Chronic use of Renin-Angiotensin-Aldosterone-System blockers and mortality in COVID-19: a multicenter prospective cohort and literature review

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Short title: RAAS blockers and mortality in COVID-19

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ABSTRACT

Aims: The role of renin-angiotensin-aldosterone system (RAAS) blockers on the course of coronavirus disease 2019 (COVID-19) is debated. We assessed the association between chronic use of RAAS blockers and mortality among inpatients with COVID-19, and explored reasons for discrepancies in the literature.

Methods and results: We included adult hypertensive patients from a prospective nationwide cohort of 3512 inpatients with COVID-19 up to June 30, 2020. Cox proportional hazard models with various adjustment or propensity weighting methods were used to estimate the Hazard Ratios (HR) of 30-day mortality for chronic users versus non-users of RAAS blockers.

We analyzed data of 1160 hypertensive patients; 719 (62%) were male, 777 (67%) were older than 65 years. The main comorbidities were diabetes (n=416, 36%), chronic cardiac disease (n=401, 35%) and obesity (n=340, 29%); 705 (61%) received oxygen therapy. We recorded 135 (11.6%) deaths within 30 days of diagnosis. We found no association between chronic use of RAAS blockers and mortality (unadjusted HR=1.13, 95% CI [0.8-1.6]; propensity inverse probability treatment weighted HR=1.09 [0.86-1.39]; propensity standardized mortality ratio weighted HR=1.08 [0.79-1.47]). Our comprehensive review of previous studies highlighted that significant associations were mostly found in unrestricted populations with inappropriate adjustment, or with biased in-hospital exposure measurement.

Conclusion: Our results do not support previous concerns regarding these drugs, nor a potential protective effect as reported in previous poorly designed studies and metanalyses. RAAS blockers should not be discontinued during the pandemic, while in-hospital management of these drugs will be clarified by randomized trials. NCT04262921

KEYWORDS: hypertension; mortality; COVID-19; angiotensin antagonists; propensity score;

RAAS blockers

LIST OF ABREVIATIONS

angiotensin converting enzyme (ACE)

angiotensin-converting enzyme 2 (ACE2)

angiotensin receptor blockers (ARBs)

confidence interval (CI)

coronavirus disease 2019 (COVID-19)

Multiple imputation by chain equations (MICE)

renin-angiotensin-aldosterone system (RAAS)

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

INTRODUCTION

The potential influence of renin-angiotensin-aldosterone system (RAAS) blockers on the course of Coronavirus Disease 2019 (COVID-19) has been a matter of controversy.

Early in the pandemic, it has been suggested that cardiovascular comorbidities such as hypertension, diabetes and coronary heart disease were risk factors for severe COVID-19 [1-3] with the potential explanation that these conditions are frequently treated with RAAS blockers. The underlying rationale came from animal studies showing an increased expression of angiotensin-converting enzyme 2 (ACE2), the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the presence of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) [4, 5]. However, other animal[6] and human [7] studies did not confirm these findings, and more importantly, there are no data demonstrating an increased expression of the transmembrane ACE2 protein in the lungs [8].

Conversely, robust animal data showed that ACE2 might be beneficial in the context of acute lung injury[9, 10]. Indeed, ACE2 converts angiotensin II to angiotensin 1-7, a peptide with vasodilating, antifibrotic and anti-inflammatory properties, opposite to those of angiotensin II. Therefore, modulating ACE-angiotensin II and ACE2-angiotensin (1-7) pathways using RAAS blockers might actually be beneficial in patients with COVID-19[11], especially as ACE2 might be downregulated during SARS-CoV-2 infection [8, 10].

While several clinical trials are ongoing to establish whether RAAS blockers should be maintained, discontinued, or even introduced *de novo* in patients with COVID-19, a number of observational studies have attempted to establish the association between chronic use of RAAS blockers and the risk of contracting the infection and/or developing a severe or lethal form of COVID-19. Several large studies consistently ruled out a significant association between the chronic use of RAAS blockers and the risk of a positive test for SARS-CoV-2 [12-14]. Conversely, studies on the association between exposure to RAAS blockers and severity of the disease have yielded discrepant results, largely explained by disparities in study design, selected populations, study size, exposure measurement, and adjustment methodologies - if any [14-23].

The aim of this pharmacoepidemiologic study was to analyze the association between the chronic use of RAAS blockers and mortality of COVID-19 in a large national multicenter prospective cohort of hospitalized patients in France.

METHODS

The French-Covid cohort (ClinicalTrials NCT04262921) of inpatients with RT-PCR virologically-confirmed COVID-19 was set-up at the end of January 2020 in 198 centers in France [24]. Patients were included at admission, and followed daily during hospital stay, and at 1, 3 and 6 months after discharge. The study was sponsored by INSERM (the French national institute for health and medical research). As at end of June 2020, 3512 patients admitted to hospital with COVID-19 were included in the cohort. We analyzed data from adult patients with a history of hypertension. The diagnosis of hypertension was gathered from the medical history based on the medical interview at admission, independently of blood pressure measurement at admission, and of the use of antihypertensive medication. In patients with hypertension, chronic treatment with RAAS blockers was collected. Patients with missing data regarding treatment prior to admission, and pregnant women were excluded from the present analyses (Figure 1). Exposure was defined as the chronic use of RAAS blockers (i.e. either ACE inhibitors or ARBs reported as part the chronic treatment at inclusion in the cohort). Patients reporting neither ACE inhibitors nor ARBs were considered as non-users. The outcome was death within 30 days of diagnosis.

Statistical analyses

Baseline characteristics were reported according to the chronic use of any RAAS blocker. Propensity score for the use of RAAS blockers was calculated by logistic regressions performed on five imputed datasets. Multiple imputations by chain equations (MICE) were performed for baseline characteristic with less than 20% missing values. Propensity score included the following variables collected at admission and assumed to be associated with the outcome: age, gender, healthcare worker, microbiology laboratory worker, geographical region of inclusion, chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, immunosuppressive

therapy, immunosuppressive disease, chronic neurological disorder including dementia, obesity, diabetes, malnutrition, and number of days with symptoms before positive RT-PCR. Overlapping of propensity score distributions among users and non-users of RAAS blockers was checked graphically. The propensity score distribution among treated and non-treated patients showed good overlap (Supplemental Figure S1). After weighting, no more imbalances are observed (Supplemental Figure S2).

Hazard ratios of mortality for patients with chronic use of RAAS blockers versus non-use and their 95% confidence interval (CI) were estimated using Cox proportional hazard models with adjustment, and two types of weighting (inverse probability of treatment – IPTW, and standardized mortality ratio – SMR), in order to control for confounding.

In secondary analyses, patients receiving both ACE inhibitors and ARBs were excluded, and ACE inhibitors and ARBs were analyzed separately.

A sensitivity analysis included additional variables in the propensity score, which reflected severity at admission, and may be intermediaries in the causal diagram leading to overfitting: symptoms at admission (respiratory rate ≥30/min; systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg), need for oxygen therapy within 2 days after admission, level of C-reactive protein at admission.

All p-values are two-sided. Statistically significant level was predefined at 5%. Detailed methods are described in the supplemental methods.

Comprehensive review of the literature

We performed a review of observational studies and meta-analyses — excluding preprints — on the association between RAAS blockers and outcome of COVID-19 published until November 2020. We systematically searched PubMed with no language restriction and starting from January 2020, using the terms “Renin-angiotensin-(aldosterone)-system”, “angiotensin converting enzyme 2”, “angiotensin converting enzyme inhibitors”, ”angiotensin receptor blockers”, “coronary artery disease” or their acronyms, and synonyms or various combinations

of those words to identify systematic reviews, observational studies, trials, and meta-analyses describing the relationship between RAAS blockers and outcome in COVID-19. We also screened cited reports from the full texts of original articles for other relevant research, and all individual studies from reviews and meta-analyses were analyzed for potential relevance. We screened reports by title and abstract, and title and full text in letters, to identify articles relevant for the study aim. Two authors independently extracted structured information on design, setting, population, exposure, outcomes, statistical methods, results, and conclusion of the authors.

RESULTS

Between February 28 and June 30, 2020, 3512 patients were included in the French-Covid cohort, of whom 1160 hypertensive patients were analyzed (Figure 1). Median age was 70 years (interquartile range 61;78), 62% (n=719) were male. The most common comorbidities, besides hypertension, were diabetes (n=416, 36%), chronic cardiac disease (n=401, 35%), and obesity (n=340, 29%); 61% (n=705) received oxygen therapy within 2 days of admission (Table 1). Detailed laboratory results are reported in Supplemental Table S1. Median follow-up was 57 (95% CI [46-77]) days, and 135 (11.6%) patients died within 30 days of diagnosis.

We found no significant association between chronic use of RAAS blockers and mortality, with any of the adjustment methods. Consistent results were found for the risk of mortality with the chronic use of ACE inhibitors or ARBs analyzed separately (Table 2), as well as in the sensitivity analyses (Supplemental Table S3).

Our comprehensive review of the literature included 65 published studies, of which 11 were meta-analyses (Supplemental Figure S3 and Table S4). Among the 56 individual studies (two of which combined an individual study and a metaanalysis [25,26]), 12 included both in- and outpatients, and 44 included only inpatients. Among the 44 inpatients studies, 30 assessed the effect of chronic use, and 12 the effect of in-hospital use, 3 of which assessed both chronic and in-hospital use [27-29]. Timing of exposure measurement was uncertain in 5 of 44. Only 34 of 56 individual studies reported results among hypertensive patients. A significant (deleterious) association between RAAS blockers and prognosis of COVID-19 was found in most studies

conducted in unselected populations before or after insufficient adjustment, but not among hypertensive patients or in properly adjusted studies. Conversely, a significant association in favor of a seemingly protective effect of treatment was found in most studies based on in-hospital use of treatment.

DISCUSSION

In this multicenter hospital-based cohort of 1160 hypertensive patients with COVID-19, using various adjustment strategies to reduce bias due to potential confounders, chronic use of RAAS blockers was not associated with an increased risk of mortality.

Previous studies conducted among inpatients with hypertension, although smaller-scaled, had mostly yielded similar conclusions [14,15,20,30-32]. Most large studies conducted in both outpatients and inpatients with hypertension were also in line with our results [14, 31, 33], except for one study reporting a protective effect of RAAS blockers among outpatients [34].

Of note, in our study, careful adjustment for comorbidities and age had no major impact on the results since even unadjusted analyses did not show a significant association between exposure to RAAS blockers and mortality. This is in line with previous studies conducted in patients with hypertension (supplementary Table S4). Indeed, RAAS blockers are among first-line antihypertensive therapies [35], so that patients receiving RAAS blockers do not drastically differ from other hypertensive patients with regards to baseline characteristics. Conversely, analyses conducted in unrestricted populations showed an increased unadjusted risk for a severe or fatal outcome of the disease in patients chronically treated with RAAS blockers [12,15,19,22,36]. However, this increased risk was systematically ironed out when proper adjustment was performed [12,15,19,20]. In unrestricted populations, patients receiving RAAS blockers had more comorbidities such as hypertension, diabetes, and chronic kidney disease, and were older than patients without these medications, so that baseline characteristics between users and non-users markedly differed. This important methodological consideration is best illustrated by studies that reported analyses both in the total population (not restricted to hypertensive patients) and in the subgroup of patients with hypertension. For instance, in a nationwide population-based cohort study using the Korean Health Insurance Review and Assessment including 5179 confirmed COVID-19 cases among whom 1157 had hypertension, the unadjusted

OR for mortality in users was 3.88 (95% CI 2.48-6.05) in the total population, and 0.74 (0.43-1.28) in hypertensive patients, whereas these ORs were 0.88 (0.53–1.44) and 0.71 (0.40-1.26) after adjustment [20].

The setting of the study – unrestricted population versus patients with an indication for RAAS blockers (hypertension in the vast majority of the studies) – is therefore crucial to take into account when interpreting the results. In our review, several meta-analyses pooled studies including total populations and hypertensive patients [37,38], which call their conclusions into question. In emulated trials, harmonization of selection criteria is one of the major recommendations when attempting to estimate the causal effect of treatments [39].

In our study, as in many previous studies, the selection of hospitalized patients may generate a collider bias, whereby patients with RAAS blockers may be admitted for less severe disease, and hence have better outcomes [28,40-42]. This bias is much more likely to occur in even more specific settings (such as intensive care unit admission [43], or in studies conducted in unrestricted populations (i.e. with no indication for RAAS blockers), due to a larger baseline imbalance, as explained above. Still, to account for potential different severity at inclusion between groups of exposure, we performed a separate adjustment for baseline severity, which did not modify the results. This sensitivity analysis has been separated from the main adjustment model because baseline severity may actually lie on the causal pathway between exposure and outcome, in which case, taking it into account would lead to overfitting.

In contrast with the studies mentioned above, others have shown results in favor of a protective effect of RAAS blockers, giving the impression of overall discrepant results. However, careful analysis of study designs showed that the vast majority of these studies did not rely in chronic exposure to treatment, before diagnosis, but rather on “in-hospital” use [23,44] or, very similarly, on chronic use continued in-hospital or after diagnosis [27,45,46]. Such study design generates a major bias because RAAS blockers are continued in patients with less severe disease and discontinued in patients with the most severe forms of the disease (for reasons such as hypotension, acute kidney injury, or ICU admission). A combination of reverse causality and immortal time bias, or the so-called “healthy user-sick stopper” bias, therefore explains this seemingly protective effect [28].

We have outlined how meta-analyses have incorporated data from different populations, with unadjusted results in unselected patients weighting towards an increased risk associated with RAAS blockers. Conversely, and probably even worse with regards to methodological considerations, most meta-analyses [37,38,47-50] have pooled studies based on chronic exposure together with studies based on in-hospital exposure. This erroneous study selection led a number of meta-analysis to conclude in favor of a beneficial effect of RAAS blockers[38, 47, 48, 50]. Further meta-analyses should take into account study populations and design as well as classification of exposure before pooling the results.

Altogether, our results, combined with a comprehensive analysis of previous studies, allow concluding that chronic use of RAAS blockers is not associated with outcome of COVID-19.

As of November 2020, seven randomized clinical trials (e.g. REPLACE-COVID in the USA, NCT04338009, BRACE CORONA in Argentina, NCT04364893, or ACORES-2 in France, NCT04329195) have been designed to study whether these drugs should be continued or discontinued upon hospital admission in chronically treated patients. The recently published results of the REPLACE-COVID and BRACE CORONA trials did not support discontinuing treatment with RAAS blockers in patients with COVID-19 admitted to hospital [51, 52].

Conversely, based on solid experimental evidence mostly published after the SARS-CoV-1 outbreak [9-11], other authors have argued that antagonizing the RAAS may actually be beneficial in patients with COVID-19, and that these drugs should not only be continued, but maybe even introduced *do novo* in previously untreated SARS-CoV-2 patients. As of November 2020, 21 trials have been designed to randomize patients with COVID-19, to receive an ARB or a comparator (e.g. CLARITY in Australia, NCT04394117, COVID-Aging, NCT04359953, and COVERAGE NCT04356495, in France, or STAR-COVID in Mexico, NCT04510662). Results of these randomized trials will be crucial to help clinicians managing ARBs and ACE inhibitors after hospital admission.

Strengths of our study include its size and multicenter design. In addition, the French-Covid cohort was implemented very early in the pandemic, so that the entire “first wave” period is reflected in the study, whereas previous studies were very often restricted to a shorter period of observation. Overall, our results reflect real-word data on the association between chronic use

of RAAS blockers and outcome of the disease in patients with hypertension admitted for COVID-19, and are not biased by inappropriate measurement of exposure and have therefore an important impact for patients care.

Our study has some limitations. First, hypertension was collected from the medical interview of the patient, so that misclassification may have occurred. However, we have no reason to believe a potential imprecision in the diagnosis of hypertension would introduce a major bias in our analysis. Importantly, blood pressure measurement at admission was not included in the definition of hypertension as we believe this stressful context may have induced elevated values in otherwise normotensive patients. Another limitation of the study is that the use of ACE inhibitors and ARBs were only collected in patients with a history of hypertension, so that their potential influence on outcome in patients with other indications for these treatments could not be assessed. However, as previously shown in several studies, most of the patients with an indication for RAAS blockers have hypertension. Moreover, blood pressure-lowering treatments other that ACEIs and ARBs were not collected, so that the association between other anti-hypertensive treatments, such as mineralocorticoid antagonists, and outcome could not be analyzed. In addition, as in all previous studies based on chronic prescription of treatment, real adherence to treatment could not be ascertained. Furthermore, our sample is far from exhaustive in France, but we ensured a nationwide coverage of centers and provide a far more representative sample than a single hospital or regional database. Finally, as our cohort did not include outpatients, the association between treatment and outcome was only assessed in the most severe patients, requiring hospital admission. Such a selection of the population may alter the association between the exposure to RAAS blockers and outcome.

In conclusion, our analysis conducted in a multicenter prospective French cohort of patients hospitalized with COVID-19 found no significant association between chronic use of RAAS blockers and mortality of COVID-19 in hypertensive patients. These results, combined with a comprehensive review of all related studies published up to end of November 2020 enabling us to provide epidemiological explanations for seemingly discrepant results, provide solid data to support that these treatments should not be discontinued during the pandemic.

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TABLES

Table 1 Patients' characteristics at admission in the total population and in users versus non-users of RAAS blockers.

Table 2 Hazard ratios of 30-day mortality in users versus non-users of RAAS blockers

FIGURE LEGENDS

Figure 1: Flow chart of patients' selection from the French-Covid cohort

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ETHICS APPROVAL, PATIENT CONSENT

The research complies with the Declaration of Helsinki. The study protocol was approved by the French Ethics Committee (CPP-Ile-de-France VI, ID RCB: 2020-A00256-33), and we obtained the consent of each participant or its surrogate.

DATA AVAILABILITY

Data can be made available upon reasonable request.

DECLARATION OF CONFLICTING INTERESTS

MR received travel funding from Pfizer, outside the submitted work. APHP, which employs JSH, has received research grants from Bioserenity, Sanofi, Servier and Novo Nordisk. JSH received

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Table 1 Patients' characteristics at admission in the total population and in users versus non-users of RAAS blockers.

	Total N = 1160	**Non-users** N = 481	**Chronic users** N = 679
Age (years)	70 [61:78]	70 [60:80]	70 [61:77]
Older than 65 years	777 (67)	314 (65.3)	463 (68.2)
Male	719 (62)	279 (58)	440 (64.8)
Healthcare worker (39 imputed data for missing values)	59 (5.1)	30 (6.2)	28 (4.2)
Microbiology laboratory worker (40 imputed data for missing values)	6 (0.6)	3 (0.7)	3 (0.4)
French region of hospitalization:			
East	98 (8.4)	33 (6.9)	65 (9.6)
North	117 (10.1)	47 (9.8)	70 (10.3)
Other	610 (52.5)	262 (54.5)	348 (51.3)
Parisian area	335 (28.9)	139 (28.9)	196 (28.9)
Smoking status (150 imputed data for missing values)			
Current smoker	65 (5.6)	32 (6.74)	33 (4.8)
Former smoker	383 (33.03)	136 (28.36)	247 (36.35)
Never smoked	712 (61.36)	312 (64.91)	400 (58.85)
Performance status* (293 missing			

	Total N = 1160	Non-users N = 481	Chronic users N = 679
values)			
0	423 (48.79)	157 (44.86)	266 (51.45)
1	226 (26.07)	89 (25.43)	137 (26.5)
2	98 (11.3)	47 (13.43)	51 (9.86)
3	73 (8.42)	34 (9.71)	39 (7.54)
4	47 (5.42)	23 (6.57)	24 (4.64)
Obesity (28 imputed data for missing values)	340 (29.28)	126 (26.15)	214 (31.55)
Diabetes (1 imputed data for missing value)	416 (35.9)	152 (31.68)	264 (38.88)
Chronic cardiac disease (4 imputed data for missing values)	401 (34.6)	158 (32.8)	243 (35.7)
Chronic pulmonary disease or asthma (3 imputed data for missing values)	231 (19.9)	96 (20)	135 (19.9)
Chronic kidney disease (4 imputed data for missing values)	199 (17.2)	83 (17.3)	115 (17)

	Total	**Non-users**	**Chronic users**
	N = 1160	N = 481	N = 679
Malnutrition (19 imputed data for missing values)	36 (3.1)	17 (3663)	19 (2.8)
Chronic neurological disorder or dementia (2 imputed data for missing values)	120 (10.3)	62 (12.8)	58 (8.5)
Immunosuppressive disease	305 (26.29)	144 (29.94)	161 (23.71)
Immunosuppressive therapy (23 imputed data for missing values)	78 (6.81)	45 (9.56)	33 (4.86)
Time from first symptoms to positive RT-PCR, median [Q1:Q3] (46 imputed data for missing values)	6 [3:9]	6 [2:9]	6 [3:10]
Anosmia (260 missing values)	94 (10.44)	33 (8.8)	61 (11.62)
Agueusia (259 missing values)	115 (12.76)	40 (10.61)	75 (14.31)
Oxygen therapy (116 imputed data for missing values)	705 (60.76)	276 (57.38)	429 (63.15)
eGFR[†] (mL/min/1.73m²), median	78.8 [53.57:91.71]	80.17 [57.18:91.67]	77.72 [48.93:91.83]

	Total	Non-users	Chronic users
	N = 1160	N = 481	N = 679
[Q1:Q3]			
(646 missing values)			
Creatinine (µmol/L), median [Q1:Q3]	84 [67:112]	82.5 [65.88:110.55]	86 [69.2:114.2]
(417 missing values)			
C-reactive protein (mg/L), median [Q1:Q3]	77.5 [32.98:135.18]	82.6 [31:138]	74.3 [36.6:132]
(352 missing values)			

*Performance status was collected according to the Eastern Cooperative Oncology Group (ECOG)[1]. †According to the Chronic Kidney Disease EPIdemiology collaboration[2]. Data are expressed with N (%) unless otherwise specified. Q1: first quartile; Q3: third quartile; sd: standard deviation

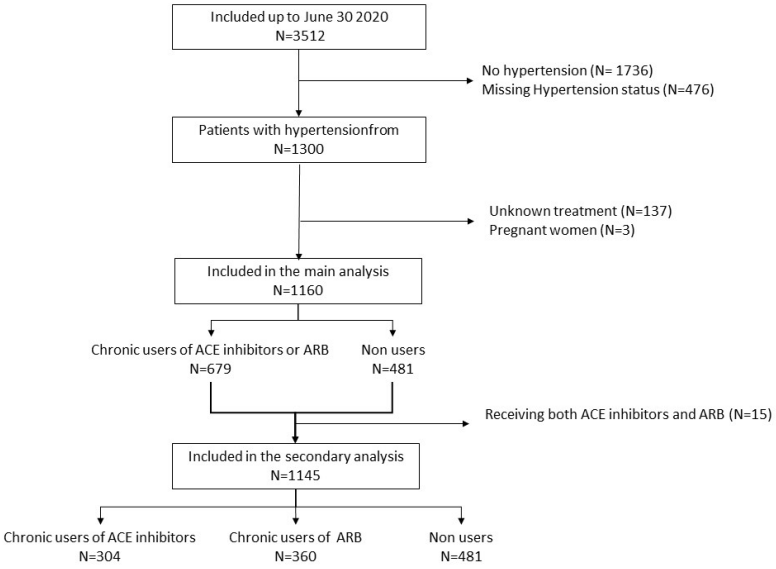
1. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5:649-55.

2. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150:604-12. DOI: 10.7326/0003-4819-150-9-200905050-00006.

Table 2 Hazard ratios of 30-day mortality in users versus non-users of RAAS blockers

	HR [95% CI]	p-value
Chronic users of ACE inhibitors or ARBs versus non-users		
Unadjusted	1.13 [0.8 - 1.6]	0.48
Adjusted*	1.07 [0.75 - 1.52]	0.71
IPT weighted	1.09 [0.86 - 1.39]	0.46
SMR weighted	1.08 [0.79 - 1.47]	0.65
Chronic users of ACE inhibitors versus non-users		
Unadjusted	1.15 [0.76 - 1.76]	0.50
Adjusted*	1.04 [0.68 - 1.6]	0.85
IPT weighted	1.06 [0.79 - 1.42]	0.72
SMR weighted	1.14 [0.71 - 1.82]	0.58
Chronic users of ARBs versus non-users		
Unadjusted	1.14 [0.76 - 1.7]	0.53
Adjusted*	1.13 [0.75 - 1.69]	0.55
IPT weighted	1.12 [0.85 - 1.48]	0.43
SMR weighted	1.07 [0.7 - 1.64]	0.75

*adjusted for age, gender, diabetes, obesity, chronic heart disease, renal failure, region of inclusion



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