QT-Prolonging Medications: Prevalence of Use and Associated Risks in CKD

Sophie Liabeuf [1,2], Jessica Berdougo-Tritz[3], Lucie Augey[3], Solène M. Laville[1,2], Aïcha Mbarek[3], Gilbert Deray[3], Ziad A. Massy[5,6,7], Michel Jadoul[4]

[1] Pharmacoepidemiology Unit, Department of Clinical Pharmacology, Amiens-Picardie University Hospital, Amiens, France
[2] MP3CV Laboratory, Jules Verne University of Picardie, Amiens, France
[3] GPR, Paris, France
[4] Department of Nephrology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[5] AURA (Association pour l'Utilisation du Rein Artificiel dans la région parisienne), Paris, France
[6] INSERM Unit 1018, Team 5, CESP, Hôpital Paul Brousse, Paris-Saclay University (UPS) and Versailles Saint-Quentin-en-Yvelines University (UVSQ), Villejuif, France
[7] Department of Nephrology, Ambroise Paré University Hospital, APHP, Boulogne-Billancourt/Paris, France

Running title: QT-prolonging medications in chronic kidney disease

Correspondence to:
Sophie Liabeuf; E-mail: liabeuf.sophie@chu-amiens.fr

ABSTRACT

Chronic kidney disease (CKD) affects over 10% of the global adult population and is associated with substantial cardiovascular morbidity and mortality. Sudden cardiac death (often precipitated by ventricular arrhythmias like torsades de pointes) is a leading cause of death in patients with CKD. Prolongation of the QT interval (a marker of delayed ventricular repolarization) is a significant risk factor for arrhythmia in patients with CKD, whether they are on dialysis or not. QT prolongation in CKD is multifactorial and may result from electrolyte imbalances, myocardial remodelling, autonomic dysfunction, and exposure to QT-prolonging drugs. Patients on haemodialysis are particularly vulnerable to QT prolongation, due to rapid intradialytic electrolyte and fluid shifts. Many drugs known to prolong the QT interval (including various selective serotonin reuptake inhibitors, antibiotics, antiemetics, and antipsychotics) are frequently prescribed to patients with CKD, even though there are few data on their safety in this population. The results of several well-designed pharmaco-epidemiological analyses (all based on data from the United States Renal Data System) have shown associations between QT-prolonging drugs and an elevated risk of sudden cardiac death among patients on dialysis. These findings are concerning, given the widespread use of such drug. The objective of this narrative review is to critically evaluate the pathophysiological relevance, prevalence, and cardiovascular consequences of QT-prolonging drug use in the CKD setting.

Keywords: chronic kidney disease, QT-prolonging medications, sudden cardiac death

1. Introduction

Chronic kidney disease (CKD) is a growing global health concern among adult populations, with an estimated prevalence exceeding 10% [1]. The prevalence of CKD increases with age and is strongly associated with common comorbidities such as hypertension, diabetes mellitus, and obesity – conditions that are also increasingly prevalent globally [2]. Despite public health efforts, the number of individuals progressing to advanced CKD continues to rise. In many countries, a large proportion of patients are only diagnosed when they develop end-stage kidney disease (ESKD), at which point renal replacement therapy (RRT) becomes necessary [3]. Haemodialysis is still the most widely used RRT modality, although peritoneal dialysis and kidney transplantation are (when available) also employed [4].

Cardiovascular disease (CVD) is the leading cause of death in patients with CKD, and the risk of CVD-related death far exceeds the risk of progression to kidney failure for most individuals [5]. Even in the early stages of CKD, patients exhibit a markedly increased risk of cardiovascular events, including myocardial infarction, stroke, heart failure, and sudden cardiac death (SCD)[6]. The pathophysiology of CVD in CKD is multifactorial and includes both conventional risk factors (such as hypertension and dyslipidaemia) and CKD-specific factors (such as chronic inflammation, vascular calcification, and electrolyte imbalances). As kidney function declines, these cardiovascular risks are amplified. Moreover, many patients with CKD are exposed to polypharmacy[7], and some of these medications (notably those which prolong the QT interval) may exacerbate the cardiac risk. The cardiovascular burden is particularly severe among patients on dialysis, and SCD is one of the most frequent causes of death in this population[8]. Haemodialysis itself may contribute to the risk of arrhythmia (including atrial fibrillation and ventricular arrhythmia), through mechanisms such as rapid electrolyte shifts, myocardial stunning, and sympathetic overactivation[8, 9]. Despite significant improvements in dialysis techniques and protocols, cardiovascular outcomes in this group remain poor. Hence, there is a clear need for more effective preventive strategies and individualized cardiovascular management.

In light of the substantial cardiovascular burden experienced by patients with CKD, the present narrative review explores a potentially modifiable cardiovascular risk factor within this population: the use of QT-prolonging medications. We begin by examining the impact of QT interval prolongation in the context of CKD. We next emphasize the pathophysiological mechanisms and key specific risk factors. Subsequently, we examine the current research

evidence from CKD cohorts on the prevalence of QT-prolonging drug use and its association with adverse cardiovascular outcomes (including arrhythmia and SCD).

2. QT interval prolongation as a risk factor in patients with CKD

The QT interval

On a standard 12-lead ECG, the QT interval represents the time from ventricular depolarization (Q wave onset) to completion of cardiac repolarization (the end of the T wave). The QT interval varies with the heart rate. A number of equations are used to correct the QT interval for the heart rate, giving a corrected QT interval (QTc) (**Table 1**). QTc is prolonged if it is greater than 440 ms in men or 460 ms in women, respectively [10]. A QTc interval over 500 ms is positively correlated with the presence of cardiac arrhythmia [11].

QT interval prolongation and its consequences

Given that QT is a measure of the cardiac repolarization time, an abnormally prolonged QT interval reflects a cardiac repolarization defect and hence greater vulnerability to left ventricular arrhythmias (i.e. torsades de pointes (TdP) – a potentially fatal form of polymorphic ventricular tachycardia – and ventricular fibrillation) and SCD. TdP typically arises when a premature ventricular contraction occurs during a prolonged repolarization phase [12]. This arrhythmia may spontaneously resolve and revert to sinus rhythm, or it can deteriorate into ventricular fibrillation. TdP often presents clinically as syncope, although it may also be asymptomatic. In cases where it progresses to ventricular fibrillation, the absence of prompt intervention typically results in sudden death [13]. In a large, representative sample of the general US population, the association between the QT interval duration on one hand and all-cause, cardiovascular disease and cardiovascular mortality on the other was U-shaped (14).

Risk factors for QT prolongation

QT interval prolongation is a multifactorial phenomenon influenced by various genetic, demographic, clinical, and pharmacological factors. Understanding the risk factors that contribute to QT prolongation is essential for preventing adverse cardiac events, especially in vulnerable populations. Several risk factors for QT interval prolongation are non-modifiable. Firstly, the main non-modifiable demographic risk factor is female sex. Compared with men, women exhibit a longer baseline QT interval and a higher incidence of TdP. This difference is attributed to hormonal influences on cardiac repolarization. Older age also increases the risk, potentially as a result of age-related changes in cardiac ion channel expression and function

[15]. Secondly, congenital long QT syndrome (LQTS) is characterized by mutations in genes encoding cardiac ion channels. Individuals with these genetic mutations have a longer baseline QT interval [16]. ~~Thirdly, non modifiable~~ Other cardiac risk factors for QT prolongation include bradycardia and underlying heart diseases such as heart failure, left ventricular hypertrophy, and myocardial infarction [17]. Other comorbidities have an influence. For example, thyroid hormones have a crucial role in modulating cardiac electrophysiology by regulating the expression and function of various cardiac ion channels, including those responsible for calcium and potassium currents. These effects influence the duration of ventricular repolarization and, consequently, the QT interval [18]. Hypothyroidism is associated with QTc prolongation and increased risk of ventricular arrhythmias, whereas hyperthyroidism has also been linked to QTc prolongation and increased QT dispersion, both of which usually normalize after restoration of euthyroidism [19]. Furthermore, patients with cirrhosis or severe liver failure often exhibit autonomic dysfunction and altered cardiac ion channel expression, which contribute to QT prolongation.

A number of modifiable risk factors can be addressed through clinical interventions, lifestyle changes, and careful medication management. Firstly, electrolyte imbalances (particularly hypokalaemia, hypomagnesaemia, and hypocalcaemia) are significant contributors to QT prolongation. These imbalances can result from various conditions, including gastrointestinal losses such as diarrhoea and/or vomiting (primarily potassium and magnesium), diuretic use (mainly potassium and sometimes magnesium), and inadequate dietary intake (potassium, magnesium, and calcium) [10]. Secondly, there are various mechanisms by which drugs can increase the risk of QT prolongation [20, 21]. One of the following sections will focus on these modifiable risk factors.

CKD is associated with several factors that predispose to QT prolongation, including electrolyte imbalances, the accumulation of uremic toxins, and secondary hyperparathyroidism. These imbalances affect cardiac ion channel function and prolong ventricular repolarization; this specific comorbidity will be extensively discussed below (**Figure 1**).

The QT interval in patients with CKD

CKD is associated with a heightened risk of cardiovascular morbidity and mortality. Among the various cardiovascular complications, QT interval prolongation has emerged as a significant concern, given its association with life-threatening arrhythmias and SCD. The

prevalence of SCD among haemodialysis patients is elevated. Indeed, the data from the Dialysis Outcomes and Practice Patterns (DOPPS) study showed that 26% of the deaths among the 3765 recorded deaths were reported as SCD [9].

QT interval prolongation is more prevalent in patients with CKD than in the general population. Studies have demonstrated that the prevalence of prolonged QT intervals increases with the CKD stage [22]. There are several possible explanations for this high prevalence, including the electrolyte imbalances and hyperparathyroidism inherent to CKD. Furthermore, CKD is linked to left ventricular hypertrophy, myocardial fibrosis, and vascular calcification, all of which can alter cardiac repolarization dynamics and lead to QT prolongation [6]. Haemodialysis patients are the category of patients with CKD with the highest risk, due to the changes in extracellular fluid and electrolyte concentrations that occur during dialysis sessions [9].

As reported in the general population, an abnormal QT interval is associated with a poor prognosis in both predialysis and dialysis patients. Based on data from 3238 participants with CKD, a 5% increment in the QTc interval was associated with a significantly greater risk of heart failure, coronary artery disease, and mortality (42% (95%CI 1.23–1.65), 22% (95%CI 1.07–1.40) and 10% (95%CI 0.98–1.22), respectively [23]. In a retrospective study of 280 patients on maintenance dialysis being evaluated for kidney transplantation, a prolonged QTc was described in 47% of the study cohort and was associated with the risk of death independently of age, sex, diabetes mellitus, myocardial infarction, the presence and severity of coronary artery disease on angiography, left ventricular hypertrophy, and left ventricular ejection fraction [24]. In the same lines, Beaubien et al.'s retrospective study of a cohort of adult ESKD patients starting peritoneal dialysis or haemodialysis showed that a prolonged QTc increased the risk of serious ventricular arrhythmias and SCD [25].

The high prevalence and serious implications of QT interval prolongation in patients with CKD necessitate a comprehensive understanding of the underlying mechanisms and clinical consequences. Although intrinsic, CKD-related, factors have a significant role, the impact of pharmacological agents (and particularly those known to prolong the QT interval) warrants detailed exploration. The subsequent section examines the use of QT-prolonging medications in patients with CKD, with regard to the prevalence and associated risks.

3. QT-prolonging medications as a risk factor in patients with CKD

Drugs and their impact on QT interval

Drug-induced QT prolongation is a well-documented phenomenon and implicates many drugs from various classes (**Table 2**). Clearly, the over 200 QT-prolonging drugs now on the market have medical value but if they are to remain available, clinicians must manage the associated risk of TdP. Major contributors include antiarrhythmics (e.g., amiodarone), certain antipsychotics (such as haloperidol), certain antidepressants (notably citalopram and escitalopram), and fluoroquinolone antibiotics. These medications can interfere with cardiac repolarization, primarily by blocking cardiac potassium channels such as hERG. The CredibleMeds® database is maintained by the Arizona Center for Education and Research on Therapeutics and provides a regularly updated, evidence-based classification of drugs by their risk of QT prolongation and TdP onset. This database is used widely in both clinical and regulatory settings to inform safe prescribing practices, even though it might not be exhaustive outside the USA. CredibleMeds® also provides alternative medication options when risk is identified. Drugs are categorized as having a known, possible, or conditional risk of causing QT-prolongation and/or TdP [21].

While the blockade of cardiac potassium channels remains the primary mechanism by which many drugs prolong the QT interval, the overall proarrhythmic risk is significantly amplified by pharmacokinetic and pharmacodynamic drug–drug interactions [26], electrolyte imbalances, and organ dysfunction, as detailed below (**Figure 2**).

Electrolyte imbalances (particularly hypokalaemia, hypomagnesaemia, and hypocalcaemia) can be induced by medications and are known risk factors for QT prolongation. Diuretics such as thiazide and loop diuretics promote the excretion of potassium and magnesium, leading to hypokalaemia and hypomagnesaemia. The long-term use of proton pump inhibitors (PPIs) has been associated with hypomagnesaemia. Corticosteroids can cause hypokalaemia through mineralocorticoid activity, further increasing the risk when combined with other QT-prolonging agents.

Pharmacokinetic interactions influence the absorption, distribution, metabolism, and excretion of drugs, which potentially leads to elevated plasma concentrations of QT-prolonging agents. Cytochrome P450 enzymes (particularly CYP3A4) metabolize many QT-prolonging drugs. Inhibitors of these enzymes, such as certain antifungals (such as ketoconazole) and macrolide antibiotics (such as clarithromycin), can increase the plasma levels of QT-prolonging

drugs and thus enhance their effects. Drugs that inhibit P-glycoprotein can affect the distribution and elimination of QT-prolonging agents, potentially leading to higher systemic exposure.

Pharmacodynamic interactions occur when drugs with similar effects on cardiac repolarization are co-administered, leading to an additive prolongation of the QT interval.

Drug accumulation can occur in patients with kidney and liver failure. The liver has a pivotal role in drug metabolism, via the cytochrome P450 enzyme system. Hepatic dysfunction can lead to decreased metabolic activity, resulting in reduced clearance and increased bioavailability of drugs metabolized by the liver. This scenario is of particular concern for medications with narrow therapeutic indices or known QT-prolonging potential. The impaired metabolism can cause drug accumulation, thereby exacerbating QT interval prolongation and increasing the risk of arrhythmogenic events. In patients with CKD, the metabolism and the clearance of drugs is affected. This pharmacokinetic alteration can prolong a drug's half-life and increases its plasma concentration. This is particularly relevant for patients with an eGFR below 30 mL/min and for those on dialysis. The resulting accumulation can enhance the QT-prolonging effects of certain drugs, especially (i) when combined with other risk factors (e.g. electrolyte imbalances) or (ii) for drugs for which QT elevation is a common adverse event or is exposure-dependant.

The *Guide de Prescription & Rein* (GPR®) database (https://sitegpr.com) is a useful French-language resource for clinicians looking for information on drug dosing and nephrotoxicity. GPR® highlights the importance of QT interval monitoring in patients with CKD when prescribing medications that may be associated with QT prolongation - particularly in the context of a potential overdose or impaired drug clearance.

Below and in Table 3, we summarize the published research data on the harmful effects of QT-prolonging medications in patients with CKD.

Prevalence of QT-prolonging drug prescriptions in patients with CKD

In the USA, the annual utilization rates of QT-prolonging medications were ~1.4 to ~2.5 times higher in haemodialysis patients than in individuals without ESKD (**Table 3**) [27] . Recently, Wang et al. analyzed large administrative databases and described the prescription and dispensation patterns for a selection of QT-prolonging medications in US haemodialysis patients. The patients were commonly prescribed QT-prolonging medications with a known TdP risk by non-nephrologist clinicians, and these prescriptions often came from nonacute care settings [28]. The three main QT-prolonging medications initiated during the study period were azithromycin, ondansetron, and levofloxacin [28]. Most drug utilization studies have been

conducted in the USA and have focused on patients on haemodialysis; data on non-dialysis patients with CKD remain limited. In the Chronic Renal Insufficiency Cohort (3,252 participants with a mean eGFR of 42 mL/min/1.73 m²), the prevalence of QT-prolonging medication use was notably high and was consistent with the well-documented burden of polypharmacy in this population[29, 30]. QT-prolonging drugs were reported at 76% of the study visits, and two or more such agents were used concurrently at 33% of the visits. Among the 30 medications analyzed, eight (amiodarone, metolazone, fluoxetine, citalopram, hydroxyzine, escitalopram, venlafaxine, and furosemide) were independently associated with significant QTc prolongation after adjustment for comorbidities and serum potassium and calcium levels [29].

QT-prolonging drug prescriptions and the associated cardiovascular risks in patients with CKD

Here and in Table 3, we summarize the results of pharmaco-epidemiological studies of the impact of selective serotonin reuptake inhibitors (SSRIs), antibiotics, antipsychotics, and antiemetics on the cardiovascular risk (and particularly the risk of SCD) in patients with CKD.

In a new-user retrospective cohort study with an active comparator from the US Renal Data System (USRDS), there was no difference in the one-year risk of SCD associated with the new use of quetiapine versus that associated with new use of oral atypical antipsychotics without an FDA warning about QT prolongation [31].

Among patients on haemodialysis, the 10-day SCD risk associated with the new use of ondansetron was greater than that associated with the new use of antiemetics with less QT-prolonging potential [32].

In a retrospective new-user cohort study from the USRDS, the short-term (14-day) risk of SCD was higher for azithromycin, levofloxacin and moxifloxacin than for oral amoxicillin-based antibiotic treatment [33, 34]. This risk was greater still for larger serum-to-dialysate potassium gradients [35].

Using the same study design, Assimon et al. reported that 1-year risk of SCD was higher for the new use of an SSRI with an elevated potential for prolonging the QT interval (citalopram or escitalopram) than for the new use of SSRIs with a lower QT-prolonging potential (fluoxetine, fluvoxamine, paroxetine, and sertraline)[36]. Furthermore, the risk was greater when a PPI was co-prescribed [37] and when the baseline dialysate potassium gradient was ≥4 mEq/L [38].

Most of these studies have focused on dialysis populations and relied solely on data from the USRDS. As a result, there are currently no published data on the risks associated with these medications in patients with CKD who are not on dialysis. These analyses were generally well conducted from a pharmaco-epidemiological standpoint but is important to note that they were observational studies rather than randomized, controlled trials.

4. Conclusion

In conclusion, QT prolongation is a significant cardiovascular risk factor in patients with CKD in general and those on dialysis in particular. The use of QT-prolonging medications (such as fluoroquinolones and macrolides, antidepressants, and antipsychotics) further exacerbates this risk. Avoiding these medications can be challenging, due to the broad range of drugs implicated, including those commonly prescribed for the treatment of infections, anxiety and depression. Although the results of observational studies have highlighted the prevalence of QT abnormalities and their link to adverse outcomes like SCD, the lack of randomized controlled trials and data from non-dialyzed patients with CKD limits the generalizability of these findings. However, we believe that the identification of drugs known to affect QT prolongation is clinically very relevant in patients with CKD, especially those on dialysis. After this identification, different aspects need to be assessed, such as drug dose adjustment, history of cardiac disease, correction of electrolyte imbalances, review of concomitant medications, and, for some drugs, performing an ECG. (**Figure 3**). Deprescribing non-essential medications should be considered, with substitution of safer or more appropriate alternatives when feasible. In addition, further research is essential for the refinement of patient management strategies.

Conflict of interest statement

SL, JBT, LA, SML and AM did not report any conflicts of interest. GD reports fees and grants to charities for research projects from Astra Zeneca and Bayer HealthCare. ZAM reports having received grants for CKD REIN and other research projects from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Sanofi-Genzyme, Lilly, Otsuka, Astra Zeneca, Vifor and the French government, as well as fees and grants to charities from Astra Zeneca, Boehringer Ingelheim, and GlaxoSmithKline. MJ reports having received consultancy/speaker fees from Astellas, Astra-Zeneca, Bayer, Boehringer-Ingelheim, Cardiorenal, CSL Vifor, GSK, Menarini, Novo Nordisk, Stada-EG and Vertex. He further reports being a cochair of Kidney Disease: Improving Global Outcomes (KDIGO) since 2019.

Authors' contributions

SL, JBT, LA and AM wrote the first draft of the manuscript. SML, GD, ZAM, and MJ revised the manuscript for critical content. All the authors approved the final version.

Data availability statement

No new data were generated or analysed in support of this research.

Table 1 : Formulas for calculating QTc [39]

Bazett formula: $QTc = QT / \sqrt{RR}$
Fridericia formula: $QTc = QT / RR^{1/3}$
Framingham formula: $QTc = QT + 0.154 (1 – RR)$
Hodges formula: $QTc = QT + 1.75$ (heart rate – 60)

The corrected QT interval (QTc) estimates the QT interval at a standard heart rate of 60 bpm. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmia. There are multiple formulas used to estimate QTc. It is not clear which formula is the most useful. QTc is prolonged if > 440ms in men or > 460ms in women. QTc > 500 is associated with an increased risk of torsades de pointes

Table 2: QT-Prolonging Medications

Known risk of torsades de pointes (n=57)
aclarubicin, **amiodarone**, anagrelide, arsenic trioxide, **azithromycin**, chloroquine, chlorpromazine, chlorprothixene, cilostazol, **ciprofloxacin**, **citalopram, clarithromycin**, disopyramide, dofetilide, **domperidone**, donepezil, dronedarone, droperidol, **escitalopram**, flecainide, **fluconazole**, halofantrine, haloperidol, hydroquinidine, **hydroxychloroquine**, ibogaine, ibutilide, ivabradine, **levofloxacin**, levomepromazine, levosulpiride, meglumine antimoniate, methadone, mobocertinib, **moxifloxacin**, nifekalant, **ondansetron**, osimertinib, oxaliplatin, papaverine HCl, pentamidine, pimozide, procainamide, propofol, quinidine, quizartinib, roxithromycin, sertindole, sevoflurane, **sotalol**, sulpiride, sultopride, terlipressin, terodiline, thioridazine, vandetanib
Possible risk of torsades de pointes (n=154)
abarelix, adagrasib, alfuzosin, alimemazine, apalutamide, apomorphine, aripiprazole, artemether/lumefantrine, artenimol/piperaquine, asenapine, atomoxetine, bedaquiline, bendamustine, betrixaban, bicalutamide, bortezomib (bortexomib), bosutinib, buprenorphine, cabozantinib, capecitabine, carbetocin, ceritinib, clotiapine, clozapine, cobimetinib, crizotinib, cyamemazine, dabrafenib, dasatinib, degarelix, delamanid, desipramine, dexmedetomidine, dextromethorphan/quinidine, dolasetron, efavirenz, eliglustat, encorafenib, entrectinib, epirubicin, eribulin mesylate, ezogabine, felbamate, fexinidazole, fingolimod, fluorouracil (5-FU), flupentixol, gemifloxacin, gepirone, gilteritinib, givinostat, glasdegib, granisetron, hydrocodone ER, iloperidone, imatinib, imipramine (melipramine), inotuzumab ozogamicin, isoflurane, isradipine, ivosidenib, ketanserin, lacidipine, lapatinib, lefamulin, lenvatinib, leuprolide, levoketoconazole, levomethadone, lithium, lofexidine, lopinavir/ritonavir, lumateperone, lurasidone, macimorelin, maprotiline, mavorixafor, melperone, mianserin, midostaurin, mifepristone, mirabegron, mirtazapine, moclobemide, motixafortide, necitumumab, **nicardipine**, nilotinib, **norfloxacin**, nortriptyline, nusinersen, **ofloxacin,** oliceridine, opipramol, osilodrostat, oxytocin, ozanimod, pacritinib, paliperidone, palonosetron, panobinostat, pasireotide, pazopanib, perphenazine, pilsicainide, pimavanserin, pipamperone, pitolisant, ponesimod, pralsetinib, pretomanid, primaquine phosphate, promethazine, prothipendyl, relugolix, remdesivir, remimazolam, revumenib, ribociclib, rilpivirine, rivastigmine, romidepsin, rucaparib, saquinavir (with ritonavir), selpercatinib, siponimod, sitafloxacin, sorafenib, sunitinib, **tacrolimus**, tamoxifen, tazemetostat, tebentafusp, telavancin, telithromycin, tetrabenazine, tiapride, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, **tramadol**, triclabendazole, trimipramine, tropisetron, valbenazine, vardenafil, vemurafenib, venlafaxine, vernakalant, voclosporin, vorinostat, zotepine, zuclopenthixol.
Conditional risk of torsades de pointes (n=52)
abiraterone, amantadine, amisulpride, **amitriptyline**, amphotericin B, amsacrine, atazanavir, bendroflumethiazide, chloral hydrate, cimetidine, clofazimine, clomipramine, **diltiazem**, diphenhydramine, doxepin, eperisone, **esomeprazole**, famotidine, **fluoxetine, fluvoxamine**, **furosemide**, galantamine, garenoxacin, **hydrochlorothiazide**, **hydroxyzine**, **indapamide, itraconazole**, **ketoconazole, lansoprazole, loperamide, metoclopramide**, metolazone, **metronidazole**, nelfinavir, olanzapine, **omeprazole, pantoprazole, paroxetine**, piperacillin/tazobactam, posaconazole, propafenone, quetiapine, quinine sulphate, ranolazine, risperidone, **sertraline**, solifenacin, telaprevir, torsemide, trazodone, **voriconazole**, ziprasidone.

***** This non-exhaustive list of medications was obtained from CredibleMeds®, which classifies medications that can prolong the QT interval as having a known, possible, or conditional risk of torsades de pointes (TdP). Drugs with a 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. Drugs with a possible TdP risk are defined as drugs that can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended. Drugs with a conditional TdP risk are defined as drugs that are associated with TdP only under certain conditions (e.g., an excessive dose, in patients with conditions such as hypokalaemia and hypomagnesaemia, or when taken with interacting drugs) or drugs that create conditions that facilitate or induce TdP (e.g. cause an electrolyte imbalance that induces TdP). This list of medications was obtained from the CredibleMeds® [21] website on May 14th, 2025.

Drugs in bold are those commonly used in CKD patients, based on European clinical experience.

Table 3: QT-prolonging drug prescriptions and the associated cardiovascular risks in patients with CKD: Summary of published studies

Authors, year, journal	Study type Population Country/countries	Primary study objective	Drugs studied	Main results
Different QT-prolonging drugs studied				
Wang V et al. JAMA Network open 2024[28]	Cross sectional study Medicare beneficiaries aged 60 or over and on in-centre **haemodialysis**. **USA**	To examine prescription and dispensation patterns of QT-prolonging medications associated with a known risk of torsades de pointes (TdP) risk, together with selected interacting medications.	**The seven most frequently filled QT-prolonging medications**: **azithromycin, levofloxacin, ciprofloxacin, fluconazole, amiodarone, ondansetron, and escitalopram.** Based on CredibleMeds® and potentially interacting drugs (from the University of Washington drug interaction database).	**52.9%** of the patients received one of the seven drugs studied. QT-prolonging medications were commonly prescribed by non-nephrologist clinicians and in nonacute settings.
Assimon et al J Am Heart Assoc. 2020[27]	Descriptive analysis of **drug utilization** according to three administrative databases: the United States Renal Data System (USRDS), MarketScan, and Medicare claims (haemodialysis and individuals without end-stage kidey disease) **USA**	To characterize the extent and patterns of QT-prolonging medication use by adult haemodialysis patients and individuals without end-stage kidney disease, annually from 2012 to 2016.	A **comprehensive list of QT-prolonging medications**, identified via the CredibleMeds® website.	Annual **utilization rates** of QT-prolonging medications with a known TdP de pointes risk in **haemodialysis** patients were **~1.4 to ~2.5 times higher** than those in individuals without end-stage kidney disease.
Snitker et al. CJASN 2017[29]	Prospective, multicentre study. The Chronic Renal Insufficiency Cohort of patients with **mild-to-**	To examine the use of electrocardiogram QT-prolonging medications in predialysis patients with	**180 QT-prolonging drugs** were identified using the CredibleMeds® website, in three categories: (i) a known risk of TdP (n=48 drugs), (ii) a	Medications classified as QT-prolonging were taken at **76% of visits**, and two or more of these taken at 33% of visits. Of 30 medications examined**, eight were associated with statistically significant QTc interva**l corrected for heart rate prolongation after adjustment

	moderate CKD and at least one study electrocardiogram between 2003 and 2011 **USA**	CKD and the medications' association with the QT duration.	possible risk of TdP (n=72), and (iii) a conditional risk of TdP (n=32).	for comorbidities, potassium, and calcium, including amiodarone (+1062 ms), metolazone (+762 ms), fluoxetine (+461 ms), citalopram (+461 ms), hydroxyzine (+461 ms), escitalopram (+362 ms), venlafaxine (+361 ms), and furosemide (+360 ms).
Jadoul et al. CJASN 2012 [9]	The Prospective Dialysis Outcomes and Practice Patterns Study of **patients on haemodialysis. 12 countries**	To explore the associations between practices and the prescription of QT–prolonging drugs on one hand and sudden death (due to cardiac arrhythmia, cardiac arrest, and/or hyperkalaemia) on the other.	**QT-prolonging drugs** (amiodarone, selected antidepressants, antipsychotics, and other drugs defined by CredibleMeds®)	The drugs were not specified. **An elevated risk** of sudden death was evidenced for the prescription of **amiodarone** (hazard ratio (HR), 1.44; 95% confidence interval (CI), 1.16–1.81; P=0.001) but not for the prescription of other QT-prolonging drugs (HR, 1.10; 95%CI, 0.94–1.28; P=0.22).
Studies of specific QT-prolonging drugs				
Antipsychotics				
Nash et al. Gen Hosp Psychiatry 2023[31]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To compare the cardiac safety (1-year risk of SCD) of atypical antipsychotics with a Food and Drug Administration (FDA) warning about QT prolongation vs. atypical antipsychotics without such a warning	**Quetiapine** vs. atypical antipsychotics without QT prolongation	**No difference in the one-year risk of SCD** associated with the new use of quetiapine vs. that associated with new use of oral atypical antipsychotics without an FDA warning about QT prolongation.
Antibiotics				
Pun et al. Kidney Medicine 2023[35]	A new-user retrospective cohort study with an active comparator from the USRDS.	To determine whether the serum-to-dialysate gradient modifies the cardiac safety (14-day SCD	Oral antibiotic treatment: **azithromycin or fluoroquinolone** (levofloxacin/moxifloxacin),	Treatment with azithromycin and, separately, respiratory fluoroquinolones were each associated with a **higher short-term risk of SCD**, this risk was augmented in the setting of **larger serum-to dialysate potassium gradients**.

	Haemodialysis patients. **USA**	risk) of azithromycin (or levofloxacin/moxifloxacin) vs. amoxicillin.	vs. an oral amoxicillin-based antibiotic (amoxicillin, amoxicillin/ clavulanic acid).	
Assimon et al. KI 2022[33]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To investigate the comparative cardiac safety (5 days SCD) of azithromycin and amoxicillin-based antibiotics and, separately, azithromycin and levofloxacin.	Antibiotic treatment: oral **azithromycin, levofloxacin** vs. amoxicillin, amoxicillin/clavulanic acid.	Patients on in-center haemodialysis treated with **azithromycin had a higher short-term risk of SCD** compared with those treated with **amoxicillin**-based antibiotics and a **lower risk** of SCD compared to those treated with **levofloxacin**.
Assimon et al. JAMA Cardiology 2022[34]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To investigate the cardiac safety (5 days SCD) of respiratory fluoroquinolones.	Respiratory fluoroquinolone (**levofloxacin** or **moxifloxacin**) vs amoxicillin-based (amoxicillin or amoxicillin with clavulanic acid) antibiotic treatment.	Compared with amoxicillin-based antibiotic treatment, respiratory **fluoroquinolone** treatment was associated with **a higher short-term risk of SCD** among patients with haemodialysis-dependent kidney failure
Antiemetics				
Ismail et al JASN 2024[32]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To investigate the 10-day risk of SCD associated with the new use of oral **ondansetron** vs. the new use of antiemetics with less QT-prolonging potential (promethazine, metoclopramide, or prochlorperazine).	Antiemetic: oral **ondansetron** vs. antiemetics with less QT-prolonging potential (promethazine, metoclopramide, or prochlorperazine)	Among people on haemodialysis, the 10-day risk of SCD was higher for the new use of **ondansetron** than for the new use of antiemetics with lesser QT-prolonging potential
Selective serotonin reuptake inhibitors (SSRIs)				
Assimon et al. NDT 2022[38]	A new-user retrospective cohort study with an active	To determine whether the serum-to dialysate potassium gradient	SSRI: **citalopram** and **escitalopram** (SSRIs with higher QT-prolonging	Among patients with serum-to-dialysate potassium gradients ≥4 mEq/l, the risk of SCD was **more than two-time greater** for SSRIs with a higher QT-prolonging

	comparator from the USRDS. **Haemodialysis patients**. **USA**	modifies the association between SSRIs with higher vs. lower QT-prolonging potential and the 1-year risk of SCD.	potential); fluvoxamine, fluoxetine, paroxetine, and sertraline (SSRIs with a lower QT-prolonging potential)	potential than for SSRIs with a lower QT-prolonging SSRIs.
Assimon et al. Pharmacoepidemiol Drug Saf 2022[37]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To examine the 1-year risk of SCD associated with new use of citalopram/escitalopram vs. new use of sertraline, in the presence and absence of PPIs.	SSRI: **citalopram** and **escitalopram** as the SSRIs of interest vs. sertraline as the comparator SSRI. Selected **PPIs** (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) were the interacting drugs of interest.	**The risk of SCD** was highest for new use of **citalopram/escitalopram with a PP**I, followed by new use of citalopram/escitalopram without a PPI and then new use of sertraline initiation without a PPI.
Assisom et al. JASN 2019[36]	A new-user retrospective cohort study with an active comparator from the USRDS. **Haemodialysis patients**. **USA**	To compare the 1-year risk of SCD among haemodialysis patients initiating SSRIs with a higher QT-prolonging potential vs. those initiating SSRIs with a lower QT-prolonging potential	**SSRIs** with a higher potential for prolonging the QT interval (**citalopram**, **escitalopram)** vs. SSRIs with a lower QT-prolonging potential (fluoxetine, fluvoxamine, paroxetine, sertraline).	The risk of SCD was higher for **SSRIs with a higher QT-prolonging potential than for SSRIs with a lower QT-prolonging potential**.

Table 4: Dialyzability and dose adjustment in dialysis patients for the most commonly used drugs in CKD patients associated with a known risk of torsades de pointes

Drugs	Dialyzability[1,2]		Dose adjustement[1]
	Haemodialysis	Peritoneal dialysis	
Amiodarone	No	No	No
Azithromycin	ND	No	No
Ciprofloxacin	No	No	Yes Usual dose: 500 to 750 mg every 8 or 12 h HD: 500 to 750 mg every 24h
Citalopram	No	Unlikely	No
Clarithromycin	Unlikely	Unlikely	Yes Usual dose: 500 mg every 12h HD: 500 mg every 24h
Domperidone	ND	ND	No
Escitalopram	ND	ND	Literature recommends initiating treatment at minimal dose and then increases depending on safety and efficacy.
Fluconazole	Yes (50 %)	Yes	Yes Dialysis: Administer the usual dose fluconazole on the first day. Then, the dosage should be adjusted depending on renal function.
Hydroxychloroquine	Unlikely	Unlikely	ND
Levofloxacin	No (24 %)	No	Yes UD: 500 mg every 12 or 24 hours depending on infection Dialysis: loading dose: 500 mg, then 125 to 250 mg every 48 hours depending on the type of infection
Moxifloxacin	No	No	No
Ondansetron	ND	ND	Yes Dialysis: Start with 4 mg
Sotalol	Yes (27-40 %)	ND	ND

Yes: dialysis enhances plasma clearance by 30 % or more during a typical 4-hour dialysis period.

No: dialysis enhances plasma clearance by less than 30 %.

Unlikely: No published data exist, but significant drug removal is unlikely based on physicochemical characteristics of the drug, such as protein binding, molecular size, volume of distribution

ND: No data, HD: haemodialysis, UD: usual dose

[1]: GPR data, [2]: Data from dialysis of drugs Bailie and Mason's, 2022

Figure 1: Risk factors of Long QT

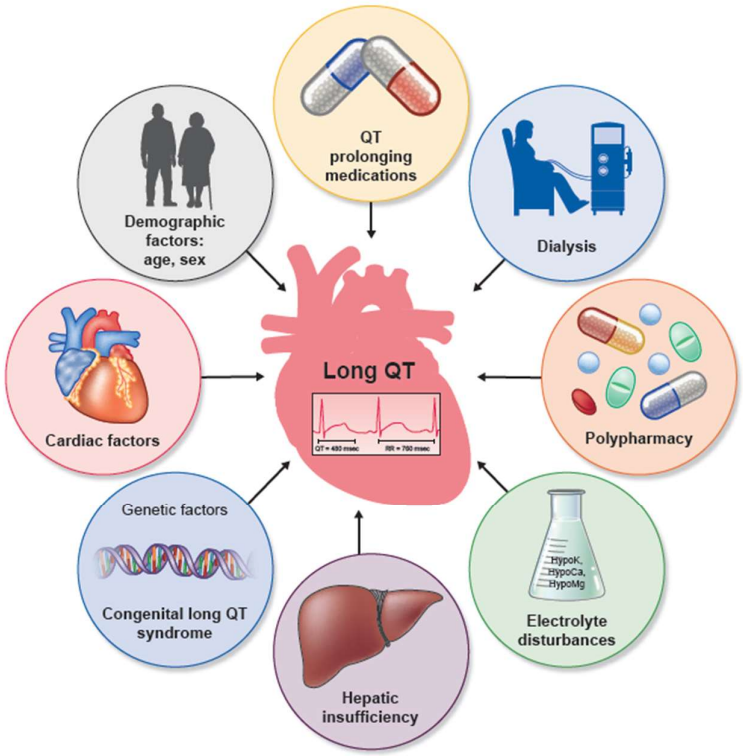


Figure 2: Drug-induced mechanisms underlying QT prolongation

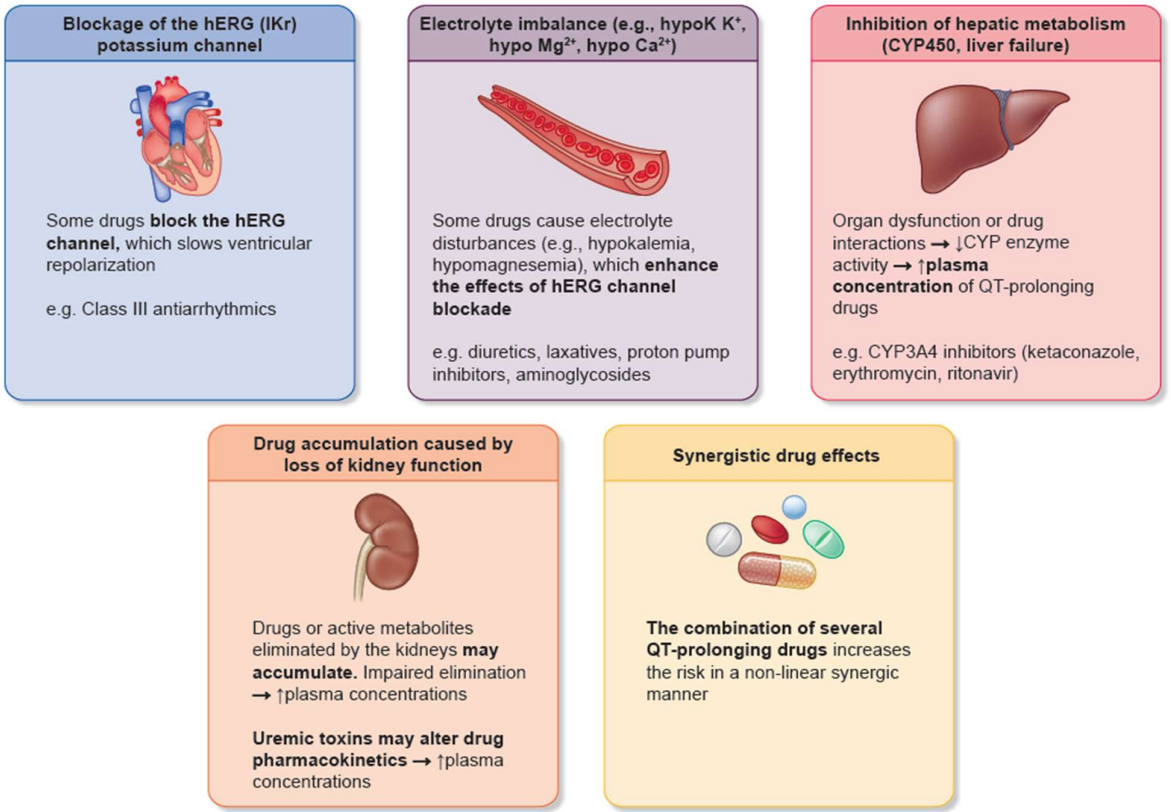
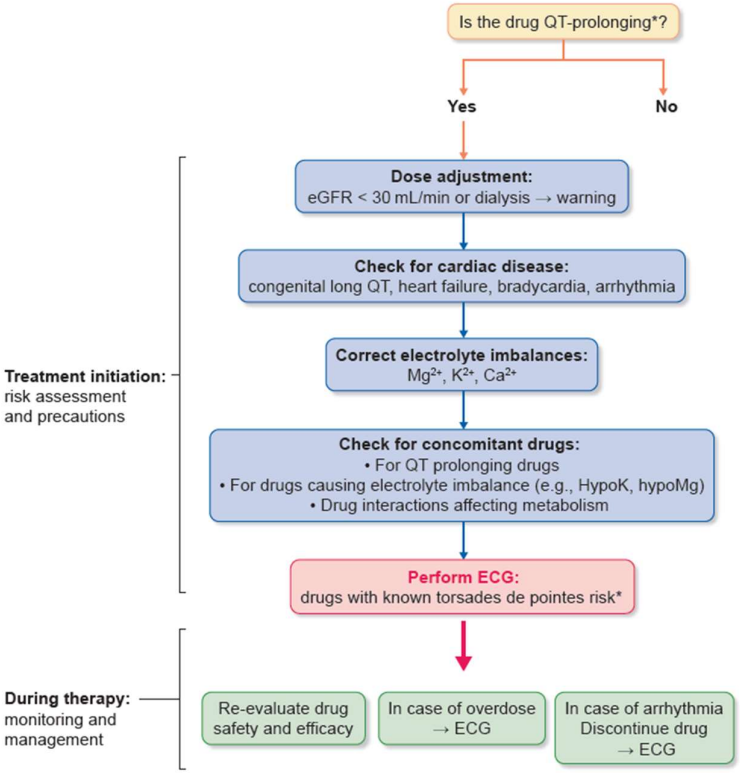


Figure 3: Recommendations before initiating treatment with drugs that carry a potential risk of QT prolongation in patients with CKD



* *Based on medications identified from CredibleMeds®

REFERENCES

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney International Supplements 2022; 12: 7–11.

2. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. The Lancet 2021; 398: 786–802.

3. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 2018; 392: 1923–1994.

4. Sanchez JJG, James G, Carrero JJ et al. Health Care Resource Utilization and Related Costs of Patients With CKD From the United States: A Report From the DISCOVER CKD Retrospective Cohort. Kidney International Reports 2023; 8: 785–795.

5. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet (London, England) 2013; 382: 339–352.

6. Zoccali C, Mallamaci F, Adamczak M et al. Cardiovascular complications in chronic kidney disease: a review from the European Renal and Cardiovascular Medicine Working Group of the European Renal Association. Cardiovascular Research 2023; 119: 2017–2032.

7. Oosting IJ, Colombijn JMT, Kaasenbrood L et al. Polypharmacy in Patients with CKD: A Systematic Review and Meta-Analysis. Kidney360 2024; 5: 841–850.

8. Drechsler C, Grootendorst DC, Pilz S et al. Wasting and Sudden Cardiac Death in Hemodialysis Patients: A Post Hoc Analysis of 4D (Die Deutsche Diabetes Dialyse Studie). American Journal of Kidney Diseases 2011; 58: 599–607.

9. Jadoul M, Thumma J, Fuller DS et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Clinical journal of the American Society of Nephrology: CJASN 2012; 7: 765–774.

10. Johnson JN, Ackerman MJ. QTc: how long is too long? British Journal of Sports Medicine 2009; 43: 657–662.

11. Moss AJ, Schwartz PJ, Crampton RS et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991; 84: 1136–1144.

12. Oksuz F, Sensoy B, Sahan E et al. The classical “R-on-T” phenomenon. Indian Heart Journal 2015; 67: 392–394.

13. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. International Journal of Clinical Practice 2018; 72: e13250.

14. Zhang Y, Post WS, Dalal D, Blasco-Colmenares E, Tomaselli GF, Guallar E. QT-Interval Duration and Mortality Rate. Archives of Internal Medicine 2011; 171: 1727–1733.

15. Drug and Therapeutics Bulletin. QT interval and drug therapy. BMJ (Clinical research ed.) 2016; 353: i2732.

16. Arora A, Zareba W, Woosley RL et al. Genetic QT score as a predictor of sudden cardiac death in participants with sleep-disordered breathing in the UK Biobank. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine 2025; 21: 549–557.

17. Locati ET. QT interval duration remains a major risk factor in long QT syndrome patients. Journal of the American College of Cardiology 2006; 48: 1053–1055.

18. Schenck JB, Rizvi AA, Lin T. Severe primary hypothyroidism manifesting with torsades de pointes. The American Journal of the Medical Sciences 2006; 331: 154–156.

19. Klein I, Danzi S. Thyroid disease and the heart. Circulation 2007; 116: 1725–1735.

20. Palsøe MK, Hansen CJ, Torp-Pedersen C et al. Proarrhythmic drugs, drug levels, and polypharmacy in victims of sudden arrhythmic death syndrome: An autopsy-based study from Denmark. Heart Rhythm 2024; 21: 1795–1802.

21. Woosley R, Heise C, Woosley R, Lambson J, Romero K. CredibleMeds, "Risk Categories for Drugs That Prolong QT & induce Torsades de Pointes (TdP)," [Internet]. *QTdrugs List* [cited 2025 May 2] Available from: https://www.crediblemeds.org/index.php/login/dlcheck

22. Wang Y, Li Q, Xu G, Yang Y, He F. Association between elevated serum parathyroid hormone and QTc interval prolongation in chronic kidney disease patients. International Urology and Nephrology 2025;

23. Kestenbaum B, Rudser KD, Shlipak MG et al. Kidney function, electrocardiographic findings, and cardiovascular events among older adults. Clinical journal of the American Society of Nephrology: CJASN 2007; 2: 501–508.

24. Hage FG, de Mattos AM, Khamash H, Mehta S, Warnock D, Iskandrian AE. QT Prolongation Is an Independent Predictor of Mortality in End-Stage Renal Disease. Clinical Cardiology 2010; 33: 361–366.

25. Beaubien ER, Pylypchuk GB, Akhtar J, Biem HJ. Value of corrected QT interval dispersion in identifying patients initiating dialysis at increased risk of total and cardiovascular mortality. American Journal of Kidney Diseases 2002; 39: 834–842.

26. Chien H-T, Lin F-J, Juang J-MJ, Lin S-W. The Impact of QT-Prolonging Medications and Drug-Drug Interactions on QTc Interval Prolongation in Hospitalized Patients: A Case-Crossover Study. Clinical Pharmacology and Therapeutics 2025; 117: 495–505.

27. Assimon MM, Wang L, Pun PH, Winkelmayer WC, Flythe JE. Use of QT Prolonging Medications by Hemodialysis Patients and Individuals Without End-Stage Kidney Disease. Journal of the American Heart Association 2020; 9: e015969.

28. Wang V, Wang C-HL, Assimon MM, Pun PH, Winkelmayer WC, Flythe JE. Prescription and Dispensation of QT-Prolonging Medications in Individuals Receiving Hemodialysis. JAMA network open 2024; 7: e248732.

29. Snitker S, Doerfler RM, Soliman EZ et al. Association of QT-Prolonging Medication Use in CKD with Electrocardiographic Manifestations. Clinical journal of the American Society of Nephrology: CJASN 2017; 12: 1409–1417.

30. Laville SM, Metzger M, Stengel B et al. Evaluation of the adequacy of drug prescriptions in patients with chronic kidney disease: results from the CKD-REIN cohort. British Journal of Clinical Pharmacology 2018; 84: 2811–2823.

31. Nash RP, Wang L, Gaynes BN, Flythe JE. Atypical Antipsychotics and the Risk of Sudden Cardiac Death among Individuals Receiving Maintenance Hemodialysis. General Hospital Psychiatry 2023; 85: 148–154.

32. Ismail S, Funk MJ, Flythe JE. Ondansetron and the Risk of Sudden Cardiac Death among Individuals Receiving Maintenance Hemodialysis. Journal of the American Society of Nephrology: JASN 2024; 35: 761–771.

33. Assimon MM, Pun PH, Wang L et al. Azithromycin use increases the risk of sudden cardiac death in patients with hemodialysis-dependent kidney failure. Kidney International 2022; 102: 894–903.

34. Assimon MM, Pun PH, Wang LC-H et al. Analysis of Respiratory Fluoroquinolones and the Risk of Sudden Cardiac Death Among Patients Receiving Hemodialysis. JAMA cardiology 2022; 7: 75–83.

35. Pun PH, Assimon MM, Wang L et al. QT-Prolonging Antibiotics, Serum-to-Dialysate Potassium Gradient, and Risk of Sudden Cardiac Death Among Patients Receiving Maintenance Hemodialysis. Kidney Medicine 2023; 5: 100618.

36. Assimon MM, Brookhart MA, Flythe JE. Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors among Individuals Receiving Maintenance Hemodialysis. Journal of the American Society of Nephrology: JASN 2019; 30: 611–623.

37. Assimon MM, Pun PH, Al-Khatib SM et al. Proton pump inhibitors may enhance the risk of citalopram- and escitalopram-associated sudden cardiac death among patients receiving hemodialysis. Pharmacoepidemiology and Drug Safety 2022; 31: 670–679.

38. Assimon MM, Pun PH, Al-Khatib SM et al. The modifying effect of the serum-to-dialysate potassium gradient on the cardiovascular safety of SSRIs in the hemodialysis population: a pharmacoepidemiologic study. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association 2022; 37: 2241–2252.

39. Vandenberk B, Vandael E, Robyns T et al. Which QT Correction Formulae to Use for QT Monitoring? Journal of the American Heart Association 2016; 5: e003264.