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Adverse Drug Reactions in Patients with Chronic Kidney Disease

Authors: Solène M Laville¹, Valérie Gras-Champel², Julien Moragny², Marie Metzger¹, Christian Jacquelinet^{1,3}, Christian Combe^{4,5}, Denis Fouque⁶, Maurice Laville⁶, Luc Frimat^{7,8}, Bruce M. Robinson⁹, Bénédicte Stengel¹, Ziad A Massy^{1,10}, Sophie Liabeuf^{2,11} on behalf of the Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) Study Group

Authors' institutions:

¹ Centre for Research in Epidemiology and Population Health (CESP), INSERM UMRS 1018, Université Paris-Saclay, Université Versailles Saint Quentin, F-94807 Villejuif, France

² Department of Clinical Pharmacology, Amiens University Hospital, F-80000 Amiens, France

³ Biomedecine Agency, F-93210 Saint Denis La Plaine, France

⁴ Service de Néphrologie Transplantation Dialyse Aphérèse, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

⁵ INSERM, U1026, Univ Bordeaux Segalen, Bordeaux, France

⁶ Nephrology Dept, Centre Hospitalier Lyon Sud, Université de Lyon, Carmes, F-69495 Pierre-Bénite, France

⁷ Nephrology Department, CHRU de Nancy, F-54000 Vandoeuvre-lès-Nancy, France

⁸ Lorraine University, APEMAC, F-54000 Vandoeuvre-lès-Nancy, France

⁹ Arbor Research Collaborative for Health, Ann Arbor MI, USA

¹⁰ Department of Nephrology, Ambroise Paré University Hospital, APHP, F-92104 Boulogne-Billancourt/Paris, France

¹¹ MP3CV Laboratory, EA7517, University of Picardie Jules Verne, Amiens, F-80000 Amiens, France

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Corresponding author:

Bénédicte Stengel

Director, Inserm U1018, Team 5

UPS-UVSQ, CESP, Centre for Epidemiology and Population Health

EpReC Team, Renal and Cardiovascular Epidemiology

16, avenue P. Vaillant Couturier

F-94 807 Villejuif cedex

France

Phone: + 33-145-595-039

E-mail: benedicte.stengel@inserm.fr

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SIGNIFICANCE STATEMENT

1. What was previously known about the specific topic of the manuscript?

Patients with CKD have complex presentations, use multiple medications, often receive inappropriate prescriptions, and are at high risk for adverse drug reactions (ADRs). Investigations of ADRs in outpatients with CKD have been sparse.

2. What were the most important findings?

Patients with CKD have a high incidence of ADR, even when they receive care from nephrologists. Some cases are serious (20%), especially those attributable to antithrombotic agents. Most ADRs resulted in discontinuation of the drug to which they were attributed (71%). As kidney function deteriorated during CKD, ADR incidence rose.

3. How does the new information advance a new understanding of the kidney and its diseases?

Many serious ADRs in patients with moderate or advanced CKD may be preventable. Greater awareness of eGFR by prescribers and pharmacists and enhanced patient education are key elements for reducing ADRs in this population at especially high risk.

ABSTRACT

Background: Little is known about the burden of adverse drug reactions (ADRs) in chronic kidney disease (CKD). We estimated the incidence of overall and serious ADRs and assessed the probability of causation, preventability, and factors associated with ADRs in patients seen by nephrologists.

Methods: The CKD-REIN cohort included 3033 outpatients (65% men) with CKD and estimated GFR (eGFR) <60 mL/min/1.73m², with follow-up for two years. ADRs were identified from hospitalization reports, medical records, and participant interviews, and finally assessed for causality, preventability, and immediate therapeutic management by experts in pharmacology.

Results: Median (interquartile range) age was 69 (60–76); 55% had eGFR ≥ 30 and 45% <30 mL/min/1.73m². Participants were prescribed a median (range) of 8 (5–10) drugs. Over 2 years, 536 patients had 751 ADRs, 150 (in 125 participants) classified as serious, for rates of 14.4 (95% confidence interval, 12.6–16.5) and 2.7 (1.7–4.3) per 100 person-years, respectively. Among the serious ADRs, 32% were considered preventable or potentially preventable; 16 caused death, directly or indirectly. Renin-angiotensin system inhibitors (15%), antithrombotic agents (14%), and diuretics (10%) were the drugs to which the most ADRs were imputed, but antithrombotic agents caused 34% of serious ADRs. The drug was discontinued in 71% of cases, at least temporarily. Adjusted hazard ratios for serious ADR were significantly higher in patients with eGFR <30 *vs* ≥ 30 mL/min/1.73m², 1.8 (1.3-2.6), in those prescribed >10 *versus* <5 medications, 2.4 (1.1-5.2), or with poor *versus* good adherence, 1.6 (1.4-2.4).

Conclusion: ADRs are common and sometimes serious in patients with CKD. Many serious ADRs may be preventable. Some specific pharmacological classes, particularly antithrombotic agents, are at risk of serious ADRs.

INTRODUCTION

Despite the highly regulated process of drug marketing authorization, no medicine is completely safe. Adverse drug reactions (ADRs) are relatively common; they cause 2–7% of overall hospitalizations.(1–4) Two French studies (2,5) have reported that 3.2% to 3.6% of hospital admissions are related to ADRs. The concept of ADR has evolved over time and today includes any harmful and unwanted reaction to a drug, occurring at doses normally used in humans, or resulting from drug misuse or error, or from accidental or willful overdose.(6) Most available studies have focused on ADR-related hospitalizations (with the ADR either the cause of admission (2,3,5,7–10) or occurring during hospitalization,(11,12) or both (1,13,14)); very few have examined ADRs in outpatient settings.(4) Although clinicians recognize ADRs as a major problem in CKD patients, few studies have investigated the incidence of and factors associated with ADRs in this population.

Drug-related nephrotoxicity is frequent and well documented.(15) But the kidney also plays an important role in the clearance of many drugs and toxic metabolites that can cause ADR due to their accumulation as kidney function declines. Despite impaired pharmacokinetics and pharmacodynamics,(16–18) patients with CKD use multiple medicines and are often exposed to some that are inappropriately prescribed.(19) Until now, studies in CKD patients have been based on self-reported ADRs,(20) or have concerned specific drugs during clinical trials,(21,22) or have been restricted to ADRs during hospitalization,(23) or to specific types of ADRs.(24) None reported therapeutic management after the ADR. No comprehensive evaluation exists of the incidence, probability of causation, and preventability of ADRs in both inpatients and outpatients belonging to this population.

The primary objective of this study was to estimate the incidence rates of overall and serious ADRs according to eGFR, in patients with moderate or advanced CKD treated by a

nephrologist. Secondary objectives aimed at assessing their causation, preventability, associated factors, and immediate therapeutic management.

METHODS

Study design and participants

Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) is a prospective cohort study conducted in 40 nationally representative nephrology outpatient facilities in France. Eligible patients were at least 18 years of age, had a confirmed diagnosis of moderate or advanced CKD, an eGFR <60 mL/min per 1.73 m², were not on dialysis, and had not been transplanted. From July 2013 to March 2016, CKD-REIN included 3033 patients. Details of the study protocol and flow chart have been published elsewhere.⁽²⁵⁾ The institutional review board of the French National Institute of Health and Medical Research (INSERM; reference: IRB00003888) approved the protocol, and the study was registered at ClinicalTrials.gov (NCT03381950).

Information

Data were collected at baseline and then annually by trained clinical research associates (CRAs) from participants interviews and medical records from the nephrology centers that included them. All of them contain patient histories, hospitalizations reports, imaging and laboratory data from every ward of the hospital/clinic, but they are not standardized and may differ between these centers. Data collected included sociodemographic characteristics and a history of hypertension, diabetes, cardiovascular disease, dyslipidemia, or acute kidney injury (AKI), as defined previously.⁽²⁵⁾ Medication adherence was assessed with the Girerd score,⁽²⁶⁾ calculated by asking 6 questions that explore the primary determinants of adherence to chronic medication (its timing, remembering to take it, and remembering to renew the prescription).

Serum creatinine, albumin, and hemoglobin were measured, as was urinary albumin or protein. We used the CKD-EPI equation to estimate GFR.(27) Participants were asked to bring to their inclusion appointment all their current drug prescriptions for the previous three months (regardless of the prescribing physician) and all prescriptions for the year to each annual follow-up appointment. In France, all prescriptions are reimbursed similarly, except for medications determined by the Ministry of Health to have only moderate or insufficient medical benefits. Some differences in reimbursement also exist for patients with chronic expensive diseases and for patients who have not purchased supplementary health insurance, but none of these differences affect the recording and processing of prescriptions. Accordingly, drug prescriptions were continuously recorded from 3 months preceding inclusion through the end of follow up. We used the international Anatomical Therapeutic and Chemical (ATC) thesaurus (28) to code treatments and recorded their start and discontinuation dates (with causes, if any). Kidney failure events, defined as dialysis start or preemptive transplantation, and deaths were reported by the participants or their families, or were identified from medical records or record linkage with the national kidney failure registry.(29)

Identification and validation of adverse drug reactions

An ADR is defined as “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product”.(6) An ADR is considered serious when the patient outcome is death (or a life-threatening situation), hospitalization (initial or prolonged), disability or permanent damage, or another important medical event.(30)

We collected ADRs over a two-year follow-up via an electronic form designed specifically to include information critical for this study. We used several sources to identify ADRs: (1) medical records (examined by CRAs) (2) participant interviews by CRAs, and (3) hospital

reports (Figure 1). Hospitalizations were identified from (1) electronic medical records, (2) nephrology records, and (3) participant interviews. For each hospitalization, we obtained a report to confirm the period and the cause. Causes of hospitalization were coded by a physician according to the 10th revision of the International Classification of Diseases (ICD-10). Every drug prescribed to the patient at the time of each ADR was recorded. Each identified ADR was reviewed by two pharmacists (SL and SML), who evaluated the potential causation of reported drug-related ADRs and coded the types of effect according to the medical dictionary for regulatory activities (MedDRA® Dictionary), the severity of the ADR (nonserious or serious), the drug suspected of responsibility for the ADR, its dosage, and immediate medication management: discontinuation of the product, dose adaptation, or no change. If the ADR was considered serious, a larger committee of expert pharmacologists (VGC, JM, SL, and SML) from the Amiens pharmacovigilance center further evaluated the potential causal relation of each drug (prescribed at the time of the ADR) and the preventability of the ADR.

Assessment of the causes and preventability of serious adverse drug reactions

We applied the Bégau imputability method (31) (Supplementary material 1A), which is the official procedure used in French pharmacovigilance centers to report serious ADRs to the French drug authorities. This algorithmic method attributes an intrinsic score based on chronological and semiological criteria. The cause-and-effect relationship is assessed independently for each drug taken by the patient before the occurrence of the event and is not influenced by the extent of imputability to other drugs. This method allowed us to identify the drug most responsible for serious ADRs, i.e., that with the highest intrinsic score. During the ADR validation process, we globally evaluated all of the risk factors for ADRs, including a review of all drugs prescribed at the time of the ADR and evaluation of potential pharmacokinetic/pharmacodynamic interactions.

In addition, we used the Naranjo 10-question algorithm (Supplementary material 1B) to confirm the causal relation of each reported serious ADR by determining the probability that an ADR is actually due to a drug rather than to any other factor.(32) This analysis considers only ADRs categorized as definite, probable, or possible with both the Bégau and Naranjo methods.

The preventability of ADRs was assessed with a seven-item ADR preventability scale (33) (Supplementary material 1C) that classified ADRs in four categories: “preventable”, “potentially preventable”, “not assessable”, “not preventable”. When items related to adherence to recommendations and the patient’s need for the prescription were uncertain, the expert committee rated preventability as “not assessable”.

Both outpatient and inpatient medical records were used to assess causality and preventability.

Statistical analyses

Baseline characteristics were described for all participants and by subgroup according to baseline eGFR (< or \geq 30 mL/min per 1.73 m²). ADRs were also described according to baseline eGFR. Results were expressed as means \pm standard deviations (SD), medians (interquartile range), or numbers (percentages). The Fisher exact, Student *t*, or Chi-squared tests were used to compare categorical variables. A sensitivity analysis was conducted by using the last eGFR preceding the ADR to describe it.

Crude incidence rates and 95% confidence intervals (95% CIs) of ADRs and serious ADRs per 100 person-years were estimated by Poisson regression for the overall population and by subgroups according to baseline eGFR; they were corrected for overdispersion by using the quasi-likelihood approach.

We used cause-specific Cox proportional hazard models to investigate patient clinical characteristics associated with the ADR risk. Data were censored at the end of the two-year follow-up, the last patient visit, death, or kidney failure, whichever came first (competing

events). Variables from Table 1, preselected by a literature review, were analyzed in a crude model. Variables with a *P* value greater than 0.10 in the crude model were excluded from the multivariable analyses. Age and sex were forced into the final model, that is, included because considered necessary for the model's validity.

Because of the possibility of multiple ADRs per patient during the follow-up, we performed a sensitivity analysis, using the Prentice, Williams, and Peterson gap-time recurrent event time-to-event analysis, with sandwich variance estimators, to determine the factors associated with ADRs.(34,35)

To deal with the missing data (Supplementary material 2), multiple imputations were performed (fully conditional specification method,(36) 10 iterations, 10 datasets) including all patient characteristics from Table 1, the total number of ADRs per patient, and the number of serious ADRs per patient. Data patterns suggest that the assumption that data were missing at random was plausible. Cox model regression coefficients were estimated separately in each imputed dataset and combined according to Rubin's rules.

Statistical analyses were performed with SAS® software (version 9.4; SAS Institute, Cary, NC) and R software (version 3.5.0, Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Participants were predominantly men; 43% had diabetes, 53% cardiovascular disease, and 91% hypertension. (Table 1) Those with eGFR < 30 mL/min per 1.73 m² at baseline were older and had less education than those with higher eGFR. They also had anemia and a history of AKI more often, and were prescribed more medications.

Incidence and description of adverse drug reactions

Over the two-year follow-up, 751 ADRs were reported in 536 (18%) of 3033 participants; 150 ADRs in 125 participants (4%) were classified as serious, i.e., 14.4 (95% CI, 12.6-16.5) and 2.7 (95% CI, 1.7-4.3) per 100 person-years, respectively. Both were nearly twice as high in participants with eGFR <30 versus \geq 30 mL/min per 1.73m² (Table 3, Table 4, and Figure 2). Five percent of participants had more than one ADR. Sixty percent of ADRs were reported only in the medical record or hospitalization report, 20% in both the medical record and participant interview, and 20% only in the participant interview.

Among the serious ADRs, 145 were associated with hospitalization: 65% as its cause and 35% as its consequence (Figure 3). Sixteen deaths resulted from an ADR, directly or indirectly, as did five life-threatening events. Five participants with serious ADRs (three medically important and two resulting in permanent disability) were not hospitalized.

Renal and urinary disorders were the most frequent type of ADR, particularly AKI, followed by gastrointestinal (mostly diarrhea), and musculoskeletal and connective tissue disorders (Table 2 and supplementary material 3). Renal disorders and hemorrhages or bleeding accounted for two thirds of the 150 serious ADRs (Figure 3). Of the 16 deaths linked to an ADR, 11 were related to hemorrhages, which also accounted for 40% of the serious ADRs in participants with baseline eGFR < 30 mL/min per 1.73m², and 19% in those with eGFR \geq 30 ($P=0.009$) (Figure 3). Using the last eGFR before the ADR did not significantly change the proportions reported in Table 2 and Figure 3 (Supplementary materials 4 and 5).

Renin-angiotensin system (RAS) inhibitors, antithrombotic agents, and diuretics were the medications most frequently responsible for both nonserious and serious ADRs (Figure 4 and supplementary material 6). Antithrombotic agents were responsible for 34% of the 150 serious ADRs: 34 were due to vitamin K antagonists, 9 to heparin, 6 to platelet aggregation inhibitors, and 2 to direct factor Xa inhibitors. Three pharmacodynamic drug interactions were identified:

two between vitamin K antagonist and heparins, and one between vitamin K antagonist and an antibiotic.

Factors associated with adverse drug reactions and serious adverse drug reactions

Participants with a baseline eGFR <30 mL/min per 1.73m^2 had a risk 1.6 times higher of an ADR than those with an eGFR ≥ 30 , after adjustment for other associated variables (Table 3). The risk of ADR also significantly increased with the participant's baseline number of prescribed drugs, history of cardiovascular disease and of AKI, and poor treatment adherence. Women were at higher risk of an ADR than men, but not of a serious ADR. There was no significant association with age.

Hazard ratios for serious ADRs were significantly higher in participants with eGFR < 30 compared to ≥ 30 mL/min per 1.73m^2 , as well as in those prescribed >10 compared with <5 medications and in participants with poor adherence (Table 4). Age and sex were not associated with a higher risk of serious ADR.

A sensitivity analysis confirmed that the factors mentioned above were associated with ADRs (Supplementary material 7A). It also showed that anemia was significantly associated with the risk of serious ADRs but that poor adherence no longer was (Supplementary material 7B).

Immediate management of adverse drug reactions and preventability

After an ADR, the drug considered responsible was discontinued in 71% of cases (e.g. in 78% of statin-linked ADRs), at least temporarily, and the dose was adjusted in 14% of cases; no change was made in the prescription in 11% (4% missing data). When the ADR was serious, 83% of the drugs blamed were discontinued at least temporarily right after the event.

The Olivier ADR preventability scale (33) allowed us to classify the 150 serious ADRs as preventable in 13% of cases ($n=19$) and potentially preventable in 19% ($n=28$). A quarter of the

preventable ADRs were associated with participant self-medication. Overall, 37% of ADRs were inevitable and 31% not assessable (Supplementary material 6).

DISCUSSION

This study presents a global descriptive view of the magnitude and diversity of ADRs in a well-phenotyped CKD population. The central message here is that ADRs are common, often serious, and potentially preventable in CKD patients and that these patients are vulnerable and their treatment is complex. It shows that three drug classes among those most prescribed in this population are responsible for almost 40% of ADRs, including RAS inhibitors, antithrombotic agents, and diuretics. The study especially points out the severity of ADRs caused by antithrombotic agents, to which one third of the serious events were imputed. In addition, we identify some care and patient characteristics that increase ADR risk; these include an eGFR ($< 30 \text{ mL/min/1.73m}^2$), a higher number of prescribed drugs, and poor adherence to medications. Importantly, a significant proportion of these ADRs may be preventable.

Our findings are difficult to compare with those of other studies, which differ from ours in several ways. Most of them assessed ADR incidence at hospital admission (1–3,5,7–10,13) or during hospitalization,(1,11–13,23) and used highly heterogeneous study settings, definitions of ADRs, and methods for ascertaining ADRs (spontaneous report, intensive chart review, or both). In this study, we evaluated ADR incidence in nephrology outpatients, with and without hospitalization; they were identified from an extensive review of medical records, hospitalization reports, and participant interviews. We compared rates according to eGFR and showed that ADR incidence increased when eGFR was lower than $30 \text{ mL/min/1.73m}^2$. Overall, renal, urinary, gastrointestinal, musculoskeletal, and connective tissue disorders were the most commonly reported ADRs in our study, but renal disorders and bleeding largely predominated among the serious ADRs. Several studies have reported similar results in hospitalized patients with unknown CKD status.(5,8–10) The known high susceptibility of patients with CKD for

AKI explains the high frequency of renal and urinary ADRs. Cardiovascular medicines stand out among the most common suspected drugs in several studies of hospitalized patients with unknown CKD status.(2–5,9,10) Similarly, we found that renin-angiotensin system inhibitors, antithrombotic agents, and diuretics were the pharmacological classes to which ADRs were most commonly imputed in our study. The high prevalence of CKD-related cardiovascular complications explains the high use of cardiovascular drugs in patients with CKD(37) despite their high risk of ADR due to the combined effect of low eGFR, hemorrhagic risk, and electrolyte disturbance. The principal drugs suspected of causing ADRs were usually not directly nephrotoxic, and most ADRs resulted from reduced renal clearance. This conclusion has important clinical implications, notably regarding drug prescriptions for CKD patients and the need to focus on regularly reassessing use or dose according to eGFR (especially when it drops below 30 mL/min/1.73m²), as well as on potential nephrotoxic agents. However, the clinical benefits of some of these drugs have been demonstrated by a high level of evidence. For instance, a moderate increase (of 20% to 30%) in creatinine can be expected with RAS inhibitors; nephrologists may find this an acceptable trade-off in view of these drugs' protective nature in the long term and their ability to slow CKD progression. This moderate increase is well below the KDIGO definition used for drug-related AKI events in our study, which is based on a rise in creatinine of at least 50%.(25)

Patients seen by nephrologists require the most complex care, because of their multiple comorbidities and the complications associated with decreased kidney function.(38) These result in the use of multiple medications, as shown here: CKD-REIN participants were prescribed a median of eight different drugs daily. Moreover, the number of prescribed drugs increases as CKD progresses.(19,39) High rates of ADRs in patients with CKD add to the complexity of their care. As we showed, treatments often need to be stopped, at least temporarily, or dosage adjusted because of ADRs, which may affect therapeutic management

and ultimately reduce the likelihood of slowing CKD progression and decreasing its complications. Lipid-lowering agents are a good example of treatments that are strongly recommended in patients with CKD due to their high cardiovascular risk, but are often discontinued because of contractures, cramps, or myalgia (stopped in 78% of statin-linked ADRs). Schneider et al. (40) noted the underprescription of statins in CKD patients, which may be partly explained by ADRs; a similar underprescription rate exists in the CKD-REIN cohort.(41) The challenge for physicians is to assess the benefit/risk ratio between treating a new complication and adding a new drug. Increased awareness by the medical community of this difficulty and of the necessity to reassess this benefit/risk ratio regularly, especially when eGFR decreases, is essential. Pharmacists too must play a role, given that most ADRs occur in outpatients. Finally, the importance of patient education in terms of drug use must be enhanced, as one quarter of preventable serious ADRs were due to participant misuse.

The major factors identified in this study associated with ADRs overall and with serious ADRs are the number of prescribed drugs, cardiovascular disease, poor adherence to treatment, and eGFR. Reports have regularly shown that the number of drugs is a risk factor in hospitalized patients with unknown CKD status.(8,9,14,23) Besides the increased risk of ADR, polypharmacy is also associated with deleterious health outcomes in elderly patients.(42) Poor adherence to medication is associated with higher ADR risk, possibly reflecting patients' misuse of drugs. However, the healthy user effect cannot be ruled out.(43) Two other studies have also described cardiovascular disease as a risk factor for ADR.(7,23) Although numerous studies show women to be at higher risk of serious ADR in populations with an unknown CKD status,(2,9,10,14) this was not the case in our CKD population. Age was not associated with the risk of either ADR or serious ADR, consistent with previous reports.(8,14,23) The risk of ADR tended to be slightly lower in older patients in the multivariable analyses, although not significantly; this finding may be related to their lower number of inappropriate

prescriptions.(19) This may indicate more careful prescriptions by physicians for elderly patients. Declining kidney function seems to be an important risk factor for CKD patients with $eGFR < 30$ mL/min per 1.73 m^2 , in line with the results reported by Sharif-Askari et al. in hospitalized CKD patients.(23) Corsonello et al. found a similar association between ADR risk and declining kidney function in elderly hospitalized patients.(44) This higher rate of ADR at $eGFR < 30$ mL/min/ 1.73m^2 appears related mainly to bleeding events due to antithrombotic agents, mostly vitamin K antagonists. This highlights the importance of reassessing prescriptions regularly as kidney function declines, especially for drugs such as vitamin K antagonists. Although these medications are metabolized by the liver, excreted in an inactive form in stool and urine,(45) and thus not renally eliminated, CKD can impair their disposition.(18) Specifically, it can cause the accumulation of uremic toxins in blood and organs with deleterious effects,(46) for example, indoxyl sulfate, which impairs platelet activity.(47)

Major strengths of this study include its large sample size of patients with confirmed CKD diagnoses, recruited from a representative sample of nephrology outpatient facilities. The high sensitivity and specificity of our process for identifying and grading ADRs is also unique. Indeed, a major limitation in ADR research is the lack of reliable data about the true burden of these reactions, related to their reporting process; the traditional ascertainment method, through the spontaneous reporting system in pharmacovigilance, results in their vast underreporting. A previous study showed that health professionals spontaneously report only 6% of serious ADRs.(48) Our study used different sources to capture these events, especially serious ADRs, through hospitalization reports, medical records, and participant interviews. Furthermore, all cases were reviewed by pharmacists, and serious cases evaluated by a committee of experts. Finally, the use of standard international coding systems for both drug classes and ADRs, the availability of start and end dates for each treatment, and the reasons for treatment discontinuation contribute to the quality and novelty of our findings.

Our study also has limitations. Despite our sensitive method for identifying ADRs, their number may still be underestimated, mainly for those not hospitalized during follow-up: these may not have been reported by physicians in medical records or by participants either to physicians or during interviews, due to memory bias or because an ADR is so well-known that it tends to be poorly reported in hospitalization reports and medical records. However, participants were probably most likely to report ADRs with the most negative impacts on their health and well-being. We may not have captured all hospitalizations and may also have missed drug effects that have never been reported as a potential ADR. Other sources of ADRs might exist, but were not available to us. Several decision algorithms for causality assessment in ADRs exist.(49) However, none of them have been accepted as a gold standard and comparing them could lead to discrepancies in results.(50) These algorithms do not replace medical diagnosis.

Another limitation of this study is the heterogeneous nature of the outcome (ADR) used in the multivariable analyses. Although these analyses allowed us to identify some specific and potentially modifiable risk factors, our basic aim here was to describe the general characteristics of patients at high risk for ADR. We will further explore risk factors associated with ADRs more specifically for a number of drug classes and outcomes.

Finally, our study is generalizable to patients with CKD seen by nephrologists, but not to all patients with an eGFR <60 mL/min per 1.73m^2 in the general population. However, because nephrologists probably handle drugs more carefully, the ADR incidence would likely have been even higher in the broader population of patients not seen by nephrologists.

CONCLUSION

The burden of ADRs is high in patients with moderate to advanced CKD, and incidence was higher when CKD was severe. Our results highlight the major risk of specific pharmacological

classes, particularly antithrombotic agents, which must be used cautiously in CKD patients, especially at low eGFRs. Greater awareness by the medical community of the importance of eGFR level in prescribing medications, increased involvement of pharmacists in systematically verifying eGFR for patient prescriptions, and enhanced patient education are key elements for preventing ADRs in this population at high risk. The impact of ADRs on health resources and patients' quality of life requires further evaluation.

Author contributions:

S.M.L., S.L., Z.A.M., B.S., and M.M. designed the present project. S.M.L., S.L., V.G-C., and J.M. evaluated the serious adverse drug reactions. S.M.L., S.L., and M.M. analyzed the data. S.M.L., S.L., V.G-C., J.M., Z.A.M., B.S., and M.M. contributed to the interpretation of the results. S.M.L., S.L., Z.A.M., and B.S. wrote the first draft of the article; S.M.L., V.G-C., J.M., M.M., C.J., C.C., D.F., M.L., L.F., B.M.R., B.S., Z.A.M., and S.L. provided critical feedback, helped shape the research, analysis and the final draft of the manuscript, and approved the version to be published; B.S. was the principal investigator.

Disclosures

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Figure legends

Figure 1: Description of the process for identifying and validating adverse drug reactions in the CKD-REIN cohort

Figure 2: Incidence rates of adverse drug reactions and serious adverse drug reactions according to baseline estimated glomerular filtration rate.

Footnote:

Incidence rates are represented with their 95% confidence interval whiskers.

P-values test the difference between incidence rates according to baseline eGFR.

Figure 3: Distribution of serious adverse drug reactions causing or resulting from hospitalization according to baseline estimated glomerular filtration rate (n=145).

Footnote:

Results are expressed as %. The denominators used are the total number of ADRs in patients with eGFR < or ≥ 30 mL/min/1.73m².

Figure 4: The most common pharmacological classes responsible for adverse drug reactions and serious adverse drug reactions according to baseline estimated glomerular filtration rate (n=751). Adverse drug reactions caused by agents acting on the renin-angiotensin system (RAS), antithrombotic agents, or diuretics accounted for 39% of adverse drug reactions. Serious adverse drug reactions caused by these three classes accounted for 58% of serious adverse drug reactions.

Footnote:

Results are expressed as %. The denominators used are the total number of ADRs in patients with eGFR < or ≥ 30 mL/min/1.73m².

Table 1: Baseline characteristics of participants in the Chronic Kidney Disease-Renal Epidemiology and Information Network

	Baseline eGFR in mL/min per 1.73m ²			Participants with missing data** (n=3033)
	All (n=3033)	≥ 30 (n=1670)	<30 (n=1363)	
Age (years)	69 [60 - 76]	68 [59 - 75]	70 [61 - 78]	0%
<60	716 (24%)	421 (25%)	295 (22%)	
60 to 75	1400 (46%)	803 (48%)	597 (44%)	
≥ 75	917 (30%)	446 (27%)	471 (35%)	
Men	1982 (65%)	1121 (67%)	861 (63%)	0%
High school diploma or higher	1094 (36%)	648 (39%)	446 (33%)	1.7%
BMI	28 [25 - 32]	28 [25 - 32]	28 [25 - 32]	2.1%
≥ 30 kg/m ²	1075 (35%)	573 (34%)	502 (37%)	
Serum Albumin	4.0 [3.8 - 4.3]	4.1 [3.8 - 4.3]	4.0 [3.7 - 4.3]	18.9%
<3.5 g/L	293 (10%)	138 (8%)	155 (11%)	
UACR				11.2%
<30 mg/g	846 (28%)	625 (37%)	221 (16%)	
30 - 300 mg/g	955 (31%)	540 (32%)	415 (31%)	
>300 mg/g	1232 (41%)	505 (31%)	727 (53%)	
Anemia*	1236 (41%)	490 (29%)	746 (55%)	0.9%
Smoking status				0.8%
Smoker	360 (12%)	197 (12%)	163 (12%)	
Non smoker	1252 (41%)	701 (42%)	551 (40%)	
Ex-smoker	1421 (47%)	773(46%)	648 (48%)	
Diabetes	1304 (43%)	702 (42%)	602 (44%)	0.2%
AKI history	710 (23%)	350 (21%)	360 (26%)	8.0%
Cardiovascular history	1611 (53%)	854 (51%)	757 (56%)	1.4%
Hypertension	2751 (91%)	1493 (89%)	1258 (92%)	0.2%
Dyslipidemia	2229 (73%)	1216 (73%)	1011 (74%)	0.5%

Number of drugs	8 [5 - 10]	7 [5 - 10]	8 [6 - 11]	0.6%
< 5 drugs	593 (19%)	412 (25%)	181 (13%)	
5 to 10 drugs	1694 (56%)	915 (54%)	779 (57%)	
> 10 drugs	747 (25%)	344 (21%)	403 (30%)	
Poor adherence to medications	1888 (62%)	1010 (60%)	878 (64%)	1.0%

AKI: Acute kidney injury, BMI: Body mass index, eGFR: estimated glomerular filtration rate, UACR: Urine albumin to creatinine ratio

Median (interquartile range, IQR) or n (%)

*Anemia is defined by the 1968 WHO definition [*World Health Organization. Nutritional anaemias. Report of a WHO scientific group. Geneva, World Health Organization; 1968*]: <12 g/dL for women and <13 g/dL for men.

**Missing data were imputed as specified in the methods section.

Table 2: Description of adverse drug reactions according to baseline estimated glomerular filtration rate.

Type of ADRs	All ADRs (n=751)	ADRs in patients with eGFR \geq 30 (n=331)	ADRs in patients with eGFR <30 (n= 420)
Renal and urinary disorders	150 (20%)	62 (19%)	88 (21%)
<i>Acute kidney injury</i>	102	41	61
<i>Increased serum creatinine</i>	40	20	20
<i>Other type of renal and urinary disorders</i>	8	1	7
Gastrointestinal disorders	119 (16%)	61 (18%)	58 (14%)
<i>Diarrhea</i>	57	35	22
<i>Gastrointestinal conditions</i>	24	8	16
<i>Other type of gastrointestinal disorders</i>	38	18	20
Musculoskeletal and connective tissue disorders	68 (9%)	34 (10%)	34 (8%)
<i>Contractures</i>	35	21	14
<i>Muscle pain</i>	22	10	12
<i>Other type of musculoskeletal and connective tissue disorders</i>	11	3	8
Hemorrhages and bleeding	67 (9%)	18 (5%)	49 (12%)
<i>Hemorrhages</i>	34	8	26
<i>Hematoma</i>	19	7	12
<i>Other type of hemorrhages and bleeding</i>	14	3	11
General disorders and administration site conditions	58 (8%)	26 (8%)	32 (8%)
<i>Peripheral edema</i>	30	11	19
<i>Drug intolerance</i>	8	3	5
<i>Other type of general disorders and administration site conditions</i>	20	12	8
Other type of ADRs	289 (38%)	130 (39%)	159 (38%)

ADRs: adverse drug reactions, eGFR: estimated glomerular filtration rate expressed in mL/min/1.73m²
Results are expressed as n (%). The denominator used in column 1 is the total number of ADRs, and in columns 2 and 3, those of the ADRs in patients with eGFR < vs \geq 30 respectively.
P-value=0.025 tests the difference in the distribution of ADR type according to patient baseline eGFR.

Table 3: Associations of participant characteristics with adverse drug reactions

	N(%) with ADRs (n=536)	Incidence rate*		Unadjusted model		Adjusted model	
		IR [95% CI]	HR [95% CI]	P-value	HR [95% CI]	P-value	
Age (years)				0.10		0.10	
<60	113 (16)	13.2 [9.9; 17.6]	Reference		Reference		
60 to 75	271 (19)	15.2 [12.5; 18.5]	1.25 [1.00; 1.56]		1.06 [0.84; 1.34]		
≥ 75	152 (17)	14.0 [10.9; 18.0]	1.08 [0.85; 1.38]		0.85 [0.65; 1.11]		
Sex				0.08		0.04	
Men	332 (17)	13.2 [11.1; 15.7]					
Women	204 (19)	16.6 [13.4; 20.6]	1.17 [0.98; 1.39]		1.21 [1.01; 1.45]		
Educational level				0.09		0.99	
High	179 (16)	13.0 [10.2; 16.5]	Reference		Reference		
Low	357 (18)	15.2 [12.8; 17.9]	1.17 [0.97; 1.40]		1.00 [0.83; 1.21]		
eGFR				<0.001		<0.001	
≥ 30 mL/min per 1.73m ²	244 (15)	10.8 [8.9; 13.2]	Reference		Reference		
< 30 mL/min per 1.73m ²	292 (21)	19.4 [16.2; 23.2]	1.74 [1.47; 2.07]		1.56 [1.30; 1.87]		
Serum Albumin				0.06		0.31	
≥3.5 g/dL	476 (17)	13.9 [12.0; 16.0]	Reference		Reference		
<3.5 g/dL	60 (20)	19.7 [12.9; 29.9]	1.38 [1.00; 1.90]		1.19 [0.85; 1.65]		
UACR				0.06		0.90	
<30 mg/g	139 (16)	13.1 [10.0; 17.1]	Reference		Reference		
30 – 300 mg/g	165 (17)	12.9 [10.0; 16.7]	1.09 [0.85; 1.39]		0.95 [0.75; 1.22]		
>300 mg/g	232 (19)	16.6 [13.5; 20.4]	1.29 [1.03; 1.62]		1.00 [0.79; 1.27]		
Anemia**				<0.001		0.06	
Without anemia	287 (16)	12.3 [10.3; 14.8]	Reference		Reference		
With anemia	249 (20)	17.7 [14.6; 21.5]	1.45 [1.23; 1.72]		1.19 [0.99; 1.42]		
Diabetes				0.01		0.78	
Without diabetes	274 (16)	12.1 [10.0; 14.7]	Reference		Reference		

<i>With diabetes</i>	262 (20)	17.4 [14.4; 21.0]	1.31 [1.10; 1.55]		1.03 [0.85; 1.24]	
AKI history				<0.001		0.01
<i>Without AKI history</i>	379 (16)	12.9 [11.0; 15.2]	Reference		Reference	
<i>With AKI history</i>	157 (22)	19.4 [15.0; 25.1]	1.48 [1.21; 1.81]		1.32 [1.08; 1.61]	
Cardiovascular history						
<i>Without cardiovascular history</i>	215 (15)	11.3 [9.1; 14.0]	Reference		Reference	
<i>With cardiovascular history</i>	321 (20)	17.2 [14.6; 20.4]	1.42 [1.19; 1.69]	<0.001	1.24 [1.02; 1.50]	0.03
Hypertension				0.06		0.71
<i>Without hypertension</i>	38 (13)	9.4 [5.4; 16.1]	Reference		Reference	
<i>With hypertension</i>	498 (18)	14.9 [13.0; 17.1]	1.37 [0.99; 1.91]		1.07 [0.76; 1.51]	
Baseline number of drugs/patient				<0.001		0.01
<i>< 5 drugs</i>	62 (10)	7.5 [5.0; 11.2]	Reference		Reference	
<i>5 to 10</i>	301 (18)	13.9 [11.6; 16.7]	1.86 [1.41; 2.44]		1.50 [1.12; 2.02]	
<i>> 10</i>	173 (9)	21.7 [17.3; 27.3]	2.59 [1.93; 3.46]		1.71 [1.21; 2.41]	
Adherence to medication				<0.001		0.01
<i>Good</i>	158 (14)	10.7 [8.3; 13.7]	Reference		Reference	
<i>Poor</i>	378 (20)	16.7 [14.3; 19.6]	1.52 [1.26; 1.83]		1.36 [1.12; 1.64]	

AKI: Acute kidney injury, CI: Confidence interval, eGFR: estimated Glomerular filtration rate, HR: hazard ratio, IR: incidence rate, UACR: Urine albumin to creatinine ratio
P-values used Wald Chi-square test for global variable effect.

*Incidence rates are expressed per 100 person-years.

**Anemia is defined by the 1968 WHO definition [*World Health Organization. Nutritional anaemias. Report of a WHO scientific group. Geneva, World Health Organization; 1968*]: <12 g/dL for women and <13 g/dL for men.

Table 4: Associations of participant characteristics with serious adverse drug reactions

	N(%) with ADRs (n=125)	Incidence rate*		Unadjusted model		Adjusted model			
		IR	[95% CI]	HR	[95% CI]	P-value	HR	[95% CI]	P-value
Age (years)					0.15		0.32		
<60	26 (4)	2.4	[0.9; 6.9]	Reference		Reference			
60 to 75	52 (4)	2.4	[1.1; 5.1]	1.02	[0.64; 1.63]	0.71	[0.44; 1.17]		
≥ 75	47 (5)	3.4	[1.6; 7.5]	1.45	[0.90; 2.34]	0.91	[0.54; 1.51]		
Sex					0.91		0.74		
Men	82 (4)	2.7	[1.5; 4.8]	Reference		Reference			
Women	43 (4)	2.8	[1.3; 6.0]	0.98	[0.68; 1.42]	1.06	[0.73; 1.55]		
eGFR					<0.001		0.01		
≥ 30 mL/min per 1.73m ²	49 (3)	1.8	[0.9; 3.4]	Reference		Reference			
< 30 mL/min per 1.73m ²	76 (6)	4.0	[2.4; 6.8]	2.17	[1.51; 3.11]	1.82	[1.25; 2.63]		
BMI					0.05		0.46		
<30 kg/m ²	70 (4)	2.4	[1.3; 4.5]	Reference		Reference			
≥30 kg/m ²	55 (5)	3.3	[1.6; 6.8]	1.42	[0.99; 2.04]	1.16	[0.79; 1.70]		
Anemia**					0.001		0.15		
Without anemia	60 (3)	2.0	[1.0; 4.1]	Reference		Reference			
With anemia	65 (5)	3.9	[2.0; 7.5]	1.77	[1.25; 2.52]	1.31	[0.91; 1.89]		
Diabetes					0.03		0.89		
Without diabetes	60 (3)	2.3	[1.2; 4.3]	Reference		Reference			
With diabetes	65 (5)	3.3	[1.8; 6.1]	1.47	[1.03; 2.09]	0.97	[0.65; 1.44]		
AKI history					0.01		0.12		
Without AKI history	84 (4)	2.3	[1.3; 4.2]	Reference		Reference			
With AKI history	41 (6)	4.0	[1.8; 9.3]	1.67	[1.12; 2.49]	1.37	[0.92; 2.05]		
Cardiovascular history					<0.001		0.01		
Without cardiovascular history	35 (2)	1.5	[0.7; 3.4]	Reference		Reference			
With cardiovascular history	90 (6)	3.9	[2.4; 6.3]	2.45	[1.65; 3.63]	1.93	[1.25; 2.98]		

Baseline number of drugs/ patients			<0.001	0.05
< 5	10 (2)	1.1 [0.2; 4.6]	Reference	Reference
5 to10	62 (4)	2.4 [1.3; 4.3]	2.29 [1.17; 4.46]	1.53 [0.76; 3.10]
> 10	53 (3)	5.0 [2.7; 9.4]	4.70 [2.39; 9.23]	2.31 [1.07; 5.01]
Adherence to medication			0.01	0.03
Good	30 (3)	1.8 [0.8; 4.3]	Reference	Reference
Poor	95 (5)	3.3 [2.0; 5.4]	1.95 [1.29; 2.94]	1.59 [1.05; 2.42]

AKI: Acute kidney injury, BMI: body mass index, CI: Confidence interval, eGFR: estimated Glomerular filtration rate, HR: hazard ratio, IR: incidence rate

P-values used Wald Chi-square test for global variable effect.

*Incidence rates are expressed per 100 person-years.

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