Adverse Drug Reactions in Patients with Chronic Kidney Disease

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Supplemental Material Table of Contents

Supplementary Material 1: Algorithms to assess causation and preventability

A. Bégaud imputability method[1]

Table a - Decision table for the chronological criteria (C)

CHALLENGE:	Event onset						
	Very suggestive			Compatible			Incompatible
DECHALLENGE (DISCONTINUE)	Rechallenge (R)						
	$R_{(+)}$	$R_{(0)}$	$R_{(-)}$	$R_{(+)}$	$R_{(0)}$	$R_{(-)}$	
Suggestive: Regression appears linked to drug discontinuation	C_3	C_3	C_1	C_3	C_2	C_1	C_0
Inconclusive: Regression seems spontaneous or induced by nonspecific treatment known to be effective, or course unknown or follow up too brief or lesions irreversible (or drug not discontinued)	C_3	C_2	C_1	C_3	C_1	C_1	C_0
Not suggestive: No regression of reversible event (or complete regression without drug withdrawal)	C_1	C_1	C_1	C_1	C_1	C_1	C_0

$R_{(+)}$: positive, the event recurs; $R_{(0)}$: no rechallenge or lack of information; $R_{(-)}$: negative, the event does not recur.
C_3: suggestive chronology; C_2: possible chronology; C_1: dubious chronology; C_0: incompatible chronology.

Table b - Decision table for the semiological criteria (S)

SEMIOLOGY (clinical or extraclinical):	Suggestive of the drug studied (and/or very favorable factor)			Other cases		
ALTERNATE NON-DRUG RELATED EXPLANATION	RELIABLE AND SPECIFIC LABORATORY TEST (L)					
	$L_{(+)}$	$L_{(0)}$	$L_{(-)}$	$L_{(+)}$	$L_{(0)}$	$L_{(-)}$
None (after an appropriate search)	S_3	S_3	S_1	S_3	S_2	S_1
Possible or present	S_3	S_2	S_1	S_3	S_1	S_1

$L_{(+)}$: positive laboratory test; $L_{(0)}$: no such test for the event-drug pair under consideration; $L_{(-)}$: negative laboratory test (if it is sensitive enough).
S_3: suggestive semiology; S_2: possible semiology; S_1: dubious semiology.

Table c - Intrinsic imputability decision table

This is obtained from the score of the chronological (C - *Table a.*) and semiological (S – *Table b.*) imputabilities.

Chronology	Semiology		
	S_1	S_2	S_3
C_0	I_0	I_0	I_0
C_1	I_1	I_1	I_2
C_2	I_1	I_2	I_3
C_3	I_3	I_3	I_4

The drug-effect relation can be: I4: very likely; I3: likely; I2: possible; I1: dubious; I0: unlikely (appears excluded).

B. Naranjo's adverse drug reaction probability scale[2]

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score				
	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

Score intervals	*Label*
≥ 9	Definite reaction
5 to 8	Probable reaction
1 to 4	Possible reaction
0	Doubtful reaction

C. Olivier adverse drug reaction (ADR) preventability scale[3]

THE DRUG	Score
A- Adherence with recommendations	
a. Neither adherence with recommendations nor lack of precaution played any role in ADR occurrence	+3
b. Not assessable	0
c. The prescriber or the patient ignored relevant recommendations	-5
THE PATIENT	
B- Other risk factors identified in the patients	
a. Present, easy to detect	-3
b. Present, difficult to detect	-1
c. Absent	+2
d. Not assessable	0
C- Adaptation of the prescription to the patient's living conditions or environment	
a. Correct	+1
b. Not assessable	0
c. Inadequate	-1
THE PRESCRIPTION	
D- This medication (prescribed or not) is probably essential for the patient	
a. Yes	+2
b. Not assessable	0
c. No	-4
TOTAL	

Score intervals	Label
-13 to -8	Preventable ADR
-7 to -3	Potentially preventable ADR
-2 to +2	Not assessable
+3 to +8	Not preventable

1. Bégaud B, Evreux JC, Jouglard J, Lagier G: Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. Therapie 40: 111–118, 1985

2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ: A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics [Internet] 30: 239–245, 1981 Available from: http://ascpt.onlinelibrary.wiley.com/doi/abs/10.1038/clpt.1981.154 [cited 2018 Sep 26]

3. Olivier P, Caron J, Haramburu F, Imbs J-L, Jonville-Béra A-P, Lagier G, Sgro C, Vial T, Montastruc J-L, Lapeyre-Mestre M: Validation d'une échelle de mesure : exemple de l'échelle française d'évitabilité des effets indésirables médicamenteux. Thérapie [Internet] 60: 39–45, 2005 Available from: http://www.sciencedirect.com/science/article/pii/S0040595716302669 [cited 2018 Sep 26]

Supplementary Material 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 1.73m² ≥30 (n=1670)	<30 (n=1363)	p-value
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/m²	*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

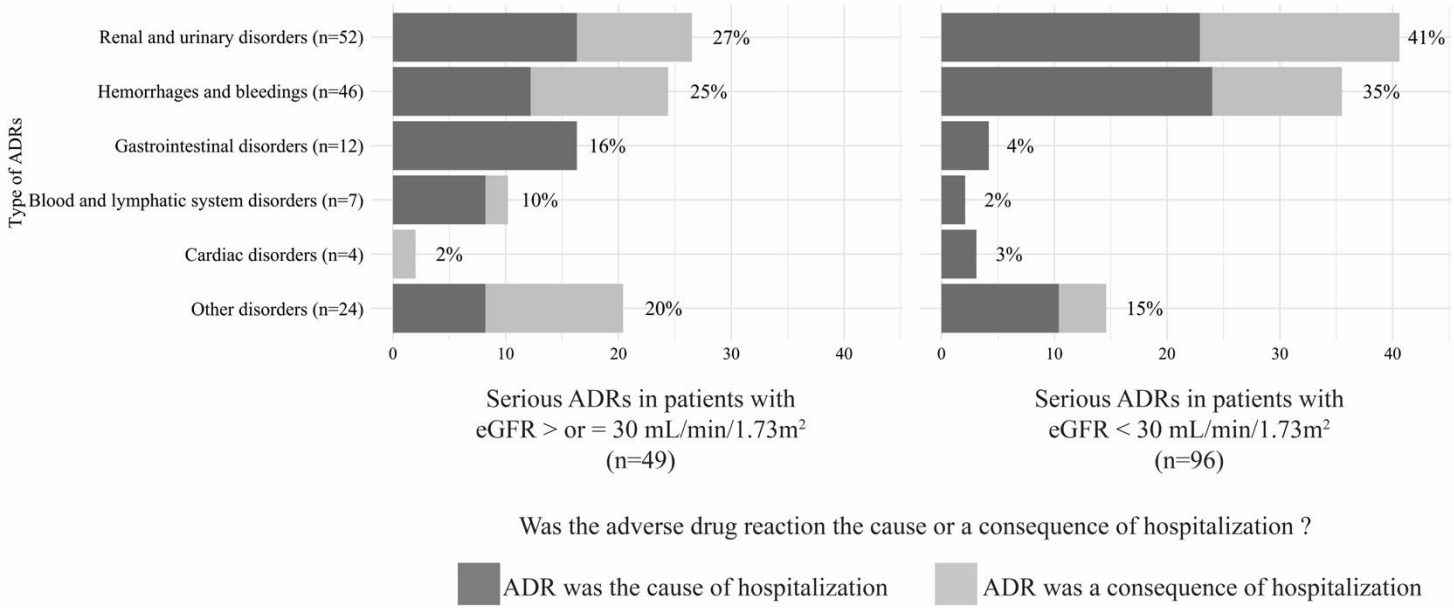
Results are expressed as n (%).

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

Type of ADRs	All ADRs (n=751)	Last eGFR before ADR in mL/min/1.73m²	
		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%)
Acute kidney injury	*102*	*32*	*70*
Increased serum creatinine	*40*	*16*	*24*
Other type of renal and urinary disorders	*8*	*3*	*5*
Gastrointestinal disorders	119 (16%)	61 (19%)	58 (13%)
Diarrhea	*57*	*35*	*22*
Gastrointestinal conditions	*24*	*8*	*16*
Other type of gastrointestinal disorders	*38*	*18*	*20*
Musculoskeletal and connective tissue disorders	68 (9%)	34 (11%)	34 (8%)
Contractures	*35*	*20*	*15*
Muscle pain	*22*	*10*	*12*
Other type of musculoskeletal and connective tissue disorders	*11*	*4*	*7*
Hemorrhages and bleeding	67 (9%)	20 (6%)	47 (11%)
Hemorrhages	*34*	*9*	*25*
Hematoma	*19*	*8*	*11*
Other type of hemorrhages and bleeding	*14*	*3*	*11*
General disorders and administration site conditions	58 (8%)	24 (8%)	34 (8%)
Peripheral edema	*30*	*12*	*18*
Drug intolerance	*8*	*3*	*5*
Other type of general disorders and administration site conditions	*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/1.73m^2.

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 1.73m²	Reference		Reference	
<30 mL/min per 1.73m²	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 1.73m²	Reference		Reference	
<30 mL/min per 1.73m²	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 to10	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.