

Adverse Drug Reactions in Patients with Chronic Kidney Disease

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Clinical Journal of the American Society of Nephrology

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Supplementary Oaterial 2: Baseline characteristics of participants in the Chronic Kidney Disease-Renal Epidemiology and Information Network (before imputation)

	All (n=3033)	Baseline eGFR in mL/min per 1.73m ²		p-value
		≥30 (n=1670)	<30 (n=1363)	
Age (years)	69 [60 - 76]	68 [59 - 75]	70 [61 - 78]	0.001
<60 years	24%	25%	22%	
60 to 75 years	46%	48%	44%	
≥ 75 years	30%	27%	35%	
Men	65%	67%	63%	0.02
High school diploma or higher	36%	38%	32%	0.001
Missing	2%	2%	1%	
BMI	28 [25 - 32]	28 [25 - 32]	28 [25 - 32]	0.30
≥ 30 kg/m ²	35%	33%	36%	
Missing	2%	2%	2%	
Serum Albumin	4.0 [3.8 - 4.3]	4.1 [3.8 - 4.3]	4.0 [3.7 - 4.3]	<0.001
<3.5 g/dL	8%	6%	9%	
Missing	19%	21%	17%	
UACR				<0.001
< 30 mg/g	5%	33%	14%	
30 - 300 mg/g	28%	29%	27%	
> 300 mg/g	36%	27%	48%	
Missing	11%	11%	11%	
Anemia*	40%	29%	55%	<0.001
Missing	1%	1%	1%	
Smoking status				0.21
Smoker	12%	12%	12%	
Nonsmoker	41%	42%	40%	
Ex-smoker	46%	46%	47%	
Missing	1%	0.5%	1%	
Diabetes	43%	42%	44%	0.43
Missing	0.2%	0.2%	0.3%	
AKI history	22%	20%	24%	0.001
Missing	8%	7%	9%	
Cardiovascular history	53%	51%	55%	0.06
Missing	1%	1%	1%	
Hypertension	91%	89%	92%	0.02
Missing	0.2%	0.3%	0.2%	
Dyslipidemia	73%	73%	74%	0.35
Missing	0.5%	1%	0.3%	
Number of drugs	8 [5 - 10]	7 [5 - 10]	8 [6 - 11]	<0.001
< 5 drugs	19%	24%	13%	
5 to 10 drugs	56%	54%	57%	
> 10 drugs	24%	21%	30%	
Missing	1%	1%	0.2%	
Poor adherence to medications	1129 (37%)	649 (39%)	480 (35%)	0.02
Missing	31 (1%)	22 (1%)	9 (1%)	

AKI: Acute kidney injury, BMI: Body mass index, eGFR: estimated glomerular filtration rate using CKD-EPI equation, 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.

Supplementary Material 3: Details of types of adverse drug reactions

Type of ADR	Frequency (n=751)
Renal and urinary disorders	150 (20%)
Acute kidney injury	102
Blood creatinine increased	40
Renal impairment	4
Chronic kidney disease	1
Renal tubular necrosis	1
Nephroangiosclerosis	1
Urinary retention	1
Gastrointestinal disorders	119 (16%)
Diarrhea	57
Gastrointestinal disorder	24
Constipation	10
Nausea	10
Vomiting	7
Abdominal pain	2
Gingival hypertrophy	2
Discolored feces	1
Colitis	1
Abdominal pain upper	1
Lip edema	1
Pancreatitis	1
Pancreatitis acute	1
Aphthous ulcer	1
Musculoskeletal and connective tissue disorders	68 (9%)
Muscle spasms	35
Myalgia	22
Arthralgia	4
Tendinous discomfort	2
Tendon pain	1
Pain in extremity	1
Muscular weakness	1
Rheumatoid arthritis	1
Periarthritis	1
Bleeding	67 (9%)
Epistaxis	11
Muscle hemorrhage	6
Hematuria	5
Hemorrhagic shock	4
Gastrointestinal hemorrhage	4
Hematoma	3
Subcutaneous hematoma	3
Peritoneal hemorrhage	3
Ecchymosis	2
Hemarthrosis	2
Cerebral hematoma	2
Subdural haematoma	2
Hemoptysis	2
Rectal hemorrhage	2
Gingival bleeding	2
Implant site hematoma	1
Injection site hematoma	1
Abdominal wall hematoma	1
Pulmonary alveolar hemorrhage	1

Incision site hemorrhage	1
Arteriovenous fistula site hemorrhage	1
Conjunctival hemorrhage	1
Eye hemorrhage	1
Adrenal hemorrhage	1
Brain stem hemorrhage	1
Wound hemorrhage	1
Upper gastrointestinal hemorrhage	1
Melena	1
Hemorrhagic esophagitis	1
General disorders and administration site conditions	58 (8%)
Edema, peripheral	30
Drug intolerance	8
Malaise	6
Fatigue	5
Asthenia	4
Injection site pain	1
General physical health deterioration	1
Vessel puncture site hematoma	1
Drug ineffective	1
Edema	1
Metabolism and nutrition disorders	44 (6%)
Hypoglycemia	11
Hyperkalemia	10
Gout	6
Hypercalcemia	5
Decreased appetite	2
Hypokalemia	2
Polydipsia	2
Metabolic acidosis	1
Weight loss poor	1
Diabetes mellitus inadequate control	1
Dehydration	1
Hypernatremia	1
Hypocalcemia	1
Vascular disorders	40 (5%)
Hypotension	21
Orthostatic hypotension	13
Hot flush	4
Flushing	1
Hypertension	1
Nervous system disorders	36 (5%)
Somnolence	9
Headache	5
Dizziness	5
Paraesthesia	3
Neuropathy peripheral	2
Cholinergic syndrome	2
Depressed level of consciousness	1
Encephalopathy	1
Toxic encephalopathy	1
Hyperreflexia	1
Burning sensation	1
Neurological symptom	1
Anticholinergic syndrome	1
Tremor	1
Nervous system disorder	1
Status epilepticus	1

Injury, poisoning and procedural complications	35 (5%)
Overdose	33
International normalized ratio increased	1
Prothrombin time shortened	1
Skin and subcutaneous tissue disorders	34 (5%)
Rash	6
Pruritus	4
Dermatitis allergic	3
Urticaria	3
Toxic skin eruption	3
Angioedema	2
Eczema	2
Skin reaction	2
Skin atrophy	1
Dermatitis bullous	1
Swelling face	1
Hyperhidrosis	1
Pemphigoid	1
Pruritus allergic	1
Photosensitivity reaction	1
Red man syndrome	1
Skin ulcer	1
Respiratory, thoracic and mediastinal disorders	21 (3%)
Cough	14
Throat irritation	2
Interstitial lung disease	2
Dyspnea	1
Nasal discomfort	1
Lung disorder	1
Blood and lymphatic system disorders	14 (2%)
Thrombocytopenia	4
Anemia	3
Eosinophilia	2
Agranulocytosis	1
Febrile bone marrow aplasia	1
Bicytopenia	1
Febrile neutropenia	1
Polycythemia	1
Cardiac disorders	10 (1%)
Bradycardia	9
Tachycardia	1
Ear and labyrinth disorders	10 (1%)
Vertigo	9
Tinnitus	1
Endocrine disorders	10 (1%)
Hyperthyroidism	4
Hypothyroidism	4
Adrenal insufficiency	1
Blood thyroid stimulating hormone decreased	1
Psychiatric disorders	9 (1%)
Confusional state	4
Insomnia	3
Abnormal behaviour	1
Loss of libido	1
Investigations	7 (1%)
Creatinine renal clearance decreased	1
Blood creatine phosphokinase increased	1
Gamma-glutamyltransferase increased	1

Electrocardiogram QT prolonged	1
Lipase increased	1
Hormone level abnormal	1
Urine output increased	1
Immune system disorders	5 (1%)
Hypersensitivity	2
Anaphylactic reaction	2
Anaphylactic shock	1
Hepatobiliary disorders	5 (1%)
Hepatocellular injury	3
Cholestasis	1
Drug-induced liver injury	1
Infections and infestations	4 (1%)
Chorioretinitis	1
Upper respiratory tract infection	1
Oral fungal infection	1
Rash pustular	1
Eye disorders	3 (1%)
Eye allergy	1
Visual acuity decreased	1
Retinal toxicity	1
Reproductive system and breast disorders	2 (0.3%)
Priapism	1
Retrograde ejaculation	1

Results are expressed as n (%).

Supplementary Material 4: Descriptions of adverse drug reactions according to the last estimated glomerular filtration rate reported before the reaction.

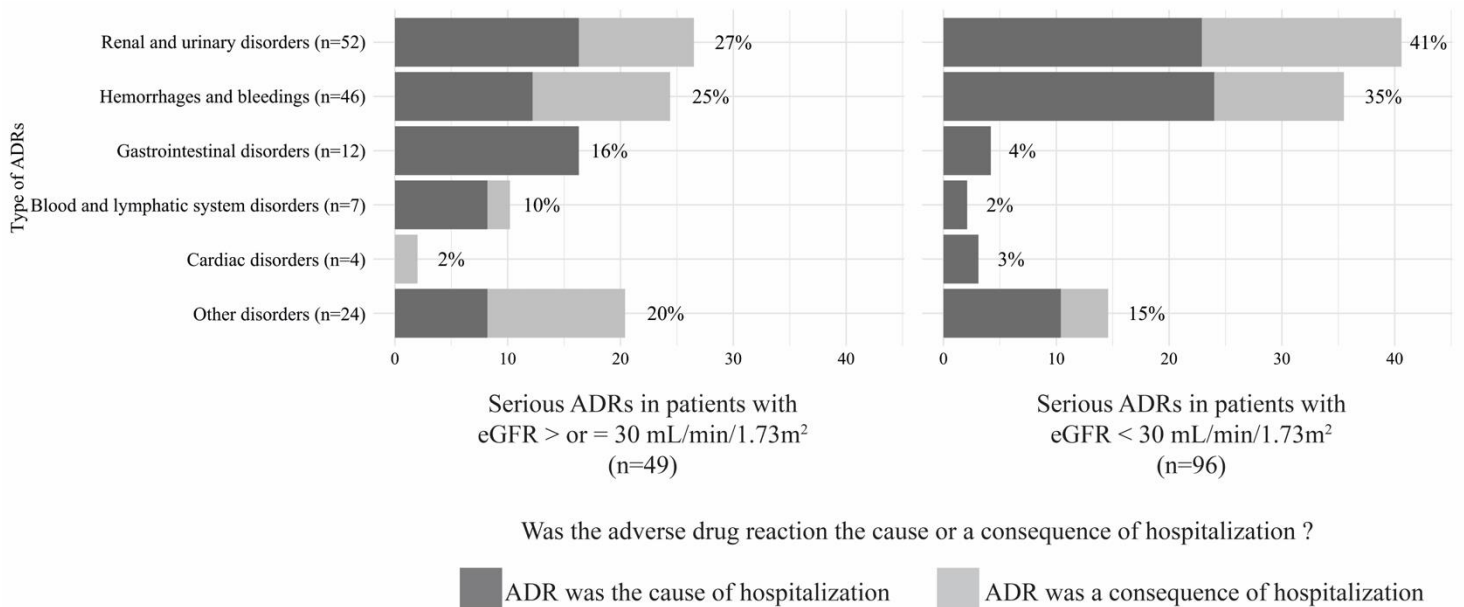
Type of ADRs	Last eGFR before ADR in mL/min/1.73m ²		
	All ADRs (n=751)	ADRs in patients with eGFR ≥30 (n=314)	ADRs in patients with eGFR <30 (n= 437)
Renal and urinary disorders	150 (20%)	51 (16%)	99 (23%)
<i>Acute kidney injury</i>	102	32	70
<i>Increased serum creatinine</i>	40	16	24
<i>Other type of renal and urinary disorders</i>	8	3	5
Gastrointestinal disorders	119 (16%)	61 (19%)	58 (13%)
<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 (11%)	34 (8%)
<i>Contractures</i>	35	20	15
<i>Muscle pain</i>	22	10	12
<i>Other type of musculoskeletal and connective tissue disorders</i>	11	4	7
Hemorrhages and bleeding	67 (9%)	20 (6%)	47 (11%)
<i>Hemorrhages</i>	34	9	25
<i>Hematoma</i>	19	8	11
<i>Other type of hemorrhages and bleeding</i>	14	3	11
General disorders and administration site conditions	58 (8%)	24 (8%)	34 (8%)
<i>Peripheral edema</i>	30	12	18
<i>Drug intolerance</i>	8	3	5
<i>Other type of general disorders and administration site conditions</i>	20	9	11
Other type of ADRs	289 (38%)	124 (40%)	165 (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 ≥ 30 respectively.

P-value=0.015 tests the difference in the distribution of ADR type according to patient eGFR at ADR occurrence. The median time between the GFR estimate and the ADR was 36 (interquartile range, 11-97) days.

Supplementary Material 5: Distribution of serious adverse drug reactions causing or resulting from hospitalization according to the last estimated glomerular filtration rate reported before the reaction (n=145).



Renal and urinary disorders were mostly acute kidney injuries or increased serum creatinine. Diarrhea was the most common gastrointestinal disorder. Blood and lymphatic system disorders consist of anemia, febrile neutropenia, thrombocytopenia, agranulocytosis, febrile aplasia, and bicytopenia. Cardiac disorders were bradycardia. Other disorders are described in the supplementary material 3.

The median time between the GFR estimate and the ADR was 36 (interquartile range, 11-97) days.

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

Supplementary Material 6: Details of imputed drugs responsible for adverse drug reactions and of type of adverse drug reaction for the 5 pharmacological classes most frequently imputed.

ATC	Pharmacological classes	Frequency (n=751)	Serious (n=150)	Preventability for serious ADR		
				Preventable*	Inevitable	Not assessable
C09	Agents acting on the renin-angiotensin system	115 (15.3%)	18	7	2	9
	Acute kidney injury	25	15	6	2	7
	Blood creatinine increased	19	0			
	Hypotension	12	0			
	Cough	12	0			
	Diarrhea	9	0			
	Other	38	3	2	0	1
B01	Antithrombotic agents	107 (14.2%)	51	13	19	19
	Overdose/INR increased/ Prothrombin time shortened	31	2	2	0	0
	Epistaxis	11	6	0	4	2
	Muscle hemorrhage	6	5	2	1	2
	Hematuria	4	3	0	1	2
	Gastrointestinal hemorrhage	4	4	1	0	3
	Other	53	31	8	13	10
C03	Diuretics	77 (10.3%)	18	6	6	6
	Acute kidney injury	40	18	6	6	6
	Blood creatinine increased	11	0			
	Gout	5	0			
	Hyperkalemia	4	0			
	Hypotension	3	0			
	Other	14	0			
C10	Lipid modifying agents	50 (6.7%)	0	0	0	0
	Muscle spasms	27	0			
	Myalgia	16	0			
	Other	7	0			
C08	Calcium channel blockers	45 (6.0%)	0	0	0	0
	Edema peripheral	26	0			
	Orthostatic hypotension	4	0			
	Other	15	0			
J01	Antibacterials for systemic use	36 (4.8%)	11	4	6	1
A10	Drugs used in diabetes	31 (4.1%)	2	2	0	0
N02	Analgesics	29 (3.9%)	6	2	3	1
L04	Immunosuppressants	27 (3.6%)	6	1	1	4
M04	Antigout preparations	26 (3.5%)	3	2	1	0
L01	Antineoplastic agents	22 (2.9%)	5	0	5	0
V08	Contrast media	21 (2.8%)	9	1	6	2
B03	Antianemic preparations	20 (2.7%)	0	0	0	0
C07	Beta blocking agents	15 (2.0%)	4	1	2	1
C02	Antihypertensives	14 (1.9%)	1	1	0	0
A12	Mineral supplements	12 (1.6%)	1	1	0	0
C01	Cardiac therapy	11 (1.5%)	1	0	1	0
H03	Thyroid therapy	8 (1.1%)	2	1	1	0
N03	Antiepileptics	8 (1.1%)	0	0	0	0
V03	All other therapeutic products	8 (1.1%)	0	0	0	0
H02	Corticosteroids for systemic use	7 (0.9%)	1	1	0	0
M01	Antiinflammatory and antirheumatic products	7 (0.9%)	1	1	0	0
J04	Antimycobacterials	6 (0.8%)	0	0	0	0
M05	Drugs for treatment of bone diseases	5 (0.7%)	2	0	1	1
G04	Urologicals	4 (0.5%)	1	0	0	1
N06	Psychoanaleptics	4 (0.5%)	1	1	0	0

N07	Other nervous system drugs	4 (0.5%)	0	0	0	0
H01	Pituitary and hypothalamic hormones and analogues	3 (0.4%)	1	0	1	0
H05	Calcium homeostasis	2 (0.3%)	0	0	0	0
J05	Antivirals for systemic use	2 (0.3%)	0	0	0	0
J06	Immune sera and immunoglobulins	2 (0.3%)	0	0	0	0
L02	Endocrine therapy	2 (0.3%)	0	0	0	0
N05	Psycholeptics	2 (0.3%)	0	0	0	0
P01	Antiprotozoals	2 (0.3%)	0	0	0	0
R03	Drugs for obstructive airway diseases	2 (0.3%)	0	0	0	0
NO CODE	No code	2 (0.3%)	0	0	0	0
A01	Stomatological preparations	1 (0.1%)	0	0	0	0
A02	Drugs for acid related disorders	1 (0.1%)	1	1	0	0
A03	Drugs for functional gastrointestinal disorders	1 (0.1%)	1	1	0	0
A07	Antidiarrheals, intestinal antiinflammatory/antiinfective agents	1 (0.1%)	0	0	0	0
A11	Vitamins	1 (0.1%)	0	0	0	0
D06	Antibiotics and chemotherapeutics for dermatological use	1 (0.1%)	0	0	0	0
D07	Corticosteroids, dermatological preparations	1 (0.1%)	0	0	0	0
G03	Sex hormones and modulators of the genital system	1 (0.1%)	0	0	0	0
M02	Topical products for joint and muscular pain	1 (0.1%)	1	0	0	1
M03	Muscle relaxants	1 (0.1%)	1	0	1	0
N01	Anesthetics	1 (0.1%)	1	0	0	1
N04	Anti-Parkinson drugs	1 (0.1%)	0	0	0	0
R06	Antihistamines for systemic use	1 (0.1%)	0	0	0	0

ADR: adverse drug reaction, ATC: Anatomical Therapeutic and Chemical

Results are expressed as n (%).

* Either definitely preventable or potentially preventable

Supplementary Material 7: Sensitivity analyses by the Prentice, Williams, and Peterson (PWP) gap-time recurrent event time-to-event analysis

A. Hazard ratios for adverse drug reactions (overall) according to patient characteristics

	Unadjusted model		Adjusted model		
	HR	[95% CI]	P-value	HR [95% CI]	P-value
Age (years)			0.494		0.15
<60	Reference			Reference	
60 to 75	1.11	[0.92; 1.35]		0.95	[0.77; 1.15]
≥ 75	1.04	[0.83; 1.29]		0.81	[0.65; 1.02]
Sex			0.05		0.02
Men	Reference			Reference	
Women	1.16	[0.99; 1.35]		1.20	[1.02; 1.40]
eGFR			<0.001		<0.001
≥ 30 mL/min per 1.73m ²	Reference			Reference	
<30 mL/min per 1.73m ²	1.59	[1.36; 1.85]		1.47	[1.26; 1.72]
Serum Albumin			0.05		0.29
≥3.5 g/dL	Reference			Reference	
<3.5 g/dL	1.29	[1.01; 1.67]		1.15	[0.89; 1.49]
UACR			0.04		0.59
< 30 mg/g	Reference			Reference	
30 – 300 mg/g	1.01	[0.81; 1.24]		0.90	[0.73; 1.12]
> 300 mg/g	1.23	[1.01; 1.50]		0.99	[0.81; 1.21]
Anemia*			<0.001		0.14
Without anemia	Reference			Reference	
With anemia	1.34	[1.15; 1.55]		1.12	[0.96; 1.31]
Diabetes			<0.001		0.35
Without diabetes	Reference			Reference	
With diabetes	1.32	[1.14; 1.52]		1.08	[0.92; 1.27]
AKI history			<0.001		0.01
Without AKI history	Reference			Reference	
With AKI history	1.35	[1.14; 1.61]		1.25	[1.05; 1.49]
Cardiovascular history			<0.001		0.01
Without cardiovascular history	Reference			Reference	
With cardiovascular history	1.39	[1.20; 1.61]		1.25	[1.06; 1.48]
Hypertension			0.01		0.30
Without hypertension	Reference			Reference	

With hypertension	1.43 [1.08; 1.90]	1.18 [0.86; 1.61]
Baseline number of drugs/ patients	<0.001	0.01
< 5	Reference	Reference
5 to10	1.65 [1.26; 2.15]	1.35 [1.04; 1.76]
> 10	2.32 [1.75; 3.07]	1.60 [1.19; 2.17]
Adherence to medication	<0.001	0.01
Good	Reference	Reference
Poor	1.40 [1.19; 1.65]	1.26 [1.06; 1.48]

AKI: Acute kidney injury, CI: confidence interval, eGFR: estimated Glomerular filtration rate, HR: hazard ratio, UACR: Urine albumin to creatinine ratio

*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.

B. Hazard ratios for serious adverse drug reactions according to patient characteristics

	Unadjusted model		Adjusted model		
	HR	[95% CI]	P-value	HR [95% CI]	P-value
Age (years)			0.33		0.33
<60	Reference			Reference	
60 to 75	0.98	[0.63; 1.52]		0.71	[0.45; 1.11]
≥ 75	1.27	[0.81; 1.98]		0.78	[0.49; 1.25]
Sex			0.92		0.63
Men	Reference			Reference	
Women	1.02	[0.72; 1.43]		1.09	[0.77; 1.54]
eGFR			<0.001		0.01
≥ 30 mL/min per 1.73m ²	Reference			Reference	
<30 mL/min per 1.73m ²	2.08	[1.47; 2.94]		1.73	[1.22; 2.44]
Anemia*			<0.001		0.04
Without anemia	Reference			Reference	
With anemia	1.83	[1.33; 2.53]		1.42	[1.01; 1.99]
Diabetes			0.04		0.88
Without diabetes	Reference			Reference	
With diabetes	1.40	[1.01; 1.94]		1.03	[0.73; 1.45]
AKI history			0.01		0.12
Without AKI history	Reference			Reference	
With AKI history	1.60	[1.11; 2.30]		1.34	[0.92; 1.95]
Cardiovascular history			<0.001		0.001
Without cardiovascular history	Reference			Reference	
With cardiovascular history	2.30	[1.56; 3.38]		1.94	[1.29; 2.90]
Baseline number of drugs/ patients			<0.001		0.06
< 5	Reference			Reference	
5 to 10	2.07	[1.06; 4.06]		1.47	[0.77; 2.81]
> 10	3.90	[1.97; 7.73]		2.11	[1.04; 4.25]
Adherence to medication			0.02		0.12
Good	Reference			Reference	
Poor	1.64	[1.09; 2.46]		1.35	[0.92; 1.97]

AKI: Acute kidney injury, CI: Confidence interval, eGFR: estimated Glomerular filtration rate, HR: hazard ratio
 *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.