Table 2. Baseline Characteristics of the 2016 Hemodialysis and General Population Cohorts

Characteristic	Younger Adults		Older Adults		All Adults
	Hemodialysis n=100 440	Non-ESKD n=13 992 738	Hemodialysis n=79 037	Non-ESKD n=3 134 841	Hemodialysis n=184 573
Age, y	51.5±9.8	42.3±13.7	75.0±6.8	75.6±7.5	61.9±14.3
Female	40 824 (40.6%)	7 362 983 (52.6%)	40 764 (51.6%)	1 900 124 (60.6%)	83 931 (45.5%)
Cause of ESKD					
Diabetes mellitus	42 905 (42.7%)	…	38 386 (48.6%)	…	84 086 (45.6%)
Hypertension	29 093 (29.0%)	…	25 655 (32.5%)	…	56 106 (30.4%)
Glomerular disease	14 091 (14.0%)	…	4974 (6.3%)	…	19 434 (10.5%)
Other	14 351 (14.3%)	…	10 022 (12.7%)	…	24 947 (13.5%)
Time on maintenance hemodialysis (years)	4.45 [2.23, 8.07]		3.52 [1.67, 6.35]		4.05 [1.95, 7.25]
Arrhythmia	13 003 (12.9%)	89 762 (0.6%)	21 269 (26.9%)	621 170 (19.8%)	35 282 (19.1%)
Conduction disorder	3153 (3.1%)	12 058 (0.1%)	4112 (5.2%)	144 389 (4.6%)	7470 (4.0%)
Heart failure	24 119 (24.0%)	25 771 (0.2%)	26 548 (33.6%)	364 289 (11.6%)	52 223 (28.3%)
Ischemic heart disease	24 438 (24.3%)	103 103 (0.7%)	30 323 (38.4%)	756 559 (24.1%)	56 525 (30.6%)
Chronic liver disease	6522 (6.5%)	38 440 (0.3%)	4594 (5.8%)	86 025 (2.7%)	11 454 (6.2%)
Has a cardiac pacemaker	1741 (1.7%)	4507 (0.0%)	4671 (5.9%)	127 477 (4.1%)	6575 (3.6%)
Has an implantable cardiac defibrillator	1968 (2.0%)	5412 (0.0%)	2154 (2.7%)	42 078 (1.3%)	4257 (2.3%)
# of baseline hospitalizations					
0	64 382 (64.1%)	13 660 222 (97.6%)	50 134 (63.4%)	2 847 101 (90.8%)	117 781 (63.8%)
1	18 448 (18.4%)	293 633 (2.1%)	15 850 (20.1%)	214 620 (6.8%)	35 259 (19.1%)
≥2	17 610 (17.5%)	38 883 (0.3%)	13 053 (16.5%)	73 121 (2.3%)	31 533 (17.1%)
Polypharmacy*	54 594 (54.4%)	976 494 (7.0%)	47 208 (59.7%)	1 200 903 (38.3%)	104 856 (56.8%)
# of medications used with any level of TdP risk†					
0	53 430 (53.2%)	11 393 516 (81.4%)	35 609 (45.1%)	1 489 263 (47.5%)	91 454 (49.5%)
1	27 919 (27.8%)	1 972 503 (14.1%)	24 645 (31.2%)	982 888 (31.4%)	54 146 (29.3%)
≥2	19 091 (19.0%)	626 719 (4.5%)	18 783 (23.8%)	662 691 (21.1%)	38 973 (21.1%)
Use of ≥1 medication with known TdP risk†	10 493 (10.4%)	538 546 (3.8%)	12 655 (16.0%)	367 736 (11.7%)	23 818 (12.9%)
Use of ≥1 medication with possible TdP risk†	8980 (8.9%)	427 635 (3.1%)	7928 (10.0%)	294 176 (9.4%)	17 385 (9.4%)
Use of ≥1 medication with conditional TdP risk†	39 759 (39.6%)	1 992 865 (14.2%)	36 160 (45.8%)	1 410 190 (45.0%)	78 186 (42.4%)

Values given are mean±SD or median [quartile 1, quartile 3] for continuous variables and as count (%) for categorical variables. ESKD indicates end-stage kidney disease; and TdP, torsades de pointes.

*Polypharmacy was defined as taking 5 or more medications.[16]

†CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1 and lists of medications falling into each category are provided in Table S3. Medications classified as having any level of TdP risk are those falling into any of the 3 CredibleMeds categories.

to ≥1 medication with conditional TdP risk was higher in younger hemodialysis patients compared with similarly aged individuals without ESKD. In contrast, rates of exposure to ≥1 medication with conditional TdP risk were similar in the older hemodialysis and non-ESKD populations. However, when thiazide/thiazide-like diuretics were excluded, annual rates of exposure to ≥1 medication with conditional TdP risk were 1.4 to 1.5 times higher in older hemodialysis patients compared with similarly aged individuals without ESKD (Figure S5 and Tables S10 through S12).

Table 3 and Table S13 display the top 5 medications with known, possible, and conditional TdP risk used by the hemodialysis and non-ESKD populations in 2016. Overall, non-antiarrhythmic QT prolonging medications, including psychotropics, antiemetics, antibiotics, diuretics, and acid suppressants, were frequently used by the hemodialysis and non-ESKD populations. However, the individual drugs comprising the top 5 medications with known, possible, and conditional TdP risk used and their respective rankings differed. For example, omeprazole was the top medication with conditional TdP

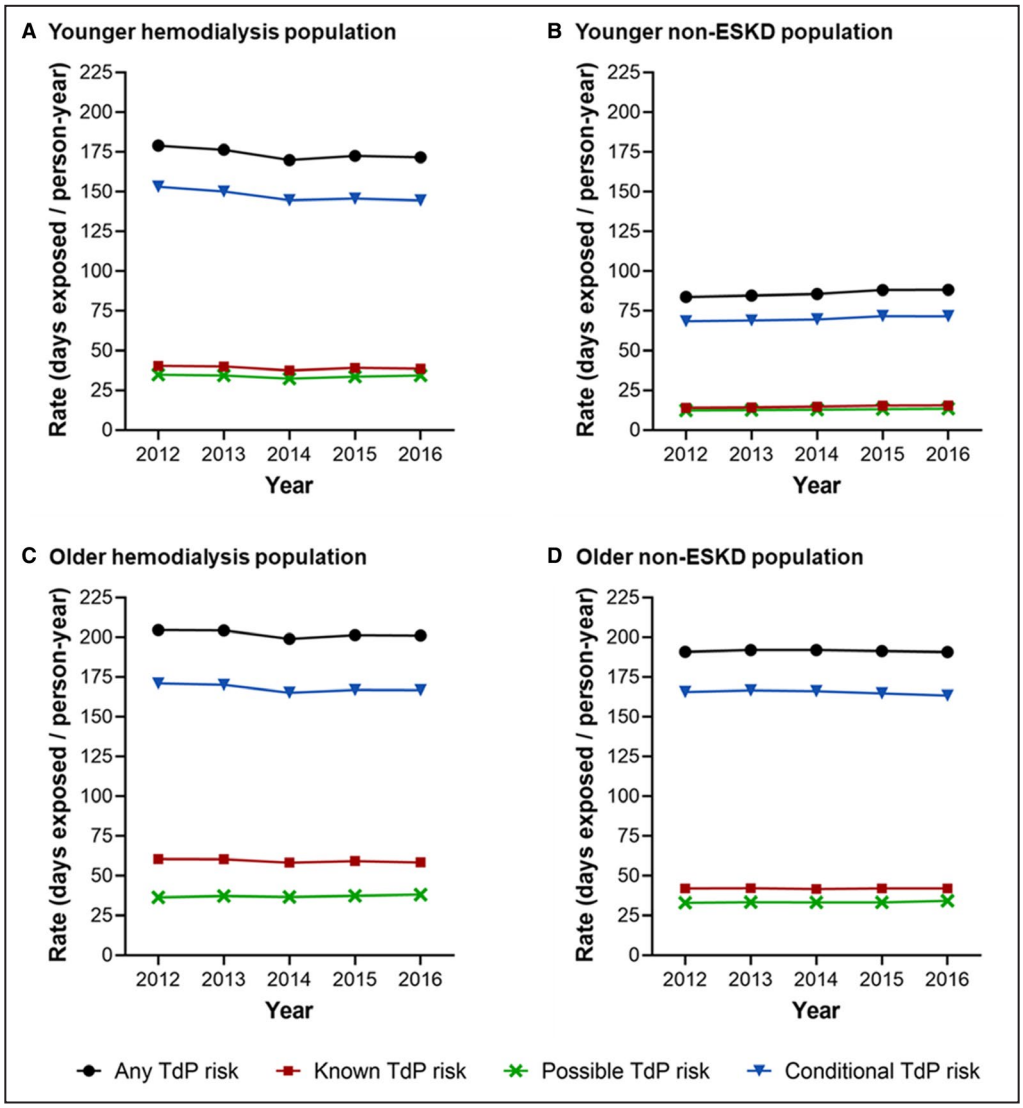

Figure 1. Use of ≥1 prescription QT prolonging medication by the hemodialysis and non-ESKD populations, 2012 to 2016.

A and **B,** Depict annual standardized rates of exposure to ≥1 QT prolonging medication in the younger hemodialysis and non-ESKD populations, respectively. **C** and **D,** Depict analogous annual rates of QT prolonging medication exposure in the older hemodialysis and non-ESKD populations. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1 and lists of medications falling into each category are provided in Table S3. Medications classified as having any TdP risk are those falling into any of the 3 CredibleMeds categories. ESKD indicates end-stage kidney disease; and TdP, torsades de pointes.

risk used by younger and older hemodialysis patients. In contrast, hydrochlorothiazide was the top medication used by similarly aged individuals without ESKD.

Table 4 shows standardized rates (95% CIs) of concurrent exposure to ≥2 QT prolonging medications in the 2016 hemodialysis and non-ESKD cohorts. Hemodialysis patients used multiple QT prolonging medications more often. For example, the standardized rate (95% CI) of concurrent exposure to ≥2 distinct medications with known TdP risk among younger hemodialysis patients was 7 times higher that of similarly aged individuals without ESKD (2.8 [2.6–3.0] versus 0.4 [0.3–0.5] days exposed per person-year). Comparable utilization patterns were seen among older individuals, albeit of lower magnitude.

Among adults with hemodialysis dependent ESKD, several high-risk patterns of QT prolonging medication use were identified. In 2016, hemodialysis patients with risk factors for drug-induced QT prolongation (eg, advanced age, female sex, heart failure) were exposed to medications with known TdP risk more often than those without such risk factors (Figure 2 and Table S14). The observed subgroup utilization patterns were

Table 3. Top 5 Medications in Each CredibleMeds Class Used by the Hemodialysis and General Populations in 2016

	Younger Adults		Older Adults		All Adults
	Hemodialysis	Non-ESKD	Hemodialysis	Non-ESKD	Hemodialysis
Known TdP risk					
1	Citalopram	Escitalopram	Amiodarone	Citalopram	Amiodarone
2	Escitalopram	Citalopram	Citalopram	Donepezil	Citalopram
3	Amiodarone	Azithromycin	Donepezil	Escitalopram	Escitalopram
4	Ondansetron	Ondansetron	Escitalopram	Amiodarone	Ondansetron
5	Levofloxacin	Ciprofloxacin	Ondansetron	Sotalol	Donepezil
Possible TdP risk					
1	Tramadol	Venlafaxine	Tramadol	Tramadol	Tramadol
2	Mirtazapine	Tramadol	Mirtazapine	Memantine	Mirtazapine
3	Promethazine	Tizanidine	Memantine	Mirtazapine	Venlafaxine
4	Venlafaxine	Aripiprazole	Venlafaxine	Venlafaxine	Promethazine
5	Tizanidine	Nortriptyline	Risperidone	Risperidone	Risperidone
Conditional TdP risk					
1	Omeprazole	Hydrochlorothiazide	Omeprazole	Hydrochlorothiazide	Omeprazole
2	Pantoprazole	Omeprazole	Pantoprazole	Omeprazole	Pantoprazole
3	Furosemide	Sertraline	Furosemide	Furosemide	Furosemide
4	Sertraline	Pantoprazole	Sertraline	Pantoprazole	Sertraline
5	Esomeprazole	Fluoxetine	Famotidine	Sertraline	Esomeprazole

CredibleMeds classifies medications that can prolong the QT interval as having a known, possible. or conditional TdP risk. Corresponding definitions are provided in Table 1 and lists of medications falling into each category are provided in Table S3. Corresponding medication utilization rates (days exposed per person-year) for each QT prolonging drug are presented in Table S13. ESKD indicates end-stage kidney disease; and TdP, torsades de pointes.

consistent when we excluded antiarrhythmic medications. In addition, the hemodialysis population was exposed to potential drug interactions involving QT prolonging medications. Concurrent use of multiple medications with known TdP risk (Figure 3 and Table S15), as well as concurrent use of medications known TdP risk and metabolic inhibitors (Figure 4 and Table S16) occurred. Citalopram and escitalopram were the QT prolonging medications with known TdP risk most frequently involved in potential pharmacodynamic and pharmacokinetic drug interactions. With regard to potential pharmacokinetic interactions, proton pump inhibitors, including omeprazole, pantoprazole, and esomeprazole, were the most common cytochrome 2C19 inhibitors used with citalopram and escitalopram.

DISCUSSION

Our study demonstrated that hemodialysis patients, a population with an extraordinarily high rate of cardiac

Table 4. Concurrent Use of Prescription Medications With Known TdP Risk and Other Drugs That Can Prolong the QT Interval by the Hemodialysis and General Populations in 2016

Medication Combinations	Younger Adults		Older Adults		All Adults
	Hemodialysis n=100 440	Non-ESKD n=13 992 738	Hemodialysis n=79 037	Non-ESKD n=3 134 841	Hemodialysis n=184 573
Known TdP risk+Any TdP risk	25.6 (25.0–26.2)	6.5 (6.2–6.9)	39.6 (38.7–40.5)	28.5 (27.8–29.2)	31.6 (31.1–32.2)
Known TdP risk+Known TdP risk	2.8 (2.6–3.0)	0.4 (0.3–0.5)	5.4 (5.1–5.7)	3.3 (3.1–3.6)	3.9 (3.7–4.1)
Known TdP risk+Possible TdP risk	6.7 (6.4–7.0)	1.4 (1.2–1.5)	10.3 (9.9–10.8)	9.0 (8.6–9.4)	8.2 (8.0–8.5)
Known risk TdP+Conditional TdP risk	22.8 (22.2–23.4)	5.7 (5.4–6.0)	34.9 (34.1–35.8)	24.6 (23.9–25.2)	28.0 (27.6–28.5)

Values presented are standardized rates (95% CIs) of exposure to specific medication combinations (ie, rates of exposure to ≥2 QT prolonging medications) in 2016 and are expressed as the number of days exposed per person-year. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1 and lists of medications in each category are provided in Table S3. Medications classified as having any TdP risk are those in any of the 3 CredibleMeds categories. ESKD indicates end-stage kidney disease; and TdP, torsades de pointes.

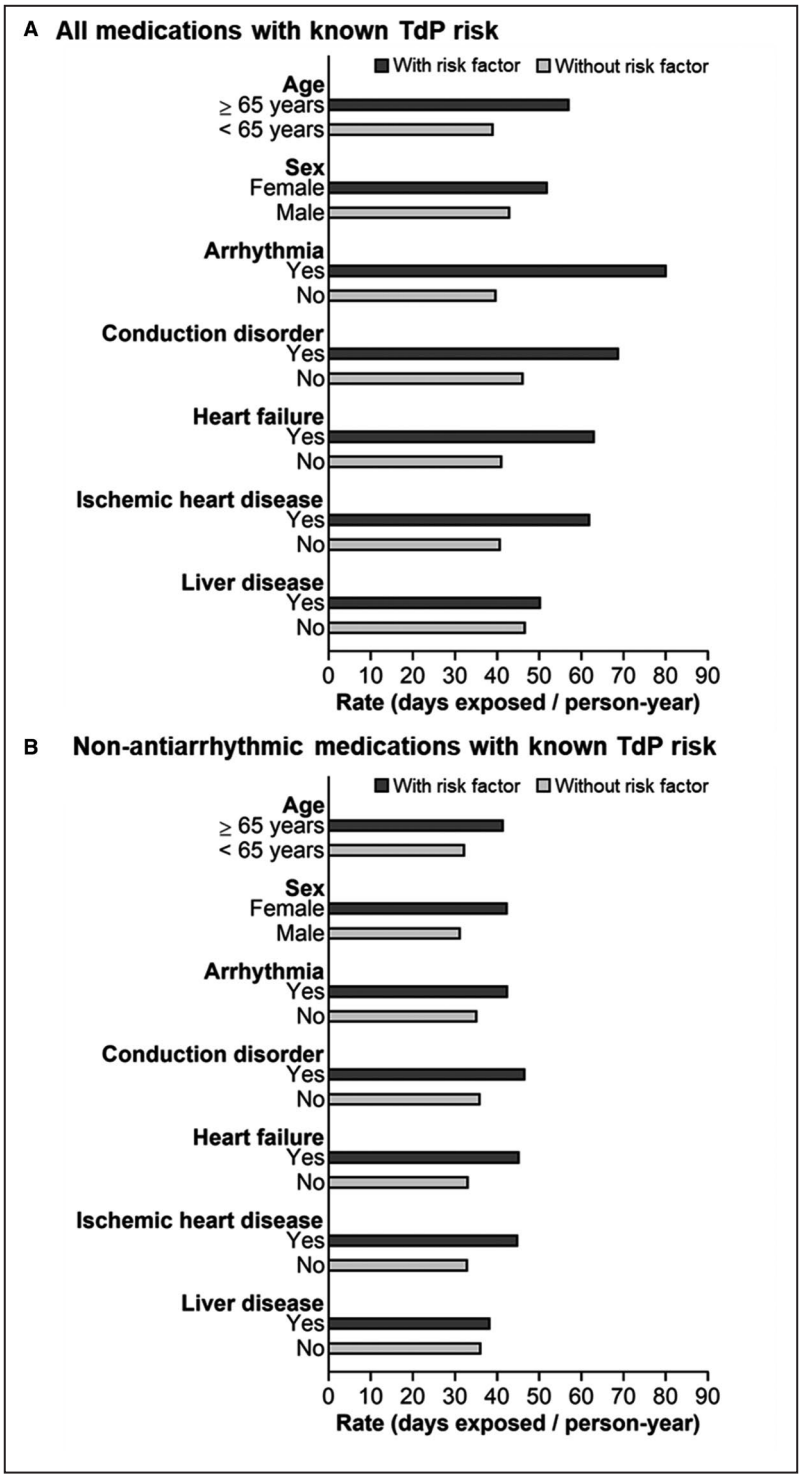

Figure 2. Use of ≥1 prescription medication with known TdP risk by hemodialysis patients with and without risk factors for drug-induced QT prolongation in 2016.

A, Depicts standardized rates of exposure to ≥1 medication with known TdP risk by hemodialysis patients with and without risk factors for drug-induced QT prolongation. **B**, Depicts analogous rates of exposure to ≥1 non-antiarrhythmic medication with known TdP risk in each subgroup. Medications with known TdP risk are listed in Table S3. Advanced age was defined as ≥65 years of age.[9] TdP indicates torsades de pointes.

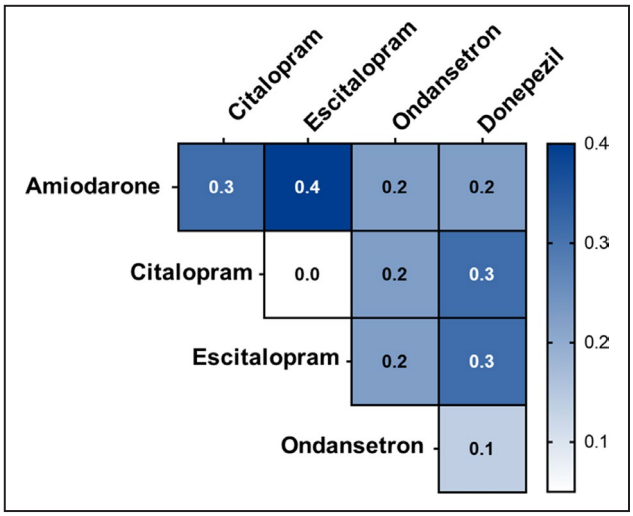

Figure 3. Concurrent use of medications with known TdP risk by the 2016 hemodialysis population.
Values presented are crude rates of exposure to a given medication combination expressed as the number of days exposed per person-year. TdP indicates torsades de pointes.

arrhythmias[20] and SCD,[1] utilize medications with known and possible TdP risk to a much greater extent than similarly aged individuals in the non-ESKD population. The use of QT prolonging medications with known TdP risk was particularly high in hemodialysis patient subgroups at risk for drug-induced QT prolongation such as the elderly, women, and individuals with underlying heart failure and ischemic heart disease. Moreover, there were frequent exposures to potential drug interactions. These findings raise concerns about high-risk and potentially unsafe prescribing patterns in the hemodialysis population. In many instances, QT prolonging medications have comparable therapeutic alternatives without QT prolonging effects, rendering alternative, and potentially safer prescribing decisions possible. Our findings underscore the need for additional research assessing the comparative safety of QT prolonging medications in the hemodialysis population.

Between the late 1980s and the early 2000s, the Food and Drug Administration removed several non-antiarrhythmic drugs (eg, terfenadine, astemizole, cisapride) from the US market because of pro-arrhythmic concerns, specifically an increased risk of TdP and SCD.[10,21] Since then, the Food and Drug Administration has required sponsors to conduct in vitro and in vivo experiments[22] as well as clinical assessments in humans[23] to evaluate and define a medication's pro-arrhythmic potential before regulatory approval. For all new drugs with systemic bioavailability, the Food and Drug Administration requires sponsors to conduct a thorough QT/QTc study, a randomized, placebo- and positive-controlled trial to determine if a drug can induce QT prolongation at therapeutic and/or supratherapeutic doses.[23] However, while informative, these studies are typically conducted in healthy volunteers, and their findings may not generalize to individuals with baseline cardiovascular vulnerability. Data from the general population support this notion. The presence of pro-arrhythmic risk factors, such as advanced age, female sex, left ventricular hypertrophy, and prior QT interval prolongation, augments the QT prolonging effects of medications with known TdP risk.[24] In fact, at least 1 such risk factor was present in >90% of drug-induced TdP cases reported in the literature.[25] Therefore, it is likely that the extent of drug-induced QT prolongation is more pronounced in populations with multiple pro-arrhythmic risk factors, such as hemodialysis patients.

Existing cardiac safety warnings on product labels[26,27] as well as a scientific statement from the American Heart Association/American College of Cardiology[28] call attention to patient populations at heightened risk for drug-induced QT prolongation, TdP, and SCD. However, these warnings do not specifically identify hemodialysis patients. The hemodialysis population carries a substantial cardiac burden. We found that >80% of hemodialysis patients had at least 1 demographic (advanced age, female sex) or

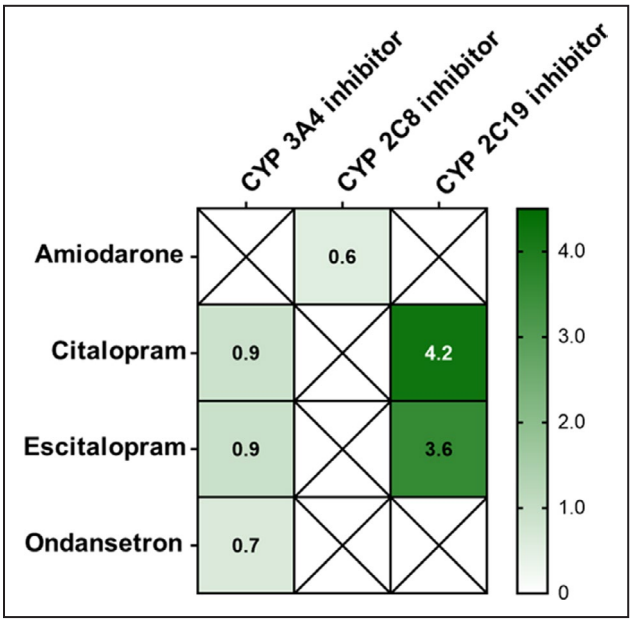

Figure 4. Concurrent use of CYP metabolized medications with known risk TdP risk and relevant metabolic inhibitors by the 2016 hemodialysis population.
Values presented are crude rates of exposure to a given medication combination expressed as the number of days exposed per person-year. Of the top 5 medications with a known TdP risk used by the adult hemodialysis population, amiodarone, citalopram, escitalopram, and ondansetron are major substrates of cytochrome isoenzymes. An "X" on the figure indicates that the QT prolonging medication is not a major substrate of specified CYP isoenzyme. Relevant CYP inhibitors are listed in Table S4. CYP indicates cytochrome P450; and TdP, torsades de pointes.

clinical (arrhythmia, conduction disorder, heart failure, ischemic heart disease, liver disease) risk factor for drug-induced QT prolongation. In addition, we found that hemodialysis patients with such risk factors were exposed to drugs with known TdP risk more often than those without. While it is certainly possible that prescribing clinicians determined that the therapeutic benefits of QT prolonging medications outweighed potential pro-arrhythmic risks, prior studies indicate that medical providers often have limited knowledge about drugs with QT liability and associated risk factors.[29–31] Thus, future investigations are needed to determine the frequency of inappropriate QT prolonging medication prescribing among high-risk hemodialysis patients and to identify effective interventions to promote safer prescribing practices.

Hemodialysis patients are clinically complex, and on average, require 10 to 12 medications per day to manage multiple comorbid conditions.[32] Such extensive polypharmacy increases the likelihood that drug interactions and adverse drug events will occur. Pharmacodynamic and pharmacokinetic drug interactions involving QT prolonging medications can result in more profound QT interval lengthening, increasing the risk of TdP and SCD.[9,10] We found that the hemodialysis population had a higher prevalence of polypharmacy and used multiple QT prolonging medications more often than the general population. Notably, among hemodialysis patients, the antidepressants citalopram and escitalopram were the medications with known TdP risk most frequently involved in potential pharmacodynamic and pharmacokinetic drug interactions. Exposure to such drug interactions may have devastating consequences. Recent pharmacoepidemiologic studies indicate that the risk of SCD associated with citalopram and escitalopram therapy is more pronounced in the setting of concurrent QT prolonging medication and metabolic inhibitor use.[12,33]

The hemodialysis population experiences an overwhelmingly high rate of SCD, which exceeds that of the general population by 20- to 30-fold.[34] To date, efforts to identify modifiable SCD risk factors have mainly focused on the dialysis procedure.[35] Despite sound biologic plausibility, the potential role of drug-induced QT prolongation in SCD among hemodialysis patients has been underappreciated.[36] Given the widespread use of QT prolonging medications in the hemodialysis population as well as their broad range of clinical indications (eg, depression, infections, nausea/vomiting), future large-scale cardiac safety studies are needed to assess the association between specific QT prolonging drugs, therapeutic alternatives, and clinical outcomes, such as sudden cardiac death.

Our findings should be considered within the context of study limitations. First, our data sources do not capture prescription medications purchased without insurance or over-the-counter medications, and thus may underestimate the frequency of QT prolonging medication use. Second, laboratory parameters, including serum electrolytes, were not available, precluding evaluation of QT prolonging medication use among hemodialysis patients with various electrolyte abnormalities associated with QT prolongation and TdP. Third, information on QT interval measurements from ECGs was not available, and thus, we were unable to determine if drug-induced QT prolongation occurred. Finally, this was a drug utilization study. Our analyses focused on patterns of medication use and did not investigate potential associations between QT prolonging drug use and clinical outcomes such as SCD.

CONCLUSIONS

Our study establishes that hemodialysis patients use QT prolonging medications with known and possible TdP risk to a greater extent than individuals without ESKD. Non-antiarrhythmic drugs (eg, psychotropics, antiemetics, acid suppressants) were the most commonly prescribed agents. Our findings highlight high-risk and potentially unsafe prescribing patterns, underscoring the need for future studies evaluating the cardiac safety of QT prolonging medications, especially non-antiarrhythmic agents, in the clinically complex hemodialysis population.

ARTICLE INFORMATION

Received January 15, 2020; accepted May 4, 2020.

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Acknowledgments

Some of 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 US government.

Sources of Funding

The project described was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health through Grant Award Number UL1 TR002489. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. M.M.A. and J.E.F. are supported grant R03 HS026801 awarded by the Agency for Healthcare Research and Quality. M.M.A., L.W., P.H.P., W.C.W., and J.E.F. are supported by grant R01 HL152034 awarded

by the National Heart, Lung, and Blood Institute of the National Institutes of Health. J.E.F. is supported by grant K23 DK109401 awarded by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH. The database infrastructure (MarketScan and Medicare data) used for this project was funded by the Department of Epidemiology, University of North Carolina Gillings School of Global Public Health; the Cecil G. Sheps Center for Health Services Research; the Comparative Effectiveness Research Strategic Initiative of University of North Carolina's Clinical and Translational Science Award (UL1 TR002489); and the University of North Carolina School of Medicine.

Disclosures

M.M.A. has received investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America and honoraria from the International Society of Nephrology. P.H.P. has received consulting fees from AstraZeneca, Janssen, and Relypsa. W.C.W. has served as an advisor to and received consulting fees from Akebia, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Janssen, Relypsa, Vifor FMC Renal Pharma, and ZS Pharma. J.E.F. has received investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America. In the past 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, and AstraZeneca. The remaining authors have no disclosures to report..

Supplementary Material

Tables S1–S16
Figures S1–S5

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SUPPLEMENTAL MATERIAL

Table S1. Diagnosis and procedure codes used to identify ESKD

Comorbid condition	Diagnosis and procedure codes
ESKD	ICD-9 codes: 585.6, 996.81, V42.0, V45.1, V56.1, V56.2, V56.3, V56.31, V56.32, V56.8, E879.1
	ICD-10 codes: N18.6, T86.10, T86.11, T86.12, T86.13, T86.19, Y84.1, Z48.22, Z49.01, Z49.02, Z49.31, Z49.32, Z94.0
	HCPCS codes: 90918-90925, 90935, 90937, 90940, 90945, 90947, 90951-90970, 90989, 90993, 90997, 90999 (only applicable if the place of service is an ESKD treatment facility)
	DRG codes: 008, 652 (only applicable for inpatient hospital claims)

Relevant diagnosis and procedure codes for ESKD are listed above. To be classified as non-ESKD, the absence of any billed ESKD diagnosis and procedure code during the 180-day baseline period was required. Individuals with ≥ 1 billed ESKD diagnosis or procedure code during the 180-day baseline period were considered to have ESKD.

Specified three-digit ICD-9 diagnosis code categories included all existing 4th and 5th digit diagnosis codes and specified four-digit ICD-9 diagnosis code categories included all existing 5th digit diagnosis codes. Specified three-digit ICD-10 diagnosis codes include all existing 4th, 5th, 6th and 7th digit diagnosis codes; specified four-digit ICD-10 diagnosis codes include all existing 5th, 6th and 7th digit diagnosis codes; specified five-digit ICD-10 diagnosis codes include all existing 6th and 7th digit diagnosis codes; and specified six-digit ICD-10 diagnosis codes include all existing 7th digit codes.

DRG, diagnosis-related group; ESKD, end-stage kidney disease; HCPCS, Healthcare Common Procedure Coding System; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table S2. ICD-9 and ICD-10 diagnosis codes used to identify relevant baseline covariates

Comorbid condition	Diagnosis codes
Arrhythmia	ICD-9 code: 427 ICD-10 codes: I46-I49
Conduction disorder	ICD-9 code: 426 ICD-10 codes: I44-I45
Heart failure	ICD-9 codes: 398.91, 402.x1, 404.x1, 404.x3, 428 ICD-10 codes: I09.81, I11.0, I13.0, I50
Ischemic heart disease	ICD-9 codes: 410-414 ICD-10 codes: I10-I16
Chronic liver disease	ICD-9 codes: 571 ICD-10 codes: K70-K76
Cardiac pacemaker	ICD-9 codes: V45.01 ICD-10 codes: Z95.0
Implantable cardiac defibrillator	ICD-9 codes: V45.02 ICD-10 codes: Z95.810

Specified three-digit ICD-9 diagnosis code categories included all existing 4th and 5th digit diagnosis codes and specified four-digit ICD-9 diagnosis code categories included all existing 5th digit diagnosis codes. Specified three-digit ICD-10 diagnosis codes include all existing 4th, 5th, 6th and 7th digit diagnosis codes; specified four-digit ICD-10 diagnosis codes include all existing 5th, 6th and 7th digit diagnosis codes; specified five-digit ICD-10 diagnosis codes include all existing 6th and 7th digit diagnosis codes; and specified six-digit ICD-10 diagnosis codes include all existing 7th digit codes.

ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table S3. List of medications with a known, possible, and conditional TdP risk

Known TdP risk*
Aclarubicin, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, hydroquinidine, ibogaine, ibutilide, levofloxacin, levomepromazine, levomethadyl, levosulpiride, mesoridazine, methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, thioridazine, vandetanib
Possible TdP risk†
Abarelix, alfuzosin, alimemazine, apalutamide, apomorphine, aripiprazole, artemether/lumefantrine, artenimol/piperaquine, asenapine, atomoxetine, bedaquiline, bendamustine, benperidol, betrixaban, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clofazimine, clomipramine, clotiapine, clozapine, cobimetinib, crizotinib, cyamemazine, dabrafenib, dasatinib, degarelix, delamanid, desipramine, deutetrabenazine, dexmedetomidine, dextromethorphan/quinidine, dolasetron, efavirenz, eliglustat, encorafenib, epirubicin, eribulin, ezogabine, felbamate, fingolimod, fluorouracil, flupentixol, gemifloxacin, gilteritinib, glasdegib, granisetron, hydrocodone ER, iloperidone, imipramine, inotuzumab ozogamicin, isradipine, ivosidenib, ketanserin, lacidipine, lapatinib, lenvatinib, leuprolide, lithium, lofexidine, lopinavir/ritonavir, maprotiline, melperone, memantine, mianserin, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/hydrochlorothiazide, necitumumab, nicardipine, nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, osimertinib, oxytocin, paliperidone, palonosetron, panobinostat, pasireotide, pazopanib, perflutren, perphenazine, pilsicainide, pimavanserin, pipamperone, primaquine, promethazine, prothipendyl, ribociclib, rilpivirine, risperidone, romidepsin, saquinavir, sertindole, siponimod, sorafenib, sunitinib, tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine, tiapride, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, tramadol, trimipramine, tropisetron, valbenazine, vardenafil, vemurafenib, venlafaxine, vorinostat, zotepine, zuclopenthixol
Conditional TdP risk‡
Amantadine, amisulpride, amsacrine, amitriptyline, amphotericin B, atazanavir, bendroflumethiazide, bendrofluazide, chloral hydrate, cimetidine, diphenhydramine, doxepin, esomeprazole, eperisone, famotidine, fluoxetine, fluvoxamine furosemide, galantamine, garenoxacin, hydrochlorothiazide, hydroxychloroquine, hydroxyzine, indapamide, itraconazole, ivabradine, ketoconazole, lansoprazole, loperamide, metoclopramide, metolazone, metronidazole, nelfinavir, olanzapine, omeprazole, pantoprazole, paroxetine, piperacillin/tazobactam, posaconazole, propafenone, quetiapine, quinine, ranolazine, sertraline, solifenacin, telaprevir, torsemide, trazodone, voriconazole, ziprasidone

Medication lists were obtained from the CredibleMeds website (www.Crediblemeds.org) on July 10, 2019.

***** Medications with known TdP risk are defined as drugs that prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

† Medications with possible risk TdP risk are defined as drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended.

‡ Medications with conditional TdP risk are defined as drugs that are associated with TdP only under certain conditions (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or medications that create conditions that facilitate or induce TdP (e.g. cause an electrolyte disturbance that induces TdP).

TdP, torsades de pointes.

Table S4. List of medications that are CYP3A4, CYP2C8, and CYP2C19 inhibitors

CYP3A4 Inhibitors
Amiodarone, amprenavir, aprepitant, atazanavir, chloramphenicol, clarithromycin, conivaptan, cyclosporine, darunavir, dasatinib, delavirdine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, quinupristin, saquinavir, tamoxifen, telithromycin, troleandomycin, verapamil, voriconazole
CYP2C8 Inhibitors
Deferasirox, gemfibrozil, lapatinib, trimethoprim
CYP2C19 Inhibitors
Chloramphenicol, cimetidine, clopidogrel, delavirdine efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, isoniazid, moclobemide, modafinil, omeprazole, oxcarbazepine, ticlopidine, topiramate, voriconazole

Medication lists were obtained from the Flockhart Table website (https://drug-interactions.medicine.iu.edu/MainTable.aspx) and the Pharmacy Times website (https://www.pharmacytimes.com) on July 10, 2019.

CYP, cytochrome P450.

Table S5. Hemodialysis population annual cohort sample sizes, 2012–2016

Hemodialysis population			
Year	**All adults**	**Younger adults**	**Older adults**
2012	165,160	96,447	64,636
2013	173,422	100,310	68,391
2014	183,252	102,786	75,523
2015	183,768	101,752	77,058
2016	184,573	100,440	79,037

We used the USRDS database to construct separate annual cohorts of center-based hemodialysis patients who were ≥ 18 years of age and met study selection criteria on January 1st of each study year (2012 to 2016). We also created annual sub-cohorts of younger (18–64 years of age) and older (≥ 66 years of age) hemodialysis patients for comparison to similarly aged individuals without ESKD.

ESKD, end-stage kidney disease; USRDS, United States Renal Data System.

Table S6. Non-ESKD population annual cohort sample sizes, 2012–2016

Non-ESKD population		
Year	**Younger adults**	**Older adults**
2012	20,358,190	2,341,761
2013	16,140,007	2,485,418
2014	16,820,990	2,875,813
2015	14,074,554	2,972,150
2016	13,992,738	3,134,841

We used 2 distinct United States-based administrative claims data sources, the Truven Health MarketScan Commercial Claims and Encounters Database and a 20% random sample of Medicare fee-for-service beneficiaries, to facilitate consideration of non-ESKD population comparator cohorts that spanned the adult age range. We generated annual cohorts (2012 to 2016) of younger and older adults without ESKD using Marketscan and Medicare data, respectively. In each study year, we identified adults without ESKD who met age specifications (18–64 years for Marketscan and ≥ 66 years for Medicare) and other study selection criteria on January 1st.

ESKD, end-stage kidney disease.

Table S7. Use of ≥ 1 prescription QT prolonging medication by the hemodialysis population, 2012–2016

Younger adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*
2012	178.3 (176.6, 180.0)	178.9 (177.3, 180.6)	40.1 (39.3, 40.9)	40.4 (39.6, 41.2)	34.8 (34.0, 35.5)	34.7 (33.9, 35.4)	152.5 (150.9, 154.1)	153.1 (151.6, 154.7)
2013	175.8 (174.2, 177.5)	176.4 (174.7, 178.0)	39.8 (39.0, 40.6)	40.0 (39.2, 40.8)	34.3 (33.6, 35.0)	34.3 (33.5, 35.0)	149.6 (148.01, 151.1)	150.1 (148.6, 151.6)
2014	169.4 (167.8, 171.0)	169.9 (168.3, 171.5)	37.3 (36.5, 38.0)	37.4 (36.7, 38.2)	32.4 (31.7, 33.1)	32.36 (31.7, 33.1)	144.1 (142.6, 145.6)	144.5 (143.02, 146.0)
2015	172.2 (170.6, 173.9)	172.4 (170.8, 174.1)	39.0 (38.2, 39.8)	39.0 (38.3, 39.9)	33.6 (32.9, 34.3)	33.6 (32.9, 34.3)	145.4 (143.9, 146.9)	145.6 (144.1, 147.1)
2016	171.6 (170.0, 173.3)	171.6 (170.0, 173.3)	38.6 (37.8, 39.4)	38.6 (37.8, 39.4)	34.4 (33.6, 35.1)	34.4 (33.6, 35.1)	144.5 (143.0, 146.0)	144.5 (143.0, 146.0)

Older adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized†	Crude	Standardized†	Crude	Standardized†	Crude	Standardized†
2012	205.5 (203.2, 207.8)	204.5 (202.5, 206.6)	60.7 (59.5, 62.0)	60.4 (59.3, 61.5)	36.7 (35.8, 37.7)	36.3 (35.5, 37.2)	171.8 (169.7, 173.9)	170.9 (169.0, 172.8)
2013	205.2 (203.0, 207.4)	204.3 (202.3, 206.4)	60.5 (59.4, 61.8)	60.3 (59.1, 61.4)	37.6 (36.6, 38.5)	37.23 (36.4, 38.1)	170.9 (168.9, 172.9)	170.1 (168.2, 172.0)
2014	199.4 (197.4, 201.5)	198.9 (196.91, 201.0)	58.4 (57.3, 59.5)	58.2 (57.1, 59.3)	36.8 (35.9, 37.7)	36.6 (35.7, 37.5)	165.5 (163.6, 167.4)	165.0 (163.2, 166.9)
2015	201.5 (199.5, 203.6)	201.3 (199.2, 203.3)	59.3 (58.2, 60.4)	59.2 (58.1, 60.3)	37.5 (36.6, 38.4)	37.4 (36.5, 38.3)	167.0 (165.1, 168.9)	166.8 (164.9, 168.7)
2016	201.1 (199.1, 203.1)	201.1 (199.1, 203.1)	58.3 (57.2, 59.4)	58.3 (57.2, 59.4)	38.0 (37.2, 38.9)	38.0 (37.2, 38.9)	166.7 (164.8, 168.5)	166.7 (164.8, 168.5)

All adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized‡	Crude	Standardized‡	Crude	Standardized‡	Crude	Standardized‡
2012	189.0 (187.6, 190.3)	189.9 (188.6, 191.2)	48.2 (47.5, 48.9)	49.0 (48.3, 49.6)	35.5 (34.9, 36.1)	35.3 (34.8, 35.9)	160.1 (158.0, 161.3)	160.8 (159.6, 161.9)

2013	187.4 (186.1, 188.7)	188.3 (187.0, 189.6)	47.9 (47.3, 48.6)	48.6 (48.0, 49.2)	35.5 (35.0, 36.1)	35.5 (34.9, 36.0)	158.1 (156.9, 159.3)	158.7 (157.6, 159.9)
2014	182.0 (180.7, 183.2)	182.5 (181.2, 183.7)	46.0 (45.4, 46.7)	46.4 (45.7, 47.0)	34.2 (33.7, 34.8)	34.2 (33.7, 34.8)	153.1 (151.9, 154.2)	153.4 (152.3, 154.6)
2015	184.6 (183.3, 185.9)	184.8 (183.6, 186.1)	47.5 (46.9, 48.2)	47.7 (47.0, 48.3)	35.2 (34.6, 35.8)	35.2 (34.6, 35.7)	154.6 (153.4, 155.7)	154.8 (153.6, 155.9)
2016	184.4 (183.2, 185.7)	184.4 (183.2, 185.7)	47.1 (46.4, 47.7)	47.1 (46.4, 47.7)	35.9 (35.3, 36.4)	35.9 (35.3, 36.4)	154.1 (153.0, 155.3)	154.1 (153.0, 155.3)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the 3 CredibleMeds classes.

* To facilitate comparisons between the younger (18-64 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 younger hemodialysis cohort was the referent population.

† To facilitate comparisons between the older (≥ 66 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 older hemodialysis cohort was the referent population.

‡ To facilitate comparisons within the adult (≥ 18 years of age) hemodialysis population across time, we age- and sex-standardized rate estimates. The 2016 adult hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; TdP, torsades de pointes.

Table S8. Use of ≥ 1 prescription QT prolonging medication by the younger non-ESKD population, 2012–2016

Younger adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*
2012	65.4 (65.3, 65.4)	83.7 (82.6, 84.8)	12.7 (12.7, 12.8)	14.0 (13.5, 14.5)	10.5 (10.4, 10.5)	12.3 (11.8, 12.7)	50.6 (50.6, 50.7)	68.4 (67.4, 69.4)
2013	66.1 (66.1, 66.2)	84.6 (83.4, 85.7)	13.0 (12.9, 13.0)	14.2 (13.8, 14.7)	10.8 (10.7, 10.8)	12.6 (12.2, 13.1)	51.1 (51.0, 51.1)	68.9 (67.9, 69.9)
2014	67.0 (66.9, 67.1)	85.59 (84.5, 86.7)	13.4 (13.3, 13.4)	14.7 (14.2, 15.1)	10.9 (10.9, 11.0)	12.8 (12.3, 13.2)	51.6 (51.5, 51.7)	69.6 (68.6, 70.6)
2015	69.7 (69.6, 69.8)	88.1 (86.9, 89.3)	14.0 (14.0, 14.0)	15.3 (14.8, 15.7)	11.4 (11.3, 11.4)	13.2 (12.8, 13.7)	53.9 (53.8, 54.0)	71.7 (70.7, 72.7)
2016	70.1 (70.2, 70.2)	88.2 (87.0, 89.4)	14.2 (14.2, 14.2)	15.4 (15.0, 15.9)	11.5 (11.5, 11.6)	13.4 (12.9, 13.8)	54.1 (54.0, 54.1)	71.5 (70.5, 72.6)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the 3 CredibleMeds classes.

* To facilitate comparisons between the younger (18-64 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 younger hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; torsades de pointes.

Table S9. Use of ≥ 1 prescription QT prolonging medication by the older non-ESKD population, 2012–2016

	Older adults							
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*
2012	197.4 (197.0, 197.7)	190.8 (188.9, 192.7)	44.7 (44.5, 44.9)	41.9 (41.1, 42.8)	35.8 (35.6, 35.9)	33.0 (32.2, 33.8)	171.2 (170.9, 171.5)	165.6 (163.9, 167.4)
2013	197.7 (197.4, 198.0)	192.0 (190.1, 193.9)	44.4 (44.2, 44.5)	42.0 (41.1, 42.9)	35.7 (35.5, 35.8)	33.3 (32.5, 34.1)	171.4 (171.0, 171.7)	166.5 (164.8, 168.3)
2014	196.6 (196.3, 197.0)	191.9 (190.1, 193.8)	43.5 (43.4, 43.7)	41.6 (40.7, 42.5)	35.2 (35.1, 35.4)	33.2 (32.5, 34.0)	170.1 (169.8, 170.4)	166.1 (164.4, 167.9)
2015	195.4 (195.0, 195.7)	191.3 (189.4, 193.2)	43.5 (43.4, 43.7)	41.9 (41.1, 42.8)	34.9 (34.8, 35.1)	33.2 (32.4, 34.0)	168.1 (167.8, 168.4)	164.7 (162.9, 166.4)
2016	194.1 (193.8, 194.4)	190.7 (188.8, 192.5)	43.3 (43.2, 43.5)	42.0 (41.1, 42.9)	35.7 (35.6, 35.8)	34.2 (33.4, 35.0)	166.2 (166.0, 166.5)	163.4 (161.6, 165.1)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the 3 CredibleMeds classes.

* To facilitate comparisons between the older (≥ 66 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 older hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; TdP, torsades de pointes.

Table S10. Use of ≥ 1 prescription QT prolonging medication by the hemodialysis population excluding thiazide/thiazide-like diuretics

Younger adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*
2012	177.3 (175.6, 179.0)	177.9 (176.3, 179.6)	40.1 (39.3, 40.9)	40.4 (39.6, 41.2)	34.8 (34.0, 35.5)	34.7 (33.9, 35.4)	151.3 (149.8, 152.9)	151.9 (150.4, 153.4)
2013	174.7 (173.0, 176.3)	175.19 (173.6, 176.9)	39.8 (39.0, 40.6)	40.0 (39.2, 40.8)	34.3 (33.6, 35.0)	34.3 (33.5, 35.0)	148.2 (146.7, 149.7)	148.7 (147.2, 150.2)
2014	168.2 (166.6, 169.8)	168.65 (167.0, 170.3)	37.3 (36.5, 38.0)	37.4 (36.7, 38.2)	32.4 (31.7, 33.1)	32.36 (31.7, 33.1)	142.7 (141.2, 144.2)	143.1 (141.5, 144.56)
2015	171.2 (169.6, 172.9)	171.42 (169.8, 173.1)	39.0 (38.2, 39.8)	39.0 (38.3, 39.9)	33.6 (32.9, 34.3)	33.6 (32.9, 34.3)	144.2 (142.7, 145.7)	144.4 (142.9, 145.9)
2016	170.7 (169.0, 172.3)	170.7 (169.0, 172.3)	38.6 (37.8, 39.4)	38.6 (37.8, 39.4)	34.4 (33.6, 35.1)	34.4 (33.6, 35.1)	143.3 (141.8, 144.8)	143.3 (141.8, 144.8)
Older adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized†	Crude	Standardized†	Crude	Standardized†	Crude	Standardized†
2012	204.1 (201.9, 206.4)	203.2 (201.1, 205.2)	60.7 (59.5, 62.0)	60.4 (59.3, 61.5)	36.7 (35.8, 37.7)	36.3 (35.5, 37.2)	170.1 (168.0, 172.2)	169.2 (167.3, 171.1)
2013	203.7 (201.5, 205.9)	202.9 (200.8, 204.9)	60.5 (59.4, 61.8)	60.3 (59.1, 61.4)	37.6 (36.6, 38.5)	37.23 (36.4, 38.1)	169.1 (167.1, 171.1)	168.3 (166.4, 170.2)
2014	198.1 (196.0, 200.2)	197.6 (195.6, 199.6)	58.4 (57.3, 59.5)	58.2 (57.1, 59.3)	36.8 (35.9, 37.7)	36.6 (35.7, 37.5)	163.8 (161.9, 165.6)	163.3 (161.5, 165.2)
2015	200.2 (198.1, 202.2)	199.9 (197.8, 201.9)	59.3 (58.2, 60.4)	59.2 (58.1, 60.3)	37.5 (36.6, 38.4)	37.4 (36.5, 38.3)	165.3 (163.4, 167.2)	165.0 (163.2, 166.9)
2016	199.8 (197.8, 201.9)	199.8 (197.8, 201.9)	58.3 (57.2, 59.4)	58.3 (57.2, 59.4)	38.0 (37.2, 38.9)	38.0 (37.2, 38.9)	165.1 (163.2, 166.9)	165.1 (163.2, 166.9)
All adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized‡	Crude	Standardized‡	Crude	Standardized‡	Crude	Standardized‡

2012	187.8 (186.5, 189.2)	188.8 (187.5, 190.0)	48.2 (47.5, 48.9)	49.0 (48.3, 49.6)	35.5 (34.9, 36.1)	35.3 (34.8, 35.9)	158.7 (157.5, 159.9)	159.3 (158.2, 160.5)
2013	186.2 (184.9, 187.5)	187.0 (185.8, 188.3)	47.9 (47.3, 48.6)	48.6 (48.0, 49.2)	35.5 (35.0, 36.1)	35.5 (34.9, 36.0)	156.4 (155.4, 157.8)	157.2 (156.0, 158.3)
2014	180.7 (179.5, 182.0)	181.2 (179.9, 182.4)	46.0 (45.4, 46.7)	46.4 (45.7, 47.0)	34.2 (33.7, 34.8)	34.2 (33.7, 34.8)	151.5 (150.4, 152.7)	151.9 (150.7, 153.0)
2015	183.4 (182.1, 184.7)	183.6 (182.4, 184.9)	47.5 (46.9, 48.2)	47.7 (47.0, 48.3)	35.2 (34.6, 35.8)	35.2 (34.6, 35.7)	153.13 (152.0, 154.3)	153.3 (152.2, 154.5)
2016	183.3 (182.1, 184.6)	183.3 (182.1, 184.6)	47.1 (46.4, 47.7)	47.1 (46.4, 47.7)	35.9 (35.3, 36.4)	35.9 (35.3, 36.4)	152.8 (151.7, 154.0)	152.8 (151.7, 154.0)

Thiazide and thiazide-like diuretics were excluded from this analysis. Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the 3 CredibleMeds classes.

* To facilitate comparisons between the younger (18-64 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 younger hemodialysis cohort was the referent population.

† To facilitate comparisons between the older (≥ 66 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 older hemodialysis cohort was the referent population.

‡ To facilitate comparisons within the adult (≥ 18 years of age) hemodialysis population across time, we age- and sex-standardized rate estimates. The 2016 adult hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; TdP, torsades de pointes.

Table S11. Use of ≥ 1 prescription QT prolonging medication by the younger non-ESKD population excluding thiazide/thiazide-like diuretics

Younger adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Year	Crude	Standardized*
2012	49.9 (49.9, 50.0)	60.0 (59.1, 61.0)	12.7 (12.7, 12.8)	14.0 (13.5, 14.5)	10.5 (10.4, 10.5)	12.3 (11.8, 12.7)	33.5 (33.4, 33.5)	42.2 (41.4, 43.0)
2013	50.9 (50.8, 50.9)	61.0 (60.1, 62.0)	13.0 (12.9, 13.0)	14.2 (13.8, 14.7)	10.8 (10.7, 10.8)	12.6 (12.2, 13.1)	34.1 (34.0, 34.1)	42.9 42.1, 43.7)
2014	51.8 (51.7, 51.9)	62.1 (61.2, 63.1)	13.4 (13.3, 13.4)	14.7 (14.2, 15.1)	10.9 (10.9, 11.0)	12.8 (12.3, 13.2)	34.6 (34.6, 34.7)	43.7 (42.8, 44.5)
2015	53.9 (53.9, 54.0)	64.1 (63.2, 65.1)	14.0 (14.0, 14.0)	15.3 (14.8, 15.7)	11.4 (11.3, 11.4)	13.2 (12.8, 13.7)	36.3 (36.2, 36.3)	45.1 (44.3, 46.0)
2016	54.3 (54.3, 54.4)	64.2 (63.2, 65.2)	14.2 (14.2, 14.2)	15.4 (15.0, 15.9)	11.5 (11.5, 11.6)	13.4 (12.9, 13.8)	36.4 (36.3, 36.4)	44.9 (44.1, 45.7)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the three CredibleMeds classes.

* To facilitate comparisons between the younger (18-64 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 younger hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; torsades de pointes.

Table S12. Use of ≥ 1 prescription QT prolonging medication by the older non-ESKD population excluding thiazide/thiazide-like diuretics

Older adults								
	Any TdP risk		Known TdP risk		Possible TdP risk		Conditional TdP risk	
Year	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*	Crude	Standardized*
2012	154.2 (153.9, 154.6)	147.8 (146.1, 149.4)	44.7 (44.5, 44.9)	41.9 (41.1, 42.8)	35.8 (35.6, 35.9)	33.0 (32.2, 33.8)	121.3 (121.1, 121.6)	116.3 (114.8, 117.7)
2013	155.4 (155.1, 155.7)	149.8 (148.1, 151.5)	44.4 (44.2, 44.5)	42.0 (41.1, 42.9)	35.7 (35.5, 35.8)	33.3 (32.5, 34.1)	122.4 (122.1,122.6)	118.0 (116.5, 119.5)
2014	154.9 (154.7, 155.2)	150.3 (148.6, 151.9)	43.5 (43.4, 43.7)	41.6 (40.7, 42.5)	35.2 (35.1, 35.4)	33.2 (32.5, 34.0)	121.8 (121.5, 122.0)	118.1 (116.6, 119.6)
2015	154.6 (154.3, 154.9)	150.6 (148.9, 152.2)	43.5 (43.4, 43.7)	41.9 (41.1, 42.8)	34.9 (34.8, 35.1)	33.2 (32.4, 34.0)	120.8 (120.6, 121.1)	117.7 (116.2, 119.2)
2016	153.9 (153.7, 154.2)	150.6 (148.9, 152.3)	43.3 (43.2, 43.5)	42.0 (41.1, 42.9)	35.7 (35.6, 35.8)	34.2 (33.4, 35.0)	119.6 (119.4, 119.8)	117.0 (115.6, 118.5)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 QT prolonging medication expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1. Supplemental Table S3 lists medications in each category. Medications with any TdP risk are those in any of the three CredibleMeds classes.

* To facilitate comparisons between the older (≥ 66 years of age) hemodialysis and non-ESKD cohorts across time, we age- and sex-standardized rate estimates. The 2016 older hemodialysis cohort was the referent population.

CI, confidence interval; ESKD, end-stage kidney disease; TdP, torsades de pointes.

Table S13. Top 5 medications in each CredibleMeds class used by the hemodialysis and non-ESKD populations in 2016

Known TdP risk				
Younger adults		**Older adults**		**All adults**
Hemodialysis n = 100,440	**Non-ESKD n = 13,992,738**	**Hemodialysis n = 79,037**	**Non-ESKD n = 3,134,842**	**Hemodialysis n = 184,573**
1) Citalopram 9.1 (9.1, 9.1)	1) Escitalopram 5.9 (5.9, 5.9)	1) Amiodarone 16.5 (16.5, 16.6)	1) Citalopram 10.9 (10.9, 10.9)	1) Amiodarone 11.1 (11.1, 11.1)
2) Escitalopram 7.4 (7.3, 7.4)	2) Citalopram 4.6 (4.6, 4.6)	2) Citalopram 10.6 (10.6, 10.6)	2) Donepezil 10.7 (10.7, 10.7)	2) Citalopram 9.8 (9.7, 9.8)
3) Amiodarone 6.9 (6.9, 6.9)	3) Azithromycin 0.9 (0.9, 0.9)	3) Donepezil 10.1 (10.1, 10.2)	3) Escitalopram 9.4 (9.4, 9.4)	3) Escitalopram 8.4 (8.3, 8.4)
4) Ondansetron 5.3 (5.2, 5.3)	4) Ondansetron 0.6 (0.6, 0.6)	4) Escitalopram 9.7 (9.7, 9.7)	4) Amiodarone 3.7 (3.7, 3.7)	4) Ondansetron 4.9 (4.9, 4.9)
5) Levofloxacin 2.1 (2.1, 2.1)	5) Ciprofloxacin 0.5 (0.5, 0.5)	5) Ondansetron 4.5 (4.5, 4.5)	5) Sotalol 2.4 (2.4, 2.4)	5) Donepezil 4.9 (4.9, 4.9)
Possible TdP risk				
Younger adults		**Older adults**		**All adults**
Hemodialysis n = 100,440	**Non-ESKD n = 13,992,738**	**Hemodialysis n = 79,037**	**Non-ESKD n = 3,134,842**	**Hemodialysis n = 184,573**
1) Tramadol 10.2 (10.2, 10.2)	1) Venlafaxine 3.5 (3.5, 3.5)	1) Tramadol 11.8 (11.8, 11.9)	1) Tramadol 9.0 (9.0, 9.0)	1) Tramadol 10.91 (10.9, 10.9)
2) Mirtazapine 5.3 (5.3, 5.4)	2) Tramadol 2.1 (2.1, 2.1)	2) Mirtazapine 11.1 (11.0, 11.1)	2) Memantine 6.9 (6.9, 67.0)	2) Mirtazapine 7.8 (7.8, 7.8)
3) Promethazine 4.6 (4.5, 4.6)	3) Tizanidine 1.0 (1.0, 1.0)	3) Memantine 4.8 (4.8, 4.8)	3) Mirtazapine 5.6 (5.6, 5.6)	3) Venlafaxine 3.2 (3.2, 3.2)
4) Venlafaxine 3.4 (3.4, 3.4)	4) Aripiprazole 0.8 (0.8, 0.8)	4) Venlafaxine 3.1 (3.1, 3.1)	4) Venlafaxine 4.9 (4.9, 4.9)	4) Promethazine 2.9 (2.9, 2.9)
5) Tizanidine 2.8 (2.8, 2.8)	5) Nortriptyline 0.6 (0.6, 0.6)	5) Risperidone 2.3 (2.3, 2.4)	5) Risperidone 2.0 (2.0, 2.0)	5) Risperidone 2.4 (2.4, 2.4)
Conditional TdP risk				
Younger adults		**Older adults**		**All adults**
Hemodialysis n = 100,440	**Non-ESKD n = 13,992,738**	**Hemodialysis n = 79,037**	**Non-ESKD n = 3,134,842**	**Hemodialysis n = 184,573**
1) Omeprazole 44.1 (44.0, 44.1)	1) Hydrochlorothiazide 22.6 (22.6, 22.6)	1) Omeprazole 51.7 (51.7, 51.8)	1) Hydrochlorothiazide 67.2 (67.2, 67.2)	1) Omeprazole 47.3 (47.3, 47.3)
2) Pantoprazole 29.2 (29.2, 29.2)	2) Omeprazole 9.5 (9.5, 9.5)	2) Pantoprazole 39.4 (39.3, 39.4)	2) Omeprazole 39.3 (39.3, 39.3)	2) Pantoprazole 33.7 (33.7, 33.7)
3) Furosemide 25.2 (25.2, 25.2)	3) Sertraline 6.5 (6.5, 6.5)	3) Furosemide 35.1 (35.0, 35.1)	3) Furosemide 31.5 (31.5, 31.6)	3) Furosemide 29.5 (29.5, 29.5)
4) Sertraline 14.8 (14.8, 14.8)	4) Pantoprazole 4.5 (4.5, 4.5)	4) Sertraline 18.3 (18.2, 18.3)	4) Pantoprazole 17.1 (17.1, 17.1)	4) Sertraline 16.3 (16.3, 16.3)
5) Esomeprazole 13.8 (13.8, 13.9)	5) Fluoxetine 4.3 (4.3, 4.3)	5) Famotidine 12.5 (12.5, 12.6)	5) Sertraline 13.2 (13.2, 13.2)	5) Esomeprazole 12.6 (12.5, 12.6)

Values presented are crude rates (95% CIs) of exposure to a given medication in 2016 and are expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample sizes. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1.

ESKD, end-stage kidney disease; TdP, torsades de pointes.

Table S14. Use of ≥ 1 prescription medication with known TdP risk by hemodialysis patients with and without risk factors for drug-induced QT prolongation in 2016

All medications with known TdP risk		
Subgroup	**Crude rate (95% CI)**	**Standardized rate (95% CI)**
Advanced age*		
Yes	57.6 (56.6, 58.7)	57.2 (56.5, 57.9)
No	38.6 (37.8, 39.4)	39.1 (38.6, 39.7)
Sex†		
Female	53.1 (52.1, 54.1)	52.0 (51.4, 52.7)
Male	42.0 (41.2, 42.9)	43.1 (42.5, 43.8)
Arrhythmia‡		
Yes	84.3 (82.3, 86.4)	80.2 (79.4, 81.1)
No	39.1 (38.5, 39.9)	39.9 (39.3, 40.4)
Conduction disorder‡		
Yes	70.6 (66.6, 74.8)	68.9 (68.1, 69.7)
No	46.2 (45.5, 46.8)	46.3 (45.7, 46.9)
Ischemic heart disease‡		
Yes	64.7 (63.4, 66.1)	62.1 (61.3, 62.9)
No	39.9 (39.2, 40.6)	40.9 (40.3, 41.5)
Heart failure‡		
Yes	65. 7 (64.2, 67.2)	63.2 (62.4, 63.9)
No	40.4 (39.7, 41.1)	41.2 (40.7, 41.8)
Liver disease‡		
Yes	50.3 (47.6, 53.1)	50.4 (49.8, 51.1)
No	46.9 (46.2, 47.5)	46.8 (46.2, 47.5)
Non-antiarrhythmic medications with known TdP risk		
Subgroup	**Crude rate (95% CI)**	**Standardized rate (95% CI)**
Advanced age*		
Yes	42.1 (41.2, 43.0)	41.6 (40.9, 42.2)
No	31.8 (31.1, 32.5)	32.4 (31.9, 32.9)
Sex†		
Female	43.0 (42.2, 44.0)	42.5 (42.0, 43.1)
Male	30.8 (30.1, 31.5)	31.4 (30.9, 31.9)
Arrhythmia‡		
Yes	44.0 (42.5, 45.5)	42.6 (42.0, 43.2)
No	34.8 (34.2, 35.4)	35.3 (34.7, 35.8)
Conduction disorder‡		
Yes	46.8 (43.6, 50.2)	46.7 (46.1, 47.4)

No	32.5 (31.9, 33.1)	33.1 (32.5, 33.6)
Ischemic heart disease‡		
Yes	64.7 (63.4, 66.1)	62.1 (61.3, 62.9)
No	39.9 (39.2, 40.6)	40.9 (40.3, 41.5)
Heart failure‡		
Yes	46.7 (45.5, 48.0)	45.3 (44.7, 46.0)
No	32.7 (32.1, 33.3)	33.3 (32.7, 33.8)
Liver disease‡		
Yes	38.3 (36.0, 40.7)	38.4 (37.8, 39.0)
No	36.3 (35.7, 36.9)	36.2 (35.7, 36.8)

Values presented are crude and standardized rates (95% CIs) of exposure to ≥ 1 medication with known TdP risk expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. Medications with known TdP risk are listed in Supplemental Table S3. Advanced age was defined as ≥ 65 years of age.[9]

***** To facilitate comparisons within the age subgroups, we sex-standardized rate estimates. The 2016 adult hemodialysis cohort was the referent population.

† To facilitate comparisons within the sex subgroups, we age-standardized rate estimates. The 2016 adult hemodialysis cohort was the referent population.

‡ To facilitate comparisons within the comorbidity subgroups, we age- and sex-standardized rate estimates. The 2016 adult hemodialysis cohort was the referent population.

CI, confidence interval; TdP, torsades de pointes.

Table S15. Concurrent use of medications with known TdP risk by the 2016 hemodialysis population

Medication combinations	Crude rate (95% CI)
Amiodarone + citalopram	0.3 (0.3, 0.3)
Amiodarone + escitalopram	0.4 (0.3, 0.4)
Amiodarone + ondansetron	0.2 (0.2, 0.2)
Amiodarone + donepezil	0.2 (0.2, 0.2)
Citalopram + escitalopram	0.0 (0.0, 0.1)
Citalopram + ondansetron	0.2 (0.2, 0.2)
Citalopram + donepezil	0.3 (0.3, 0.3)
Escitalopram + ondansetron	0.2 (0.2, 0.2)
Escitalopram + donepezil	0.3 (0.3, 0.3)
Ondansetron + donepezil	0.1 (0.1, 0.1)

Values presented are crude rates (95% CIs) of exposure to a given medication combination expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size.

CI, confidence interval; TdP, torsades de pointes.

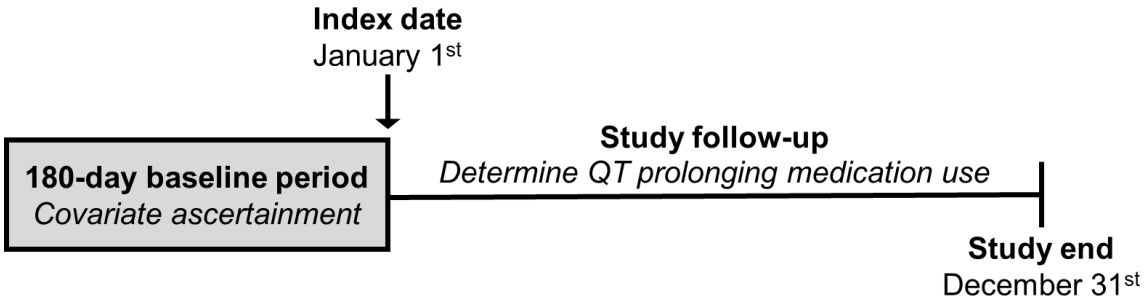
Table S16. Concurrent use of CYP metabolized medications with known risk TdP risk and relevant metabolic inhibitors by the 2016 hemodialysis population

Medication combinations	Crude rate (95% CI)
Amiodarone + CYP 2C8 inhibitor	0.6 (0.5, 0.6)
Citalopram + CYP 3A4 inhibitor	0.9 (0.9, 0.9)
Citalopram + CYP 2C19 inhibitor	4.2 (4.2, 4.2)
Escitalopram + CYP 3A4 inhibitor	0.9 (0.9, 0.9)
Escitalopram + CYP 2C19 inhibitor	3.6 (3.6, 3.6)
Ondansetron + CYP 3A4 inhibitor	0.7 (0.7, 0.7)

Values presented are crude rates (95% CIs) of exposure to a given medication combination expressed as the number of days exposed per person-year. The observed 95% CIs are very precise (i.e. narrow) due to the large sample size. CYP inhibitors are listed in Supplemental Table S4.

CI, confidence interval; CYP, cytochrome P450; TdP, torsades de pointes.

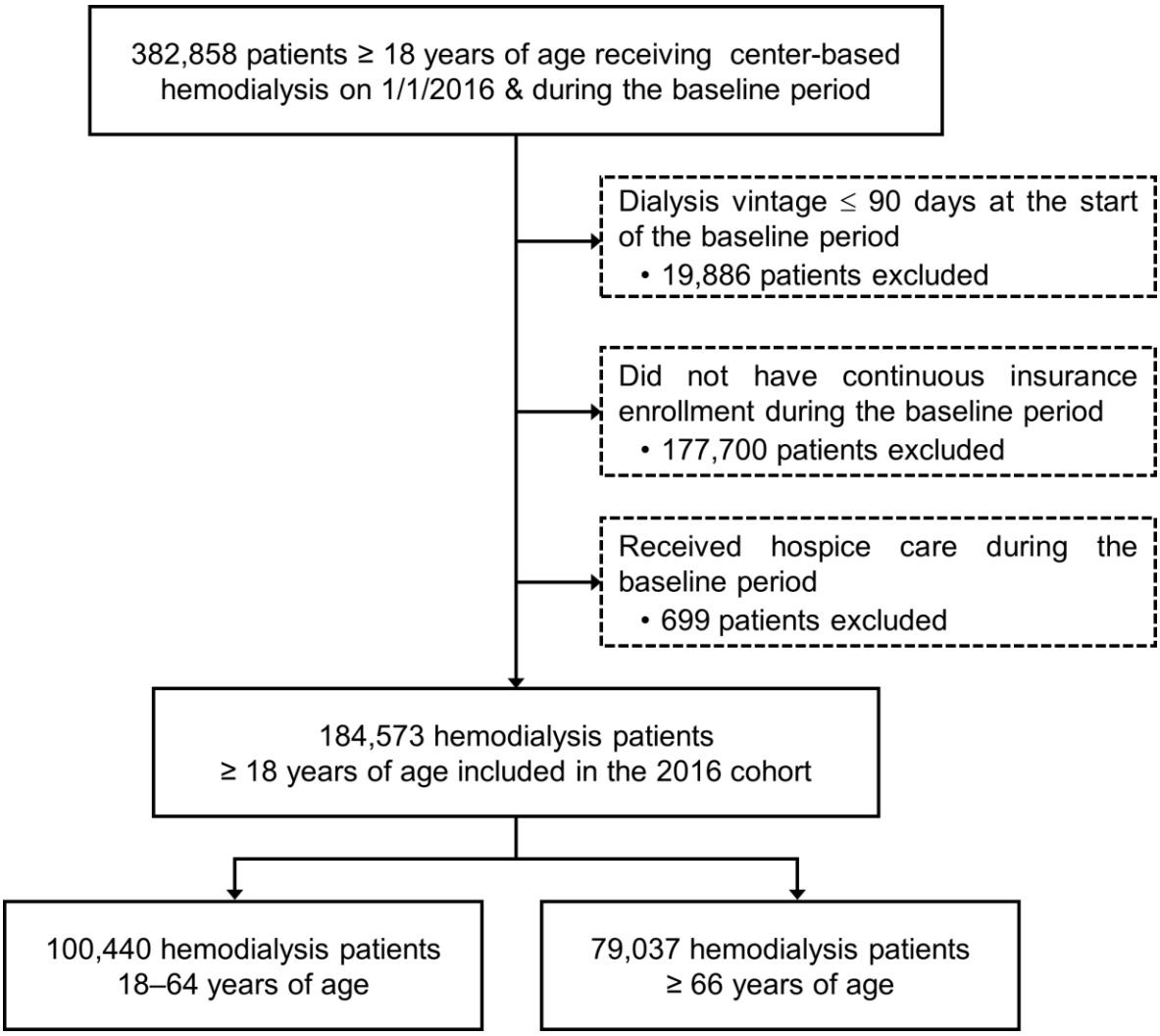
Figure S1. Study design



We conducted a drug utilization study to describe the magnitude of prescription QT prolonging medication use by hemodialysis patients relative to individuals without ESKD on an annual basis from 2012 to 2016. In each study year, we tracked QT prolonging medication use on a daily basis starting from January 1st (the index date) until December 31st. We defined the baseline period as the 180 days prior to January 1st.

ESKD, end-stage kidney disease.

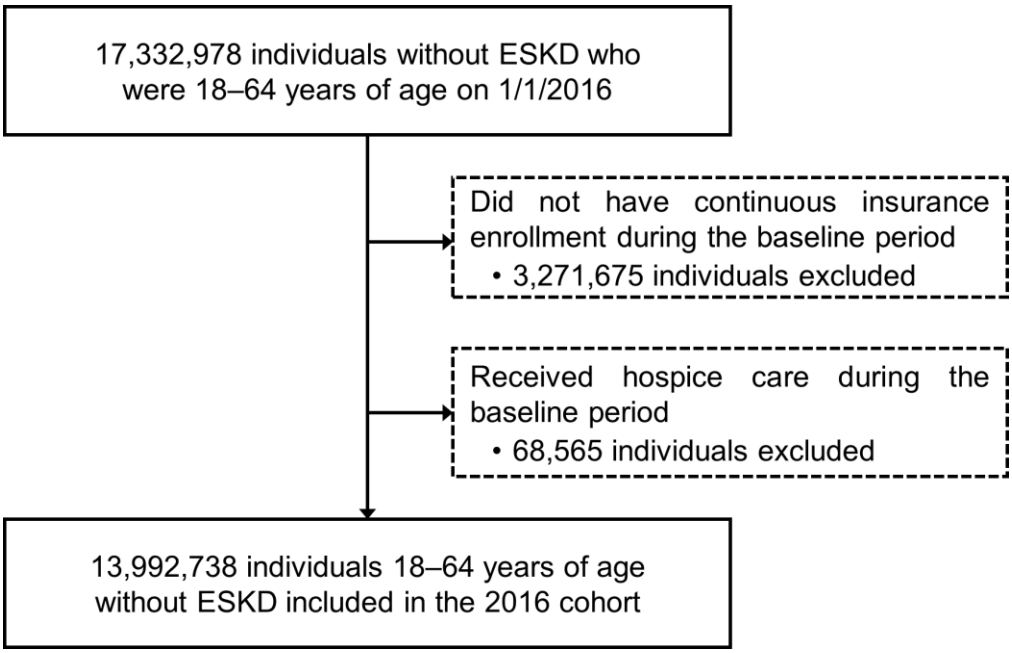
Figure S2. Assembly of the hemodialysis cohorts, 2016



We used the USRDS database to generate the 2016 hemodialysis cohorts.

USRDS, United States Renal Data System.

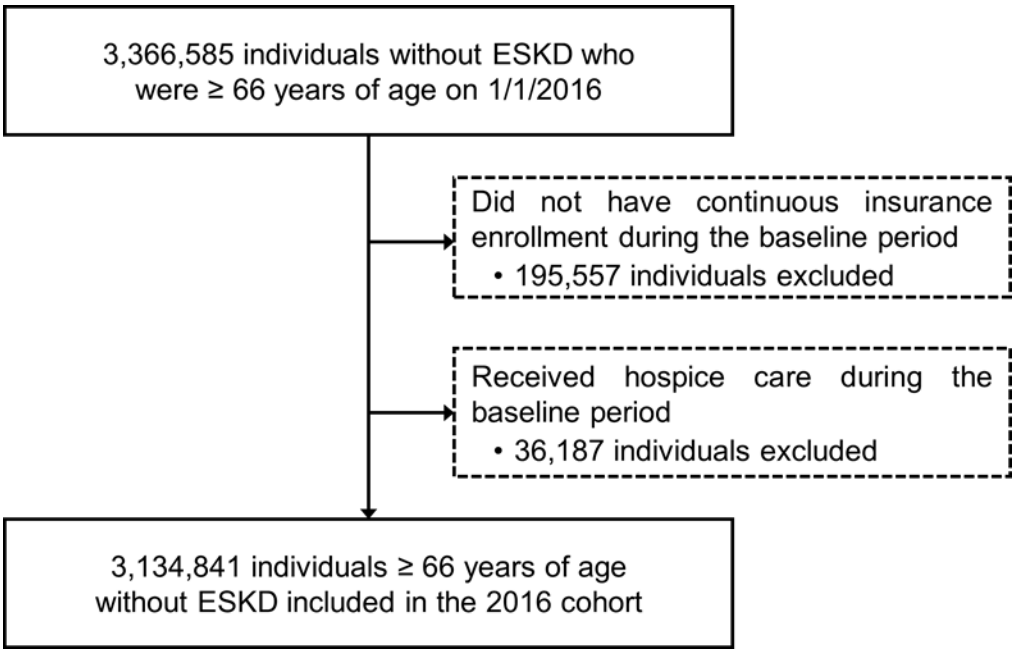
Figure S3. Assembly of the younger non-ESKD cohort, 2016



We used the MarketScan Commercial Claims and Encounters Database to generate the 2016 non-ESKD cohort comprised of younger individuals.

ESKD, end-stage kidney disease.

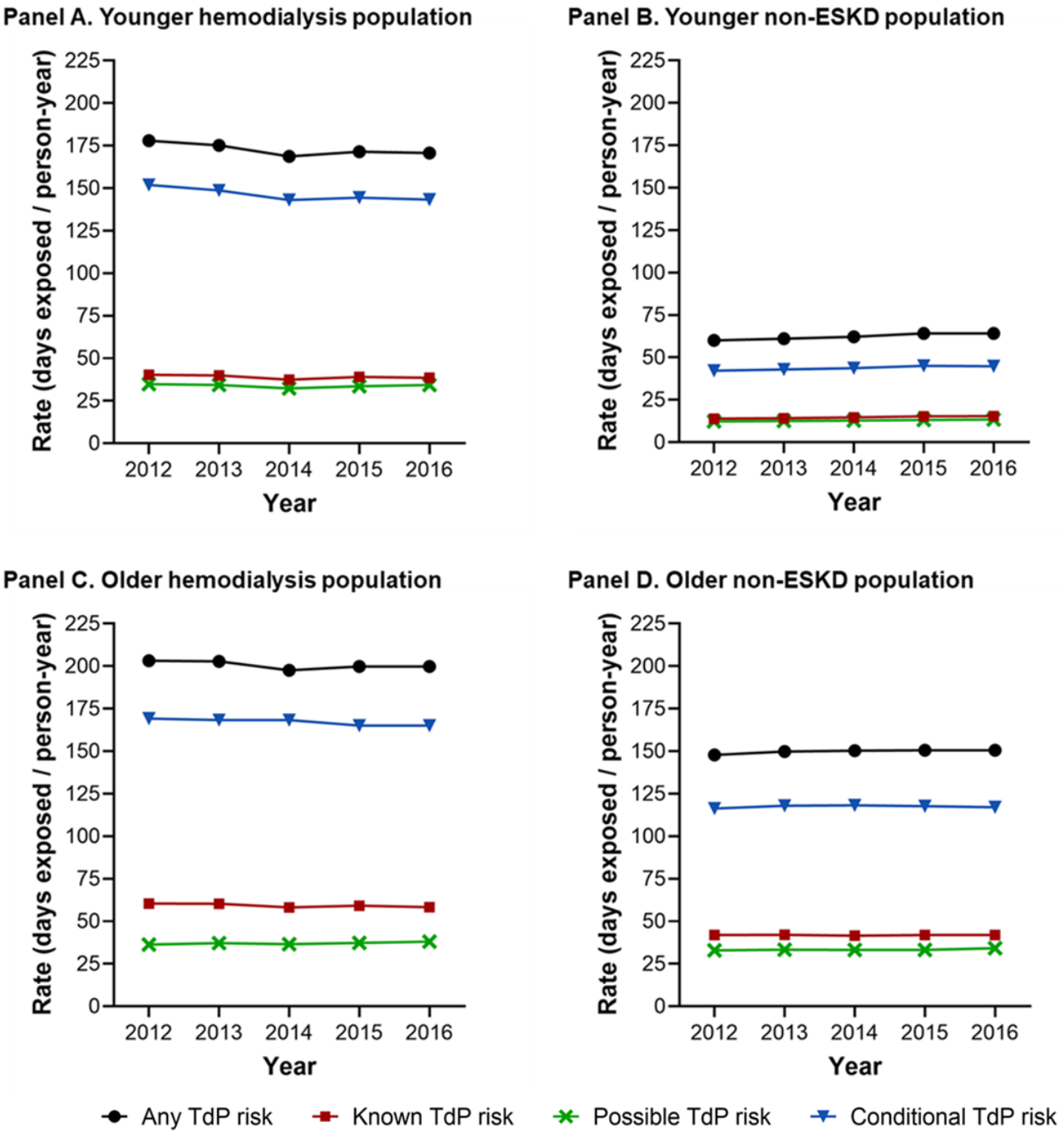
Figure S4. Assembly of the older non-ESKD population cohort, 2016



We used the Medicare database (a 20% random sample of fee-for-service beneficiaries) to generate the 2016 non-ESKD cohort comprised of older individuals.

ESKD, end-stage kidney disease.

Figure S5. Use of ≥ 1 QT prolonging medication by the hemodialysis and non-ESKD populations excluding thiazide/thiazide-like diuretics



Thiazide and thiazide-like diuretics were excluded from this analysis. Panels A and B depict annual standardized rates of exposure to ≥ 1 QT prolonging medication in the younger hemodialysis and non-ESKD populations respectively. Panels C and D depict analogous annual rates of QT prolonging medication exposure in the older hemodialysis and non-ESKD populations. CredibleMeds classifies medications that can prolong the QT interval as having a known, possible, or conditional TdP risk. Corresponding definitions are provided in Table 1 and lists of medications falling into each category are provided in Supplemental Table S3. Medications classified as having any TdP risk are those falling into any of the 3 CredibleMeds categories.

ESKD, end-stage kidney disease; TdP, torsades de pointes.