

Table 1 – Total number of reported drugs with either renal dose adjustment recommendation or contraindication, and number of exposed participants with eGFR below threshold for each drug at baseline

WHO- ATC classification	Overall N=8701 N (%)	Recommendation for renal dose adjustment		Renal contraindication	
			N*		N*
Alimentary tract and metabolism	3488 (40.1)				
Antiacids and other drugs for acid-related disorders	319 (3.7)	No		Yes †	-
H2-receptor antagonists	117 (1.3)	Yes †§	11	No	
Propulsives	171 (2.0)	Yes †	-	No	
Intestinal antiinflammatory agents	24 (0.3)	No		Yes †	-
Biguanides (metformin)	209 (2.4)	No		Yes †	32
Sulfonamides, urea derivatives	398 (4.6)	No		Yes †	1
Alpha glucosidase inhibitors	75 (0.9)	No		Yes †	-
Blood and blood-forming organs	1960 (22.5)				
Vitamin K antagonists and Heparin group	332 (3.8)	No		Yes †	1
Cardiovascular system	6727 (77.3)				
Digitalis glycosides	205 (2.4)	Yes †	45	No	
Antiarrhythmics, class Ia and Ic	283 (3.3)	Yes †	20	No	
Antiadrenergic agents, centrally acting	241 (2.8)	Yes † ¶	121	Yes †	-
Antiadrenergic agents, peripherally acting	140 (1.6)	Yes †	-	Yes †	-
Antihypertensives and diuretics in combination	13 (0.1)	No		Yes †	-
Low-ceiling diuretics and thiazides	195 (2.2)	No		Yes †	-
High-ceiling diuretics	467 (5.4)	Yes †	13	No	
Potassium-sparing agents	224 (2.6)	Yes †	-	Yes †	2
Diuretics and potassium-sparing agents in combination	591 (6.8)	No		Yes †	4
Peripheral vasodilators	2038 (23.4)	Yes †	9	No	
Beta-blocking agents	1452 (16.7)	Yes †	6	No	
Beta-blocking agents and thiazides or other diuretics	29 (0.3)	No		Yes †	-
ACE inhibitors, plain and combinations	1244 (14.3)	Yes † ‡	33	Yes †	3
Angiotensin II antagonists and diuretics	248 (2.8)	No		Yes †	-
HMG CoA reductase inhibitors (statin)	1351 (15.5)	Yes †	52	Yes †	-
Fibrates	1191 (13.7)	Yes †	225	No	
Other lipid modifying agents	121 (1.7)	No		Yes ¶	4
Genitourinary system and sex hormones	1583 (18.2)	Yes †	-	Yes †	-
Antibacterials and antivirals for systemic use	148 (1.7)	Yes † §	-	No	
Antineoplastic agents	112 (1.3)	Yes †	-	No	
Musculoskeletal system	2067 (23.7)				
Antiinflammatory and antirheumatic products, non-steroids	763 (8.7)	Yes †	-	Yes †	-
Propionic acid derivatives	222 (2.6)	No		Yes †	-
Coxibs	52 (0.6)	No		Yes †	-
Other (including gold salt and penicillamine)	238 (2.7)	Yes †	-	Yes †	-
Antigout preparations	442 (5.1)	Yes ¶	298	Yes †¶	6
Bisphosphonates	248 (2.8)	Yes †	35	Yes †	1
Nervous system	3540 (40.7)				
Opioids	255 (2.9)	Yes †	7	No	
Aspirin and derivatives	181 (2.1)	Yes †	24	No	
Acetaminophen and derivatives	987 (11.3)	Yes §	52	No	
Antiepileptics	71 (0.8)	Yes †	4	No	
Dopaminergic agents	93 (1.1)	Yes †	11	No	
Psycholeptics (including lithium)	1300 (14.9)	Yes † **	358	Yes †	-
Psychoanaleptics	335 (3.8)	Yes †	4	Yes †	-
Antiparasitic products, insecticides, repellents	41 (0.5)				
Antiprotozoals	38 (0.4)	Yes ¶	3	No	
Respiratory system	827 (9.5)				
Adrenergics for systemic use	23 (0.3)	Yes †	1	No	
Antihistamines for systemic use	119 (1.4)	No		Yes †	16
Sensory organs	628 (7.2)				
Antiglaucoma preparations and miotics	337 (3.9)	No		Yes †	-

eGFR : estimated glomerular filtration rate;

*Number of participants whose eGFR level would require either contraindication or renal dose adjustment for each drug ; for example, 209 participants reported using biguanides, which were contraindicated in 32 of them who had an eGFR < 60 mL/min/1.73 m²;

† Recommended eGFR threshold for dose adjustment or contraindication < 30 mL/min/1.73m²; ‡ < 40; § < 50; || < 60; ¶ < 80; ** < 90; different eGFR thresholds are indicated for drug categories including substances with various recommended levels, e.g., H2-receptor antagonists or antiarrhythmics

Table 2 - Baseline characteristics of the Three-City study participants

	Overall (N=8701)	Subsample with 4-year follow-up (N=2915)
	% or mean \pm sd	% or mean \pm sd
Age (year)	74.3 \pm 5.4	73.3 \pm 4.5
Women	60.5	62.3
Household income per month (\$)		
<1084	5.3	5.3
[1084 – 2168[28.8	31.0
[2168 – 3253[26.8	25.7
\geq 3253	33.1	32.5
missing	6.0	5.6
Body mass index (kg/m ²)	25.7 \pm 4.0	25.9 \pm 4.0
Body surface area (m ²)	1.71 \pm 0.2	1.71 \pm 0.2
Number of visits to the GP (per year)		
\leq 2	17.0	17.8
3 or 4	41.9	40.1
> 4	41.1	42.1
Mean number of reported drugs	4.4 \pm 2.9	4.3 \pm 2.8
History of cardiovascular disease**	29.6	30.7
Hypertension [†]	77.3	77.2
Hypercholesterolemia [‡]	56.6	57.0
Diabetes [§]	9.7	9.0
MDRD eGFR (mL/min/1.73m ²)		
\geq 60	86.4	88.1
30 – 60	13.4	11.7
<30	0.3	0.1
Cockcroft-Gault eGFR (mL/min) (N=8632)		
\geq 60	63.1	
30 – 60	36.0	
<30	0.9	

* *including myocardial infarction, angioplasty, stroke, cardiac surgery, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, heart failure, coronary heart disease, and dysrhythmia

[†] Hypertension defined as blood pressure >140/90 mm Hg or antihypertensive drug treatment

[‡] Fasting cholesterol concentration \geq 6.2mmol/L or lipid lowering drug treatment

[§] Diabetes was either self-reported or defined as fasting glycemia \geq 7 mmol/L or nonfasting glycemia \geq 11 mmol/L or antidiabetic drug treatment

^{||} eGFR : glomerular filtration rate estimated with the MDRD equation

Table 3 - Percentage of participants with an eGFR below threshold for at least one contraindicated drug or requiring dose adjustment or either, by eGFR* level

	Overall	eGFR* in mL/min/1.73m ²		
		≥ 60	30 - 60	< 30
N	8701	7510	1166	25
Participants with eGFR below threshold for	N (%)	n (%)	n (%)	n (%)
at least one contraindicated drug	70 (0.8)	6 [†] (0.1)	52 (4.5)	12 (48.0)
at least one drug requiring dose adjustment	1135 (13.0)	520 (6.9)	591 (50.7)	24 (96.0)
at least one or the other	1161 (13.3)	525 (7.0)	612 (52.5)	24 (96.0)

* eGFR: glomerular filtration rate estimated with the MDRD equation

[†] two participants who reported use of benzbromarone (antigout) and 4 of tiadenol (lipid modifying agent), both contraindicated for eGFR < 80 mL/min/1.73 m²

Table 4 - Determinants of exposure to the risk of any* drug use inappropriate to kidney function

	Overall 8701	Any inappropriate drug use (%)	City-adjusted OR [95% CI]	Fully-adjusted^l OR [95% CI]
Sociodemographic factors				
Gender				
men	3438	13.5	1.0 [0.9-1.1]	1.3 [1.1-1.5]
women	5263	13.3	1	1
Age (years)				
[65-75 [5082	10.5	1	1
[75-85 [3190	16.7	1.7 [1.5-2.0]	1.4 [1.2-1.6]
> 85	429	22.1	2.4 [1.9-3.1]	1.9 [1.5-2.5]
Household income per month (\$)				
<1084	461	17.8	1.6 [1.2-2.1]	1.1 [0.8 – 1.5]
1084 – 2168	2506	14.6	1.3 [1.1-1.5]	1.1 [0.9 -1.3]
2168 – 3253	2329	13.1	1.2 [1.0-1.4]	1.1 [0.9 – 1.3]
>3253	2882	11.5	1	1
Missing	523	14.5	1.2 [0.9-1.6]	1.1 [0.8 – 1.5]
Clinical care indicators				
Number of visits to the GP per year				
>4	3266	18.2	3.7 [3.0-4.6]	1.2 [0.9-1.5]
3 or 4	3338	13.5	2.5 [2.1-3.2]	1.0 [0.8-1.3]
≤2	2063	5.6	1	1
Number of reported drugs				
≤1	731	1.8	1	1
2 - 3	2150	6.9	4.0 [2.6-6.0]	2.9 [1.9-4.5]
4 - 5	2296	13.5	8.2 [5.5-12.3]	5.2 [3.4-7.9]
6 - 9	2321	22.5	15.2 [10.3-22.6]	8.5 [5.5-13.0]
>10	462	33.1	25.9 [16.9-39.8]	13.7 [8.6-22.0]
Comorbidities				
History of cardiovascular disease				
No	6128	11.0	1	1
Yes	2571	19.1	2.0 [1.6-2.3]	1.0 [0.9-1.2]
Hypertension [†]				
No	1974	8.4	1	1
Yes, untreated	2454	7.2	0.8 [0.7-1.0]	0.9 [0.7-1.1]
Yes, treated	4268	19.2	2.5 [2.1-3.0]	1.5 [1.2-1.8]
Hypercholesterolemia [‡]				
No	3773	10.4	1	1
Yes, untreated	2305	10.3	1.0 [0.8-1.2]	1.1 [0.9-1.4]
Yes, treated	2619	20.4	2.2 [1.9-2.5]	1.7 [1.5-2.0]
Diabetes [§]				
no	7814	12.8	1	1
Yes, untreated	285	14.7	1.2 [0.8-1.6]	0.8 [0.6-1.1]
Yes, treated	553	20.1	1.7 [1.4-2.1]	0.9 [0.7-1.1]

OR [CI 95%]: odds ratio [95% confidence interval]

* Either a contraindicated drug or one requiring dose adjustment to kidney function

[†] Hypertension defined as blood pressure >140/90 mm Hg or antihypertensive drug treatment

[‡] Fasting cholesterol concentration ≥6.2mmol/L or lipid-lowering drug treatment

[§] Diabetes was either self-reported or defined as fasting glycemia ≥ 7 mmol/L or nonfasting glycemia ≥ 11 mmol/L or antidiabetic drug treatment

^lAdjusted for all variables

Table 5: Hazard ratios for 6-year mortality related to the exposure to the risk of inappropriate drug use, by eGFR level

		N	Deaths	Crude	Adjusted*	Adjusted†
		8693	859	HR (95%CI)	HR (95%CI)	HR (95%CI)
eGFR ≥ 60 mL/min/1.73 m²						
At least one drug requiring dose adjustment	No	6985	597	1	1	1
	Yes	519	57	1.3 (1.0-1.7)	1.2 (0.9-1.6)	1.1 [0.8-1.4]
At least one contraindicated drug	No	7498	653	-	-	-
	Yes	6	1	-	-	-
At least one or the other	No	6980	596	1	1	1
	Yes	524	58	1.3 (1.0-1.8)	1.2 (0.9-1.6)	1.1 [0.8-1.5]
eGFR < 60 mL/min/1.73 m²						
At least one drug requiring dose adjustment	No	575	85	1	1	1
	Yes	614	120	1.4 (1.1-1.9)	1.4 (1.1-1.9)	1.4 [1.1-1.9]
At least one contraindicated drug	No	1125	186	1	1	1
	Yes	64	19	2.0 [1.3-3.3]	1.9 [1.2-3.1]	1.5 [0.9-2.6]
At least one or the other	No	554	80	1	1	1
	Yes	635	125	1.5 (1.1-1.9)	1.5 (1.1-2.0)	1.4 [1.0-1.9]

* adjusted for age, sex and city

† adjusted for age, sex, city, income, body mass index, alcohol drinking, smoking, history of cardiovascular disease, hypertension, diabetes, and hypercholesterolemia