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## **Effectiveness and Tolerance of Renin-Angiotensin System Inhibitors with Aging in Chronic Kidney Disease**

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**Brief summary:**

In a cohort of CKD patients, RASi prescription was significantly associated with a lower combined risk of end-stage kidney disease and death, without excess risk of adverse effects. Age did not modify these relations.

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## **Conflicts of interest**

CV, MM, SL, AH, NM, CC, DF, LF, CJ, ML, SB, CA, RPF, and TH have no disclosures relative to this study.

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## 1 **Abstract**

### 2 **Objectives**

3 Renin-angiotensin system inhibitors (RASi) are recommended for slowing chronic kidney  
4 disease (CKD) progression to kidney failure. Their effectiveness and tolerance as patients age  
5 remain uncertain because older patients have often been excluded from clinical trials.

### 6 **Design**

7 CKD-REIN cohort study.

### 8 **Setting and Participants**

9 We studied 2762 patients with CKD stages 3–4 and a clinical indication for RASi enrolled  
10 between 2013 and 2016 in 40 nephrology clinics nationally representative in France.

### 11 **Methods**

12 The primary outcome was the occurrence of kidney failure or death. The secondary outcomes  
13 were the occurrence of cardiovascular events and hospitalizations with acute kidney injury  
14 (AKI) or hyperkalemia. A propensity score analysis was performed. We used Cox models to  
15 estimate hazard ratios (HRs) for each outcome associated with RASi prescription and tested  
16 interactions with age.

### 17 **Results**

18 Patients' mean age was 67 years, including 841 (30%) aged 75 years and older; 2178 (79%)  
19 were prescribed RASi. During a median follow-up of 4.6 years, 33% of patients reached  
20 kidney failure or died. RASi prescription was associated with a lower risk of kidney failure or  
21 death (HR, 0.79; 95%CI, 0.66-0.95), an association not modified by age (P for  
22 interaction=0.72). It was not significantly associated with cardiovascular events. During the  
23 first 3 years of follow-up, 14% of patients were hospitalized with AKI or hyperkalemia, but

24 risk was not higher among those prescribed RASi (HR, 0.75; 95%CI, 0.55-1.02) and age did  
25 not modify its effect (P for interaction=0.28).

## 26 **Conclusions and Implications**

27 This study shows that aging does not appear to modify either RASi's beneficial effects on  
28 major CKD outcomes or their potential adverse effects.

29

## 30 **Introduction**

31 Renin-angiotensin system inhibitors (RASi, including angiotensin-converting enzyme [ACE]  
32 inhibitors and angiotensin II receptor blockers [ARBs]) are the main drugs recommended for  
33 reduction of blood pressure and albuminuria in patients with chronic kidney disease (CKD).<sup>1</sup>  
34 Since the early 1990s, several randomized trials in patients with CKD have shown that RAS  
35 blockade can slow the progression to kidney failure, mainly through their effect on blood  
36 pressure and albuminuria.<sup>2-11</sup> Reduction in mortality and cardiovascular risk is still  
37 controversial in patients with CKD.<sup>2,4,8,9,12,13</sup>

38 Chronic kidney disease is frequent in older people and affects 28% of patients aged 65 years  
39 or more in France.<sup>14</sup> In the United States, nearly half of people aged 80 years or older have  
40 CKD stages 3-5.<sup>15</sup> Age has been associated with the underuse of RASi in CKD but data on  
41 their effectiveness and tolerance are scarce in older patients.<sup>16,17</sup> In those randomized  
42 controlled trials that did not explicitly limit age for study inclusion, the mean age of included  
43 patients has not exceeded 67 years.<sup>2,4-10,13</sup> As most older patients with CKD have low  
44 albuminuria and a low risk of progression to kidney failure, but a higher risk of death, the  
45 benefit of RASi in this population are questionable.<sup>18,19</sup> In a randomized trial assessing the  
46 nephroprotective efficacy of ARBs in patients with diabetes and nephropathy, those aged 65  
47 to 74 years had the same advantages as those younger than 65 years.<sup>20</sup> Observational studies,  
48 however, report conflicting findings about RASi's benefits in delaying kidney failure and  
49 mortality in older patients with CKD.<sup>21-24</sup> This population is also particularly exposed to  
50 drug-related adverse effects.<sup>25</sup> Randomized controlled trials have not consistently reported the  
51 adverse effects of RASi and their frequency. The trial on ARBs mentioned above found  
52 similar incidence rates of acute kidney injury (AKI) and hyperkalemia in patients aged 65 to



53 74 years and in those younger than 65 years,<sup>20</sup> but none of the observational studies assessed  
54 the impact of age on RASi safety in CKD.<sup>21–24</sup>

55 Accordingly, current evidence about the benefits and risks of RASi use in older patients with  
56 CKD is limited, although these may well differ from those in younger patients. We used a  
57 propensity score analysis to investigate the impact of age on the effectiveness and tolerance of  
58 RASi in patients with CKD enrolled in the CKD-REIN cohort study.

59

## 60 **Methods**

### 61 *Population*

62 This study used data from the CKD-REIN cohort (ClinicalTrials.gov identifier:  
63 NCT03381950), the design of which has previously been described.<sup>26</sup> Briefly, 3033 patients  
64 with CKD were recruited from 40 nephrology clinics in France between July 2013 and April  
65 2016. During a census phase, we screened all adults with a proven CKD diagnosis and two  
66 measures of estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min/1.73m<sup>2</sup> at  
67 least 1 month apart, with no prior chronic dialysis or kidney transplantation. Eligible patients  
68 were recruited within the next few weeks during a routine nephrology visit, excluding those  
69 who had started kidney replacement therapy in the meantime. Patients under the age of 18 or  
70 unable to give informed consent were also excluded. The study protocol was approved by the  
71 INSERM institutional review board (reference: IRB00003888), and all participants provided  
72 informed consent.

73 For this analysis, we excluded 121 patients with baseline eGFR <15 ml/min/1.73m<sup>2</sup> and 32  
74 treated by renin inhibitors, which also act on the RAS but have a different benefit-risk ratio  
75 than ACE inhibitors and ARBs.<sup>27</sup> We also excluded 118 patients who had no indication for  
76 RASi at baseline, because they did not have hypertension, heart failure, coronary artery  
77 disease, severely increased albuminuria, or moderately increased albuminuria associated with  
78 diabetes. Finally, this analysis included 2762 patients (Figure 1).

### 79 *Data Collection*

80 Data were collected from medical records and patient interviews by trained clinical research  
81 associates. RASi included ACE inhibitors and ARBs. We calculated eGFR using the Chronic  
82 Kidney Disease–Epidemiology Collaboration (CKD-EPI) creatinine equation with correction  
83 for ethnicity. Albuminuria or proteinuria were collected either from 24-h or spot urine

84 samples and expressed according to the Kidney Disease: Improving Global Outcomes  
85 (KDIGO) albuminuria categories (A1, normal; A2, moderately increased; A3, severely  
86 increased).<sup>1</sup> When data on the albumin-to-creatinine ratio were missing, they were imputed  
87 from the results of the 24-hour urine collection or the protein-to-creatinine ratio, as described  
88 elsewhere.<sup>28</sup> Participants were classified as having diabetes if it was reported in their medical  
89 records, or they were prescribed a glucose-lowering medication, or they had an HbA1c level  
90  $\geq 7\%$ . Hypertension was defined as a history of hypertension or antihypertensive medication  
91 prescription without a concurrent indication. The Charlson Comorbidity Index was  
92 computed.<sup>29</sup> Data were available for five activities of daily living (ADL) from the Katz Index  
93 (bathing, dressing, going to the toilet, transfer, and feeding) and four instrumental ADL  
94 (IADL: ability to use the telephone, handle finances, take medication, and travel).<sup>30,31</sup>  
95 Educational level was classified in two categories:  $\leq 12$  versus  $> 12$  years. Medication  
96 compliance was evaluated with a self-administered questionnaire.<sup>32</sup> The method used to  
97 collect and assess any adverse drug reactions occurring during follow-up in the cohort has  
98 been described previously.<sup>33</sup> Exhaustive data on adverse drug reactions were available for the  
99 first three years of follow-up.

#### 100 *Outcomes*

101 The primary outcome was defined as death or kidney failure, defined as initiation of kidney  
102 replacement therapy (i.e., kidney transplantation or maintenance dialysis), during follow-up.  
103 Secondary outcomes included: i) kidney failure; ii) death before kidney failure occurrence; iii)  
104 major cardiovascular events, defined as cardiovascular death, stroke, myocardial infarction, or  
105 hospitalization or an emergency department visit for heart failure; iv) AKI or hyperkalemia  
106 requiring or occurring during hospitalization. Major cardiovascular events, AKI or  
107 hyperkalemia events were identified from medical records and hospital discharge reports.

108 AKI events were further adjudicated by three nephrologists (AH, LF, and ML) using the  
109 current KDIGO definition for AKI.<sup>34</sup> Data on death and kidney failure were available until  
110 February 1, 2020. Data on major cardiovascular events and AKI or hyperkalemia requiring  
111 hospitalizations were available for the first three years of follow-up.

### 112 *Statistical Analysis*

113 We first described patient baseline characteristics according to RASi prescription. Cumulative  
114 incidence curves were then computed and compared according to age and RASi prescription  
115 for each outcome. To evaluate the impact of age on the effectiveness and tolerance of RASi in  
116 patients with CKD and to minimize indication bias due to the observational design of the  
117 study, we performed a propensity score analysis using the inverse probability of treatment  
118 weighting (IPTW) method.<sup>35</sup> A specific propensity score was performed for each outcome as  
119 detailed in Appendix 1.<sup>36</sup> Hazard ratios (HR) for each outcome were then estimated by using  
120 Cox models. Confidence intervals (CI) were obtained by bootstrapping. Interaction between  
121 age as a continuous variable and RASi prescription was tested. Hazard ratios were also  
122 computed for 4 age groups (<60, 60-69, 70-79, and  $\geq 80$  years) and 2 groups according to  
123 eGFR level (<30 and  $\geq 30$  ml/min/1.73m<sup>2</sup>).

124 We conducted secondary analyses to test the robustness of the associations by subgroups  
125 according to sex, diabetic status, albuminuria category, and the presence of a cardiovascular  
126 disease (CVD) for which RASi are indicated, i.e., heart failure and coronary artery disease.  
127 We also tested the interaction by introducing age as a binary variable (< or  $\geq 75$  years). We  
128 also assessed the effect of ACE inhibitors and ARBs separately. For the analysis of secondary  
129 outcomes, Fine and Gray competing risk regression models were used with the propensity  
130 scores. The events considered for the competing risk analyses were (i) kidney failure for the  
131 analysis of death before kidney failure, (ii) death not related to kidney disease for the analysis

132 of kidney failure, (ii) death not related to cardiovascular diseases for the analysis of major  
133 cardiovascular events, and (iv) death and kidney failure for the analysis of AKI or  
134 hyperkalemia. Lastly, we used time-varying Cox models weighted for the propensity score.  
135 We calculated a propensity score for each patient at each time point. Given that the variables  
136 other than age, eGFR, and RASi prescription were not available for all the time points, the  
137 propensity score was mainly computed with baseline values. Missing data were considered by  
138 using multiple imputations. All statistical analyses were performed with R software (R  
139 Foundation, Vienna, Austria, version 3.5.1).<sup>37</sup> A *P*-value <0.05 was considered statistically  
140 significant.

## 141 **Results**

### 142 *Baseline Patient Characteristics*

143 Among the 2762 studied patients, 2178 (79%) were prescribed RASi at baseline (Table 1 and  
144 Table A1). Their mean age was  $67.0 \pm 12.8$  years; 841 (30%) were aged 75 years or older.

145 Compared to patients to whom RASi were prescribed, those whose physicians did not  
146 prescribe it for them were significantly older, more often women and dependent for ADL and  
147 IADL, had visited a cardiologist in the past year more often, and had more AKI, heart failure,  
148 dysrhythmia, stroke history, and lower levels of both eGFR and blood potassium.

### 149 *Crude Risk of Kidney Failure, Death, or Major Cardiovascular Events*

150 Over a median follow-up of 4.6 years [interquartile range (IQR) 3.6-5.2], 539 (19.5%)  
151 patients reached kidney failure and 377 (13.6%) patients died before kidney failure.

152 Prescription of RASi was significantly associated with a lower risk of the combined outcome  
153 of kidney failure or death, and of death before kidney failure, but not of kidney failure alone  
154 (Figures A1 to A3). During a median follow-up of 3.0 years (IQR 2.9-3.0), 306 (11.1%)  
155 patients experienced a major cardiovascular event, including 29 (9.5%) cardiovascular deaths,  
156 49 (16.0%) strokes, 51 (16.7%) myocardial infarctions, and 177 (57.8%) hospitalizations or  
157 emergency department visits for heart failure. In the crude analysis, RASi prescription was  
158 significantly associated with a lower risk of major cardiovascular events (Figure A4).

### 159 *Adverse drug reactions*

160 Of the 2178 patients who were prescribed RASi at baseline, 164 experienced at least one  
161 RASi-related adverse drug reaction during follow-up; these were mainly serum creatinine  
162 elevation, AKI, hypotension, cough, and high serum potassium. Adverse drug reactions  
163 occurred in 8.2%, 8.0%, 7.6%, and 5.2% of RASi users in the <60, 60-69, 70-79, and  $\geq 80$  age  
164 classes, respectively ( $p=0.47$ ). In 73% of cases, the drug was discontinued (at least

165 transiently) after the occurrence of the adverse drug reaction, and dose adjustment was  
166 necessary in 10% of cases. Over a median follow-up period of 3.0 years, a total of 380  
167 (13.8%) patients were hospitalized with AKI (n=322; 11.7%) and/or hyperkalemia (n=104;  
168 3.8%). RASi prescription was significantly associated with a lower risk of hospitalization for  
169 AKI or hyperkalemia (Figure A5). Patients aged 75 years or older had a higher risk of both  
170 events than younger patients.

#### 171 *Propensity Score Analyses*

172 Propensity scores were computed for each outcome. The standardized differences of <10%  
173 for each covariate in each score indicate that the treated and untreated patients were well  
174 balanced for all variables after weighting (Tables 1 and A2). The propensity score analyses  
175 showed a statistically significant association between the prescription of RASi and the risk of  
176 kidney failure or death (Table 2). Age was not a significant effect modifier in this association.  
177 However, the prescription of RASi was not significantly associated with any of the secondary  
178 outcomes and age did not modify these associations. In subgroups of age, RASi prescription  
179 was associated with a decreased risk of death or kidney failure, and a decreased risk of kidney  
180 failure in patients aged 60-69 years, but all the others studied association were not statistically  
181 significant (Table 3). Considering age as a binary variable (< or  $\geq$  75 years) did not change  
182 our findings, and all the p values for the interaction between age and RASi prescription were  
183 >0.15 for all outcomes studied. The HRs estimated for time-varying Cox models were  
184 consistent with those found in the main analysis, for all outcomes studied (Table A3).

#### 185 *Subgroups Analyses*

186 According to eGFR level, RASi prescription was associated with a decreased risk of death or  
187 kidney failure in patients with an eGFR <30 ml/min/1.73m<sup>2</sup>, but the others studied association  
188 were not statistically significant (Table 4). Age did not modify the association between the

189 outcomes and RASi prescription in the subgroups of eGFR. In patients with and without  
190 diabetes, and with and without CVD for which RASi was indicated, as well as with and  
191 without moderate or severe albuminuria, this prescription was not significantly associated  
192 with the primary outcome but HRs were similar between both groups, and age did not modify  
193 the associations (Figure A6). The prescription of RASi was significantly associated with a  
194 lower risk of the primary outcome in men, but not in women; nonetheless, these HRs were of  
195 the same order of magnitude in both subgroups. Finally, a decrease in the risk of kidney  
196 failure or death appeared more strongly associated with prescription of ARBs than ACE  
197 inhibitors, but the difference in the risk of this primary outcome between these two classes of  
198 RASi was not statistically significant.



199 **Discussion**

200 Using propensity score analyses on data from the CKD-REIN cohort, we found that RASi  
201 prescription at baseline was significantly associated with a lower risk of the combined  
202 outcome of kidney failure or death in patients with CKD and that age did not modify the  
203 effect of the prescription on the outcome. This cohort of patients with CKD receiving  
204 nephrology care had no higher risk of hospitalization with AKI or hyperkalemia than those  
205 not prescribed RASi. The originality of this study was to assess the impact of age on the  
206 effectiveness and tolerance of RASi in this population; a key finding was the lack of an  
207 association between older age and a higher risk of RASi-related adverse effects.

208 In our study, prescription of RASi was not associated with a significant decrease in the risk of  
209 kidney failure alone. However, in studies evaluating RASi, CKD progression was often  
210 defined by multiple endpoints also including a percentage decline of eGFR or a doubling in  
211 serum creatinine. Limiting our analysis to kidney failure may have underestimated the  
212 association between RASi and CKD progression and reduced statistical power. Moreover,  
213 RASi has shown stronger benefits against CKD progression in patients with high levels of  
214 albuminuria.<sup>38,39</sup> In our study, the HRs for the association between the primary outcome and  
215 RASi prescription did not differ by albuminuria level. This result should nonetheless be  
216 interpreted with caution in these patients whose history of albuminuria before they began  
217 RASi treatment is unknown.

218 In older patients with CKD, the risk of death is often higher than the risk of progression to  
219 kidney failure, as we observed in our cohort.<sup>40</sup> Moreover, as conservative management is  
220 increasingly proposed to older CKD patients reaching kidney failure, the initiation of kidney  
221 replacement therapy may not be an appropriate outcome in this specific population. For this  
222 reason, we considered that a combined endpoint (i.e., death or kidney failure) was the most

223 relevant primary outcome. In our study, the prescription of RASi was not significantly  
224 associated with a lower risk of death alone, but rather with the risk of the combined primary  
225 outcome, and age did not change this association. These results are at odds with a previous  
226 study using the same combined endpoint to evaluate RASi prescription in a cohort of  
227 veterans.<sup>21</sup> Like the randomized controlled trials including patients with CKD and  
228 intermediate cardiovascular risk, our study did not find a lower risk of cardiovascular events  
229 associated with RASi prescription.<sup>4,8</sup>

230 In our study, prescription of RASi was not associated with a higher risk of hospitalization for  
231 AKI or hyperkalemia. This unexpected result may be explained by a selection bias in patients  
232 receiving RASi for a long time before inclusion in the study. This bias could be suspected  
233 from the observation of a higher prevalence of AKI history in patients not prescribed RASi at  
234 baseline, compared to their counterparts with prescriptions. This variable was, however, taken  
235 into account in the propensity score and was well balanced after weighting. Another major  
236 reason for stopping RASi is hyperkalemia, which usually occurs early after starting the  
237 treatment, but the patients' history of hyperkalemia was not available.<sup>41,42</sup> The fact that  
238 patients were receiving nephrology care may also explain this result. However, the main focus  
239 of this study was on the potential effect modification by age of the association we studied. Its  
240 lack of significance indicates that older patients did not experience more adverse effects  
241 related to RASi than younger ones.

242 This study has several strengths. The analysis was based on a large cohort of CKD patients  
243 including a high proportion of patients aged 75 years or older. The use of propensity scoring  
244 including numerous variables well-balanced between treated and untreated patients minimized  
245 indication bias linked to the observational design of the study. Confounding by indication,  
246 however, cannot be totally excluded, which is the first limitation of our analysis.

247 Nevertheless, this study population is closer to that of nephrology outpatients than that of  
248 controlled randomized trials. The second limitation is that patients receiving RASi at baseline  
249 may have been treated for a long time before the study began, and those not receiving them  
250 may have used them previously and stopped them due to adverse effects like hyperkalemia  
251 and AKI. This may have biased our results, even though AKI history and duration of kidney  
252 disease were included in the propensity scores. However, this should not have biased our key  
253 finding, which is the lack of interaction with age in these associations. Thirdly, all the  
254 variables were not available at each follow-up visit, which might have biased the analyses  
255 based on time-varying Cox models. Finally, patient recruitment from nephrology  
256 consultations restricts the generalizability of our results.

### 257 **Conclusions and Implications**

258 To conclude, in CKD patients receiving nephrologist-led care, RASi prescription, compared  
259 with its nonprescription, was associated with a lower risk of the combined outcome of death  
260 or kidney failure with no apparent increase in the risk of AKI or hyperkalemia requiring  
261 hospitalization. RASi are recommended in CKD to control blood pressure and albuminuria,  
262 but are often underused in older patients.<sup>1,16,17</sup> The finding that age did not modify the  
263 associations we studied indicates that prescription of RASi appears to be equally beneficial  
264 and safe in young and old patients with CKD.

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**Figure legend**

**Figure 1 – Flow chart of the study population.** eGFR, estimated glomerular filtration rate according to the CKD EPI equation; RASi, renin-angiotensin system inhibitors.

## Tables

Table 1 – Baseline characteristics of the study population

Variable	RASi prescription*	No RASi prescription*	P <sup>†</sup>	Standardized differences after weighting*	Age <60 years	Age 60-69 years	Age 70-79 years	Age ≥80 years
Sample size (%)	2178 (78.9)	584 (21.1)			640 (23.2)	818 (29.6)	887 (32.1)	417 (15.1)
ACE users	999 (45.9)	0 (0.0)			295 (46.1)	308 (37.7)	281 (31.7)	115 (27.6)
ARB users	1310 (60.1)	0 (0.0)			294 (45.9)	397 (48.5)	435 (49.0)	184 (44.1)
ACE or ARB users	2178 (100.0)	0 (0.0)			537 (83.9)	664 (81.2)	686 (77.3)	291 (69.8)
<b>Sociodemographic characteristics and functional status</b>								
Age (years)	66.3 ± 12.7	69.4 ± 12.9	<.001	0.7	48.3 ± 9.1	65.3 ± 2.7	74.4 ± 2.9	83.1 ± 2.8
Men	1474 (67.7)	343 (58.7)	<.001	0.7	373 (58.3)	552 (67.5)	623 (70.2)	269 (64.5)
Sub-Saharan African origin	64 (2.9)	10 (1.7)	<.001	0.7	39 (6.1)	20 (2.4)	13 (1.5)	2 (0.5)
Dependence for ≥1 ADL	175 (8.0)	82 (14.0)	.01	2.8	38 (6.0)	80 (9.8)	88 (9.9)	50 (12.1)
Dependence for ≥1 IADL	522 (24.0)	206 (35.2)	<.001	2.5	105 (16.4)	173 (21.1)	278 (31.4)	171 (41.1)
<b>CKD characteristics</b>								
Baseline eGFR (ml/min/1.73m <sup>2</sup> )	34.0 ± 11.6	31.9 ± 11.3		3.6	34.9 ± 12.6	34.9 ± 12.0	32.9 ± 11.0	30.1 ± 9.5
Albuminuria								
A1	600 (27.6)	163 (28.0)	.21	0.4	124 (19.4)	222 (27.1)	288 (32.4)	129 (31.0)
A2	662 (30.4)	199 (34.0)		0.2	166 (25.8)	236 (28.9)	297 (33.5)	162 (38.8)
A3	916 (42.0)	222 (38.0)		0.6	350 (54.7)	360 (44.0)	302 (34.0)	126 (30.2)
Value (mg/g of urine creatinine)	464 ± 1011	384 ± 771	0.08		594 ± 1066	504 ± 1215	353 ± 692	310 ± 669
Causal nephropathy								
Diabetes	493 (22.7)	106 (18.2)	<.001	0.3	91 (14.2)	205 (25.1)	225 (25.4)	78 (18.8)
Glomerulopathy	432 (19.8)	81 (13.8)		0.6	202 (31.6)	155 (19.0)	120 (13.5)	36 (8.5)
Nephroangiosclerosis	504 (23.1)	138 (23.6)		1.1	63 (9.8)	161 (19.6)	251 (28.3)	167 (40.1)
Renal artery stenosis	165 (7.6)	57 (9.7)		0.5	19 (2.9)	54 (6.6)	83 (9.3)	66 (15.9)
Tubulointerstitial nephritis	231 (10.6)	104 (17.8)		0.1	105 (16.4)	102 (12.4)	98 (11.1)	31 (7.4)
Polycystic kidney disease	137 (6.3)	24 (4.1)		0.0	84 (13.1)	52 (6.4)	18 (2.1)	6 (1.4)
Other or unknown	216 (9.9)	74 (12.7)		1.3	77 (12.0)	88 (10.8)	92 (10.4)	33 (8.0)
Duration of kidney disease (years)	8.4 ± 8.9	6.5 ± 7.6	<.001	2.7	10.0 ± 9.4	7.5 ± 8.7	7.5 ± 8.1	6.8 ± 8.0
History of acute kidney injury	432 (19.8)	218 (37.3)	<.001	3.2	156 (24.4)	174 (21.2)	227 (25.6)	93 (22.4)
Serum kalemia (mmol/l)	4.6 ± 0.5	4.4 ± 0.5	<.001		4.6 ± 0.5	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.5
<b>Cardiovascular diseases and risk factors</b>								
Hypertension	1966 (90.3)	505 (86.5)	.01	1.8	527 (82.3)	742 (90.7)	815 (91.9)	388 (93.0)
Systolic blood pressure (mmHg)	142 ± 20	144 ± 20	.08		136 ± 19	143 ± 20	145 ± 21	147 ± 20
Diastolic blood pressure (mmHg)	78 ± 12	78 ± 12	.73		81 ± 12	79 ± 12	76 ± 12	76 ± 12
Diabetes	993 (45.6)	240 (41.1)	.05	0.7	167 (26.1)	399 (48.8)	476 (53.7)	190 (45.6)
Body-mass index (kg/m <sup>2</sup> )	29.0 ± 5.8	28.2 ± 5.9	.003	1.2	27.4 ± 6.0	29.8 ± 6.4	29.4 ± 5.3	28.0 ± 4.9
Nonsmoker	872 (40.0)	252 (43.1)	.07	2.4	290 (45.3)	281 (34.3)	348 (39.3)	204 (49.0)
Former smoker	1029 (47.3)	278 (47.5)		1.5	206 (32.2)	424 (51.9)	478 (53.9)	198 (47.5)
Current smoker	277 (12.7)	55 (9.4)		0.9	144 (22.5)	113 (13.8)	60 (6.8)	15 (3.5)
Heart failure	252 (11.6)	121 (20.6)	<.001	3.4	46 (7.2)	100 (12.2)	138 (15.6)	88 (21.1)
Coronary artery disease	544 (25.0)	162 (27.7)	.19	1.4	57 (8.9)	205 (25.0)	301 (33.9)	143 (34.3)
Atrial fibrillation	217 (10.0)	107 (18.4)	<.001	1.2	15 (2.4)	76 (9.3)	135 (15.2)	98 (23.5)
Peripheral arteritis	283 (13.0)	87 (14.9)	.23	1.6	35 (5.4)	116 (14.1)	153 (17.3)	66 (15.8)
Ischemic stroke or transient ischemic attack	203 (9.3)	75 (12.8)	.01	0.3	30 (4.6)	73 (9.0)	117 (13.2)	58 (14.0)
Cardiology consultation in the past year	1494 (68.6)	434 (74.3)	.01	3.8	302 (47.2)	574 (70.2)	707 (79.8)	344 (82.5)
<b>Other medical characteristics</b>								
COPD	191 (8.8)	69 (11.8)	.03	1.7	30 (4.7)	88 (10.8)	97 (11.0)	44 (10.6)
History of cancer	436 (20.0)	139 (23.8)	.05	0.6	60 (9.3)	175 (21.3)	224 (25.2)	117 (28.0)
Serum hemoglobin (g/dl)	12.9 ± 2.1	12.9 ± 2.0	.85	3.6	12.9 ± 2.2	13.0 ± 2.3	12.9 ± 2.0	12.7 ± 1.4

Serum albumin (g/l)	40.2 ± 4.2	40.1 ± 4.4	.90	0.8	40.5 ± 4.8	40.2 ± 4.3	40.0 ± 3.9	39.8 ± 4.0
Charlson Comorbidity Index	6.6 ± 2.7	7.3 ± 2.7	<.001		4.0 ± 2.1	6.6 ± 2.2	7.9 ± 2.0	8.9 ± 2.1
<b>Drug prescriptions</b>								
Antiplatelet agents	937 (43.0)	232 (39.7)	.17	1.5	121 (18.9)	353 (43.2)	473 (53.3)	222 (53.2)
Oral anticoagulant	286 (13.1)	126 (21.6)	<.001	1.0	36 (5.6)	99 (12.1)	171 (19.3)	106 (25.4)
Beta blockers	891 (40.9)	282 (48.3)	.002	3.8	210 (32.8)	369 (45.1)	398 (44.9)	196 (47.0)
Statins or ezetimibe	1461 (67.1)	323 (55.3)	<.001	3.3	307 (48.0)	576 (70.4)	628 (70.8)	273 (65.5)
Calcium channel blockers	1061 (48.7)	276 (47.3)	.56	2.4	244 (38.1)	420 (51.3)	451 (50.8)	222 (53.2)
Thiazide diuretics	509 (23.4)	25 (4.3)	<.001	6.0	130 (20.3)	176 (21.5)	176 (19.8)	52 (12.5)
Loop diuretics	769 (35.3)	254 (43.4)	<.001	3.2	123 (19.2)	289 (35.3)	381 (43.0)	230 (55.2)
Potassium-sparing diuretics	95 (4.4)	40 (6.8)	.02	0.6	33 (5.2)	38 (4.6)	48 (5.4)	16 (3.8)
Erythropoietin-stimulating agent	133 (6.1)	58 (9.9)	.002	1.0	43 (6.7)	51 (6.2)	59 (6.7)	38 (9.1)
Total number of drugs used	8.2 ± 3.8	7.8 ± 4.1	.01	0.3	6.4 ± 3.8	8.3 ± 4.0	8.9 ± 3.7	9.0 ± 3.4
Good drug adherence	796 (36.6)	246 (42.1)	.03	1.0	215 (33.5)	294 (35.9)	352 (39.6)	182 (43.6)
Moderate drug adherence	1218 (55.9)	295 (50.5)		1.7	339 (52.9)	478 (58.4)	484 (54.6)	213 (51.1)
Poor drug adherence	163 (7.5)	43 (7.4)		0.7	87 (13.6)	47 (5.7)	51 (5.7)	22 (5.3)

\* expressed as sample sizes (percentages) for categorical variables and means ± standard

deviations for continuous variables; † comparison of patients who were prescribed renin-angiotensin system inhibitors (RASi) and those who were not, by logistic regression models for categorical variables and linear regression models for continuous variables; ‡ standardized differences (percentages) between patients who were prescribed RASi and those who were not after weighting with a propensity score for the variables included in the analysis of the primary outcome (mean standardized differences from 20 imputations); ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin ii receptor blockers; ADL, activities of daily living; IADL, instrumental activities of daily living; eGFR, estimated glomerular filtration rate, with the CKD EPI equation; albuminuria expressed as the KDIGO grade (A1: normal; A2: moderately increased; A3: severely increased); LDL, low density lipoprotein; HDL, high density lipoprotein; COPD, chronic obstructive pulmonary disease; MMSE, mini-mental state examination.

**Table 2 – Hazard ratios (HRs) for primary and secondary outcomes assessing effectiveness and tolerance associated with renin-angiotensin system inhibitors (RASi) prescription in patients with CKD and impact of age on these associations. Propensity score analyses.**

	Cox models with propensity score	Age-RASi interaction	Fine and Gray models with propensity score	Age-RASi interaction
	HR (95% CI)*	P	sHR (95% CI)*	P
<i>Primary outcome</i>				
<b>Death or kidney failure</b>	0.79 (0.66-0.95)	.72		
<i>Secondary outcomes</i>				
<b>Death before kidney failure</b>	0.84 (0.65 to 1.08)	.92	0.82 (0.63 to 1.06)	.71
<b>Kidney failure</b>	0.80 (0.61 to 1.04)	.25	0.82 (0.63 to 1.06)	.31
<b>Major cardiovascular events</b>	1.06 (0.79-1.43)	.29	1.08 (0.79-1.48)	.30
<b>AKI or hyperkalemia</b>	0.75 (0.55 to 1.02)	.28	0.80 (0.59 to 1.10)	.37

\* For prescription of RASi; hazard ratios (95% confidence intervals) (HR [95%CI]) were computed by using models weighted for propensity scores according to the Inverse Probability of Treatment Weighting method and bootstrapping; major cardiovascular events included cardiovascular death, stroke, myocardial infarction, and hospitalization for heart failure; sHR, subdistribution HR; AKI, acute kidney injury; CKD, chronic kidney disease.

**Table 3 – Hazard ratios (HRs) for primary and secondary outcomes assessing effectiveness and tolerance associated with renin-angiotensin system inhibitors (RASi) prescription in patients with CKD according to age groups.**

	Age category	Event in the RASi prescription group	Event in the RASi nonprescription group	HR (95% CI)*
<b>Death or kidney failure</b>	<60 years	182/537 (33.9)	37/103 (35.9)	0.91 (0.50-1.66)
	60-69 years	172/664 (25.9)	59/154 (38.3)	0.66 (0.45-0.97)
	70-79 years	214/686 (31.2)	76/201 (37.8)	0.88 (0.64-1.21)
	≥80 years	117/291 (40.2)	59/126 (46.8)	0.83 (0.56-1.24)
<b>Death before kidney failure</b>	<60 years	11/537 (2.0)	8/103 (7.8)	0.27 (0.06-1.22)
	60-69 years	65/664 (9.8)	15/154 (9.7)	0.81 (0.34-1.91)
	70-79 years	107/686 (15.6)	46/201 (22.9)	0.78 (0.50-1.19)
	≥80 years	78/291 (26.8)	47/126 (37.3)	0.81 (0.51-1.27)
<b>Kidney failure</b>	<60 years	171/537 (31.8)	26/103 (28.2)	1.27 (0.72-2.25)
	60-69 years	107/664 (16.1)	44/154 (28.6)	0.58 (0.37-0.90)
	70-79 years	107/686 (15.6)	30/201 (14.9)	1.04 (0.65-1.66)
	≥80 years	39/291 (13.4)	12/126 (9.5)	1.24 (0.55-2.81)
<b>Major cardiovascular events</b>	<60 years	22/537 (4.1)	6/103 (5.8)	0.96 (0.10-9.37)
	60-69 years	70/664 (10.5)	13/154 (8.4)	1.56 (0.72-3.37)
	70-79 years	86/686 (12.5)	35/201 (17.4)	0.95 (0.60-1.49)
	≥80 years	45/291 (15.5)	29/126 (23.0)	0.72 (0.40-1.29)
<b>AKI or hyperkalemia</b>	<60 years	52/537 (9.7)	11/103 (10.7)	0.86 (0.36-2.10)
	60-69 years	90/664 (13.6)	23/154 (14.9)	0.73 (0.39-1.35)
	70-79 years	103/686 (15.0)	41/201 (20.4)	0.81 (0.50-1.31)
	≥80 years	38/291 (13.1)	22/126 (17.5)	0.81 (0.42-1.53)

\* For prescription of RASi; hazard ratios (95% confidence intervals) (HR [95%CI]) were computed by using models weighted for propensity scores according to the Inverse Probability of Treatment Weighting method and bootstrapping; major cardiovascular events included cardiovascular death, stroke, myocardial infarction, and hospitalization for heart failure; AKI, acute kidney injury; CKD, chronic kidney disease.

**Table 4 – Hazard ratios (HRs) for primary and secondary outcomes assessing effectiveness and tolerance associated with renin-angiotensin system inhibitors (RASi) prescription in patients with CKD according to estimated glomerular filtration (eGFR) groups.**

	eGFR category	Event in the RASi prescription group	Event in the RASi nonprescription group	HR (95% CI)*	P for age-RASi interaction
<b>Death or kidney failure</b>	<b>≥30 ml/min/1.73m<sup>2</sup></b>	217/1264 (17.2)	60/300 (20.0)	0.77 (0.53-1.13)	0.59
	<b>&lt;30 ml/min/1.73m<sup>2</sup></b>	468/914 (51.2)	171/284 (60.2)	0.79 (0.64-0.98)	0.67
<b>Death before kidney failure</b>	<b>≥30 ml/min/1.73m<sup>2</sup></b>	124/1264 (9.8)	44/300 (14.7)	0.84 (0.53-1.31)	0.54
	<b>&lt;30 ml/min/1.73m<sup>2</sup></b>	137/914 (14.9)	72/284 (25.4)	0.71 (0.50-1.01)	0.52
<b>Kidney failure</b>	<b>≥30 ml/min/1.73m<sup>2</sup></b>	93/1264 (7.4)	16/300 (5.3)	0.68 (0.33-1.41)	0.07
	<b>&lt;30 ml/min/1.73m<sup>2</sup></b>	331/914 (36.2)	99/284 (34.9)	0.92 (0.70-1.22)	0.56
<b>Major cardiovascular events</b>	<b>≥30 ml/min/1.73m<sup>2</sup></b>	102/1264 (8.1)	26/300 (6.7)	1.19 (0.70-2.01)	0.21
	<b>&lt;30 ml/min/1.73m<sup>2</sup></b>	121/914 (13.2)	57/284 (20.1)	1.00 (0.67-1.48)	0.66
<b>AKI or hyperkalemia</b>	<b>≥30 ml/min/1.73m<sup>2</sup></b>	124/1264 (9.8)	35/300 (11.7)	0.68 (0.41-1.13)	0.89
	<b>&lt;30 ml/min/1.73m<sup>2</sup></b>	159/914 (17.4)	62/284 (21.8)	0.89 (0.62-1.28)	0.38

\* For prescription of RASi; hazard ratios (95% confidence intervals) (HR [95%CI]) were computed by using models weighted for propensity scores according to the Inverse Probability of Treatment Weighting method and bootstrapping; major cardiovascular events included cardiovascular death, stroke, myocardial infarction, and hospitalization for heart failure; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate, with the CKD EPI equation.



Figure 1

