Acute Kidney Injury in Elderly Patients With Chronic Kidney Disease: Do Angiotensin-Converting Enzyme Inhibitors Carry a Risk?

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In contrast to angiotensin receptor blockers (ARBs), mainly excreted by the liver, the dosage of angiotensin-converting enzyme (ACE) inhibitors, cleared by the kidney, must be adapted to account for renal clearance in patients with chronic kidney disease (CKD) to avoid acute kidney injury (AKI). Community-acquired AKI and the use of ACE inhibitors or ARBs in the emergency department were retrospectively assessed in 324 patients with baseline stage 3 or higher CKD. After stepwise regression analysis, the use of ACE inhibitors (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.1–3.1; *P*=.02) and the presence of dehydration (OR, 30.8; 95% CI, 3.9–239.1) were associated with AKI. A total of 45% of patients using ACE inhibitors experienced overdosing, which causes most of the excess risk of AKI. These results suggest that dosage adjustment of ACE inhibitors to renal function or substitution of ACE inhibitors with ARBs could reduce the incidence of AKI. Moreover, ACE inhibitors and ARBs should be stopped in cases of dehydration. *J Clin Hypertens (Greenwich).* 2016;18:514–521. © 2016 Wiley Periodicals, Inc.

Renin-angiotensin system (RAS) blockers are some of the most prescribed drugs for patients with chronic kidney disease (CKD). In patients with CKD, RAS blockers are recommended mainly for both arterial hypertension and proteinuria to slow the rate of CKD progression.[1] However, RAS blockers may induce acute kidney injury (AKI) in certain clinical situations such as dehydration or sepsis, which are frequently reported in elderly patients with CKD.[2–4] In turn, AKI itself may hasten the progression of the underlying CKD by causing cell cycle arrest of tubular cells and the development of interstitial renal fibrosis.[5] Thus, the risk/benefit ratio of RAS blockers must be evaluated in elderly CKD patients. Accordingly, some authors recommend a dose reduction of angiotensin-converting enzyme (ACE) inhibitors to minimize adverse renal events.[6,7] In contrast to ACE inhibitors, angiotensin receptor blockers (ARBs) are predominantly cleared by the liver rather than the kidney.[7] Thus, ARBs do not require dose adaptation, even in severe CKD. In order to minimize the risk of ACE inhibitor–induced AKI and hyperkalemia, manufacturers provide adjustment recommendations that are summarized in Table I. In the present study, we tested the hypothesis that overdosing of ACE inhibitors in CKD outpatients is associated with an increased risk of community-acquired AKI if an intercurrent disease occurs. We also evaluated how the prescribed daily dose of ACE inhibitors matched with the dose reduction recommended by the manufacturer in CKD patients.

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MATERIAL AND METHODS

Study Design

We performed a retrospective, cross-sectional study in the emergency department of our academic center (Hôpital Erasme, Brussels, Belgium) between October 2010 and the end of April 2013. All data were retrieved from our hospital biochemistry and electronic medical databases. The study was approved by the local ethics committee in compliance with the Declaration of Helsinki 2000 as well as the Declaration of Istanbul 2008.

Patients

Every adult patient who was admitted to the emergency department with an estimated glomerular filtration rate (GFR) <45 mL/min/1.73 m^2 (as defined by the Chronic Kidney Disease Epidemiology Collaboration 2009 equation)[8] measured within 48 hours of hospital admission was considered for analysis. Baseline renal function was defined by the lowest plasma creatinine values (or highest estimated GFR), which was reported between 3 to 12 months before admission. A global cohort of 1897 patients was identified. From this global cohort, patients with either unknown or baseline renal function ≥60 mL/min/1.73 m^2 were excluded (n=224 [14.2%] and n=498 [31.6%], respectively). Other exclusion criteria were lacking or incomplete medical records (n=98), end-stage renal disease on dialysis (n=291), solid organ transplant (n=196), metastatic cancer (n=131), or

TABLE I. Dosing of Most Prescribed ACE Inhibitors and ARBs

Drug Name	Renal/Hepatic Excretion	Maximal Dosage in Renal Dysfunction, mL/min[a]	Maximal Dosage Across All Indications	American Manufacturer's Recommendations[b]
ACE inhibitors				
Captopril	100%/0%	≥50: 100 mg/d 20–49: 50 mg/d <20 or HD or DP: contraindicated except for specialist	150 mg/d	10–50: 75% normal dosage <10: 50% normal dosage Maximal dosage: 450 mg/d
Lisinopril	100%/0%	Adaptation of the starting dose then titrate to a maximum dosage of 40 mg/d	40 mg/d HTN: 80 mg/d	Idem
Perindopril arginine	100%/0%	≥60: 5 mg/d 30<Clr<60: 2.5 mg/d 15<Clr<30: 2.5 mg 1 d/2 HD: 2.5 mg dialysis day	10 mg/d	Not found
Ramipril	100%/0%	≥60: 10 mg/d 30<Clr<60: 5 mg/d 15<Clr<30: 5 mg/d HD: 5 mg dialysis day	10 mg/d	<40: 5 mg/d <10: 25% to 50% of the normal dosage Maximal dosage: 20 mg/d
ARBS				
Candesartan	33%/67%	Adaptation of the starting dosage then titrate <15: limited experience	32 mg/d	Idem
Losartan	10%/90%	Dosage adjustment not required unless patient is volume depleted	150 mg/d	Maximal dosage: 100 mg/d
Olmesartan		20–60: 20 mg/d <20: contraindicated to limited experience	40 mg/d	Dosage adjustment not required
Telmisartan	0%/100%	Mild to moderate CKD: dosage adjustment not required Severe CKD: adaptation of the starting dosage	80 mg/d	Idem
Valsartan	30%/70%	>10: dosage adjustment not required <10: caution	320 mg/d	<30: caution

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; Clr, clearance; DP, peritoneal dialysis; HD, hemodialysis; HTN, hypertension; Idem, same as European manufacturer's recommendations.

[a]Adapted from official European manufacturer's recommendations (May 21, 2015).

[b]Adapted from official American manufacturer's recommendations (May 21, 2015).

subsequent admission to the intensive care unit (n=135). A total of 324 patients with moderate to severe CKD constituted the final data set.

Assessment of AKI

AKI was defined and classified into three stages according to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.[4] We did not consider urinary output criteria because it was not reported in many cases and the risk of it being inaccurately reported could not be estimated in a retrospective design. Presence or absence of AKI at admission was defined by the comparison between baseline and admission plasma creatinine levels as defined by KDIGO guidelines.[4] Causes of AKI were defined on the basis of the admission emergency medical records and were subdivided into four groups: prerenal (ie, dehydration, low circulating volume), septic, renal origin, and obstructive. The length of AKI was defined as the time needed to reach the baseline value. If the length of AKI was greater than 3 months or if AKI resulted in permanent dialysis, length of AKI was considered to be permanent. The length of AKI was unknown in 14 of the 129 AKI patients identified (10.8%).

Assessment of RAS Blocker Intake

The use of RAS blockers was noted from the admission emergency medical record and confirmed from an additional medical record dating back at least 3 months. RAS blockers were classified into two groups: ACE inhibitors and ARBs. Only one patient was taking a combination of a direct renin inhibitor (aliskiren) and an ACE inhibitor. Dose adjustment of RAS blockers according to baseline renal function was assessed in accordance with manufacturer's recommendations (Table I). Then, ACE inhibitor intake was subdivided in two groups: overdose and normal dose (including submaximal dose and maximum daily dose). Finally, in cases of AKI, suspension of the RAS blocker prescription by the emergency doctor was noted.

Data Collection

The main clinical and biological characteristics reported in the literature as risk factors for AKI were considered.[4] A detailed cross-sectional analysis of electronic medical records was undertaken for demographic and clinical data, which included age, sex, hemodynamic parameters at admission, medical history (hypertension, diabetes, dyslipidemia, CKD, coronary artery disease, peripheral artery disease, stroke, heart failure and reduced left ventricular ejection fraction, respiratory disease, malignancy), medication history (eg, diuretics, aldosterone antagonists, β-blockers, calcium channel blockers, α-blockers, sympathetic blockers, antithrombotic therapies, calcium supplements, nonsteroidal anti-inflammatory drugs), emergency diagnosis, and admission and baseline laboratory data including plasma creatinine and potassium. Peak systolic blood pressure, diastolic blood pressure, and heart rate were noted from admission emergency medical system field records. The primary diagnosis from the emergency admission record was retrieved. The most common emergency diagnoses were cardiovascular disease, sepsis, trauma, neurologic disease, and dehydration. The diagnosis of sepsis was confirmed according to standard criteria.[9] The diagnosis of dehydration was considered according to the fact that diagnosis of dehydration was clearly mentioned within the emergency admission report or the diagnosis of dehydration could be strongly supported by a combination of the following items that were found within the emergency report: (1) medical history (diarrhea, vomiting, blood loss, thirsty, heat wave, history of a lack of access to water because of disability, sweat, burns, and third-space sequestration, including intestinal obstruction, fracture, and acute pancreatitis);[10] (2) physical examination (severe postural dizziness, dry axilla, dry mouth, dry skin, dry mucous membranes, decreased skin turgor, prolonged capillary refill time, reduced jugular venous pulse);[10] (3) hemodynamic parameters (postural hypotension); (4) laboratory data (serum urea nitrogen/creatinine ratio >20:1, natremia >150 mmol/L, hematocrit >50%, serum albumin concentration >50 g/L, urine sodium concentration <20 meq/L, fractional excretion of sodium <1%, fractional excretion of urea <35%, and urine osmolality >450 mOsm/kg). When available, proteinuria was retrieved from the 24-hour or spot urine collection closest to the index admission. When available, left ventricular ejection fraction as assessed by transthoracic echocardiography (biplane Simpson, Teicholz method) was also collected from the medical records. Finally, the hospital length of stay was assessed.

Statistical Analysis

Analyses were conducted on the total number of index admissions (n=324). The admissions were stratified into two groups: AKI vs no AKI. Gaussian distribution was evaluated by Kolmogorov-Smirnov test.

Comparisons between nonbinary variables were performed with either two-sample *t* tests (parametric parameters) or Mann-Whitney *U* test for nonparametric parameters, otherwise a Wilcoxon rank-sum test was used. Categorical variables were studied using the chi-square test. Results were expressed as percentage of the total for nominal variables and as mean and standard deviation or as medians with interquartile (25th and 75th percentiles) range for parametric and nonparametric numerical variables. The variables included in the analyses were age, sex, hemodynamic parameters at admission, medical history, chronic treatments, emergency diagnosis, admission, and baseline laboratory data including plasma creatinine and potassium. Thereafter, the variables with *P* values <.05 in the univariate analysis were inserted into a stepwise logistic regression analysis to identify risk factors for AKI. A second univariate analysis was also performed in the groups of patients with and without RAS blockers. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were derived from the final logistic models. All analyses were performed with Stata software (Stata, version 11.2; StataCorp, College Station, TX), and a *P* value <.05 was considered statistically significant.

RESULTS

Incidence and Risk Factors for AKI

A total of 324 patients were included in the final data set (Table II). Most of the patients were elderly, with a mean age of 77±12.1 years, and 49.1% were male. Accordingly, moderate to severe CKD was frequent (eg, 70.4% were stage 3B, ie, <45 mL/min/1.73 m^2) with a mean baseline GFR of 34.5±7.8 mL/min/1.73 m^2. AKI was observed in 40% of cases (129 of 324). Most AKI patients (91.5%) presented with stage 1 disease, mainly of prerenal (68.6%) or septic (26.3%) origin. After univariate analysis, the main risk factors for AKI were younger age, male sex, chronic use of three or more different antihypertensive drugs, peripheral arterial disease, low systolic blood pressure at the time of admission, and dehydration (Table II and Table III). Interestingly, only the chronic use of ACE inhibitors was associated with both AKI (OR, 2.1; 95% CI, 1.2–3.7; *P*=.0054) and hyperkalemia (ie, >5 mmol/L; OR, 2.63; CI, 95%: 1.25–5.93; *P*=.006), whereas ARBs were not (Table II and Table III). After stepwise regression analysis (for the above variables), both ACE inhibitors (OR, 1.9; 95% CI, 1.1–3.1; *P*=.02) and dehydration (OR, 30.8; 95% CI, 3.9–239.1) were independently associated with AKI.

The Role of ACE Inhibitor Overdose in the Occurrence of AKI

We identified 210 patients who took long-term RAS blockers. ACE inhibitors were more frequently noted than ARBs (59% vs 41%). As expected, patients taking RAS blockers had a higher prevalence of arterial hypertension (92.2% vs 74.8%; *P*<.0001), diabetes mellitus (42.4% vs 29.4%; *P*=.02), dyslipi-

TABLE II. Baseline Demographic and Clinical Characteristics of Admissions According to the Presence or Absence of AKI

Ville	All Patients (N=324)	No AKI (n=195)	AKI (n=129)	*P* Value
Age, y	77±12.1	77.9±12	75.6±12.2	**.0379**
Men, %	49.1	44.6	55.8	**.0484**
Baseline biochemistry				
Baseline serum creatinine, mg/dL	1.77±0.5	1.8±0.6	1.8±0.5	.22
Baseline eGFR, mL/min/1.73 m^2	34.6±7.8	34.5±8.2	34.6±7.2	.64
Baseline K^+, mmol/L	4.3±0.5	4.3±0.6	4.3±0.5	.72
Comorbidities				
Hypertension, %	86	82.6	90.7	**.04**
Refractory hypertension, %	19.1	16.4	23.3	.13
Hypertension with triple therapy, %	43.2	36.4	53.5	**.002**
Diabetes, %	37.6	34.4	42.6	.13
Dyslipidemia, %	49.4	46.7	53.5	.23
CKD stage 4, %	28.4	28.7	29.5	.89
Proteinuria, %	71.2	71.7	70.5	.91
Proteinuria stage 3, %	4.9	5.1	4.6	.85
Coronary artery disease, %	33	32.3	34.1	.74
Peripheral artery disease, %	17.3	13.85	22.48	**.04**
Stroke, %	14.2	11.3	18.6	.07
Heart failure, %	25.3	26.15	24.03	.67
LVEF <45%, %	21.3	23.7	17.8	.3051
Cardiovascular disease, %	25.3	26.1	24	.76
Respiratory disease, %	36.1	18.5	19.4	.84
Malignancy, %	19.1	20.5	17	.53
Medications				
RAS blockade, %	63.3	58.5	70.5	**.04**
Maximal dosage, %	87.3	84.2	91.2	.2
Overdose, %	29.8	24.6	36.3	.1
ACE inhibitor, %	37.3	31.3	46.5	**.006**
Maximal dosage, %	89.3	86.9	91.7	.58
Overdose, %	45.5	41	50	.42
ARBs, %	25.9	26.2	25	.76
Maximal dosage, %	84.5	81.1	90.3	.42
Overdose, %	7.1	5.7	9.7	.8
Diuretics, %	54.3	51.8	58.1	.26
Aldosterone blockers, %	11.7	10.3	13.95	.31
β-Blockers, %	57.7	53.85	63.6	.08
Calcium channel blockers, %	39.8	36.4	45	.124
α-Blockers, %	2.5	0	6.2	**<.0001**
Sympathetic blockers, %	10.2	8.2	13.2	.147
Three or more antihypertensive drugs, %	18.6	16.4	23.3	.125
Antithrombotic therapy, %	73.5	70.3	78.3	.109
Calcium supplement, %	26.8	22.6	33.3	**.032**
Erythropoietin, %	5.6	4.6	7	.364
Nonsteroidal anti-inflammatory drugs, %	2.5	1.5	3.9	.184

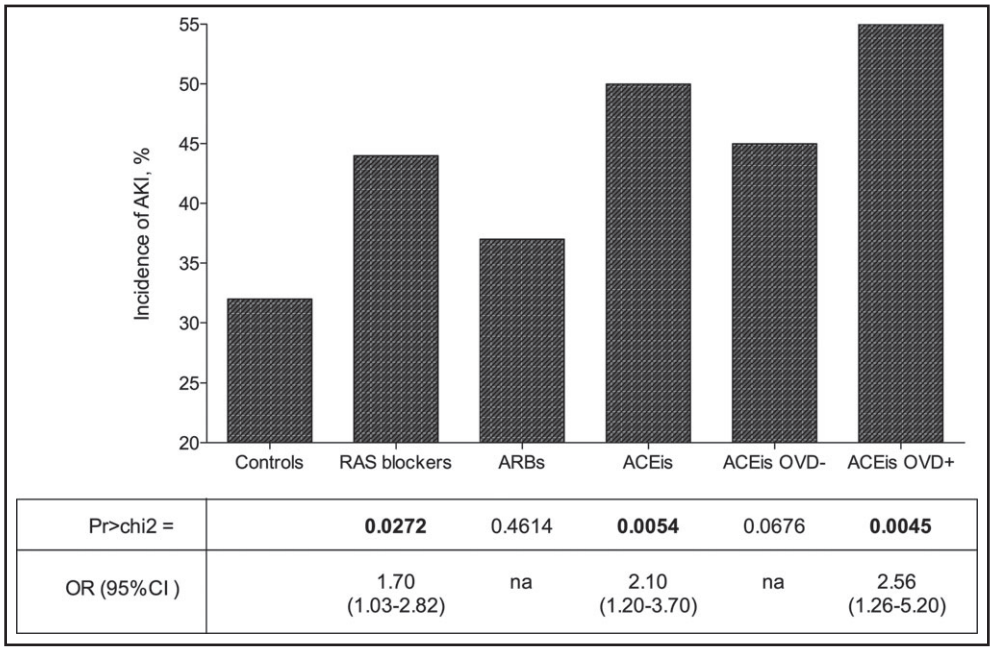
Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; K+, potassium; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system. Bold values indicate significance.

demia (54.6% vs 40.3%; *P*=.01), and proteinuria (ie, >300 mg/g creatinine or 300 mg/24 h) (6.8% vs 1.7%; *P*=.04). Patients taking RAS blockers were also more likely to take diuretics (59.5% vs 45.4%; *P*=.01), calcium channel blockers (43.9% vs 32.8%; *P*=.0485), three or more antihypertensive drugs (57.6% vs 18.5%; *P*<.0001), or antithrombotic therapy (77.6% vs 66.4%; *P*=.03). Interestingly, overdose of RAS blockers in relation to baseline renal function was observed in 45% of patients taking ACE inhibitors but was negligible (0.07%) in patients taking ARBs. In comparison to the patients who were naive for RAS blockers, patients who were taking an overdose of ACE inhibitors exhibited a higher risk for

TABLE III. Clinical Characteristics of Patients According to the Presence or Absence of AKI on Admission

	All Patients (N=324)	No AKI (n=195)	AKI (n=129)	*P* Value
Admission biochemistry				
eGFR, mL/min/1.73 m^2	30.1±9.1	34.7±7.6	23.2±6.4	**<.0001**
Serum creatinine, mg/dL	2.1±0.8	1.7±0.5	2.6±0.8	**<.0001**
K^+, mmol/L	4.3±0.6	4.2±0.5	4.4±0.77	**.0023**
Admission hemodynamic parameters				
SBP, mm Hg	138±28	142±28	132±27	**.0028**
SBP <120 mm Hg, %	25.4	21.35	32	**.0474**
Heart rate, beats per min	83±19	83±18	84±20	.6582
Temperature, °C	36.5±0.7	36.5±0.7	36.5±0.8	.6926
Emergency diagnostics				
Unknown, %	2.1	3.1	0.8	.163
Sepsis, %	22.8	21	25.6	.339
Trauma, %	9.3	11.3	6.2	.122
Cardiovascular disease, %	21.9	25.6	16.3	.046
Dehydration, %	5.2	0.5	12.4	**<.0001**
Ionic disturbance, %	1.8	0.5	3.9	.028
Various, %	24.7	22.6	27.9	.275
Decompensated liver disease, %	1.8	2.05	1.55	.743
Neurologic disease, %	8.6	11.3	4.65	.038
Outcomes				
Hospitalization length, d	10.5±14	9.3±11.6	12.4±16.9	**.0042**
Stop RAS blockade, %	10.1	5.3	15.4	**.01**
Stop RAS blockade if overdose, %	8.7	4.2	13.2	.03
Stop RAS blockade if AKI recognized, %			17.6	
Stop RAS blockade if AKI no recognized, %			5.6	

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; K^+, potassium; RAS, renin-angiotensin system; SBP, systolic blood pressure. Bold values indicate significance.



Pr>chi2 =	**0.0272**	0.4614	**0.0054**	0.0676	**0.0045**
OR (95%CI)	1.70 (1.03-2.82)	na	2.10 (1.20-3.70)	na	2.56 (1.26-5.20)

FIGURE. Incidence of acute kidney injury (AKI) compared with controls depending on the class and dose of renin-angiotensin-aldosterone system (RAS) blockers. OR indicates odds ratio; ARB, angiotensin receptor blockers; ACEis, angiotensin-converting enzyme inhibitors; OVD, overdosed; CI, confidence interval; na, not available.

AKI (OR, 2.56; 95% CI, 1.26–5.20; *P*=.0045) (Figure).

Outcomes of AKI and the Use of RAS Blockers

Mean length of stay was prolonged by 3 days in the case of AKI (Table III). In cases of AKI, the chronic use of RAS blockers was associated with longer length of AKI (3.5±4.5 days [n=17] vs 5.4±6.5 days [n=42], *P*=.0474). However, despite the association of RAS blocker use with both AKI and subsequent prolonged length of stay, overdosing was not a determinant in length of stay. In this context, a trend in longer AKI was observed when an overdose of RAS blockers was prescribed in comparison to optimal doses of RAS blockers (6.8±8.9 [n=19] vs 4.2±3.1 [n=23], *P*>.05). Early recognition of AKI was missed in 42% of cases (54 of 129) in the emergency department. Moreover, early suspension of RAS blocker administration was performed in only 16% of AKI cases, regardless of whether AKI was identified (22%) or not (8%).

Prevalence of Antihypertensive Drugs Other Than RAS Blockers

Calcium channel blockers (CCBs) and diuretics were prescribed in 39.8% and 57% of our patients, respectively. Diuretics alone or in combination found in our study were hydrochlorothiazide (43% of patients taking diuretics) and/or one of the following (57% of patients taking diuretics): indapamide, chlorthalidone, furosemide, or bumetamide. Neither CCBs or diuretics alone or CCBs or diuretics plus RAS blockers were associated with AKI (*P*>.05). Overall, β-blockers and spironolactone were prescribed in 57.7% and 11.7% of patients, respectively. Spironolactone or β-blockers were not associated with RAS blocker use or with AKI (*P*>.05).

DISCUSSION

Limited data exist regarding community-acquired AKI. In our study, 40% of patients with CKD admitted to the emergency department had community-acquired AKI. Although this rate is far higher than the incidence rate found in the largest study on community-acquired AKI,[11] this is likely explained by our selection criteria that focused our study on patients most susceptible to AKI who present with frequent comorbidities such as moderate to severe CKD, diabetes mellitus, arterial hypertension, and older age.[3,4] Accordingly, the mean age of our cohort was 77 years, which is consistent with other epidemiologic studies on community-acquired AKI.[11,12] Elderly patients taking RAS blockers are prone to AKI and hyperkalemia because of their specific risk for complete inhibition of RAS.[13] Although some trials have suggested that RAS blockers are safe in patients with severe CKD,[14,15] our data clearly contrast with this observation, as more than 44% of our CKD patients taking a RAS blocker experienced AKI. Trials on RAS blockers may have observed fewer adverse events attributable to close monitoring of highly selected patients included in the trial. This situation differs significantly from our study, which involved unselected elderly patients with a high comorbidity burden. Unfortunately, these frail patients are usually excluded from almost all trials and scientific data on them are missing.[16–19] Furthermore, the specific effect of RAS blockers on slowing CKD may be inadequate in the elderly because they have a slow renal deterioration rate and often die before reaching end-stage renal disease.[20] RAS blocker discontinuation may even delay the progression of CKD to end stage renal disease in the elderly.[21,22] However, the debate is not closed, as the benefit of using RAS blockers may exceed the risks in patients with high proteinuria (ie, ≥1 g/d).[23] From this point of view, the incidence of AKI that we report in this population highlights the need to assess the risk-benefit balance and to monitor these patients carefully.

ARBs and ACE inhibitors present substantial pharmacologic differences.[7] ACE inhibitors block ACE and therefore may inhibit both receptors of angiotensin II (ie, AT_1 and AT_2) but also affect the degradation of kinins. In contrast to ARBs, the antihypertensive effect of ACE inhibitors can be blurred by different factors. Accordingly, ACE inhibitors lead to a fall in circulating angiotensin II, with a subsequent increase in renin release that partially returns angiotensin II levels toward baseline. Moreover, alternative enzymatic pathways (eg, chymase) may produce angiotensin II independently of ACE (eg, within the myocardium and blood vessels). In contrast, ARBs inhibit most of the biological effects of angiotensin II, without modifying the amount of circulating angiotensin II. Because of this action on the terminal effector (ie, angiotensin II), ARBs provide a more complete and powerful blockade of RAS in comparison to ACE inhibitors. In our data, despite these effects that lead to the strong inhibition of the AT_1 receptor, ARBs were not associated with an excess risk of AKI, whereas ACE inhibitors did. More accurately, excess risk of AKI is almost exclusively caused by overdose in ACE inhibitors. Contrary to ARBs, which are cleared by the liver, ACE inhibitors are mainly cleared by the kidneys (Table I) and can accumulate in cases of CKD and induce a chronically maximal RAS inhibition. If this is associated with a minimal insult (eg, mild dehydration), it could compromise renal function. From a pharmacologic point of view, it is reasonable to assume that a long-term accumulation of an overdose of ACE inhibitor in cases of CKD could lead to higher RAS inhibition than ARBs. In addition, we noted a trend in longer AKI in cases of ACE inhibitor overdose (6.8±8.9 [n=19] vs 4.2±3.1 [n=23], *P*>.05). This suggests that the elimination rate of the drug (ie, ACE inhibitors or ARBs) could be an important determinant of AKI and that renal clearance of ACE inhibitors could be an important difference in this case. Certainly many other factors related to the differences between ACE inhibitors and ARBs pharmacokinetics and pharmacodynamics could contribute to the occurrence of AKI. However, we did not find any literature comparing the

blockade of AT_1 by ACE inhibitors and ARBs in the context of AKI, and our retrospective design is limiting in this context. Despite this limitation, as mentioned in some guidelines on AKI, strategies to avoid potential drug accumulations and subsequent AKI should be encouraged.[3,4] Accordingly, the preferential use of drugs metabolized primarily by the liver such as ARBs should be discussed. This question should be specifically addressed in large-scale prospective studies. In addition, the dose adjustment to renal function, the regular monitoring of kidney function, and the interruption of drug administration during intercurrent illness are mandatory when using ACE inhibitors, especially in patients who are at high risk for intravascular volume depletion.[24]

Unfortunately, roughly 42% of AKI cases were not diagnosed at the time of admission in the emergency department. This proportion of missed AKI is in line with a recent epidemiological study.[25] This could be explained by the fact that almost all AKIs were stage 1. Despite clear statement in the KDIGO guidelines, this small increase in plasma creatinine was likely not considered clinically relevant by the clinicians in charge of the patients. However, delay in recognizing mild AKI often leads to more severe AKI by delaying nephrotoxic drug withdrawal and sufficient increase in volume perfusion. As has been reported previously, we observed that even stage 1 AKI increased the risk of adverse outcome.[26] For instance, it was associated with a doubling of the time of length of stay in our cohort.

Despite the acute rise in plasma creatinine, RAS blockers were rarely suspended at the time of emergency admission. Although this might be expected in cases of missed AKI, it was more surprising to observe the same scenario in cases of identified AKI. This resulted in prolonged administration of RAS blockers in situations of AKI, which require optimal renal hemodynamics to recover. Although our study was not powered to detect this type of difference, we noted a trend showing that sustained administration of RAS blockers in cases of AKI may result in prolonged length of AKI. Absence of RAS blocker discontinuation despite the occurrence of AKI could be attributable to two main factors: first, some may argue that stage 1 AKI is an expected result of introduction of RAS blockers.[27] However, the study design excluded this misdiagnosis and all patients were taking RAS blockers at the time of CKD stage evaluation at least 3 months before index admission. Second, the RAS blockers were not stopped because AKI was often not recognized. The practice of suspending RAS blockers during mild AKI is still debated.[28–31] Inhibiting angiotensin II using RAS blockers raises the risk of prerenal AKI but may reduce the risk of renal AKI. Indeed, they may decrease tubular cell necrosis during ischemic insults such as dehydration or sepsis by increasing renal blood flow and oxygenation through the vasodilation of efferent arterioles.[30,31] Nevertheless, CKD is accompanied by failure of vascular autoregulation, which probably does not permit an increase of renal blood flow because of RAS blockers.[32] In this study, RAS blockers doubled AKI duration. We postulated that, in CKD patients, RAS blockers could promote the evolution from a prerenal AKI to true tubular injury, which would take longer to be resolved. Duration of AKI seems to be an independent predictor of in-hospital mortality in several studies.[33,34] Adapting the dosing of ACE inhibitors to renal function and discontinuing ACE inhibitor administration in cases of AKI could minimize the duration of AKI.

STUDY STRENGTHS AND LIMITATIONS

Our study has several strengths. First, to the best of our knowledge, this is the only study to describe the association between AKI and RAS blockers according to the method of dose adaptation to estimated GFR and the category of RAS blockers. Second, only patients with true CKD, as defined by KDIGO guidelines, were included in the study (ie, based on the definition of baseline renal function).[1] Third, we included information on causes of AKI, which is important to interpret the results of RAS blocker side effects. Finally, a particular strength of our study was to include elderly patients who are underrepresented in the main trials on RAS blockers. This model also has limitations for a single-center retrospective study. The sample size is relatively small. The population in this study excluded severely ill patients who were admitted to the intensive care unit or patients who underwent transplantation. Thus, results may lack external validity. In addition, we limited the definition of AKI to the modification in plasma creatinine level because exact data regarding urine output were not available.[4] Finally, we have not been able to control our model for all known confounders, which may attenuate the relationship between AKI and ACE inhibitors.

CONCLUSIONS

The main results from this study show that the frequency of dose adjustment of ACE inhibitors to actual renal function of patients with CKD is insufficient. The lack of dose adjustment increased the risk of community-acquired AKI, which led to prolonged hospital length of stay. In contrast, ARBs seem to be less harmful in moderate to severe CKD, possibly in part because of their hepatic clearance, which reduces the risk of accumulation in patients with acute-on-chronic renal failure. Current strategies that can be used to minimize the risk of AKI include stopping RAS blockers in case of dehydration, respecting manufacturer recommendations on dose adjustment of ACE inhibitors to renal function, and perhaps the preferential use of ARBs in patients with CKD. However, these questions should be addressed in large prospective studies. Finally, there is a need to systematically determine the risks and benefits of RAS blockers to prevent progression of proteinuric CKD in elderly patients.

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References

1. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825–830.
2. Onuigbo MAC, Onuigbo NTC. Late-onset renal failure from RAAS blockade. *Kidney Int*. 2006;70:1378–1379.
3. Ftouh S, Thomas M. Acute kidney injury: summary of NICE guidance. *BMJ*. 2013;347:f4930.
4. Eknoyan G, Lameire N, Eckardt KU, Kasiske BL. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
5. Canaud G, Bonventre JV. Cell cycle arrest and the evolution of chronic kidney disease from acute kidney injury. *Nephrol Dial Transplant*. 2015;30:575–583.
6. Suzuki H, Kanno Y, Ikeda N, et al. Selection of the dose of angiotensin converting enzyme inhibitor for patients with diabetic nephropathy depends on the presence or absence of left ventricular hypertrophy. *Hypertens Res*. 2002;25:865–873.
7. Smith TW, Morgan JP. Differences between angiotensin-converting enzyme inhibitors and receptor blockers. In: Bakris JP, ed. *UpToDate*. http://www.uptodate.com/contents/differences-between-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers. Accessed December 29, 2015.
8. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
9. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med*. 2015;372:1629–1638.
10. McGee S, Abernethy WB III, Simel DL. Is this patient hypovolemic? *JAMA*. 1999;281:1022–1029.
11. Wonnacott A, Meran S, Amphlett B, et al. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol*. 2014;9:1007–1014.
12. Talabani B, Zouwail S, Pyart RD, et al. Epidemiology and outcome of community-acquired acute kidney injury. *Nephrology*. 2014;19:282–287.
13. Abdel-Kader K, Palevsky PM. Acute kidney injury in the elderly. *Clin Geriatr Med*. 2009;25:331–358.
14. GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*. 1997;349:1857–1863.
15. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med*. 2006;354:131–140.
16. Brody H, Light DW. The inverse benefit law: how drug marketing undermines patient safety and public health. *Am J Public Health*. 2011;101:399–404.
17. Suzuki H, Kikuta T, Inoue T, Hamada U. Time to re-evaluate effects of renin-angiotensin system inhibitors on renal and cardiovascular outcomes in diabetic nephropathy. *World J Nephrol*. 2015;4:118.
18. O'Hare AM, Hailpern SM, Pavkov ME, et al. Prognostic implications of the urinary albumin to creatinine ratio in veterans of different ages with diabetes. *Arch Intern Med*. 2010;170:930–936.
19. Sarafidis PA, Bakris GL. Does evidence support renin-angiotensin system blockade for slowing nephropathy progression in elderly persons? *Ann Intern Med*. 2009;150:731–733.
20. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol*. 2007;18:2758–2765.
21. Onuigbo MA, Onuigbo NT. Late-onset renal failure from angiotensin blockade (LORFFAB) in 100 CKD patients. *Int Urol Nephrol*. 2008;40:233–239.
22. Ahmed AK, Kamath NS, El Kossi M, El Nahas AM. The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant*. 2010;25:1344–1345.
23. Kent DM, Jafar TH, Hayward RA, et al. Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. *J Am Soc Nephrol*. 2007;18:1959–1965.
24. Stirling C, Houston J, Robertson S, et al. Diarrhoea, vomiting and ACE inhibitors–an important cause of acute renal failure. *J Hum Hypertens*. 2003;17:419–423.
25. National Confidential Enquiry Into Patient Outcome and Death Smith N, Stewart J, Findlay G. *Acute kidney injury: adding insult to injury*. http://www.ncepod.org.uk/2009aki.htm. Accessed January 27, 2016.
26. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365–3370.
27. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor–associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160:685–693.
28. Coca SG, Garg AX, Swaminathan M, et al; TRIBE-AKI Consortium. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. *Nephrol Dial Transplant*. 2013;28:2787–2799.
29. Auron M, Harte B, Kumar A, Michota F. Renin-angiotensin system antagonists in the perioperative setting: clinical consequences and recommendations for practice. *Postgrad Med J*. 2011;87:472–481.
30. Barodka V, Silvestry S, Zhao N, et al. Preoperative renin-angiotensin system inhibitors protect renal function in aging patients undergoing cardiac surgery. *J Surg Res*. 2011;167:e63–e69.
31. Shah M, Jain AK, Brunelli SM, et al. Association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use prior to major elective surgery and the risk of acute dialysis. *BMC Nephrol*. 2014;15:53.
32. Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012;379:165–180.
33. Wu HC, Wang WJ, Chen YW, Chen HH. The association between the duration of postoperative acute kidney injury and in-hospital mortality in critically ill patients after non-cardiac surgery: an observational cohort study. *Ren Fail*. 2015;37:985–993.
34. Coca SG, King JT, Rosenthal RA, et al. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. *Kidney Int*. 2010;78:926–933.