Kidney Function Decline and Serious Adverse Drug Reactions in Patients With CKD

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Rationale & Objective: Adverse drug reactions (ADRs) are common in patients with chronic kidney disease (CKD). The impact of kidney function decline on serious ADR risk has been poorly investigated. We comprehensively describe ADRs and assess the relationship between estimated glomerular filtration rate (eGFR) and serious ADR risk.

Study Design: Prospective cohort study.

Setting & Participants: 3,033 participants in French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study, a nationwide sample of nephrology outpatients with moderate to advanced CKD.

Predictors: Demographic and biological data (including eGFR), medication prescriptions.

Outcome: ADRs (preventable or not) were prospectively identified from hospital discharge reports, medical records, and patient interviews. Expert pharmacologists used validated tools to adjudicate ADRs.

Analytical Approach: Restricted cubic splines in fully adjusted cause-specific Cox proportional hazard models were used to evaluate the relationship between eGFR and the risk of serious ADRs (overall and by subtype).

Results: During a median follow-up period of 4.7 years, 360 patients experienced 488 serious ADRs. Kidney and urinary disorders (n = 170) and hemorrhage (n = 170) accounted for 70% of serious ADRs. The most common medications classes were antithrombotics and renin-angiotensin system inhibitors. The majority of those serious ADRs were associated with hospitalization (n = 467), with 32 directly or indirectly associated with death and 22 associated with a life-threatening event. More than 27% of the 488 serious ADRs were preventable or potentially preventable. The eGFR is a major risk factor for serious ADRs. The risk of acute kidney injury was 2.2% higher and risk of bleeding ADRs was 8% higher for each 1 mL/min/1.73 m^2 lower baseline eGFR.

Limitations: The results cannot be extrapolated to patients who are not being treated by a nephrologist.

Conclusions: ADRs constitute a major cause of hospitalization in CKD patients for whom lower eGFR level is a major risk factor.

Visual Abstract online

Complete author and article information provided before references.

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Drugs provide therapeutic benefits but can also cause adverse drug reactions (ADRs), which range from frequent but nonserious events with mild symptoms to rare, serious events including disability and death. Randomized clinical trials, pharmacovigilance, and pharmacoepidemiology studies enable the initial and continuous assessment of a drug's risk-benefit ratio—the balance between safety risks and therapeutic effectiveness. Patients with chronic kidney disease (CKD) are excluded from many clinical trials, and they are highly susceptible to ADRs.[1-4]

Older age and polypharmacy are common in patients with CKD and raise the risk of ADRs.[5] However, it is not clear whether the level of kidney function per se affects the risk of ADRs. Relative to patients with normal kidney function, the pharmacodynamic and pharmacokinetic parameters of many medications change in CKD. For instance, various uremic toxins that accumulate as kidney function deteriorates can alter drug bioavailability, effectiveness, and safety.[6-8]

In this study, our hypothesis is that lower kidney function is associated with an elevated risk of serious ADRs independent of age and polypharmacy in patients with moderate to advanced CKD. We tested this hypothesis in the French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study, a national sample of patients with moderate to advanced CKD and 5 years of prospective follow-up observation. The objectives of this study were to (1) provide a comprehensive description of serious ADRs and their short-term consequences, (2) identify ADRs that were preventable, and (3) determine the relationship between kidney function and the most common serious ADRs.

Methods

Study Design and Participants

CKD-REIN is a prospective cohort study conducted in 40 nationally representative outpatient nephrology centers in

PLAIN-LANGUAGE SUMMARY

Patients with chronic kidney disease (CKD) have complex clinical presentations, take multiple medications, and often receive inappropriate prescriptions. Using data from a large, prospective CKD cohort, we found a high incidence of serious adverse drug reactions (ADRs). The 2 most common serious ADRs were drug-induced acute kidney injury and bleeding. A large proportion of serious ADRs required hospital admission, and 11% led to death or were life threatening. Lower kidney function was a major risk factor for serious ADRs. Many of these serious ADRs were determined to be partly preventable through greater adherence to prescription guidelines. This report enhances our understanding of the potential toxicity of drugs taken by patients with moderate to advanced CKD. It emphasizes the importance of monitoring kidney function when prescribing drugs, particularly for high-risk medications such as antithrombotic agents.

France. Eligible patients were at least 18 years of age, had a confirmed diagnosis of moderate or advanced CKD with an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2, were not on dialysis, and had not received a kidney transplant. From July 2013 to March 2016, CKD-REIN enrolled 3,033 patients, who gave their written, informed consent. Details of the study protocol and flow chart have been published previously.[9,10] The study was approved by the institutional review board at the French National Institute of Health and Medical Research (INSERM; reference: IRB00003888) and was registered at ClinicalTrials.gov (NCT03381950). The results of this cohort study are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11]

Study Data

Data were collected at baseline and then annually by trained clinical research associates (CRAs) from patient interviews and medical records. The study data included baseline sociodemographic characteristics and any history of hypertension, diabetes, heart disease (such as heart failure and coronary disease), peripheral artery disease, cerebrovascular disease, stroke or transit ischemic attack, dyslipidemia, or acute kidney injury (AKI), as defined in the Table S1. Patients were classified with heavy alcohol use if they reported drinking at least 10 g per day (for women) or 20 g per day (for men). Medication adherence was assessed with the validated, questionnaire-based Girerd score (Table S1).[12] Blood hemoglobin and serum creatinine and albumin levels were measured, as were urinary albumin-creatinine or protein-creatinine ratios (Table S1). We used the 2009 creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation to estimate the baseline GFR.[13]

Patients were asked to bring all their current drug prescriptions for the 3 months preceding their enrollment visit and all the year's prescriptions to each annual follow-up visit. Accordingly, drug prescriptions were continuously recorded from 3 months preceding study inclusion through the end of the follow-up period. We used the international Anatomical Therapeutic and Chemical (ATC) thesaurus[14] to code medications and recorded their start and discontinuation dates (with causes, if any). Kidney replacement therapy (KRT) initiation (defined as dialysis initiation or preemptive kidney transplantation) and deaths were reported by the patients or their families or were identified from medical records or linkage to the French national death registry and that of patients receiving KRT.[15]

Identification and Adjudication of Adverse Drug Reactions

According to the World Health Organization, 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."[16] An ADR is considered serious when the patient's outcome is death or a life-threatening situation, hospitalization, disability or permanent damage, or another important medical event (the ADR was considered serious but did not require hospitalization, required a short stay in the emergency department, or occurred during a hospital stay without prolonging it).[17] A serious ADR was considered to be the cause of the hospital admission when the medical condition was the reason the patient was admitted, and it was considered to occur during the hospital stay when the patient did not present with the medical condition on admission to the hospital.

Considering the high risk of drug-induced AKI and bleeding in patients with CKD, these events have been defined further as follows. Drug-linked AKIs were defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) AKI criteria: "an increase in serum creatinine (SCr) by ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours or an increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days."[18] A hemorrhage was considered to be serious if it was fatal, symptomatic in a critical area or organ, or caused anemia (according to the International Society on Thrombosis and Haemostasis definition of major bleeding).[19]

We collected data on ADRs over a 5-year follow-up period via an electronic form designed specifically to include essential information for this study. The workflow involved an initial process to identify potential ADRs, followed by pharmacist review for confirmation. We used

several sources to identify potential ADRs: (1) medical records (examined by CRAs), (2) patient interviews with CRAs, and (3) hospital reports. The causes of hospital admissions were coded by a study physician according to the *International Classification of Diseases, Tenth Revision* (ICD-10) and on the basis of the hospital reports. Each drug prescribed to the patient at the time of each ADR was recorded. The medical record for each identified ADR was reviewed by 1 of 2 pharmacists (S.L. and S.M.L.), who evaluated the potential causal relationship with the patient's drugs, coded the event according to the *Medical Dictionary for Regulatory Activities* (MedDRA), and rated the seriousness of the ADR (nonserious or serious), the drug thought to be responsible for the ADR, the dose level, and the immediate drug management action (discontinuation, dose adjustment, or no change).

For serious ADRs, a larger committee of expert pharmacologists from the Amiens Pharmacovigilance Center (V.G-C., J.M., S.L., and S.M.L.) further evaluated (1) the potential causal relationships between the ADR and the drugs prescribed before and/or at the time of occurrence; (2) the short-term consequence of the ADR (hospitalization, death, life-threatening situation, disability, permanent damage) and the course of ADR (resolved with no sequelae or with sequelae, ongoing recovery, unresolved, death, unknown); and (3) the preventability of the ADR. Consensus among the committee was used to classify these features.

Assessment of the Causes and Preventability of Serious Adverse Drug Reactions

The pharmacovigilance committee applied the method of Bégaud et al[20-22] for the causality assessment of ADRs. The causal relationship was assessed independently for each drug taken by the patient before the occurrence of the event and was not influenced by possible causal links to other drugs. This method allowed us to identify the drug most likely to be responsible for a serious ADR. During the overall ADR validation process, we evaluated all the risk factors for ADRs; this included a review of all the drugs prescribed at the time of the ADR and an evaluation of potential pharmacokinetic/pharmacodynamic interactions. We also used the 10-item algorithm of Naranjo et al[23] to assess the causal relationship between a drug and a serious ADR. Finally, we selected only ADRs categorized as being at least possible with both the Bégaud and Naranjo methods.

The preventability of ADRs was rated on a 7-item scale[24] that classified ADRs into 4 categories: preventable, potentially preventable, not assessable, and not preventable. The preventability scale is based on criteria of compliance with prescription guidelines, the presence or absence of risk factors for ADRs at the time of prescription, adaptation of the prescription to the conditions of the patient's life and environment, and the inescapable nature of taking the implicated drug. When there was doubt concerning the prescriber's or patient's compliance with treatment guidelines and/or the patient's real need for the prescription, the expert committee rated the preventability as "not assessable." When preventable or potentially preventable were in question, the criteria of preventability were searched: appropriateness of the prescription, medication error from patient, self-medication (ie, self-administration of a medication in the absence of a current prescription and/or without consulting a health care professional).

Statistical Analyses

Baseline characteristics were described for all participants. Data were expressed as the mean ± SD, median [IQR], or number (percentage). The crude incidence rates (95% CI) for all serious ADRs, and by type of ADRs, per 100 person-years were estimated for the overall study population. Quasi-Poisson model deviance tests were used to compare incidence rates according to baseline eGFR (≥30 vs <30 mL/min/1.73 m^2).

We used cause-specific Cox proportional hazard models to report the association between the baseline eGFR and the first-occurring serious ADR after adjustment for patients' baseline characteristics. Data were censored at the date of death or KRT or the date of last follow-up visit, whichever came first (ie, competing events). Variables implemented in models were preselected through literature review, and variables with a $P > 0.1$ in the crude model were excluded from the multivariable analyses. Hazard ratios were adjusted for multiple variables according to the outcome studied. Hazard ratios were adjusted for age at baseline, sex, serum albumin, diabetes, hypertension, history of heart failure, coronary disease, peripheral artery disease, stroke or transient ischemic attack, number of drugs per patient, and adherence to medication. Hazard ratios for serious ADRs (whatever the type) were further adjusted on education level, alcohol misuse, serum albumin, anemia, history of AKI, history of gastrointestinal bleeding, and cirrhosis. Hazard ratios for AKI were further adjusted for anemia, albumin-creatinine or protein-creatinine ratio, and history of cerebrovascular disease. Hazard ratios for drug-induced bleeding were further adjusted for alcohol misuse, history of gastrointestinal bleeding, and cirrhosis. The proportional hazard assumption was checked by testing the Schoenfeld residuals. We used restricted cubic splines in adjusted Cox models to explore the functional form of the relationship between baseline eGFR and the risks of serious ADRs, drug-linked bleeding, and drug-linked AKI (using the rms package in R software[25]). We performed a secondary analysis of first-occurring preventable serious ADRs and first-occurring nonpreventable serious ADRs.

To address missing data, we performed multivariate imputation by chained equations (20 iterations and 40

Table 1. Baseline Characteristics of Study Participants

	Total (N = 3,033)	eGFR, mL/min/1.73 m²			Imputed data (n = 3,033)
		<30 (n = 1,367)	30-45 (n = 1,127)	≥45 (n = 539)	
Age at baseline, y	69 [60-76]	70 [61-78]	69 [62-76]	65 [57-72]	—
Male	65 %	63 %	66 %	70 %	—
High school diploma or higher	35 %	33 %	36 %	42 %	1.7%
Smoking					0.8%
Never smoker	41%	41%	42%	42%	
Current smoker	12%	12%	11%	13%	
Former smoker	47%	47%	47%	45%	
Alcohol consumption	6%	6%	5%	6%	0.2%
Body mass index, kg/m²	28.7 ± 5.85	28.8 ± 5.95	28.8 ± 5.90	28.1 ± 5.44	2.1%
eGFR at baseline, mL/min/1.73 m²	33.0 ± 12.2	22.1 ± 4.92	36.9 ± 4.19	52.3 ± 6.16	—
ACR or PCR					9.1%
A1, normal to mildly increased	28%	16%	35%	44%	
A2, moderately increased	31%	30%	33%	31%	
A3, severely increased	41%	54%	32%	26%	
Anemia	41%	55%	33%	21%	0.8%
Serum albumin, g/L	40.1 ± 4.33	39.7 ± 4.38	40.4 ± 4.34	40.7 ± 4.04	16.1%
Comorbidities					
Diabetes	43%	44%	44%	39%	0.2%
Hypertension	91%	92%	91%	86%	0.2%
Dyslipidemia	74%	74%	74%	70%	0.5%
History of AKI	24%	26%	23%	17%	8.0%
Coronary artery disease	25%	27%	24%	20%	2.1%
Heart failure	13%	15%	13%	8%	0.3%
Peripheral artery disease	17%	18%	17%	14%	2.2%
Cerebrovascular disease	12%	13%	11%	10%	2.5%
History of stroke or TIA	10%	12%	9%	9%	2.5%
GI bleeding	4%	5%	4%	4%	5.8%
Cirrhosis	2%	1%	2%	2%	5.7%
Medications					
Prescriptions at baseline					
Antithrombotic	52%	54%	52%	46%	0.3%
NSAID	1%	1%	1%	2%	0.3%
SSRI	5%	5%	4%	4%	0.3%
PPI	33%	35%	34%	26%	0.3%
Diuretic	55%	62%	52%	42%	0.3%
RAS inhibitor	76%	75%	77%	76%	0.3%
Antibacterial	6%	6%	6%	7%	0.3%
No. of daily drugs	8 [5-10]	8 [6-11]	7 [5-10]	6 [4-9]	0.3%
<5	20%	13%	23%	30%	
5-10	56%	57%	54%	55%	
>10	25%	30%	23%	15%	
Poor adherence to medications	62%	65%	62%	57%	1.0%

Values for continuous variables given as mean ± SD or median [IQR], and for categorical variables as percentage. Abbreviations: AKI, acute kidney injury; ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PCR, protein-creatinine ratio; PPI, proton pump inhibitor; RAS, renin-angiotensin system; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack.

datasets) and included all patient variables used in adjusted models.[26] The data patterns suggested that the "data missing at random" assumption was plausible. In 37% of patients, at least 1 missing data occurred. The proportion of missing data by variable is presented in Table 1. Fitted Cox models were generated for each dataset, and pooled regression coefficients were obtained using Rubin's rules. All statistical analyses were performed with R software.[27]

Results

Baseline Characteristics

Two-thirds of the study participants were men (Table 1). At baseline, the median age was 69 years (IQR, 60-76), and patients were taking a median of 8 medications (IQR, 5-10); hence, the prevalence of polypharmacy (5 or more drugs per day) and hyperpolypharmacy (10 or more drugs

Table 2. Description of Adverse Drug Reactions According to Their Seriousness

	All (N = 1,672)	Adverse Drug Reaction	
		Nonserious (n = 1,184)	Serious (n = 488)
Kidney and urinary disorders	310 (18.5%)	140 (11.8%)	170 (34.8%)
Acute kidney injury[a]	224	64	160
Creatinine serum increased[a]	66	65	1
Aggravated chronic kidney failure[a]	11	4	7
Gastrointestinal disorders	253 (15.1%)	225 (19.0%)	28 (5.7%)
Diarrhea[a]	105	93	12
Gastrointestinal disorder (not specified)[a]	43	42	1
Nausea[a]	29	27	2
Hemorrhages and bleeding	213 (12.7%)	43 (3.6%)	170 (34.8%)
Epistaxis[a]	26	6	20
Hematuria[a]	19	3	16
Rectal bleeding[a]	15	4	11
Musculoskeletal and connective tissue disorders	137 (8.2%)	134 (11.3%)	3 (0.6%)
Muscle spasms[a]	81	81	0
Myalgia[a]	35	35	0
Arthralgia[a]	7	7	0
General disorders and administration site conditions	137 (8.2%)	134 (11.3%)	3 (0.6%)
Peripheral edema[a]	70	70	0
Drug intolerance (not specified)[a]	20	20	0
Fatigue[a]	16	16	0
Metabolism and nutrition disorders	118 (7.1%)	95 (8.0%)	23 (4.7%)
Injury, poisoning and procedural complications	85 (5.1%)	79 (6.7%)	6 (1.2%)
Skin and subcutaneous tissue disorders	78 (4.7%)	61 (5.2%)	17 (3.5%)
Vascular disorders	73 (4.4%)	70 (5.9%)	3 (0.6%)
Nervous system disorders	63 (3.8%)	55 (4.6%)	8 (1.6%)
Respiratory, thoracic and mediastinal disorders	40 (2.4%)	37 (3.1%)	3 (0.6%)
Blood and lymphatic system disorders	32 (1.9%)	13 (1.1%)	19 (3.9%)
Cardiac disorders	26 (1.6%)	16 (1.4%)	10 (2.0%)
Psychiatric disorders	25 (1.5%)	16 (1.4%)	9 (1.8%)
Ear and labyrinth disorders	18 (1.1%)	18 (1.5%)	0 (0%)
Endocrine disorders	17 (1.0%)	12 (1.0%)	5 (1.0%)
Infections and infestations	11 (0.7%)	8 (0.7%)	3 (0.6%)
Immune system disorders	10 (0.6%)	7 (0.6%)	3 (0.6%)
Hepatobiliary disorders	9 (0.5%)	6 (0.5%)	3 (0.6%)
Reproductive system and breast disorders	7 (0.4%)	6 (0.5%)	1 (0.2%)
Investigations	6 (0.4%)	6 (0.5%)	0 (0%)
Eye disorders	4 (0.2%)	3 (0.3%)	1 (0.2%)

[a]Three most frequently reported disorders: 1,184 nonserious adverse drug reactions were reported in 773 patients, and 488 serious adverse drug reactions were reported in 360 patients.

per day) was high (81% and 25%, respectively). Hypertension was very common (91%), as were diabetes (43%) and cardiovascular disease (53%).

Characteristics of Adverse Drug Reactions

Over a median follow-up time of 4.7 (IQR, 3.0-5.1) years, 1,672 ADRs were reported in 973 (32%) of 3,033 participants; 488 ADRs in 360 participants (12%) were classified as serious (Table 2).

When considering nonserious ADRs only (n = 1,184) (Table 2), gastrointestinal disorders (n = 225) were the most frequent, followed by kidney and urinary disorders (n = 140) and then musculoskeletal and connective tissue disorders (n = 134). The incidence rate of nonserious kidney and urinary disorders was significantly higher in patients with a baseline eGFR < 30 mL/min/1.73 m^2 than in patients with an eGFR ≥ 30 mL/min/1.73 m^2 (P = 0.003; Table S2). This difference of incidence rate according to baseline eGFR was not significant for gastrointestinal disorders (P = 0.3).

When considering serious ADRs only (n = 488), kidney and urinary disorders (n = 170) and bleeding events (n = 170) were most frequent and together accounted for 70% of the reactions (Table 2). The incidence rates of serious kidney and urinary disorders and bleeding events were significantly higher in patients with a baseline

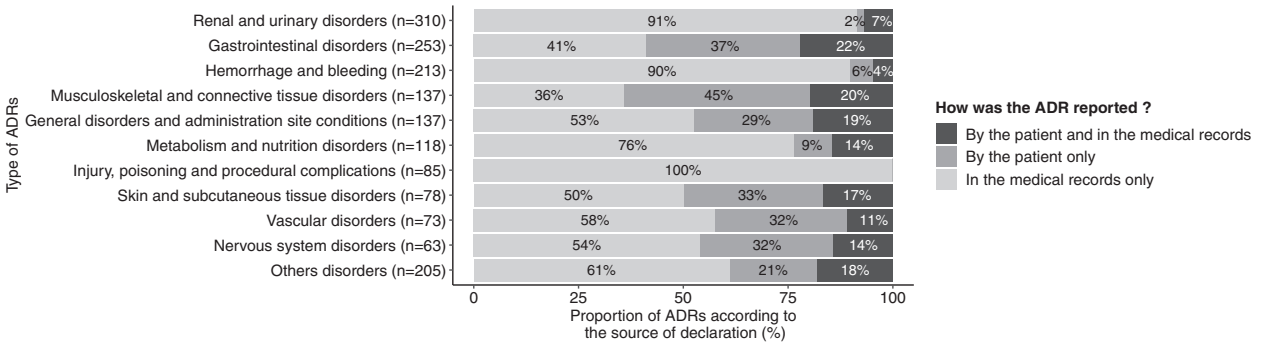

Figure 1. Distribution of source of adverse drug reaction report, by type of ADR (n = 1,672). Abbreviation: ADR, adverse drug reaction.

eGFR < 30 mL/min/1.73 m^2 than in patients with an eGFR ≥ 30 mL/min/1.73 m^2 ($P < 0.001$; Table S3). Of the 145 patients with a serious drug-induced bleeding events, 19 (13%) experienced at least 1 further event of this type during the follow-up period: 15 patients had 2 events, 3 patients had 3 events, and 1 patient had 5 events. Of the 149 patients with a serious drug-linked AKI, 21 (14%) experienced at least 1 further injury of this type during the follow-up period.

Patients reported only one-third of total ADRs. Nonserious ADRs were more frequently reported by patients (44% of nonserious ADRs), especially gastrointestinal, musculoskeletal, and connective tissue disorders, compared with serious ADRs (mainly AKI and bleeding) which were reported by patients in only 8% of cases (Fig 1; Table S4).

Regardless of the seriousness of ADRs, antithrombotic agents (18%) and renin-angiotensin system (RAS) inhibitors (14%) were the main drugs responsible for ADRs (Table 3). A single drug was implicated for 237 of the 488 serious ADRs, and 2 or 3 drugs were implicated for the remaining 251 serious ADRs. Of these 251 serious ADRs, 179 (71%) featured a drug interaction—most of which were additive, synergy-type pharmacodynamic interactions (Table S5). Drug-related AKI and hemorrhages accounted for 90% of the ADRs with interactions. Concomitant use of multiple diuretics, the combination of a diuretic with RAS inhibitors, and the combination of nonsteroidal anti-inflammatory drugs (NSAIDs) with a RAS inhibitor or a diuretic were the main pharmacodynamic interactions noted in drug-related AKI. The concomitant use of 2 antithrombotic agents (ie, an oral anticoagulant and an antiplatelet agent) and the combination of an oral anticoagulant with a selective serotonin reuptake inhibitor (SSRI) were the drug interactions most often noted in bleeding ADRs.

In 224 of the serious ADRs (46%), the implicated drug had been taken by the patient for more than 1 year. In 73 serious ADRs (15%), the patient had been taking the implicated drug for between 31 and 365 days before the reaction. In 20 cases (4%), the drug had been introduced on the same day as the ADR. In 63 cases (13%), the drug had been introduced in the 7 days preceding the ADR. Lastly, in 108 cases (22%), the drug had been introduced between 7 and 30 days previously. In the majority of cases, the treatment was chronic. Acute clinical situations often disturbed the sometimes precarious balance and made the chronic treatment toxic.

Discontinuation (at least temporarily) of the drug responsible for ADRs was the most frequently reported response (68%), followed by dose adjustment (14%) and, lastly, no change (12%). Discontinuation was more frequent (80%) when the ADR was serious.

Short-term Consequences and Preventability of Serious Adverse Drug Reactions

Among 488 serious ADRs, only 21 were not associated with hospitalization but were considered medically significant. Within the 467 serious ADRs associated with hospitalization, the most common short-term consequence of serious ADRs was hospitalization or prolonged hospitalization (n = 365). A number of life-threatening ADRs were reported (n = 22), and 32 ADRs were directly or indirectly linked to the death of 30 patients (2 patients had 2 ADRs that could independently have contributed indirectly to death) (Table S4). Nearly a third of the serious ADRs (and notably 38% of the drug-induced AKIs) occurred during hospitalization (Table 4). After a serious ADR, patients recovered without sequelae in 73% of cases (Table S4).

More than 27% of the serious ADRs were preventable (n = 54) or potentially preventable (n = 78), with the 2 most common reactions being drug-related AKI (n = 48) and bleeding (n = 23). Another 250 were not preventable; but, again, the 2 most common reactions were drug-related AKI (n = 82) and bleeding (n = 107) (Table S6). Preventability differed slightly according to whether the serious ADR was the cause of hospitalization or occurred during the hospital stay. Indeed, 32% of ADRs causing a hospitalization were preventable or potentially preventable, whereas this was the case for only 18% of ADRs that occurred during hospitalization (Table 4).

The most frequent preventability criteria were prescriptions that did not comply with the summary of product characteristics (SPC), such as contraindications

Table 3. Drug Classes and Active Compounds Responsible for Adverse Drug Reactions According to the Latter's Seriousness

			Adverse Drug Reaction	
		Total (N = 1,672)	Nonserious (n = 1,184)	Serious (N = 488)
B01	Antithrombotic agents	302 (18.1%)	125 (10.6%)	177 (36.3%)
	Fluindione[a]	128	36	92
	Warfarin[a]	54	19	35
	Heparin[a]	38	10	28
C09	Agents acting on the renin-angiotensin system	238 (14.2%)	161 (13.6%)	77 (15.8%)
	Ramipril[a]	44	25	19
	Irbesartan[a]	36	20	16
	Candesartan[a]	27	15	12
C03	Diuretics	155 (9.3%)	92 (7.8%)	63 (12.9%)
	Furosemide[a]	95	33	62
	Hydrochlorothiazide[a]	20	14	6
	Spironolactone[a]	18	13	5
C10	Lipid-modifying agents	105 (6.3%)	104 (8.8%)	1 (0.2%)
	Atorvastatin[a]	35	25	10
	Rosuvastatin[a]	24	16	8
	Pravastatin[a]	11	7	4
C08	Calcium channel blockers	96 (5.7%)	94 (7.9%)	2 (0.4%)
	Amlodipine[a]	54	25	29
	Lercanidipine[a]	22	13	9
	Manidipine[a]	10	8	2
J01	Antibacterials for systemic use	78 (4.7%)	51 (4.3%)	27 (5.5%)
	Amoxicillin and β-lactamase inhibitor[a]	15	6	9
	Amoxicillin[a]	12	5	7
	Sulfamethoxazole and trimethoprim[a]	11	8	3
A10	Drugs used in diabetes	68 (4.1%)	57 (4.8%)	11 (2.3%)
	Metformin[a]	21	20	1
	Insulin[a]	11	6	5
	Repaglinide[a]	8	3	5
N02	Analgesics	57 (3.4%)	42 (3.5%)	15 (3.1%)
M04	Antigout preparations	56 (3.3%)	45 (3.8%)	11 (2.3%)
L01	Antineoplastic agents	54 (3.2%)	40 (3.4%)	14 (2.9%)
L04	Immunosuppressants	40 (2.4%)	29 (2.4%)	11 (2.3%)
V08	Contrast media	40 (2.4%)	22 (1.9%)	18 (3.7%)
C07	β-Blocking agents	39 (2.3%)	31 (2.6%)	8 (1.6%)
B03	Antianemic preparation	33 (2.0%)	32 (2.7%)	1 (0.2%)
C02	Antihypertensives	32 (1.9%)	31 (2.6%)	1 (0.2%)
V03	Drugs for treatment of hyperkalemia and hyperphosphatemia	30 (1.8%)	29 (2.4%)	1 (0.2%)
C01	Cardiac therapy	27 (1.6%)	21 (1.8%)	6 (1.2%)
H03	Thyroid therapy	22 (1.3%)	18 (1.5%)	4 (0.8%)
H02	Corticosteroids for systemic use	19 (1.1%)	17 (1.4%)	2 (0.4%)
N03	Antiepileptics	17 (1.0%)	13 (1.1%)	4 (0.8%)
	Other therapeutic classes		130 (11.0%)	34 (7.0%)

[a]Three most frequently reported active ingredients.

(n = 35) and an inappropriately high dose level (n = 28) relative to the patient's level of kidney function (Table S7). The patient was causally involved in 22 preventable cases because of medication errors (n = 14), self-medication (n = 6 of which 4 involved NSAIDs, 1 involved tramadol, and 1 involved colchicine), and self-induced drug intoxication (n = 2).

Kidney Function and Serious Adverse Drug Reactions

The incidence rate of serious ADRs was significantly higher in patients with a baseline eGFR < 30 mL/min/1.73 m^2 than in patients with eGFR ≥ 30 mL/min/1.73 m^2 ($P < 0.001$; Table S8). The incidence rate for serious ADRs associated with antithrombotics (the drugs primarily

Table 4. Preventability of Serious Adverse Drug Reactions Causing or Resulting From Hospitalization (n = 488)

		Did the Serious ADR Cause the Hospital Admission or Occur During the Hospital Stay?		
	Total (N = 488)	Cause of Hospitalization (n = 317)	Occurred During the Stay (n = 150)	NA (n = 21)[a]
Preventable or potentially preventable	132 (27%)	100 (32%)	27 (18%)	5 (24%)
Not preventable	250 (51%)	142 (45%)	95 (63%)	13 (62%)
Not assessable	106 (22%)	75 (24%)	28 (19%)	3 (14%)

Abbreviations: ADR, adverse drug reaction; NA, not applicable.
[a]In 21 cases of serious ADR, management of the ADR did not require hospitalization.

responsible for bleeding events) was significantly higher in patients with eGFR < 30 mL/min/1.73 m^2 than in patients with eGFR ≥ 30 mL/min/1.73 m^2 ($P < 0.001$); the incidence rate of serious ADRs associated with RAS inhibitors did not significantly differ according to the baseline eGFR ($P = 0.4$) (Table S8).

After multiple adjustment and a modeling of the relationship between baseline eGFR and hazard ratio of serious ADR globally and by subtypes (serious bleeding ADR and serious drug-linked AKI) by 4-knot restricted cubic splines regressions, we graphically investigated the shapes of the relationships with a reference value at 45 mL/min/1.73 m^2.

Graphical inspection of the relationship led us to consider a linear relationship between eGFR and hazard ratio of serious ADRs of any type only between 25 and 38 mL/min/1.73 m^2 and not over the whole range of eGFR values (Fig 2). Within this range, each decrease in baseline eGFR of 1 mL/min/1.73 m^2 resulted in a 2.8% increase in the risk of serious ADRs. Beyond this interval, the confidence intervals go in opposite directions, making the trend of the relationship unclear. Risk factors and the associated hazard ratios (both unadjusted and adjusted) are shown in Table S9.

When focusing on the 2 main subtypes of serious ADRs, (1) the risk of serious drug-induced AKI was increased by 2.2% for each decrease of 1 mL/min per 1.73 m^2 in baseline eGFR, with nonsignificant nonlinearity test ($P = 0.8$) indicating a linear relationship (Fig 3); (2) the relationship between hazard ratio of serious bleeding ADR and baseline eGFR was nonlinear (global nonlinearity test, $P = 0.01$). However, Figure 4 led us to estimate a range of eGFR (between 25 and 38 mL/min/1.73 m^2) where a linear relationship could be considered: each decrease of 1 mL/min/1.73 m^2 increased the risk of serious bleeding ADR by 8%. Risk factors and the associated hazard ratios (both unadjusted and adjusted) for both outcomes are shown in Tables S10 and S11.

The results of the secondary analysis according to preventability are given in Tables S12 and S13. The risk factors identified were very similar to those found in the overall analysis of serious ADRs.

Discussion

In a large cohort of well-characterized patients with nondialysis CKD, we used validated measurement tools (including measures of causality and preventability) to adjudicate ADRs and provide a comprehensive, in-depth description of the ADRs that occurred over a 5-year active follow-up period. ADRs and serious ADRs in particular were common (respectively, 32% and 12% of patients were affected). Many serious ADRs were considered preventable, and noncompliance with prescription

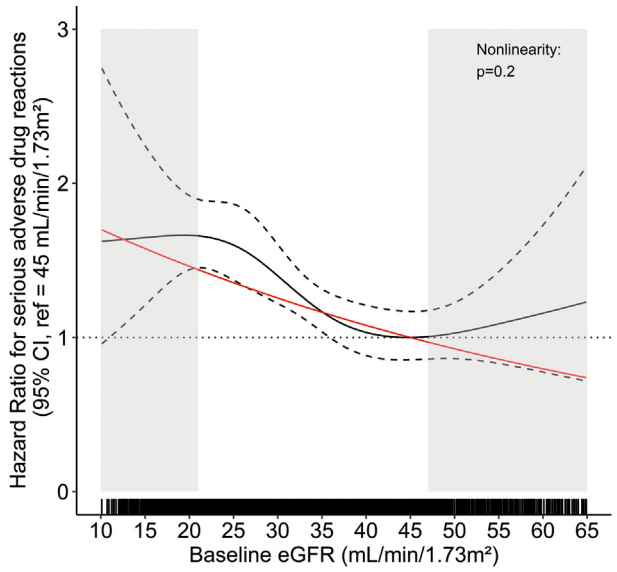

Figure 2. Adjusted hazard ratio for serious adverse drug reactions according to the baseline eGFR (mL/min/1.73 m^2). Reported were 360 first-occurring serious adverse drug reactions. The continuous line represents predictions with restricted cubic splines in Cox models (95% CI). Ticks on the *x*-axis represent the distribution of the baseline eGFR. The shaded areas represent areas where the confidence intervals are too wide to interpret the relationship. Due to nonsignificant nonlinearity test, we add a red curve corresponding to the relationship between hazard ratio and baseline eGFR, when eGFR is considered as a linear continuous variable in the model (ie, no spline applied). Hazard ratios are adjusted for age at baseline, sex, education level, alcohol misuse, serum albumin, anemia, diabetes, hypertension, history of acute kidney injury, history of heart failure, coronary disease, peripheral artery disease, stroke or transient ischemic attack, history of gastrointestinal bleeding, cirrhosis, number of drugs per patient, and adherence to medication. Abbreviation: eGFR, estimated glomerular filtration rate.

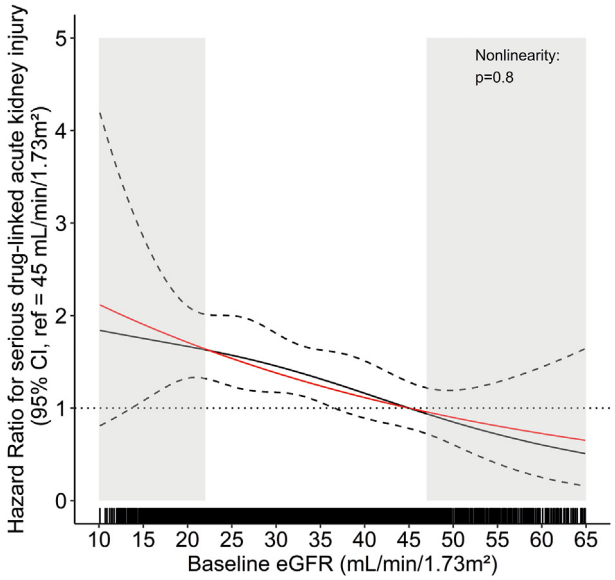

Figure 3. Adjusted hazard ratio for serious drug-linked acute kidney injury events according to the baseline eGFR (mL/min/1.73 m²). Reported were 149 first-occurring serious drug-linked acute kidney injury. The continuous line represents predictions with restricted cubic splines in Cox models (95% CI). Ticks on the *x*-axis represent the distribution of the baseline eGFR. The shaded areas represent areas where the confidence intervals are too wide to interpret the relationship. Due to nonsignificant nonlinearity test, we add a red curve corresponding to the relationship between hazard ratio and baseline eGFR, when eGFR is considered as a linear continuous variable in the model (ie, no spline applied). Hazard ratios are adjusted for age at baseline, sex, albumin-creatinine or protein-creatinine ratio, serum albumin, anemia, diabetes, hypertension, history of heart failure, coronary disease, peripheral artery disease, cerebrovascular disease, stroke or transient ischemic attack, number of drugs per patient, and adherence to medication. Abbreviation: eGFR, estimated glomerular filtration rate.

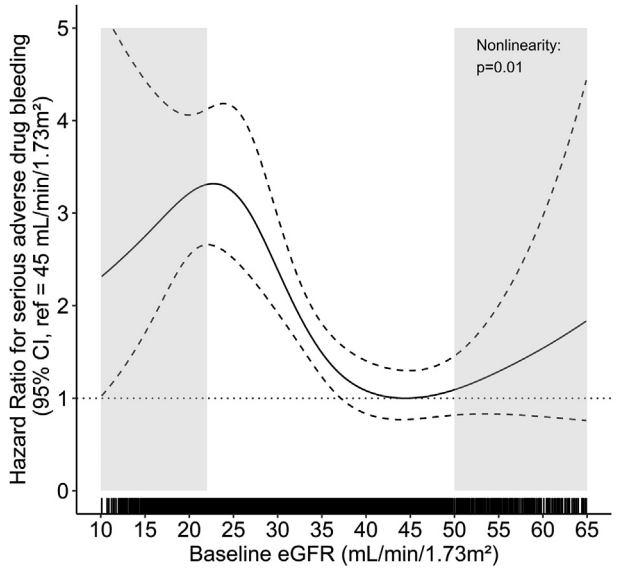

Figure 4. Adjusted hazard ratio for serious adverse drug-linked bleeding events according to the baseline eGFR (mL/min/1.73 m²). Reported were 145 first-occurring serious adverse drug-linked bleeding events. The continuous line represents predictions with restricted cubic splines in Cox models (95% CI). Ticks on the *x*-axis represent the distribution of the baseline eGFR. The shaded areas represent areas where the confidence intervals are too wide to interpret the relationship. Hazard ratios are adjusted for age at baseline, sex, alcohol misuse, serum albumin, diabetes, hypertension, history of heart failure, coronary disease, peripheral artery disease, stroke or transient ischemic attack, history of gastrointestinal bleeding, cirrhosis, number of drugs per patient, and adherence to medication. Abbreviation: eGFR, estimated glomerular filtration rate.

guidelines was the main factor in preventability. The 2 most common serious ADRs were drug-induced AKI and bleeding. A large proportion of serious ADRs required hospitalization, and 11% led to death or were life threatening. In this population of patients with CKD, lower eGFR level was a major risk factor for serious ADRs, especially for serious bleeding ADRs and serious drug-linked AKI after accounting for other risk factors such as age and polypharmacy.

We reported high incidence rates for serious ADRs, mainly driven by AKI and bleeding events. Furthermore, our results showed that ADRs can have major consequences in a CKD population, such as hospitalization, life-threatening events, or death. Even though the majority of serious ADRs were not fatal in the present study, the markedly elevated incidence of serious ADRs in patients with CKD compared with the general population will result in a substantial number of fatal events at the population level. This proportion is also in line with literature reports on ADRs in hospitalized patients whose CKD status was unknown.[28-31] A retrospective US study based on the Mortality Statistics Database found that anticoagulants were the drug most often responsible for ADR-related deaths.[32] In France, a recent prospective study in a sample of public hospitals, collecting causes of hospitalization over 14 days, reported that 8.5% of hospitalizations were linked to an ADR, the most common ADR being bleeding.[33] A large part of reported serious ADRs led to hospitalization in our study. In addition to their impact on patient's health, ADRs are a significant burden on the health care systems. A recent US study showed that hospitalizations linked to antithrombotic ADRs were the most expensive,[34] which is consistent with a French analysis of the economic burden of serious ADRs.[35] However, the true burden of ADRs is difficult to estimate and generalize.

We judged that more than a quarter of the serious ADRs were preventable or potentially preventable. This proportion is in line with other literature, although the methods used to assess preventability differ significantly.[28,33,36-39] In a large meta-analysis, Hodkinson et al[40] found that the highest prevalence rate of preventable ADRs was observed in elder care units, which often involved patients

with high comorbidity and polypharmacy rates in addition to a potential age-associated decline of eGFR; however, the meta-analysis did not consider CKD status. We found that the most frequently encountered preventability criteria were prescriptions that did not comply with the SPC, such as contraindications and an inappropriately high dose level relative to the patient's level of kidney function. A recent study of the preventability of ADRs inducing hospital admission in the general population found that insufficient monitoring and inappropriate dosing were the factors most frequently associated with preventable ADRs.[41] In the present study, self-medication was a preventability criterion in 4.5% of ADRs. In the general population, self-medication is often inappropriate and is associated with drug-related problems.[42-46] Furthermore, self-medication is prevalent among CKD patients,[47] and some specific drugs are particularly harmful for the kidney; these include painkillers, which accounted for most of the preventable serious ADRs linked to self-medication in the present study. Given the elevated risk of ADRs (and especially AKI) in a CKD setting, patient education about non-recommended drugs needs to be improved.

Another important aspect of patient education is the instruction on how to identify the signs and symptoms that herald an ADR. Indeed, we found that only 33% of ADRs were reported by patients and that the majority of patient-reported ADRs were nonserious (eg, muscle cramps and gastrointestinal symptoms). Serious ADRs such as the bleeding associated with antithrombotic agents and drug-induced AKI were only reported by the patient in 10 and 8 cases, respectively. Better education could help patients identify early signs of ADRs, allowing for earlier management. Moreover, patient awareness could increase the ADR notification rate and reduce ADR underreporting.

One of the main findings of our study was that lower eGFR is a major risk factor for serious ADRs in patients with CKD. This association was evident even after adjusting for well-known factors to be linked to the ADR risk in various populations, such as age and polypharmacy.[5,38,48-50] Most of the studies evaluating ADR risk factors have been performed in non-CKD patients in hospitals; some studies found that impaired kidney function was associated with ADRs,[51-53] whereas others failed to find an association.[48,54] To the best of our knowledge, our study is the first to have assessed the relationship between eGFR and ADRs (overall and by subtype) in a large cohort of CKD patients. Indeed, we have also demonstrated inverse associations of eGFR with the 2 main subtypes of serious ADRs (ie, bleeding reactions and AKI). This finding has an important clinical implication: the risk-benefit ratio for antiplatelet agents and anticoagulants must be systematically reassessed when kidney function deteriorates in patients with CKD.

It is well known that patients with CKD present a high risk of bleeding. The main abnormalities concern primary hemostasis and platelet-platelet or platelet–vessel-wall interactions.[55] The use of antithrombotic agents increases this bleeding risk in patients with CKD, especially when 2 antithrombotic agents are prescribed concomitantly.[56] CKD patients are at high risk of toxic drug events due to alterations in pharmacokinetics and pharmacodynamics and even for drugs that are not cleared by the kidneys.[57,58] Although warfarin is metabolized and eliminated by the liver and not directly excreted by the kidney,[59] a recent study indicated that moderate to severe renal impairment was associated with a reduction in the required dose of warfarin.[60] Although, direct oral anticoagulants seem to have a better safety profile, there is a need to improve the benefit-risk ratio of anticoagulants.[61]

Baseline eGFR was inversely and linearly associated with the risk of drug-induced AKI. The majority of these events were related to RAS inhibitors and loop diuretics. RAS inhibitors and diuretics are well-known risk factors for hemodynamically mediated AKI.[62,63] RAS inhibitors lead to AKI by inhibiting efferent arteriolar vasoconstriction and reducing the eGFR, whereas loop diuretics decrease the effective circulating volume through venodilation/diuresis and can cause a decrease in renal blood flow and the GFR.[64,65] In our present study, most of the AKIs associated with RAS inhibitors or diuretics did not have sequelae. Indeed, volume-related AKI has a good prognosis, and a rapid recovery is usually observed after the discontinuation of potentially nephrotoxic drugs and adequate management (volume support).[66] However, evidence suggests that the consequences of AKI (drug-induced or not) are not trivial, especially in relation to the progression of CKD and all-cause mortality.[67]

Regarding the clinical management of RAS inhibitors and because this drug class is strongly indicated for use in many CKD patients (notably for reducing the disease progression), different reports have suggested that these drugs could be reinitiated after an episode of AKI so long as kidney function is closely monitored.[68-70] Many cases of drug-linked AKI were related to acute illness (with volume depletion), which momentarily increased the drug's toxicity. A randomized clinical trial in a population of veterans with stages 3-5 CKD who were taking RAS inhibitors, diuretics, metformin, or NSAIDs did not highlight a significant reduction in AKI episodes or kidney function loss when a sick day protocol was implemented.[71] However, reinforcing patient education on medication management in a sick day protocol (eg, during vomiting and episodes of diarrhea) could prevent some ADRs. Primary care providers such as family physicians and pharmacists should advise CKD patients on drugs that induce volume depletion on these situations.[72]

The main strengths of our study include the comprehensive, standardized, and adjudicated evaluation of a large number of patients with CKD and the generation of data on both serious and nonserious adjudicated ADRs in inpatients and outpatients. Although other studies have provided information on ADRs in patients with CKD, the process used to capture and check data in our study provided additional insights. In particular, the inclusion of several sources of data on ADRs and the review of these

data by expert pharmacologists enhanced the robustness of our findings. Lastly, the quantity and quality of the data collected enabled us to assess many cases reported in hospital discharge reports and medical records, and/or by patients. The long period of active follow-up observation enabled us to better model the relationship between the baseline eGFR and the risk of the most frequently observed serious ADRs.

The study had some limitations. Even though our ADR identification process was rigorous, we may have missed some events—especially out-of-hospital events that might not have been recognized clinically, were not reported by physicians in medical records, were not mentioned by participants to physicians or during study coordinator interviews, or were an ADR was so well known that it tended to be underreported. Underreporting is likely more pertinent to nonserious ADRs, though some hospital-associated ADRs may also have been uncaptured. Finally, given the nature of the CKD-REIN cohort, we cannot extrapolate our results to (1) patients who did not have follow-up visits with a nephrologist and so might have experienced more ADRs, and (2) patients with an eGFR greater than 60 mL/min/1.73 m or less than 15 mL/min/1.73 m^2.

Our results (1) highlight the high burden of serious ADR, (2) show that serious ADRs are a major cause of hospital admission in this population, and (3) emphasize the importance of monitoring kidney function over time when prescribing drugs, especially antithrombotic agents. Greater awareness among clinicians of the heightened risk of ADRs in advanced CKD, more resources directed toward support for patients, and implementation of other pharmaceutical-related risk mitigation strategies should be targeted to improve safety and outcomes in this high-risk population.

Supplementary Material

Supplementary File (PDF)

Table S1: Definitions of variables.

Table S2: The most common types of nonserious ADRs according to eGFR.

Table S3: The most common types of serious ADRs according to eGFR.

Table S4: Course and source of serious ADRs by type and by drug involved.

Table S5: Description of pharmacological interactions in ADR cases.

Table S6: Description of serious ADRs type according to preventability.

Table S7: Preventability criteria for preventable serious ADRs.

Table S8: Incidence rates of ADRs according to seriousness or to the drug class involved.

Table S9: Hazard ratios for first serious ADR.

Table S10: Hazard ratios for first serious drug-linked bleeding.

Table S11: Hazard ratio for serious drug-linked AKI.

Table S12: Hazard ratio for preventable serious adverse drug events.

Table S13: Hazard ratio for not preventable serious adverse drug events.

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contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work—even one in which the author was not directly involved—are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Kidney Function Decline and Serious ADRs in Patients With CKD

Setting & Participants

CKD-REIN:
Prospective cohort study conducted in 40 outpatient nephrology centers in France

N = 3,033 patients with moderate to advanced CKD

July 2013-March 2016

Analysis

Adverse Drug Reactions (ADRs) prospectively identified from:
- Hospital discharge reports
- Medical records
- Patient interviews

Pharmacologists used validated tools to adjudicate ADRs

Restricted cubic splines in fully adjusted Cox proportional hazard models

Results

Median follow-up: 4.7 years

488 serious ADRs
- 35% (N = 170) kidney and urinary disorders
- 35% (N = 170) hemorrhages
- 96% (N = 467) associated with hospitalizations
- 27% (N = 132) preventable/potentially preventable

Main drugs responsible for ADRs:
- Antithrombotics (18%)
- RAS inhibitors (14%)

eGFR is a major risk factor for serious ADRs
For each 1 mL/min/1.73 m^2 lower baseline eGFR:
- Risk of AKI was 2.2% higher
- Risk of bleeding ADRs were 8% higher

CONCLUSION: ADRs constitute a major cause of hospitalization in CKD patients for whom lower eGFR level is a major risk factor.

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