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Inappropriate drug use and mortality in community-dwelling elderly with impaired kidney function--the Three-City population-based study

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Abstract

Backgrouncd

Glomerular filtration rate (GFR) decline with age increases the risk of inappropriate dosing of drugs. We investigated the determinants and the mortality associated with the use of drugs that are contraindicated or require dose adjustment according to kidney function among the community-dwelling elderly.

Methods

The Three-City population-based study included 8701 participants ≥ 65 years from 1999 to 2001. Exposure to the risk of inappropriate drug dosage was defined as reported use of either a contraindicated drug or one requiring dose adjustment according to the individual baseline glomerular filtration rate estimated (eGFR) with the Modification of Diet in Renal Disease study equation. Six-year mortality was analyzed using Cox models adjusted for several sociodemographic, biologic and clinical risk factors.

Results

The overall percentage of exposure to the risk of inappropriate drug use was 13.3% (contraindication, 0.8%): it was 52.5% (4.5%) in those with eGFR of 30–59, and 96% (48%) in those <30 mL/min/1.73 m^2 . Antihypertensive agents, fibrates and psycholeptics accounted for most of the drugs with dosing recommendations, and antidiabetic agents and antihistamines for those contraindicated. Individuals at risk were more likely to be men, older, and under treatment for hypertension or hypercholesterolemia. Exposure to either risk was independently related to higher all-cause mortality (Hazard Ratio1.4, 95% confidence interval 1.0–1.9) in participants with eGFR < 60 mL/min/1.73m^2 .

Conclusions

Contraindicated drug prescription was uncommon but > 10% of the population took drugs requiring renal dosing adjustments. Regular monitoring of eGFR may prevent excess mortality associated with inappropriate drug prescription in the elderly.

MESH Keywords Aged ; Cohort Studies ; Community Health Planning ; Drug Toxicity ; Female ; Follow-Up Studies ; France ; epidemiology ; Glomerular Filtration Rate ; Humans ; Inappropriate Prescribing ; adverse effects ; Kidney ; physiopathology ; Kidney Failure, Chronic ; epidemiology ; mortality ; pathology ; Kidney Function Tests ; Longitudinal Studies ; Male ; Prognosis ; Prospective Studies ; Risk Factors ; Survival Rate

Introduction

Impairment of kidney function with age increases both vulnerability to drug toxicity and the risk of dosing too high for many drugs cleared renally.[1,2] Chronic kidney disease (CKD), as defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) 2002 classification system,[3] by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 , is common in the elderly.[4–6] Because it is often undiagnosed, older people with multiple diseases and consequently polymedication are at particularly high risk of inappropriate drug use.[7,8]

The prevalence[9–13] and outcomes[14–16] of inappropriate drug use, based on the Beers criteria[17,18] or the Inappropriate Prescribing in the Elderly Tool [[19], have been studied among the community-dwelling elderly, but CKD is rarely considered as a risk modifier for adverse drug events. [18,20] Specifically, the prevalence and the impact of inappropriate drug dosing on mortality among them is unknown, although it has been examined in selected inpatient populations. [21–23] Moreover, although pharmacokinetic studies usually referred to the Cockcroft-Gault formula, [24,25] evidence today shows that the Modification of Diet in Renal disease (MDRD) study equation[26] is more accurate than others for estimating GFR in the elderly. [27] Which of them should be used for adjusting drug doses is still a topic of debate. [28–30]

Our primary objective was therefore to assess the prevalence among the community-dwelling elderly of drug use inappropriate for their kidney function level, determinants of this use and the mortality associated with it as well as its trends before and after the 2002 CKD guidelines.[3] We also studied the impact of the eGFR estimation equation on the evaluation of the need to adjust drug dosages.

Methods

Design, setting, and participants

The Three City (3C) study is a population-based prospective cohort that included 9294 non-institutionalized individuals aged ≥65 years, randomly selected from the electoral rolls of Bordeaux, Dijon, and Montpellier (France) from March 1999 through March 2001. Details of the study design are reported elsewhere.[31] We studied 8701 participants with available baseline eGFR; a subsample of 2915 from two cities (limited to those < 80 in one of them) was also seen at 4 years and had blood taken for laboratory measurements including eGFR. The study protocol was approved by the Ethics Committee of Bicetre University Hospital, and written informed consent was obtained from all participants.

Information

Baseline data were recorded from face-to-face interviews and physical examinations. Participants reported demographic information, number of visits to their general practitioners (GP) and history of cardiovascular diseases and risk factors. Height and weight were measured; seated blood pressure (BP) was measured twice after 5 minutes rest and averaged. Hypertension was defined by a mean systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or by the use of antihypertensive drugs. Diabetes was either self-reported or defined as fasting glucose ≥ 7 mmol/L or nonfasting ≥ 11 mmol/L (in 1% of the participants) or antidiabetic drug use; hypercholesterolemia, as fasting cholesterol > 6.2 mmol/L or lipid-lowering drug use. Serum creatinine was measured both times with the colorimetric Jaffe method. It was remeasured with an isotope dilution mass spectrometry (IDMS) standardized enzymatic assay from 1720 frozen serum specimens at baseline and 325 at 4 years. This assay provided very reliable eGFR when compared with measured GFR in a clinical CKD patient cohort.[32] We used these values to develop equations relating the Jaffe and IDMS standardized measurements and standardized all baseline (1) and follow-up (2) values as follows (with S_{cr} in μmol/L): (1) $S_{crIDMS} = 0.86 \times S_{crJaffe} + 4.40$; (2) $S_{crIDMS} = 0.87 \times S_{crJaffe} + 7.85$

We then calculated eGFR in mL/min/1.73 m^2 with the IDMS creatinine-based MDRD equation.[26]

Assessment of exposure to the risk of drug use inappropriate to kidney function

At both baseline and 4 years, participants were asked to provide their prescriptions and drug packages for all medications, including over-the-counter, taken more than once a week during the previous month.[13] Up to 15 substances were recorded per participant and coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system.[33] For each of the 958 different registered substance codes, a pharmacist (GB) searched for any dosing recommendation or contraindication according to eGFR level through the principal French drug dictionaries (Vidal[34] and Dorosz[35]), as well as from *Information Conseil Adaptation Renale* (ICAR) website, [36] a database updating renal dose adjustment guidelines based on international pharmacokinetic studies. With the help of senior ICAR pharmacists, an eGFR threshold was assigned to each substance that was either contraindicated or required dose adjustment (Appendix). Pharmacokinetic studies were unavailable for 225 substances. Exposure to the risk of inappropriate drug use was defined as reported use of either a contraindicated drug or one requiring dose adjustment according to the participant's eGFR level. In a multicomponent medication or an ATC class, each substance could involve either type of risk. Moreover, eGFR threshold may vary according to substance within an ATC class. In that case, each substance was assigned its own specific eGFR threshold. (Table 1) Finally, because drug doses were not recorded, only renal contraindications were certain. However, the 3C study started before the publication of CKD guidelines,[3] at a time when French laboratories did not routinely report eGFR and primary care physicians had a relatively low level of awareness of CKD. Thus, although some may indeed have monitored eGFR and adjusted drug dosage accordingly, it is likely that most did not. This justifies our analysis of baseline exposure to drugs for which dose adjustment is required as a surrogate for actual inappropriate dosage.

Outcome measures

Six-year mortality was assessed by active follow-up of all participants and by appropriate vital status searches. It remained unknown for only eight participants.

Statistical analysis

We compared baseline characteristics of participants with and without baseline eGFR. The latter were older than the former (76.6 *versus* 74.2 years), had significantly more cardiovascular diseases but did not differ for other studied characteristics after adjustment for age (data not shown). Baseline CKD prevalence, defined as an eGFR <60 mL/min/1.73m^2 , and prevalence of exposure to the risk of drug use inappropriate to kidney function were assessed in all participants with the MDRD equation and in 8632 with the Cockcroft-Gault formula, because of missing weight.[25] Crude and adjusted odds ratios and their 95% confidence intervals (CIs) were then estimated from logistic regression for inappropriate drug use exposure associated with demographic variables, number of GP visits, number of reported drugs, and comorbidities. We also used Cox models to assess mortality hazard ratios (HRs, 95% CI) related to the risk of inappropriate drug use before and after adjusting for several confounders including sociodemographic and behavioral factors, history of cardiovascular diseases and cardiovascular risk factors, in participants with and without CKD. In participants without CKD (eGFR ≥ 60 mL/min/1.73m^2), those classified as exposed to the risk of inappropriate drug use reported using drugs requiring dose adjustment for eGFR between 60 and 80 mL/min/1.73m^2 , such as allopurinol, used to treat hyperuricemia (antigout preparation). Finally, in the subsample, we compared exposure to inappropriate drug use according to MDRD eGFR at both baseline and 4 years, that is before and after 2002. Analyses were performed with SAS-PC (9.1; SAS Institute Inc, Cary, NC).

Results

Baseline characteristics

In the overall population, the prevalence of eGFR < 60 mL/min/1.73m^2 was 13.7% with the MDRD equation and with the Cockcroft-Gault formula, 36.9% (Table 2). Participants reported an average of 4.4 medications: 44.7% ≥ 5, and 5.3% ≥ 10. Mean drug use increased as eGFR decreased: 4.2 ± 2.9 for eGFR ≥ 60, 5.5 ± 2.9 for 30–59 and 7.1 ± 2.7 for < 30 mL/min/1.73m^2 . As expected in view of the selection of participants studied at 4 years, they were significantly younger (73.3 ± 4.5 *versus* 74.8 ± 5.9 years, P < 0.001) than those who were not; more of them were women (P < 0.01), but their other characteristics were similar (Table 2).

Exposure to the risk of drug use inappropriate for kidney function level

The most commonly reported drugs with dosing recommendations were those for the cardiovascular system, psycholeptics and acetaminophen (Table 1). Rilmenidine, fibrates, allopurinol, and bromazepam accounted for >80% of these drugs. The contraindicated drugs were mainly antidiabetic agents and antihistamines. Forty-four participants (0.5%) had both a contraindicated drug and one requiring dose adjustment. The observed overall prevalence of 13.3% was thus slightly lower than the sum of both (Table 3). Contraindications mainly concerned participants with eGFR < 60 mL/min/1.73m^2 . In contrast, 45% of the participants with at least one drug requiring dose adjustment had an eGFR ≥ 60 mL/min/1.73m^2 . About half of the participants with eGFR of 30 – 59 (CKD stage 3) and all but one with eGFR < 30 mL/min/1.73m^2 (CKD stages 4–5) reported at least one inappropriate use; contraindications accounted for 4.5% and 48% of those, respectively. The number of drugs either contraindicated or requiring dose adjustment ranged from 1 to 6; it was 1.2 ± 0.6 on average, increasing from 1.0 ± 0.2 for eGFR ≥ 60 to 1.4 ± 0.6 for 30–59, and 2.6 ± 1.3 for < 30 mL/min/1.73m^2 . The prevalence of exposure to the risk of inappropriate drug use was much higher, 21.3%, when estimated with Cockcroft-Gault formula-based eGFR.

Determinants of exposure to the risk of drug use inappropriate to kidney function

Participants with at least one contraindicated drug or requiring dose adjustment were more likely to be men and older than those not taking such drugs (Table 4). As expected, they were also more likely to be under treatment for hypertension or hypercholesterolemia. Moreover, the higher the number of reported medications, the higher the risk.

Mortality associated with exposure to the risk of drug use inappropriate to kidney function

In participants with an eGFR < 60 mL/min/1.73m^2 , the mortality risk significantly increased, by 40%, with the use of drugs requiring dose adjustment, after adjustment for confounders, and was of borderline significance for contraindicated drugs. In those with an eGFR ≥ 60, neither exposure was associated with mortality after adjustment (Table 5).

Trend in exposure to the risk of drug use inappropriate to kidney function in the subsample

Of the 2915 participants with two eGFR measures, 12.9% (0.5%) were exposed to the risk of inappropriate drug use (contraindication) at baseline and 17.9% (0.3%) at 4 years. Only one participant reported contraindication both times. It is worth noting that contraindications at 4 years did not result from decreased eGFR in treated participants, but from new prescriptions in participants with CKD.

Discussion

This study showed that although use of contraindicated drugs was uncommon among community-dwelling older people, that of drugs requiring dose adjustment may concern more than 10%. This exposure was independently associated with a 40% increased mortality in

those with impaired kidney function. It was encouraging to observe that all but one of those in the subsample seen twice who reported contraindicated drugs at baseline were no longer using them at follow-up, but new prescriptions of contraindicated drug resulted in this prevalence remaining stable over time. This study also pointed out an opposite risk of concern — that of overadjusting doses by underestimating true GFR with the Cockcroft-Gault formula rather than using the MDRD equation. These findings have major clinical and public health implications.

Assessment of exposure to the risk of inappropriate renal drug use strongly depends on CKD prevalence and the number of medications used in the study population. The prevalence of CKD that we found in those 65 years or older was about 10 to 25% lower than reported in most earlier studies. [4,5] Although we cannot rule out the possibility that 3C participants were healthier than other study populations,[31] this is probably due mainly to our use of the IDMS standardized creatinine-based MDRD equation, which proved to provide lower S_{cr} values, but more reliable estimates of true GFR at higher eGFRs. [26] Indeed, using the Cockcroft-Gault formula raised our prevalence estimate by 23%. In contrast, compared to the Norwegian HUNT II study, which used the same method as here to assess eGFR, our prevalence in those older than 70 years was very similar: 16.0% *vs* 18.6% in Hunt II. [6] Drug consumption among the participants was similar to, albeit somewhat lower than, that in other studies: 44.7% of the 3C participants reported the use of 5 or more prescription and nonprescription drugs, compared with the 44% and 57% observed in the late 1990s among noninstitutionalized US men and women aged 65 years and older, respectively;[11] the 5.3% of those reporting at least 10, however, was lower than the 12%[11] and 17.8%[10] reported for both sexes in two US studies. Therefore, our prevalence estimate of elderly at risk of being prescribed inappropriate drug doses should be seen as rather conservative, especially given the number of substances for which no pharmacokinetic studies exist.

It has been argued in the geriatric community[29] that, because pharmacokinetic studies and dosing recommendations were established with reference to the Cockcroft-Gault formula,[25] it should also be used for adjusting drug doses. These studies, however, were performed in young healthy volunteers, a population in whom, unlike the elderly, the MDRD and Cockcroft-Gault equations perform equally well for estimating true GFR. [3,27,30] Because the former has clearly been shown to perform better than the latter in the elderly, [27] this prompted recommendations to adopt the MDRD equation for renal dose adjustment in the elderly. This equation has now been added to assess renal function in the revised draft guidance for industry on pharmocokinetic study in patients with CKD. [25] In this study, the prevalence of exposure to the risk of inappropriate drug use based on the Cockcroft-Gault formula was nearly twice that obtained with the IDMS standardized creatinine-based MDRD equation. Its use may thus potentially expose a larger number of elderly individuals to overadjusted dosing. It might also be argued that using the MDRD equation can introduce errors in renal dose adjustment in the very obese or the very lean, because it is adjusted for 1.73 m^2 body surface area while GFR reference levels for dose adjustment are not. In this study, the participants' mean body surface area was very close to this reference, 1.71 ± 0.2 m^2 , which would not much bias our prevalence estimate of people at risk at the population level. However, at the individual level, body surface area-unadjusted eGFR should certainly be used for renal dose adjustment, particularly in those lean or obese.

We note that this risk adds to, rather than being included in, the risk of inappropriate drug use defined by Beers which more than a third of the 3C study participants were exposed to.[13] His list concerns different drugs with a few exceptions, including disopyramide, carbutamide, glipizide, cimetidine, methyldopa, monoxidine, bromazepam, and buflomedil.[17,18] The profile of individuals at risk was also different. While men were at higher risk than women and social factors were not associated with drug use inappropriate to kidney function, the reverse has previously been observed for Beer's criteria in this study.[13] Moreover, because several drugs requiring dose adjustment are prescribed for hypertension or dyslipidemia, which are also associated with CKD, individuals with these conditions were more specifically at higher risk for this type of inappropriate use. Not surprisingly, however, the higher the total number of reported drugs the higher the risk with either definition of inappropriate drug use.

Although adverse outcomes related to inappropriate drug use according to Beer's criteria is well documented,[14–16] this study is the first to point out that using drugs requiring dose adjustment is associated with excess mortality among community-dwelling elderly with impaired kidney function, regardless of age, gender, and several potential confounders. The hazard ratio for contraindicated drugs was of the same order of magnitude, but not statistically significant, possibly because of the small sample size for this subgroup. These findings are consistent with those from Hug et al,[8] showing that adverse drug events were common among hospitalized adult patients with impaired kidney function, half of which classified as either serious or life-threatening. Interestingly, these investigators considered that more than 90% of these adverse events were potentially preventable with renal dose checking.[8] Of note, among all the inappropriate drug use we studied, 45% concerned participants with eGFR above 60 mL/min/1.73m^2 . These were drugs, such as allopurinol, requiring dose adjustment for eGFR of 60 to 80 mL/min/1.73m^2 , and were not associated with increased mortality.

The large sample size of this population and the low number of participants lost to follow-up (8 out of 8,705 at six years) are major strengths of this study. It also has some limitations. First, it is possible that we underestimated the extent of the problem for two reasons. The participation rate was low (37%), and those who participated were younger, more often women, and had a higher socioeconomic level than in the elderly in general.[31] While we found no or little association between sex or socioeconomic factors and exposure to the risk of drug use inappropriate to kidney function, older age was an important determinant and might have biased our prevalence estimates towards lower values. Recall bias of drug use is also possible, but we sought to limit it by asking participants to provide drug packages and

prescriptions. Moreover, medication data were further validated in a subsample, by comparing participant reports with health insurance claims: agreement was good, at least for drugs prescribed for chronic conditions, which account for most of those considered here.[37]

Second, drug doses were not recorded. While this did not prevent us from assessing the prevalence of contraindications, we could not formally estimate the prevalence of doses *truly* inappropriate for kidney function level. Several reasons, however, beyond the absence of eGFR levels on laboratory reports at the time of the study start, lead us to believe that the *true* risk may be close to the need for dosing adjustment that we actually measured. Several recent studies show that awareness of CKD among both physicians and patients in ambulatory population is poor, thereby indicating that eGFR monitoring before drug prescriptions is likely to be uncommon even today. [38–41] Patients with CKD were also shown to be at particularly high risk for adverse safety events that may influence outcomes. [42] The excess mortality we observed in participants with CKD using drugs requiring dose adjustment indeed argues for the reality of this risk. It may have been, however, underestimated if some participants were misclassified.

Third, GFR was estimated and not measured. However, creatinine measurements were IDMS standardized, and eGFR was estimated with the IDMS creatinine-based MDRD equation, which has proved more accurate than previously used equations.[26]

In conclusion, the risk of elderly people receiving inappropriate drug dosages is high, especially the very old and those with cardiovascular risk factors. Our study provides new evidence that this exposure is associated with significantly higher mortality risk. These findings should prompt more regular monitoring of eGFR in the elderly than is currently recommended and thus allow drug doses to be carefully monitored and adjusted, thereby preventing adverse events due to overdosing.

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Footnotes:

Disclaimers : None

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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	Recommendation for renal dose adjustment		Renal contraindication	
	N (%)		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-ceilling diuretics and thiazides	195 (2.2)	No		Yes †	-
High-ceilling 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 vasodilatators	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)**				
Adrenegics 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 m^2 ;

† Recommended eGFR threshold for dose adjustment or contraindication < 30 mL/min/1.73m^2 ;

‡ < 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 ± sd	% or mean ± sd
Age (year)	74.3 ± 5.4	73.3 ± 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
≥3253	33.1	32.5
missing	6.0	5.6
Body mass index (kg/m^2)	25.7 ± 4.0	25.9 ± 4.0
Body surface area (m^2)	1.71 ± 0.2	1.71 ± 0.2
Number of visits to the GP (per year)		
≤ 2	17.0	17.8
3 or 4	41.9	40.1
> 4	41.1	42.1
Mean number of reported drugs	4.4 ± 2.9	4.3 ± 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)		
≥ 60	86.4	88.1
30–60	13.4	11.7
<30	0.3	0.1
Cockcroft-Gault eGFR‖ (mL/min) (N=8632)		
≥ 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 ≥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

‖ 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 m^2

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‖ 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

‖ Adjusted 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 m^2						
At least one drug requiring	No	6985	597	1	1	1
dose adjustment	Yes	519	57	1.3 (1.0–1.7)	1.2 (0.9–1.6)	1.1 [0.8–1.4]
At least one	No	7498	653	-	-	-
contraindicated drug	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 m^2						
At least one drug requiring	No	575	85	1	1	1
dose adjustment	Yes	614	120	1.4 (1.1–1.9)	1.4 (1.1–1.9)	1.4 [1.1–1.9]
At least one	No	1125	186	1	1	1
contraindicated drug	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