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Association between Cardiovascular Drugs and Chronic Kidney Disease in Non-Institutionalized Elderly Patients

Laurent Becquemont[1], Bernard Bauduceau[2], Linda Benattar-Zibi[3], Gilles Berrut[4], Philippe Bertin[5], Sophie Bucher[6], Emmanuelle Corruble[7], Nicolas Danchin[8], Abdallah al-Salameh[1], Geneviève Derumeaux[9], Jean Doucet[10], Bruno Falissard[11], Francoise Forette[12], Olivier Hanon[13], Florence Pasquier[14], Michel Pinget[15], Rissane Ourabah[6] and Celine Piedvache[1]

[1]Pharmacology Department, Faculty of Medicine Paris-Sud, APHP, Bicêtre university Hospital, University Paris-Sud, Le Kremlin Bicêtre, France, [2]Endocrinology Department, Bégin hospital, Saint-Mandé, France, [3]ORPEA/CLINEA, Puteaux, France, [4]Clinical Gerontology, Nantes university hospital, Nantes, France, [5]Rheumatology Department, Limoges University Hospital, Limoges, France, [6]General Practice Department, Faculty of Medicine Paris-Sud, University Paris-Sud, Le Kremlin-Bicêtre, France, [7]INSERM U 669, Faculty of Medicine Paris-Sud, Department of Psychiatry, Bicêtre University Hospital, APHP, University Paris-Sud, Le Kremlin Bicêtre, France, [8]Coronary Diseases, HEGP, Paris, France, [9]Cardiovascular Functional Exploration, Louis Pradel Hospital, HCL, Bron, France, [10]Internal Medicine, Geriatrics and Therapeutics, Saint Julien University Hospital, Rouen University, Rouen, France, [11]INSERM U 669, Faculty of Medicine Paris-Sud, Biostatistics Department, APHP, Hôpital Paul Brousse, University Paris-Sud, Le Kremlin-Bicêtre, France, [12]National Foundation of Gerontology, University Paris Descartes, Paris, France, [13]Geriatrics Department, EA 4468, AP-HP, Broca university hospital, University Paris Descartes, Paris, France, [14]UDSL, EA 1046, CHU, University of Lille Nord de France, Lille, France and [15]Endocrinology, Diabetes and Diseases of Nutrition, University Hospital of Strasbourg, European Centre for the Study of Diabetes (CeeD), University of Strasbourg, Strasbourg, France

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Abstract: Concern about the renal safety of commonly used cardiovascular drugs with demonstrated clinical benefit appears to be an obstacle to their use in the elderly. The objective was to describe the relationship between cardiovascular drugs and chronic kidney disease (CKD) in elderly individuals in the real-life setting. This is an ancillary study of the prospective non-interventional S.AGE (aged individuals) cohort. General physicians were free to prescribe any drug their patients needed. The participants were non-institutionalized patients aged 65 years and older treated by their primary physician for either chronic pain or atrial fibrillation or type 2 diabetes mellitus. The estimated glomerular filtration rate (eGFR) derived from the CKD-EPI formula was determined at inclusion and every year during 2 years of follow-up. This study comprised 2505 patients aged 77.8 ± 6.2 years. At inclusion, the factors associated with CKD (eGFR < 60 ml/min/1.73 m^2) in multivariate analysis were age, female gender, hypertension, heart failure, history of atherothrombotic disease and renin angiotensin system blockers, loop diuretics and calcium channel inhibitors. Introduction of each of these three drug classes during the follow-up period led to only a small decrease in the eGFR: −3.8 ± 12.7 ($p < 0.0006$), −2.2 ± 12.0 ($p < 0.003$) and −1.0 ± 13.4 ml/min./1.73 m^2 (NS), respectively. Only the introduction of loop diuretics was associated with CKD (OR 1.91, 95% CI: 1.25–2.90; $p = 0.002$). Renal safety of cardiovascular drugs in the elderly appears acceptable and should not be a barrier to their use.

With the ageing of the population in the developed countries, the prevalence of chronic kidney disease (CKD) is increasing significantly. While the prevalence of CKD is roughly 7% in persons aged 30 years or older, it raises to 35% in those over 65 years of age [1]. This age-related reduction in the glomerular filtration rate (GFR) is a result of the physiological ageing of the kidneys involving a progressive loss of nephrons and can be accelerated by chronic diseases such as diabetes, hypertension and dyslipidaemias [1–3].

Screening of CKD, especially in individuals at risk such as elderly persons [4], is important in several respects. First of all, as part of a preventive approach, many medicines require dose adjustment according to renal function in order to avoid adverse drug reactions [5]. Secondly, from a prognostic viewpoint, renal dysfunction is a major predictor of overall and cardiovascular mortality [2], especially in the elderly [3]. Lastly, from a therapeutic angle, the deterioration of renal function can be slowed by appropriate management of hypertension (HT), in particular with nephroprotective drugs such as renin angiotensin system blockers (RAS blockers), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB).

Although appropriate management of hypertension and heart failure in the elderly is essential, as emphasized in all the international recommendations, particularly with diuretic and RAS blocker therapy [6,7], these drugs are clearly underused, mainly because physicians are wary of causing a deterioration of renal function in this frail population [8,9]. Indeed, diuretics and RAS blockers are known to reversibly alter renal function (pre-renal kidney injury) that represents the second most common cause of acute renal failure in the elderly, accounting for nearly one-third of all hospitalized cases [10]. This perceived risk of kidney injury in the elderly [11,12] constitutes a true obstacle to the use of these drugs and therefore a loss of

Author for correspondence: Laurent Becquemont, Clinical Research Center, Bicêtre University Hospital, 78 General Leclerc road, le jremlin Bicêtre 94270 France, France (fax +33 1 45 21 36 51, e-mail laurent.becquemont@bct.aphp.fr).

Laurent Becquemont had full access to all of the data and had the final responsibility for the decision to submit the publication.

opportunity for these already frail individuals with multiple cardiovascular comorbidities [13,14].

This ancillary study to the S.AGES cohort performed in the real-life primary care setting is aimed to describe the association between long-term therapy with cardiovascular drugs and CKD, and to evaluate the extent to which these drugs contribute to the reduction in estimated glomerular filtration rate (eGFR), in ambulatory elderly patients living at home.

Patients and Methods

The S.AGE ('Sujets ages', i.e. aged individuals) study is a multi-centre, prospective cohort study conducted in France [15,16]. The main objective of the S.AGES cohort was specifically to describe the real-life therapeutic management of non-institutionalized elderly individuals. This cohort consists of 3434 non-institutionalized patients aged 65 years and older with either chronic pain (n = 1379), type 2 diabetes mellitus (n = 983) or atrial fibrillation (n = 1072). The inclusion criteria were men or women aged 65 years or older living in France who were able to understand the goal of the study, agreed to participate in the study and signed the informed consent. Patients included in the study also had one of the three following conditions that defined three subcohorts:

- Chronic pain (CP) present for more than 3 months and requiring care.
- Type 2 diabetes mellitus (T2DM) treated at inclusion by any hypoglycaemic drug.
- Atrial fibrillation (AF) (defined by ECG or Holter ECG).

Patients could not participate if they were residents of a nursing home at the time of inclusion, could not be followed after inclusion (planned move, homeless) or had a short life expectancy (<3 months).

Patients were recruited by their general practitioners (GP) throughout France. A total of 760 GPs responded favourably and were randomized into one of the three S.AGE subcohorts. Inclusion of patients began in June 2009 and ended in September 2011 [15]. Patients returned to their GP every 6 months (planned follow-up visits) for a 3-year period.

The present work is an ancillary study that analysed the data obtained at baseline (inclusion) and during the first 2 years of follow-up. To be eligible for this study, patients had to have a serum creatinine blood sample at inclusion and every year during the first 2 years of follow-up. We also excluded those who were haemodialysed at baseline or started dialysis during the first year of follow-up.

Study variables.

1. Estimated glomerular filtration rate (eGFR) was derived from the CKD-EPI formula [17]. CKD was defined in this study by an eGFR < 60 ml/min./1.73 m^2.
2. Heart failure was evaluated by the GP according to the NYHA classification [18].
3. Hypertensive patients were defined by use of an antihypertensive treatment or systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg.
4. Studied drugs were grouped into several classes as follows: non-steroidal anti-inflammatory drugs (NSAIDs) (ATC code M01A) and aspirin at doses above 350 mg/day (aspirin used as platelet anti-aggregant at doses below 350 mg/day was not included in this group); RAS blockers: ACEi, ARB and renin inhibitors (ATC code C09); beta blockers (ATC code C07); loop diuretics (ATC code C03C); other diuretics, including thiazide and anti-aldosterone diuretics (ATC code C03A, C03B, C03D); calcium channel inhibitors (CCI) including diltiazem, verapamil and dihydropyridines (ATC code C08); and other antihypertensive treatments including alpha-adrenergic blockers (ATC code C02C) and centrally acting drugs (ATC code C02A).
5. To demonstrate an eventual dose effect of loop diuretics, RAS blockers and CCI, dose equivalences between molecules in a same pharmacological class were established. For loop diuretics, widely represented by furosemide, 1 mg and 5 mg bumetanide were considered equivalent to 40 and 200 mg furosemide. For RAS blockers, daily doses were divided into three categories: low, intermediate and high. For CCI, the doses of the different molecules were divided into low and high.
6. Treatments: All prescribed drugs were reported by the GP at each visit, indicating when the drug was started or stopped, but compliance was not assessed.

The study was approved by the Ethics Committee and by the French Medicines Agency. The clinical trial reference of this study is NCT01065909. All the patients signed the informed consent form before participation. Further details about the study have been provided in previously published papers [15,16].

Statistical analysis. Statistical analyses were carried out with SAS software release 9.3 (SAS version 9.0 SAS institute, France).

In a first step, a descriptive analysis of the different baseline variables (mean and standard deviation for quantitative variables, frequencies and percentages for qualitative variables) was carried out. Patients were divided into two groups: eGFR < 60 ml/min./1.73 m^2 and eGFR ≥ 60 ml/min./1.73 m^2, and their characteristics were compared using Wilcoxon or chi-squared tests.

In a second step, multivariate analysis (stepwise descending logistic regression) on baseline variables was performed in which any statistically significant variable by univariate analysis at $p < 0.05$ was introduced to determine its association with an eGFR below 60 ml/min./1.73 m^2.

Odd ratios and their 95% confidence intervals were determined.

The change in the eGFR after introduction of a treatment (loop diuretic, RAS blocker, calcium channel inhibitor) was also determined. To do this, the change in the eGFR was compared either between baseline and the 1-year follow-up or between the 1-year and 2-year follow-up visits. For each patient, the choice of the period studied depended on the eventual introduction of a loop diuretic, with priority given to the period during which a loop diuretic was introduced so as to obtain the largest number of patients for whom loop diuretics were introduced. For patients for whom none of the three drug classes was introduced, the period studied corresponded to the period from baseline to the 1-year follow-up. A Wilcoxon test for paired samples was used for comparison of the means.

A value of $p < 0.05$ was considered significant for all statistical tests.

Results

Study population.

Of the 3434 patients initially enrolled in the S.AGE cohort, 2509 had a serum creatinine determination at inclusion, 1 and 2 years of follow-up. Four patients were excluded because they were haemodialysed or started dialysis during the first year of follow-up. Among the 2505 patients retained in the study, 726 (29%), 777 (31%) and 1002 (40%) were from the T2DM, AF and CP subcohorts, respectively. Mean age was 77.8 ± 6.2 years and 54% of the population was

female. Apart from their disease that led to their inclusion in the S.AGES cohort, the study patients also suffered from additional diseases: 2059 patients (82.3%) were hypertensive, 1024 (40.9%) had type 2 diabetes, 1774 (70.8%) were taking antihypertensive drugs, and 1029 (41.1%) were treated with cholesterol-lowering drugs. The mean BMI was 28 ± 5 kg/m^2 and the eGFR was 66.38 ± 17.16 ml/min./1.73 m^2. Table 1 shows the general baseline characteristics of the study population, which was divided into two groups: eGFR ≥ and <60 ml/min./1.73 m^2. The percentage of patients in the latter group did not differ in the three subcohorts: 34.6%, 37.7% and 35.2% in the T2DM, AF and CP subcohorts, respectively.

Association between heart failure and eGFR.

We first looked for an association between baseline eGFR and heart failure. In patients without heart failure, with NYHA stage I–II heart failure and with severe NYHA stage III–IV heart failure, the mean eGFR was 68 ± 17, 59 ± 19 and 55 ± 17 ml/min./1.73 m^2, respectively ($p < 0.0001$) (Figure S1).

Association between cardiovascular drugs and eGFR.

We then studied the association between cardiovascular drugs known to induce pre-renal kidney injury and the baseline eGFR (fig. 1). Patients taking one or more antihypertensive treatments had a lower eGFR than those who did not take these drugs ($p < 0.001$). Aspirin at platelet anti-aggregant

Table 1.

Baseline characteristics of patients.

	eGFR < 60 ml/min./1.73 m^2 (%)	eGFR ≥ 60 ml/min./1.73 m^2 (%)	*p* Value
N	897	1608	
Gender (female)	548 (61.1)	840 (52.2)	<0.0001
Age	79.8 ± 5.8	76.7 ± 6.1	<0.0001
Education level – high school diploma or higher[a]	474 (52.8)	801 (49.8)	NS
Marital status[b]			
Single	62 (6.9)	111 (6.9)	<0.001
With partner	484 (54.1)	990 (61.6)	
Widowed	349 (39.0)	505 (31.4)	
Lives alone at home[c]	358 (46.7)	528 (39.6)	<0.01
Beneficiary of long-term/major illness (ALD) coverage[d]	702 (78.3)	1172 (73.4)	<0.01
Beneficiary of Personalised Autonomy Allowance (APA)[e]	83 (9.4)	68 (4.4)	<0.0001
Household help[f]	204 (23.1)	226 (14.4)	<0.0001
Home nurse[g]	221 (24.9)	287 (18.2)	<0.0001
Physiotherapy[h]	249 (28.1)	382 (24.3)	0.04
Pedicure[i]	263 (29.6)	387 (24.5)	<0.01
BMI (kg/m^2)[j]	28.1 ± 5.0	27.9 ± 5.1	NS
Current smoker[k]	33 (3.7)	65 (4.1)	NS
Regular alcohol consumption[l]	217 (24.4)	456 (28.7)	0.02
History of atherothrombotic disease[m]	200 (22.4)	271 (16.9)	<0.001
History of venous thromboembolic disease[n]	88 (10.0)	90 (5.7)	<0.0001
Atrial fibrillation[o]	363 (40.5)	570 (35.5)	<0.01
Arterial hypertension[p]	789 (88.1)	1270 (79.0)	<0.0001
Heart failure NYHA classification[q]			
None	723 (80.8)	1475 (91.8)	<0.0001
I–II	104 (11.6)	100 (6.2)	
III–IV	68 (7.6)	32 (2.0)	
Type 2 diabetes mellitus[r]	358 (40.0)	666 (41.5)	NS
Liver cirrhosis	0 (0)	0 (0)	NS
Antidiabetic treatment	329 (36.7)	630 (39.2)	NS
Cholesterol-lowering treatments	407 (45.4)	622 (38.7)	<0.01
Loop diuretics	213 (23.7)	159 (9.9)	<0.0001
Other diuretics	111 (12.4)	156 (9.7)	0.04
Beta blockers	286 (31.9)	435 (27.1)	<0.01
Calcium channel inhibitors	217 (24.2)	282 (17.5)	<0.0001
Renin angiotensin system (RAS) blockers (ACEi or ARB or aliskiren)	556 (62.0)	808 (50.2)	<0.0001
Other antihypertensive agents	73 (8.1)	87 (5.4)	<0.01
NSAIDs or aspirin >350 mg/day	51 (5.7)	123 (7.6)	NS

Missing values: a = 38; b = 4; c = 406; d = 12; e = 66; f = 53; g = 38; h = 43; i = 34; j = 103; k = 8; l = 23; m = 10; n = 32; o = 5; p = 2; q =3; r = 3.

The number of patients suffering from atrial fibrillation (AF) was superior to the number of patients providing from the AF subcohort, as some patients included in the T2DM or CP subcohort also suffered from additional disease such as AF; same finding for the number of patients suffering from T2DM.

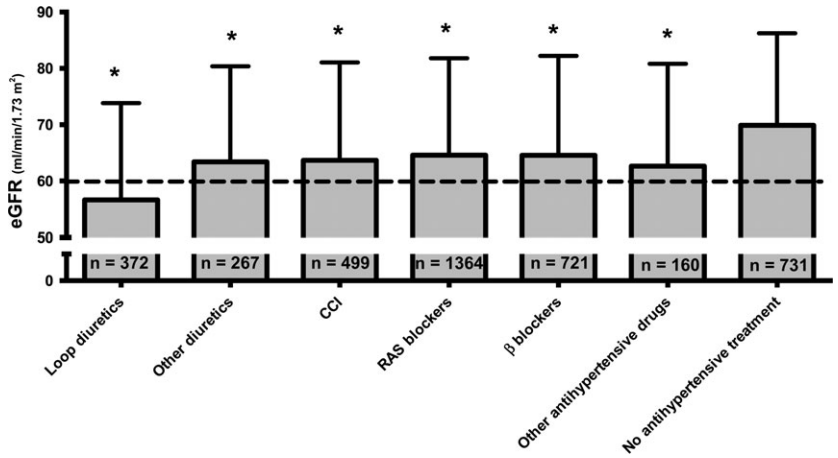

Fig. 1. Association between cardiovascular drugs and baseline eGFR. *: $p < 0.001$ *versus* no antihypertensive drugs; CCI: calcium channel inhibitors; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; RAS blockers: ACEi/ARB/aliskiren.

doses was not associated with a lower eGFR, even when NSAIDs were taken into account (Figure S2).

Factors associated with an eGFR < 60 ml/min./1.73 m² after multivariate analysis.

We identified the factors associated with an eGFR < 60 ml/min./1.73 m² (table 1). In the multivariate analysis, eight independent factors associated with chronic kidney disease (eGFR < 60 ml/min./1.73 m²) were identified (table 2), including three drugs (loop diuretics, RAS blockers and CCI).

Diabetes was not found to be associated with CKD. However, there were more patients on insulin (10.6% *versus* 6.2%, $p < 0.0001$) and disease duration of diabetes was longer (11.5 ± 8.5 *versus* 10.6 ± 8.2 years, $p = 0.053$) in the group with eGFR < 60 ml/min./1.73 m² compared to the group with eGFR > 60 ml/min./1.73 m².

Hypothetical causal relationship between drugs and an eGFR < 60 ml/min./1.73 m².

To find indirect evidence of a possible causal relationship between loop diuretics, RAS blockers and CCI and CKD, we studied:

(a) whether these drugs displayed a dose effect on the eGFR at baseline and
(b) whether the eGFR decreased when these drugs were introduced during follow-up.

The dose effect was only found for loop diuretics (fig. 2). Although there was a negative correlation between the dose of loop diuretics and the eGFR ($r = -0.23$, $p < 0.0001$), this explained only 4% of the variance of the eGFR.

Between the first and second visits separated by 12 ± 2 months, 430 patients who were not taking loop diuretics, RAS blockers or CCI at the first visit (V1) had started one of these drugs by the time of the second visit. The eGFR was determined again at the second visit (V2), after introduction of one of these three drug classes (Figure S3). In the 160 patients who started a loop diuretic between the two visits, the eGFR decreased by an average of −3.8 ± 12.7 ml/min./1.73 m² ($p < 0.0006$). In the 186 patients who began an RAS blocker between the two visits, the eGFR decreased by an average of -2.2 ± 12.0 ml/min./1.73 m² ($p < 0.003$). On the other hand, in the 84 patients who began a CCI between the two visits, the eGFR did not significantly decrease [−1.0 ± 13.4 ml/min./1.73 m² ($p = 0.90$)].

We then determined whether introduction of these drugs was associated with an eGFR < 60 ml/min./1.73 m² at the second visit (V2) by adjusting for factors previously identified as associated with an eGFR < 60 ml/min./1.73 m² (Table S1): only the introduction of loop diuretics was still associated with a decrease in the eGFR (OR = 1.91, 95% CI: (1.25–2.90), $p = 0.002$). All patients who started a loop diuretic during the first year of follow-up were still taking this treatment after 2 years of follow-up, testifying to the good tolerability of this drug class. Ninety-seven per cent of patients who started an RAS blocker and 83% of those who started a CCI during the first year were still taking their treatment at 2 years.

Table 2.
Independent factors associated with an estimated glomerular filtration rate (eGFR) below 60 ml/min./1.73 m².

	OR	95% CI	*p* Value
Age	1.08	1.06–1.10	<0.0001
Female gender	1.42	1.18–1.70	0.0001
Hypertension	1.35	1.03–1.77	0.03
History of atherothrombotic disease	1.28	1.02–1.60	0.03
Heart failure (NYHA I–II)	1.45	1.06–1.99	0.02
Heart failure (NYHA III–IV)	2.55	1.59–4.08	<0.0001
Renin angiotensin system (RAS) blockers (ACEi or ARB or aliskiren)	1.35	1.11–1.64	0.003
Loop diuretics (furosemide 10–40 mg/day)	1.76	1.33–2.33	<0.0001
Loop diuretics (furosemide > 40 mg/day)	2.22	1.39–3.56	0.0009
Calcium channel inhibitors	1.33	1.07–1.65	0.01

The categories of loop diuretics, furosemide 10–40 mg/j and furosemide >40 mg/j, were compared to patients not taking loop diuretics. The categories of heart failure, NYHA I–II and NYHA III–IV, were compared to patients without heart failure.

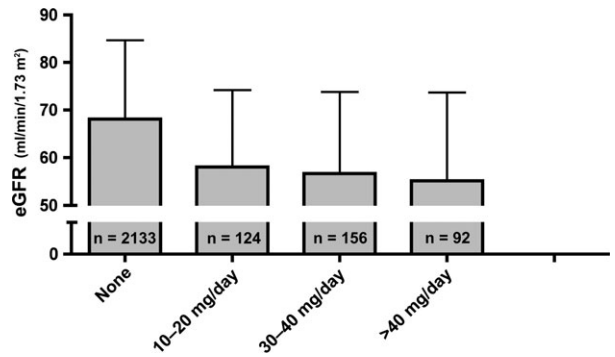

Fig. 2. Loop diuretics: dose effect.

Discussion

This study aimed to describe the association between cardiovascular drugs known to alter renal function and CKD in non-institutionalized elderly patients in the real-life primary care setting. Three classes of cardiovascular drugs (loop diuretics, RAS blockers and CCI) were identified as independent factors associated with CKD (defined as eGFR < 60 ml/min./1.73 m^2), although they only caused a small reduction in the eGFR of less than 5 ml/min./1.73 m^2.

Diuretics, RAS blockers and NSAIDs are classically known to cause pre-renal kidney injury [11,19,20]. In our study, univariate analysis showed that all these antihypertensive drugs were associated with a lower eGFR (fig. 1) than that seen in patients not taking antihypertensive treatment. This lower eGFR value is probably a simple reflection of the fact that hypertension is one of the two leading risk factors for chronic kidney disease [21]. Moreover, in the multivariate analysis, only three pharmacological classes of antihypertensives were still independent factors associated with CKD, which nonetheless raises the question of the causality of these drugs in the development of CKD. In fact, loop diuretics are more widely prescribed when eGFR is <30 ml/min./1.73 m^2 because they are the only diuretics that remain active; RAS blockers are also recommended as front-line treatment for their nephroprotective effect in case of CKD and/or diabetes. The association between the three drug classes and CKD, despite an adjustment for hypertension, heart failure and history of atherothrombotic disease, could be merely a consequence of their increased prescription in case of CKD and not the cause of CKD.

This is why we looked for evidence in favour of a causal link between each of these three drug classes and CKD. As far as dose effect is concerned, loop diuretics was the only class to fulfil this criterion. Concerning the temporal relationship between introduction of one of the three drug classes and a subsequent decrease in the eGFR, both loop diuretics and RAS blockers led to a lower eGFR but, after adjustment for confounding factors, only loop diuretics remained significantly associated with CKD. Thus, among the common cardiovascular drugs, loop diuretics are the only class to show a causal relation with CKD. However, it must be emphasized that regardless of the drug class, the decrease in the eGFR attributable to the drug was small (<5 ml/min./1.73 m^2), signifying that the renal tolerability of these drugs is satisfactory in this elderly population with multiple comorbidities. For loop diuretics, all patients who started the drug during the first year of follow-up were still taking their treatment 1 year later, another indication of good tolerability. Our observations in the real-life primary care setting are consistent with the findings from other large, randomized studies in elderly populations taking diuretics or RAS blockers [14,22,23].

Surprisingly, we did not find a correlation between chronic NSAID therapy and CKD, even though these drugs are known to alter intraglomerular haemodynamics, especially in older individuals [11,19,20]. This can be explained by the fact that the prescription of these drugs in the chronic pain subcohort followed international recommendations restricting their use to a small subset of patients at low risk, that is with satisfactory renal function [16]. Indeed, the eGFR of patients on NSAIDs was similar to that of patients without antihypertensive treatment.

On the other hand, the absence of an association between T2DM and CKD in our study is more difficult to explain, especially considering that patients with diabetes made up around 40% of the study population. However, diabetic patients with CKD were more often on insulin therapy and had a longer disease duration, which nonetheless suggests a relation between T2DM and CKD in this study. It should be noted that CKD is often defined by an eGFR < 60 ml/min./1.73 m^2 and/or the presence of proteinuria. As we did not have proteinuria data for the patients with diabetes in our study, we were unable to use this composite criterion; if proteinuria had been taken into account, it is likely that T2DM would have been identified as a CKD risk factor.

This study has several limitations. First of all, it is not representative of the general population of patients over 65 years of age because only patients with chronic pain, AF or T2DM were included. Furthermore, patients with T2DM were not found to be at greater risk for CKD, which undoubtedly represents a confusion bias. Proteinuria was not systematically tested in the non-diabetic patients, which may have modified the classification of individuals with CKD. More than half of the population was already treated with RAS blockers at baseline, most likely with a good renal tolerance, which may represent a selection bias concerning their tolerance. Lastly, the safety profile of loop diuretics and RAS blockers is not restricted to renal function; we did not investigate other adverse effects of these drugs such as orthostatic hypotension and dyskalaemia, to which elderly individuals may be more susceptible.

In conclusion, in view of the good renal tolerability of loop diuretics and RAS blockers in elderly patients in the real-life setting, concern about drug-induced kidney injury appears unjustified.

Conflict of Interest

This study was financed and sponsored by SANOFI drug company. The sponsor did not interfere with the present analyses nor with the writing section.

Becquemont L received consulting fees from Sanofi-Aventis, Pfizer, Servier and lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp and Dohme. His close family member is working at Sanofi France. Bauduceau B received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, Novo Nordisk. Berrut G received fees from Sanofi, Lundbeck, Eisai, Novartis, Merck Sharp and Dohme, Amgen, Boehringer-Ingelheim, Bayer. Bertin P received consulting fees from Sanofi-Aventis, Pfizer, Ethypharm, Reckitt-Benkiser and speaking fees from Genevrier, Roche, Bristol-Myers Squibb, Merck Sharp and Dohme. Corruble E received consulting fees from Servier, Lundbeck, Sanofi-Aventis, Bristol-Myers Squibb, Eisai. Danchin N received consulting or speaking fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, MSD-Schering Plough, Novartis, Novo-Nordisk, Pierre Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, The Medicines Company. Derumeaux G received consulting or speaking fees from Actelion, Boehringer-Ingelheim, Pfizer, Sanofi-Aventis and Servier, and research grant from Actelion and AstraZeneca. Doucet J received speaking fees from Novo Nordisk and consulting fees from Sanofi-Aventis, Novo Nordisk, Merck-Serono and has the research partnership with Lilly. Falissard B received consulting fees from Sanofi-Aventis, Servier, Roche, AstraZeneca, Grünenthal, Lilly, HRA, Boehringer-Ingelheim, Bayer, Novartis, Genzyme, Stalergène, Daiichi, Otsuka, Bristol-Myers Squibb. Forette F received speaking and consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Eisaï, Exonhit, Pierre Fabre, Ipsen, Janssen-Cilag, Lilly, Lundbeck, Novartis, Merck Sharp and Dohme, Merz, Pfizer, Roche, Sanofi-Aventis, Servier, Schwarz-Pharma, Specia, Warner-Lambert, Wyeth. Hanon O received speaking and consulting fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer, Eisaï, Exonhit, Janssen-Cilag, Lundbeck, Novartis, Pfizer, Sanofi-Aventis, Servier. Pasquier F is the investigator for Eisai, Exonhit, Novartis, Ipsen, Medivation, Pfizer, Bayer, Noscira, Sanofi, Roche, GE Healthcare. He received consulting fees from Lilly, Bayer, Janssen, Sanofi. Pinget M received speaking and consulting fees from Asdia, AstraZeneca, Bristol-Myers Squibb, Medtronic, Merck Sharp and Dohme, Novo Nordisk, Novartis, Roche Diagnostics, Ypsomed. Benattar-Zibi L, Sophie Bucher, Abdallah al-Salameh, Delespierre T, Ourabah R and Piedvache C have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Introduction of drugs associated with an eGFR below 60 ml/min./1.73 m^2.

Figure S1. Association between eGFR and heart failure. $p < 0.0001$; 3 missing values.

Figure S2. No association between NSAIDs and eGFR.

Figure S3. Change in eGFR after introduction of loop diuretics, RAS blockers or CCI.