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

Short title: RAAS blockers and mortality in COVID-19

Nathalie **Gault**^{1,2,*}, Marina **Esposito-Farese**^{1,3}, Matthieu **Revest**⁴, Jocelyn **Inamo**⁵, André **Cabie**⁶,
Élisabeth **Polard**⁷, Jean-Sébastien **Hulot**^{8,9}, Jade **Ghosn**¹⁰, Catherine **Chirouze**¹¹, Laurène
Deconinck¹², Jean-Luc **Diehl**^{13,14}, Julien **Poissy**¹⁵, Olivier **Epaulard**¹⁶, Benjamin **Lefèvre**^{17,18}, Lionel
Piroth¹⁹, Etienne **de Montmollin**^{20,21}, Eric **Oziol**²², Manuel **Etienne**²³, Cédric **Laouenan**^{1,2,21},
Patrick **Rosignol**²⁴, Dominique **Costagliola**²⁵, Emmanuelle **Vidal-Petiot**^{26,27,*}, and the French-
Covid cohort investigators and study group[#]

¹INSERM, Centre d'Investigations cliniques-Epidémiologie Clinique 1425, Hôpital Bichat, F-75018 Paris, France

²AP-HP, Hôpital Bichat, Département Epidémiologie Biostatistiques et Recherche Clinique, F-75018 Paris, France

³AP-HP, DRCI, URC Paris Nord, F-75018 Paris, France

⁴Service des Maladies Infectieuses et Réanimation Médicale, CHU Rennes, Univ Rennes, INSERM UMR 1230, Bacterial Regulatory RNA and Medicine, F-35000 Rennes, France

⁵CHU Martinique, Département de Cardiologie, EA7525, F-97200 Fort-de-France, France

⁶Inserm CIC 1424, Université des Antilles EA 7524, Service de maladies infectieuses et tropicales, CHU de Martinique, F-97200 Fort-de-France, France

⁷Pharmacovigilance, Pharmacoepidemiology and Drug Information Centre, Department of Clinical Pharmacology, Rennes University Hospital, F-35033 Rennes, France

⁸Université de Paris, INSERM, PARCC, F-75006 Paris, France

⁹INSERM Centre d'Investigations cliniques-plurithématique 1418 and DMU CARTE, AP-HP, Hôpital Européen Georges-Pompidou, F-CRIN INI-CRCT network, F-75015, Paris, France

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¹⁰AP-HP, Service de Maladie Infectieuses et Tropicales, Hôpital Bichat, F-75018, Paris, France

¹¹CHU Besançon, Service de Maladie Infectieuses et Tropicales, F-25000, Besançon, France

¹²AP-HP, Service de Maladie Infectieuses et Tropicales, Hôpital Bichat, F-75018, Paris, France

¹³AP-HP, Service de Médecine Intensive Réanimation, Laboratoire de Recherche Biochirurgicale (Fondation Carpentier), Hôpital Européen Georges-Pompidou, F-75015 Paris, France

¹⁴Université de Paris, INSERM, UMR_S 1140, Innovations thérapeutiques en Hémostase, F-75006 Paris, France

¹⁵Univ. Lille, Inserm U1285, CHU Lille, Pôle de réanimation, CNRS, UMR 8576 - UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, F-59000 Lille, France

¹⁶CHU Grenoble Rhône Alpes, Service de Maladies Infectieuses et Médecine Tropicale, F-38000 Grenoble, France

¹⁷Université de Lorraine, CHRU Nancy, Service des Maladies Infectieuses et Tropicales, F-54000 Nancy, France

¹⁸Université de Lorraine, APEMAC, F-54000 Nancy, France

¹⁹CHU Dijon Bourgogne, Université de Bourgogne, Département d'infectiologie, F-21000 Dijon, France

²⁰AP-HP, Service de réanimation médicale et des maladies infectieuses, Hôpital Bichat, F-75018 Paris, France

²¹Université de Paris, INSERM, IAME UMR 1137, F-75018 Paris, France

²²CHU Beziers, Service de Médecine Hospitalière, F-34500 Beziers, France

²³CHU Rouen, Service des Maladies Infectieuses et Tropicales, F-76000 Rouen, France

²⁴Université de Lorraine, INSERM, Centre d'Investigations cliniques-plurithématique 1433, INSERM U1116; CHRU Nancy; F-CRIN INI-CRCT network, F-54000 Nancy, France

²⁵Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique (IPLESP), F-75013 Paris, France

²⁶AP-HP, Hôpital Bichat, Service de Physiologie rénale, F-75018 Paris, France

²⁷Université de Paris, INSERM U1149, F-75018 Paris, France

Author contributors are listed in the Appendix.

***Corresponding author and request of reprints:** Dr Nathalie Gault (MD, PhD). INSERM CIC-EC
1425, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris. Tel. +33140257932. Fax
+33140256773.nathalie.gault@aphp.fr

***Alternate corresponding author:** Dr Emmanuelle Vidal-Petiot (MD, PhD), Service de
Physiologie-Explorations Fonctionnelles, CHU Bichat-Claude Bernard, 46, rue Henri Huchard,
75877 Paris cedex 18, Tel +33140256986/8408, Fax: +33140258856. emmanuelle.vidal-
petiot@aphp.fr

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 meta-analyses. 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 ABBREVIATIONS

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 than 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

APPENDIX

The French-Covid cohort study group (scientific, executive and steering committees)

<i>Name</i>	<i>Last name</i>	<i>Mail address @</i>	<i>Affiliation</i>
Marie	BARTOLI	marie.bartoli@anrs.fr	ANRS, Paris, France
Alpha	DIALLO	alpha.diallo@inserm.fr	ANRS, Paris, France
Soizic	LE MESTRE	soizic.le mestre@inserm.fr	ANRS, Paris, France
Noémie	MERCIER	noemie.mercier@inserm.fr	ANRS, Paris, France
Christelle	PAUL	christelle.paul@inserm.fr	ANRS, Paris, France
Ventzislava	PETROV-SANCHEZ	ventzislava.petrov-sanchez@anrs.fr	ANRS, Paris, France
Catherine	CHIROUZE	catherine.chirouze@univ-fcomte.fr	CHRU Jean Minjot, Besançon, France
Claire	ANDREJAK	andrejak.claire@chu-amiens.fr	CHU Amiens, France
Denis	MALVY	denis.malvy@chu-bordeaux.fr	CHU Bordeaux, France
François	DUBOS	Francois.DUBOS@CHRU-LILLE.FR	CHU Lille, France
Patrick	ROSSIGNOL	p.rossignol@chru-nancy.fr	CHU Nancy, France
Manuel	ETIENNE	Manuel.Etienne@chu-rouen.fr	CHU Rouen, France
François	BOMPART	fbompart@dndi.org	Drugs for Neglected Diseases initiative, Geneva, Switzerland
Tristan	GIGANTE	T.GIGANTE@chru-nancy.fr	F-CRIN INI-CRCT, Nancy, France
Morgane	GILG	M.GILG@chru-nancy.fr	F-CRIN INI-CRCT, Nancy, France
Bénédicte	ROSSIGNOL	B.ROSSIGNOL@chru-nancy.fr	F-CRIN INI-CRCT, Nancy, France
Claire	LEVY-MARCHAL	claire.levy-marchal@inserm.fr	F-CRIN INI-CRCT, Paris, France
Marine	BELUZE	marine.beluze@aphp.fr	F-CRIN Partners Platform, Paris, France
Delphine	BACHELET	delphine.bachelet@aphp.fr	Hôpital Bichat, Paris, France
Krishna	BHAVSAR	krishna.bhavsar@aphp.fr	Hôpital Bichat, Paris, France
Lila	BOUADMA	lila.bouadma@aphp.fr	Hôpital Bichat, Paris, France
Anissa	CHAIR	anissa.chair@aphp.fr	Hôpital Bichat, Paris, France
Camille	COUFFIGNAL	camille.couffignal@aphp.fr	Hôpital Bichat, Paris, France
Charlene	DA SILVEIRA	charlene.dasilveira@aphp.fr	Hôpital Bichat, Paris, France
Marie-Pierre	DEBRAY	marie-pierre.debray@aphp.fr	Hôpital Bichat, Paris, France
Diane	DESCAMPS	diane.descamps@aphp.fr	Hôpital Bichat, Paris, France
Xavier	DUVAL	xavier.duval@aphp.fr	Hôpital Bichat, Paris, France
Philippine	ELOY	philippine.eloy@aphp.fr	Hôpital Bichat, Paris, France
Marina	ESPOSITO-FARESE	marina.esposito-farese@aphp.fr	Hôpital Bichat, Paris, France
Nadia	ETTALHAOUI	nadia.ettalhaoui@aphp.fr	Hôpital Bichat, Paris, France
Nathalie	GAULT	nathalie.gault@aphp.fr	Hôpital Bichat, Paris, France
Jade	GHOSN	jade.ghosn@aphp.fr	Hôpital Bichat, Paris, France
Isabelle	GORENNE	isabelle.gorenne@aphp.fr	Hôpital Bichat, Paris, France
Isabelle	HOFFMANN	isabelle.hoffmann@aphp.fr	Hôpital Bichat, Paris, France
Ouifiya	KAFIF	ouifiya.kafif@aphp.fr	Hôpital Bichat, Paris, France
Sabrina	KALI	sabrina.kali@aphp.fr	Hôpital Bichat, Paris, France
Antoine	KHALIL	antoine.khalil@aphp.fr	Hôpital Bichat, Paris, France
Cédric	LAOUÉNAN	cedric.laouenan@aphp.fr	Hôpital Bichat, Paris, France

<i>Name</i>	<i>Last name</i>	<i>Mail address @</i>	<i>Affiliation</i>
Samira	LARIBI	samira.laribi@aphp.fr	Hôpital Bichat, Paris, France
Minh	LE	minh.le@aphp.fr	Hôpital Bichat, Paris, France
Quentin	LE HINGRAT	quentin.lehingrat@aphp.fr	Hôpital Bichat, Paris, France
François-Xavier	LESCURE	xavier.lescure@aphp.fr	Hôpital Bichat, Paris, France
Jean Christophe	LUCET	jean-christophe.lucet@aphp.fr	Hôpital Bichat, Paris, France
France	MENTRÉ	france.mentre@inserm.fr	Hôpital Bichat, Paris, France
Jimmy	Mullaert	jimmy.mullaert@inserm.fr	Hôpital Bichat, Paris, France
Nathan	PEIFFER-SMADJA	nathan.peiffer-smadja@inserm.fr	Hôpital Bichat, Paris, France
Gilles	PEYTAVIN	gilles.peytavin@aphp.fr	Hôpital Bichat, Paris, France
Carine	ROY	carine.roy@aphp.fr	Hôpital Bichat, Paris, France
Marion	SCHNEIDER	marion.schneider2@aphp.fr	Hôpital Bichat, Paris, France
Nassima	SI MOHAMMED	nassima.simohammed@aphp.fr	Hôpital Bichat, Paris, France
Lysa	TAGHERSET	lysa.tagherset@aphp.fr	Hôpital Bichat, Paris, France
Coralie	TARDIVON	coralie.tardivon@aphp.fr	Hôpital Bichat, Paris, France
Marie-Capucine	TELLIER	marie-capucine.tellier@aphp.fr	Hôpital Bichat, Paris, France
Jean-François	TIMSIT	jean-francois.timsit@aphp.fr	Hôpital Bichat, Paris, France
Théo	TRIOUX	theo.trioux@aphp.fr	Hôpital Bichat, Paris, France
Sarah	TUBIANA	sarah.tubiana@aphp.fr	Hôpital Bichat, Paris, France
Benoit	VISSEAU	benoit.visseaux@aphp.fr	Hôpital Bichat, Paris, France
Yazdan	YAZDANPANA	yazdan.yazdanpanah@aphp.fr	Hôpital Bichat, Paris, France
Dominique	DEPLANQUE	Dominique.DEPLANQUE@chru-lille.fr	Hôpital Calmette, Lille, France
Jean-Sébastien	HULOT	jean-sebastien.hulot@aphp.fr	Hôpital Européen Georges Pompidou, Paris, France
Noémie	VANEL	Noemie.VANEL@ap-hm.fr	Hôpital la Timone, Marseille, France
Romain	BASMACI	romain.basmaci@aphp.fr	Hôpital Louis Mourier, Colombes, France
Olivier	PICONE	olivier.picone@aphp.fr	Hôpital Louis Mourier, Colombes, France
François	ANGOULVANT	francois.angoulvant@aphp.fr	Hôpital Necker, Paris, France
Florentia	KAGUELIDOU	florentia.kaguelidou@aphp.fr	Hôpital Robert Debré, Paris, France
Justine	PAGES	justine.pages@aphp.fr	Hôpital Robert Debré, Paris, France
Christelle	TUAL	christelle.tual@chu-rennes.fr	Inserm CIC-1414, Rennes, France
Auréli	VEISLINGER	Aurilie.VEISLINGER@chu-rennes.fr	Inserm CIC-1414, Rennes, France
Sandrine	COUFFIN-CADIERGUES	sandrine.couffin-cadiergues@inserm.fr	Inserm sponsor, Paris, France
Hélène	ESPEROU	helene.esperou@inserm.fr	Inserm sponsor, Paris, France
Ikram	HOUAS	ikram.houas@inserm.fr	Inserm sponsor, Paris, France
Salma	JAAFOURA	salma.jaafoura@inserm.fr	Inserm sponsor, Paris, France
Auréli	PAPADOPOULOS	aurelie.papadopoulos@inserm.fr	Inserm sponsor, Paris, France
Alexandra	COELHO	alexandra.coelho@inserm.fr	Inserm UMR 1018, Paris, France
Alphonsine	DIOUF	alphonsine.diouf@inserm.fr	Inserm UMR 1018, Paris, France
Alexandre	HOCTIN	alexandre.hoctin@inserm.fr	Inserm UMR 1018, Paris, France
Marina	MAMBERT	marina.mambert@inserm.fr	Inserm UMR 1018, Paris, France
Maude	BOUSCAMBERT	maude.bouscambert-duchamp@chu-lyon.fr	Inserm UMR 1111, Lyon, France
Alexandre	GAYMARD	alexandre.gaymard@chu-lyon.fr	Inserm UMR 1111, Lyon, France
Bruno	LINA	bruno.lina@chu-lyon.fr	Inserm UMR 1111, Lyon, France

<i>Name</i>	<i>Last name</i>	<i>Mail address @</i>	<i>Affiliation</i>
Manuel	ROSA-CALATRAVA	manuel.rosa-calatrava@univ-lyon1.fr	Inserm UMR 1111, Lyon, France
Olivier	TERRIER	olivier.terrier@univ-lyon1.fr	Inserm UMR 1111, Lyon, France
Dehbia	BENKERROU	dehbia.benkerrou@iplesp.upmc.fr	Inserm UMR 1136, Paris, France
Céline	DORIVAL	celine.dorival@iplesp.upmc.fr	Inserm UMR 1136, Paris, France
Amina	MEZIANE	amina.meziane@iplesp.upmc.fr	Inserm UMR 1136, Paris, France
François	TÉOULÉ	francois.teoule@iplesp.upmc.fr	Inserm UMR 1136, Paris, France
Jérémie	GUEDJ	jeremie.guedj@inserm.fr	Inserm UMR 1137, Paris, France
Hervé	LE NAGARD	herve.lenagard@inserm.fr	Inserm UMR 1137, Paris, France
Guillaume	LINGAS	guillaume.lingas@inserm.fr	Inserm UMR 1137, Paris, France
Nadège	NEANT	nadege.neant@inserm.fr	Inserm UMR 1137, Paris, France
Laurent	ABEL	laurent.abel@inserm.fr	Inserm UMR 1163, Paris, France
Mathilde	DESVALLÉE	mathilde.desvallees@u-bordeaux.fr	Inserm UMR 1219, Bordeaux, France
Coralie	KHAN	coralie.khan@u-bordeaux.fr	Inserm UMR 1219, Bordeaux, France
Sylvie	BEHILILL	sylvie.behillil@pasteur.fr	Pasteur Institute, Paris, France
Vincent	ENOUF	vincent.enouf@pasteur.fr	Pasteur Institute, Paris, France
Hugo	MOUQUET	hugo.mouquet@pasteur.fr	Pasteur Institute, Paris, France
Sylvie	VAN DER WERF	sylvie.van-der-werf@pasteur.fr	Pasteur Institute, Paris, France
Minerva	CERVANTES-GONZALEZ	minerva.cervantes@inserm.fr	REACTing, Paris, France
Eric	d'ORTENZIO	eric.dortenzio@inserm.fr	REACTing, Paris, France
Oriane	PUÉCHAL	oriane.puechal@inserm.fr	REACTing, Paris, France
Caroline	SEMAILLE	caroline.semaille@anses.fr	REACTing, Paris, France
Marion	NORET	mnoret@ch-annecygenevois.fr	RENARCI, Annecy, France
Yves	LEVY	yves.levy@inserm.fr	Vaccine Research Institute (VRI), Inserm UMR 955, Créteil, France
Aurélie	WIEDEMANN	aurelie.wiedemann@inserm.fr	Vaccine Research Institute (VRI), Inserm UMR 955, Créteil, France

The French-Covid cohort investigators group

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Mélanie	RORIZ	Rorizm@ch-agen-nerac.fr	Agen - Médecine Interne
Patrick	RISPAL	risalp@ch-agen-nerac.fr	Agen - Médecine Interne
Sarah	REDL	redls@ch-agen-nerac.fr	Agen - Médecine Interne
Laurent	LEFEBVRE	llefebvre@ch-aix.fr	Aix en Provence - SMIT
Pascal	GRANIER	pgranier@ch-aix.fr	Aix en Provence - SMIT
Laurence	MAULIN	lmaulin@ch-aix.fr	Aix en Provence - SMIT
Cédric	JOSEPH	joseph.cedric@chu-amiens.fr	Amiens - SMIT/Réanimation
Julien	MOYET	moyet.julien@chu-amiens.fr	Amiens - SMIT/Réanimation
Cynthia	RAMES	rames.cynthia@chu-amiens.fr	Amiens - SMIT/Réanimation
Rafael	MAHIEU	Rafael.Mahieu@chu-angers.fr	Angers - SMIT
Alexandra	DUCANCELLE	alexandra.ducancelle@univ-angers.fr	Angers - SMIT
Vincent	DUBEE	vincent.dubee@chu-angers.fr	Angers - SMIT
Stéphane	SALLABERRY	ssallaberry@ch-annecygenevois.fr	Annecy - Réanimation
Aldric	MANUEL	amanuel@ch-annecygenevois.fr	Annecy - SMIT
Gabriel	MACHEDA	gmacheda@ch-annecygenevois.fr	Annecy - SMIT
Mylène	MAILLET	mmaillet@ch-annecygenevois.fr	Annecy - SMIT
Patrick	IMBERT	pimbert@ch-annecygenevois.fr	Annecy - SMIT
Amélie	VALRAN	avalran@ch-annecygenevois.fr	Annecy - SMIT
Jean-Charles	GAGNARD	jeancharles.gagnard@gmail.com	Antony - Médecine interne
Guillermo	GIORDANO	GIORDANO.Guillermo@ch-avignon.fr	Avignon - SMIT
Clara	MOUTON PERROT	mouttonperrot.clara@gmail.com	Avignon - SMIT
Vincent	PESTRE	PESTRE.Vincent@ch-avignon.fr	Avignon - SMIT
Cécile	FICKO	cecile.ficko@gmail.com	Bégin - SMIT
Marie	GOMINET	marie.gominet@intradef.gouv.fr	Bégin - SMIT
Aurore	BOUSQUET	aurorebousquet@yahoo.fr	Bégin - SMIT
Charline	VAUCHY	cvauchy@chu-besancon.fr	Besancon - SMIT
Kévin	BOUILLER	kbouiller@chu-besancon.fr	Besancon - SMIT
Maïder	PAGADOY	mpagadoy@chu-besancon.fr	Besancon - SMIT
Quentin	LEPILLER	q1lepiller@chu-besancon.fr	Besancon - SMIT
Noémie	TISSOT	noemie.tissot@univ-fcomte.fr	Besancon - SMIT
Cyril	LE BRIS	cyril.le-bris@ch-beziers.fr	Beziers - SMIT/Réanimation
Benoît	THILL	benoit.thill@ch-beziers.fr	Beziers - SMIT/Réanimation
Marie-Laure	CASANOVA	marie-laure.casanova@ch-beziers.fr	Beziers - SMIT/Réanimation
Georges	LE FALHER	georges.le-falher@ch-beziers.fr	Beziers - SMIT/Réanimation
Eric	OZIOL	eric.oziol@ch-beziers.fr	Beziers - SMIT/Réanimation
Hugues	CORDEL	hugues.cordel@aphp.fr	Bobigny - Avicenne - SMIT
Nathalie	DOURNON	nathaliedournon@gmail.com	Bobigny - Avicenne - SMIT
Olivier	BOUCHAUD	olivier.bouchaud@aphp.fr	Bobigny - Avicenne - SMIT
Duc	NGUYEN	duc.nguyen@chu-bordeaux.fr	Bordeaux - SMIT
Segolene	GREFFE	segolene.grefe@aphp.fr	Boulogne Billancourt - A. Paré - Médecine interne

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Camille	BOUISSE	cbouisse@ch-bourg01.fr	Bourg en Bresse - Infectiologie/Réanimation
Nicholas	SEDILLOT	nsedillot@ch-bourg01.fr	Bourg en Bresse - Infectiologie/Réanimation
Damien	BOUHOURL	dbouhour@ch-bourg01.fr	Bourg en Bresse - Infectiologie/Réanimation
Camille	CHASSIN	cchassin@ghnd.fr	Bourgoin-Jallieu - Médecine interne
Erwan	L'HER	erwan.lher@chu-brest.fr	Brest - Réanimation
Laetitia	BODENES	Laetitia.bodenes@chu-brest.fr	Brest - Réanimation
Nicolas	FERRIERE	nicoferriere@yahoo.fr	Brest - Réanimation
Séverine	ANSART	severine.ansart@chu-brest.fr	Brest - SMIT
Cécile	TROMEUR	cecile.tromeur@chu-brest.fr	Brest - SMIT
Dewi	GUELLEC	dewi.guellec@chu-brest.fr	Brest - SMIT
Antoine	MERCKX	antoine.merckx@ch-cahors.fr	Cahors - SMIT
Felix	DJOSSOU	felix.djossou@ch-cayenne.fr	Cayenne - SMIT/Réanimation
Mayka	MERGEAYFABRE	mayka.mergeayfabre@ch-cayenne.fr	Cayenne - SMIT/Réanimation
Arsène	KPANGON	amadohoue.kpangon@ch-cayenne.fr	Cayenne - SMIT/Réanimation
Vincent	PEIGNE	vincent.peigne@ch-metropole-savoie.fr	Chambery - SMIT
Carola	PIEROBON	carola.pierobon@ch-metropole-savoie.fr	Chambery - SMIT
Marie-Christine	CARRET	mariechristine.carret@ch-metropole-savoie.fr	Chambery - SMIT
Florence	JEGO	florence.jego@ch-metropole-savoie.fr	Chambery - SMIT
Margaux	ISNARD	margaux.isnard@ch-metropole-savoie.fr	Chambery - SMIT
Johann	AUCHABIE	johann.auchabie@ch-cholet.fr	Chollet - Réanimation
Anthony	Lemeur	anthony.lemeur@ch-cholet.fr	Chollet - Réanimation
Thierry	MAZZONI	thierry.mazzoni@ch-cholet.fr	Chollet - Réanimation
Roxane	COURTOIS	roxane.courtois@ch-cholet.fr	Chollet - SMIT
Olivier	LESENS	olesens@chu-clermontferrand.fr	Clermont-Ferrand - SMIT
Martin	MARTINOT	Martin.martinot@ch-colmar.fr	Colmar - SMIT
Jeanne	SIBIUDE	Jeanne.sibiude@aphp.fr	Colombes - Louis Mourier - Gynécologie
Laurent	MANDELBROT	laurent.mandelbrot@aphp.fr	Colombes - Louis Mourier - Gynécologie
Marie	LACOSTE	mlacoste@ch-alpes-leman.fr	Contamine sur Arve - Infectiologie/Réanimation
Jean-Daniel	LELIEVRE	jean-daniel.lievre@aphp.fr	Créteil - Mondor - SMIT
Brigitte	ELHARRAR	Brigitte.elharrar@chicreteil.fr	Créteil CHIC - Médecine interne
Valerie	GARRAIT	valerie.garrait@chicreteil.fr	Créteil CHIC - Médecine interne
Isabelle	DELACROIX	isabelle.delacroix@chicreteil.fr	Créteil CHIC - Médecine interne
Thomas	MAITRE	thomas.maitre@chicreteil.fr	Créteil CHIC - Médecine interne
Jean Baptiste	ASSIE	jean-baptiste.assie@inserm.fr	Créteil CHIC - Médecine interne
Elsa	NYAMANKOLLY	NYAMANKOLLYe@ch-dax.fr	Dax - SMIT/Réanimation
Adrien	AUVET	auveta@ch-dax.fr	Dax - SMIT/Réanimation
Anne-Hélène	BOIVIN	helene.boivin@ght40.fr	Dax - SMIT/Réanimation
Younes	KERROUMI	ykerroumi@hopital-dcss.org	Diaconesses CSS - Médecine interne
Vanina	MEYSSONNIER	vmeyssonnier@hopital-dcss.org	Diaconesses CSS - Médecine interne
Oryane	MABIALA	omabiala@for.paris	Diaconesses CSS - Médecine interne

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
François Xavier	CATHERINE	francois-xavier.catherine@chu-dijon.fr	Dijon - SMIT
Mathieu	BLOT	mathieu.blot@chu-dijon.fr	Dijon - SMIT
Sophie	MAHY	sophie.mahy@chu-dijon.fr	Dijon - SMIT
Marielle	BUISSON	marielle.buisson@chu-dijon.fr	Dijon - SMIT
Lionel	PIROTH	lionel.piroth@chu-dijon.fr	Dijon - SMIT
Valentine	CAMPANA	Valentine.CAMPANA@chu-martinique.fr	Fort de France - SMIT
Jérémie	PASQUIER	jeremie.pasquier@chu-martinique.fr	Fort de France - SMIT
André	CABIE	andre.cabie@chu-martinique.fr	Fort de France - SMIT
Pierre-François	SANDRINE	sandrine.pierre-francois@chu-martinique.fr	Fort de France - SMIT
Jean-Marie	TURMEL	jean-marie.turmel@chu-martinique.fr	Fort de France - SMIT
Simon	BESSIS	simon.bessis@aphp.fr	Garches - SMIT
Olivier	EPAULARD	OEpaulard@chu-grenoble.fr	Grenoble - SMIT
Nicolas	TERZI	nterzi@chu-grenoble.fr	Grenoble - SMIT
Jean-François	PAYEN	JFPayen@chu-grenoble.fr	Grenoble - SMIT
Laurence	BOUILLET	lbouillet@chu-grenoble.fr	Grenoble - SMIT
Rebecca	HAMIDFAR	rhamidfar@chu-grenoble.fr	Grenoble - SMIT
Marion	LE MARECHAL	mlemarechal@chu-grenoble.fr	Grenoble - SMIT
Elodie	CURLIER	elodie.curlier@chu-guadeloupe.fr	Guyane - Guadeloupe - Réanimation - SMIT
Rachida	OUISSA	rachida.ouissa@chu-guadeloupe.fr	Guyane - Guadeloupe - Réanimation - SMIT
Isabelle	FABRE	mfabre@ghnd.fr	Guyane - Guadeloupe - Réanimation - SMIT
Pierre-Marie	ROGER	pierre-marie.roger@chu-guadeloupe.fr	Guyane - Guadeloupe - Réanimation - SMIT
Samuel	Markowicz	samuel.markowicz@chu-guadeloupe.fr	Guyane - Guadeloupe - Réanimation - SMIT
Olivier	PICONE	olivier.picone@aphp.fr	Gynécologie, Hôpital Louis Mourrier, Colombe
Cécile	GOUJARD	cecile.goujard@aphp.fr	Kremlin-Bicêtre - SMIT/Médecine interne
Stéphane	JAUREGUIBERRY	stephane.jaureguiberry@aphp.fr	Kremlin-Bicêtre - SMIT/Médecine interne
Antoine	CHERET	antoine.cheret@aphp.fr	Kremlin-Bicêtre - SMIT/Médecine interne
Gwenhaël	COLIN	gwenhael.colin@chd-vendee.fr	La Roche Sur Yon - Infectiologie
Romain	DECOURS	romain.decours@chd-vendee.fr	La Roche Sur Yon - Infectiologie
Thomas	GUIMARD	thomas.guimard@chd-vendee.fr	La Roche Sur Yon - Infectiologie
Vincent	Langlois	vincent.langlois@ch-havre.fr,	Le Havre - MI / Pneumologie
Laure	GOUBERT	laure.goubert@ch-havre.fr	Le Havre - MI / Pneumologie
Stéphanie	COUSSE	stephanie.cousse@ch-havre.fr	Le Havre - MI / Pneumologie
Hikombo	HITOTO	hhitoto@ch-lemans.fr	Le Mans CH - SMIT
Julien	POISSY	julien.poissy@chru-lille.fr	Lille - Réanimation
Saad	NSEIR	saadalla.nseir@chru-lille.fr	Lille - Réanimation
Sébastien	PREAU	sebastien.preau@chru-lille.fr	Lille - Réanimation
Mercé	JOURDAIN	merce.jourdain@chru-lille.fr	Lille - Réanimation
Raphaël	FAVORY	raphael.favory@chru-lille.fr	Lille - Réanimation

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Karine	FAURE	karine.faure@chru-lille.fr	Lille - SMIT
Fanny	VUOTTO	Fanny.VUOTTO@CHRU-LILLE.FR	Lille - SMIT
Marie-Charlotte	CHOPIN	Mariecharlotte.CHOPIN@CHRU-LILLE.FR	Lille - SMIT
Sarah	STABLER	stabler.sarah@gmail.com	Lille - SMIT
Jules	BAUER	bauerjules@gmail.com	Lille - SMIT
Marc	LAMBERT	Marc.LAMBERT@chru-lille.fr	Lille Calmette - SMIT
Arnaud	SCHERPEREEL	Arnaud.SCHERPEREEL@chru-lille.fr	Lille Calmette - SMIT
Ryadh	POKEERBUX	ryadh.pokeerbux@chru-lille.fr	Lille Calmette - SMIT
Stéphanie	FRY	Stephanie.FRY@chru-lille.fr	Lille Calmette - SMIT
Cécile	YELNIK	CECILE.YELNIK@chru-lille.fr	Lille Calmette - SMIT
Laurent	BITKER	laurent.bitker@chu-lyon.fr	Lyon - Réanimation
Mehdi	MEZIDI	mehdi.mezidi@chu-lyon.fr	Lyon - Réanimation
Hodane	YONIS	hodane.yonis@chu-lyon.fr	Lyon - Réanimation
Nicolas	BENECH	nicolas.benech@chu-lyon.fr	Lyon - SMIT
Thomas	PERPOINT	thomas.perpoint@chu-lyon.fr	Lyon - SMIT
Anne	CONRAD	anne.conrad@chu-lyon.fr	Lyon - SMIT
Muriel	DORET-DION	muriel.doret-dion@chu-lyon.fr	Lyon - Hôpital Mère Enfant - Gynécologie
Pierre-Adrien	BOLZE	pierre-adrien.bolze@chu-lyon.fr	Lyon Sud - Obstétrique
Simon-Djamel	THIBERVILLE	thiberville.sd@ch-manosque.fr	Manosque - SMIT
Moïse	MACHADO	mmachado@ghef.fr	Marne la Vallee- SMIT
Audrey	BARRELET	abarrelet@ghef.fr	Marne la Vallee- SMIT
Alexandra	BEDOSSA	abedossa@ghef.fr	Marne la Vallee- SMIT
Stanislas	REBAUDET	s.rebaudet@hopital-europeen.fr	Marseille - SMIT
Frédérique	RETORNAZ	f.retornaz@hopital-europeen.fr	Marseille - SMIT
Myriam	BENNANI	M.BENNANI@hopital-europeen.fr	Marseille - SMIT
Hortense	DROUET	h.drouet@hopital-europeen.fr	Marseille - SMIT
Bertrand	DUSSOL	bertrand.dussol@ap-hm.fr	Marseille conception - Néphrologie
Marc	LEONE	marc.leone@ap-hm.fr	Marseille Nord - La Timone - Réanimation
Bruno	PASTENE	bruno.pastene@ap-hm.fr	Marseille Nord - La Timone - Réanimation
Karine	BEZULIER	karine.bezulier@ap-hm.fr	Marseille Nord - La Timone - Réanimation
Axelle	BRACONNIER	a.braconnier@hotmail.fr	Mayotte - Gynécologie
Sylvain	DIAMANTIS	Sylvain.diamantis@ghsif.fr	Melun - SMIT
Catherine	CHAKVEATZE	eka.chakvetadze@aphp.fr	Melun - SMIT
Clara	FLATEAU	clara.flateau@ghsif.fr	Melun - SMIT
Vincent	DINOT	v.dinot@chr-metz-thionville.fr	Metz - Réanimation
Rostane	GACI	r.gaci@chr-metz-thionville.fr	Metz - Réanimation
Nadia	OAMARA	n.ouamara@chr-metz-thionville.fr	Metz - Réanimation
Guillaume	LOUIS	g.louis@chr-metz-thionville.fr	Metz - Réanimation
Cyril	CADOZ	c.cadoz@chr-metz-thionville.fr	Metz - Réanimation
Hajnal-Gabriela	ILLES	gabriela.illes@ch-mdm.fr	Mont de Marsan - SMIT
Bouchra	LOUTFI	bouchra.loutfi@ch-mdm.fr	Mont de Marsan - SMIT
Jérôme	DIMET	jerome.dimet@ght40.fr	Mont de Marsan - SMIT
Vincent	LE MOING	v-le_moing@chu-montpellier.fr	Montpellier - SMIT

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Nathalie	PANSU	n-pansu@chu-montpellier.fr	Montpellier - SMIT
Clément	LE BIHAN	c-lebihan@chu-montpellier.fr	Montpellier - SMIT
Antoine	KIMMOUN	a.kimmoun@chru-nancy.fr	Nancy - Réanimation
Bruno	LEVY	b.levy@chru-nancy.fr	Nancy - Réanimation
Maximilien	SAINT GILLES	M.SAINTGILLES@chru-nancy.fr	Nancy - Réanimation
François	GOEHRINGER	f.goehringer@chru-nancy.fr	Nancy - SMIT
Christian	RABAUD	c.rabaud@chru-nancy.fr	Nancy - SMIT
Sibylle	BEVILACQUA	s.bevilacqua@chru-nancy.fr	Nancy - SMIT
Benjamin	LEFEVRE	B.LEFEVRE@chru-nancy.fr	Nancy - SMIT
Anne	GUILLAUMOT	a.guillaumot@chru-nancy.fr	Nancy - SMIT
Anne Sophie	BOUREAU	annesophie.boureau@chu-nantes.fr	Nantes - Gériatrie
Clotilde	ALLAVENA	Clotilde.ALLAVENA@chu-nantes.fr	Nantes - SMIT
Sabelline	BOUCHEZ	Sabelline.BOUCHEZ@chu-nantes.fr	Nantes - SMIT
Romain	GUERY	dr.guery@groupeconfluent.fr	Nantes - SMIT
Paul	LE TURNIER	Paul.LETURNIER@chu-nantes.fr	Nantes - SMIT
Cécile	MEAR-PASSARD	cecile.passard@chu-nantes.fr	Nantes - SMIT
Christophe	RAPP	christophe.rapp@ahparis.org	Neuilly sur Seine - Médecine Interne
Stéphane	LASRY	stephane.lasry@ahparis.org	Neuilly sur Seine - Médecine Interne
Thierry	CARMOI	thierry.carmoi@ahparis.org	Neuilly sur Seine - Médecine Interne
Elisa	DEMONCHY	demonchy.e@chu-nice.fr	Nice - SMIT
Céline	MICHELANGELLI	michelangeli.c@chu-nice.fr	Nice - SMIT
Karine	RISSO	risso.k@chu-nice.fr	Nice - SMIT
Paul	LOUBET	Paul.LOUBET@chu-nimes.fr	Nimes - SMIT
Alberto	SOTTO	albert.sotto@chu-nimes.fr	Nimes - SMIT
Didier	Laureillard	didier.laureillard@chu-nimes.fr	Nimes - SMIT
Etienne	DE MONTMOLLIN	etienne.demontmollin@aphp.fr	Paris - Bichat - Réanimation
Juliette	PATRIER	juliette.patrier@aphp.fr	Paris - Bichat - Réanimation
Paul Henri	WICKY	paul-henri.wicky@aphp.fr	Paris - Bichat - Réanimation
Lucie	LE FEVRE	lucie.lefevre@aphp.fr	Paris - Bichat - Réanimation
Pierre	JACQUET	Pierre.jaquet@aphp.fr	Paris - Bichat - Réanimation
Raphael	BORIE	raphael.borie@aphp.fr	Paris - Bichat - SMIT
Tiphaine	GOULENOK	tiphaine.goulenok@aphp.fr	Paris - Bichat - SMIT
Dominique	LUTON	dominique.luton@aphp.fr	Paris - Bichat - SMIT
Lauren	DECONINCK	bastien.deconninck@aphp.fr	Paris - Bichat - SMIT
Sylvie	LE GAC	sylvie.legac@aphp.fr	Paris - Bichat - SMIT
Cécile	AZOULAY	cecile.azoulay@aphp.fr	Paris - Cochin - CIC Vaccinologie
Nicolas	CARLIER	nicolas.carlier@aphp.fr	Paris - Cochin - CIC Vaccinologie
Liem	LUONG	liem.luong@aphp.fr	Paris - Cochin - CIC Vaccinologie
Marie	LACHATRE	marie.lachatre@aphp.fr	Paris - Cochin - CIC Vaccinologie
Odile	LAUNAY	odile.launay@aphp.fr	Paris - Cochin - CIC Vaccinologie
Jean-Luc	DIEHL	jean-luc.diehl@aphp.fr	Paris - HEGP - Réanimation
Marine	LIVROZET	marine.livrozet@aphp.fr	Paris - HEGP - Réanimation
Bernard	CHOLLEY	bernard.cholley@aphp.fr	Paris - HEGP - Réanimation

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Jean-Benoit	ARLET	jean-benoit.arlet@aphp.mssante.fr	Paris - HEGP - Réanimation
Olivier	SANCHEZ	manuel.sanchez@aphp.fr	Paris - HEGP - Réanimation
Victoria	MANDA	victoria.manda@aphp.fr	Paris - Lariboisière - SMIT
Laurène	AZEMAR	laurene.azemar@aphp.fr	Paris - Lariboisière - SMIT
Guylaine	CASTOR-ALEXANDRE	guylaine.alexandre@aphp.fr	Paris - Lariboisière - SMIT
Jeanne	TRUONG	jeanne.truong@aphp.fr	Paris - Robert Debré - Pédiatrie
Karine	LACOMBE	karine.lacombe2@aphp.fr	Paris - Saint Antoine - SMIT
Thibault	CHIARABINI	Thibault.chiarabini@aphp.fr	Paris - Saint Antoine - SMIT
Bénédicte	LEFEBVRE	benedicte.lefebvre2@aphp.fr	Paris - Saint Antoine - SMIT
Nathalie	DE CASTRO	nathalie.de-castro@aphp.fr	Paris - Saint Louis - Réanimation
Geoffrey	LIEGEON	geoffroy.liegeon@aphp.fr	Paris - Saint Louis - Réanimation
Diane	PONSCARME	diane.ponscarme@aphp.fr	Paris - Saint Louis - Réanimation
Julie	CHAS	julie.chas@aphp.fr	Paris - Tenon - SMIT
Valérie	GABORIEAU	valerie.gaborieau@ch-pau.fr	Pau - SMIT/Réanimation
Eve	LE COUSTUMIER	eve.lecoustumier@ch-pau.fr	Pau - SMIT/Réanimation
Walter	PICARD	walter.picard@ch-pau.fr	Pau - SMIT/Réanimation
Jean-Benoit	ZABBE	marion.zabbe@ch-perigueux.fr	Perigueux - SMIT
Florent	PEELMAN	florent.peelman@ch-perigueux.fr	Perigueux - SMIT
Edouard	SOUM	edouard.soum@ch-perigueux.fr	Perigueux - SMIT
Hugues	AUMAÎTRE	hugues.aumaitre@ch-perpignan.fr	Perpignan - SMIT
Blandine	RAMMAERT	blandine.rammaert@chu-poitiers.fr	Poitiers - SMIT
Gwenaël	Le Moal	Gwenaël.LEMOAL@chu-poitiers.fr	Poitiers - SMIT
Isabelle	PIRONNEAU	Isabelle.PIRONNEAU@chu-poitiers.fr	Poitiers - SMIT
Anne Sophie	RESSEGUIER	annesophie.resseguier@ch-lepuy.fr	Puy en Velay - Médecine interne
Nadia	SAIDANI	n.saidani@ch-cornouaille.fr	Quimper - MIIS
Firouzé	BANI-SADR	fbanisadr@chu-reims.fr	Reims - SMIT
Maxime	HENTZIEN	mhentzien@chu-reims.fr	Reims - SMIT
Yohan	N'GUYEN	ynguyen@chu-reims.fr	Reims - SMIT
Juliette	ROMARU	jromaru@chu-reims.fr	Reims - SMIT
Kévin	DIDIER	kdidier@chu-reims.fr	Reims - SMIT
Isabelle	ENDERLE	Isabelle.ENDERLE@chu-rennes.fr	Rennes - Gynécologie
Fabrice	LAINÉ	Fabrice.Laine@chu-rennes.fr	Rennes - SMIT
Matthieu	LESOUHAITIER	mathieu.LESOUHAITIER@chu-rennes.fr	Rennes - SMIT
Matthieu	REVEST	matthieu.revest@chu-rennes.fr	Rennes - SMIT
Pierre	TATTEVIN	pierre.tattevin@chu-rennes.fr	Rennes - SMIT
Jean-Marc	CHAPPLAIN	jean-marc.chaplain@chu-rennes.fr	Rennes - SMIT
Manuel	ETIENNE	Manuel.Etienne@chu-rouen.fr	Rouen - SMIT
Véronique	LEMEE	Veronique.Lemee@chu-rouen.fr	Rouen - SMIT
Eglantine	FERRAND DEVOUGE	E.Ferrand-Devouge@chu-rouen.fr	Rouen - SMIT
Kévin	ALEXANDRE	kevin.alexandre@chu-rouen.fr	Rouen - SMIT
Elise	ARTAUD-MACCARI	Elise.Artaud-Macari@chu-rouen.fr	Rouen - SMIT
Nathalie	ALLOU	nathalie.allou@chu-reunion.fr	Saint Denis - Saint Pierre - SMIT
Marie	LAGRANGE	marie.lagrange-xelot@chu-reunion.fr	Saint Denis - Saint Pierre - SMIT

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Julien	JABOT	jabot974@gmail.com	Saint Denis - Saint Pierre - SMIT
Elisabeth	BOTELHO-NEVERS	elisabeth.botelho-nevers@chu-st-etienne.fr	Saint Etienne - SMIT
Amandine	GAGNEUX-BRUNON	amandine.gagneux-brunon@chu-st-etienne.fr	Saint Etienne - SMIT
Tiffany	TROUILLON	tiffany.trouillon@chu-st-etienne.fr	Saint Etienne - SMIT
Corinne	DANIEL	c.daniel@chsaintmartin.fr	Saint Martin - Médecine UDSMT
Benoît	ROZE	b.roze@ch-saintonge.fr	Saintes - Réanimation
Delphine	BREGEAUD	d.bregeaud@ch-saintonge.fr	Saintes - Réanimation
Younes	AIT TAMLIHAT	y.ait-tamlihat@ch-saintonge.fr	Saintes - Réanimation
Ali	HACHEMI	ali.hachemi@ch-soissons.fr	Soissons - Infectiologie
Hélène	SALVATOR	h.salvator@hopital-foch.org	Suresnes - Hopital Foch - DRCI
Erwan	FOURN	e.fourn@hopital-foch.org	Suresnes - Hopital Foch - DRCI
David	ZUCMAN	d.zucman@hopital-foch.org	Suresnes - Hopital Foch - DRCI
Marie-Laure	CHABI-CHAVILLAT	ml.chabi-charvillat@hopital-foch.com	Suresnes - Hopital Foch - DRCI
Auréli	MARTIN	a.martin@hopital-foch.com	Suresnes - Hopital Foch - DRCI
Eric	DELAVEUVE	e.delaveuve@chr-metz-thionville.fr	Thionville - Bel Air - SMIT/Réanimation
Coline	JAUD-FISCHER	C.JAUDFISCHER@chru-nancy.fr	Thionville - Bel Air - SMIT/Réanimation
Paul	DUNAND	paul.m.dunand@gmail.com	Thionville - Bel Air - SMIT/Réanimation
François	BISSUEL	f.bissuel@ch-hopitauxduleman.fr	Thonon les Bains - Pneumologie
Karen	DELAVIGNE	delavigne.karen@iuct-oncopole.fr	Toulouse - Hématologie/Médecine interne
Alexa	DEBARD	debard.a@chu-toulouse.fr	Toulouse - SMIT
Pierre	DELOBEL	delobel.p@chu-toulouse.fr	Toulouse - SMIT
Benjamine	SARTON	sarton.b@chu-toulouse.fr	Toulouse - SMIT
Stella	Rousset	rousset.st@chu-toulouse.fr	Toulouse - SMIT
Guillaume	MARTIN-BLONDEL	martin-blondel.g@chu-toulouse.fr	Toulouse - SMIT
Laurent	GUILLEMINAULT	guilleminault.l@chu-toulouse.fr	Toulouse Larrey - Pneumologie
Marlène	MURRIS	murris.m@chu-toulouse.fr	Toulouse Larrey - Pneumologie
Agnès	SOMMET	agnes.sommet@univ-tlse3.fr	Toulouse Larrey - Pneumologie
Olivier	LAIREZ	lairez.o@chu-toulouse.fr	Toulouse-cardiologie
Eric	SENNEVILLE	esenneville@ch-tourcoing.fr	Tourcoing - SMIT
Olivier	ROBINEAU	olivier.robineau82@gmail.com	Tourcoing - SMIT
Agnès	MEYBECK	ameybeck@ch-tourcoing.fr	Tourcoing - SMIT
Denis	GAROT	d.garot@chu-tours.fr	Tours - Réanimation
Laurent	PLANTIER	laurent.plantier@univ-tours.fr	Tours - Réanimation
Valérie	GISSOT	valerie.gissot@univ-tours.fr	Tours - Réanimation
Emmanuelle	MERCIER	emercier@med.univ-tours.fr	Tours - Réanimation
Charlotte	SALMON GANDONNIERE	charlotte.salmon.gandonniere@gmail.com	Tours - Réanimation
Adrien	LEMAIGNEN	adrien.lemaignen@chu-tours.fr	Tours - SMIT
Julie	MANKIKIAN	J.MANKIKIAN@chu-tours.fr	Tours - SMIT
Thomas	FLAMENT	T.FLAMENT@chu-tours.fr	Tours - SMIT
Grégory	CORVAISIER	gregory.corvaisier@ch-bretagne-atlantique.fr	Vannes - SMIT
Delphine	LARIVIERE	delphine.lariviere@ch-bretagne-atlantique.fr	Vannes - SMIT
Marie	LANGELOT-RICHARD	marie.langelot-richard@ch-bretagne-atlantique.fr	Vannes - SMIT

<i>Name</i>	<i>Last name</i>	<i>Mail adress @</i>	<i>Affiliation</i>
Pauline	CARAUX PAZ	pauline.caraux-paz@chiv.fr	Villeneuve Saint Georges - SMIT
Laurent	RICHIER	laurent.richier@aphp.fr	Villeneuve Saint Georges - SMIT
Danielle	JAAFAR	danielle.jaafar@chiv.fr	Villeneuve Saint Georges - SMIT
Claudine	BADR	claudine.Badr@chiv.fr	Villeneuve Saint Georges - SMIT
Fara	DIOP	Fara.Diop@chiv.fr	Villeneuve Saint Georges - SMIT

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AUTHOR CONTRIBUTIONS

MG, MEF, MR, JI, AC, EP, CL, PR, DC and EVP contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. MG, MEF, MR, JI, EP, JSH, CL, PR, DC and EVP drafted the manuscript. All authors critically revised the manuscript; gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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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	Non-users	Chronic users
	N = 1160	N = 481	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)
<i>French region of hospitalization:</i>			
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)
<i>Smoking status (150 imputed data for missing values)</i>			
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)
<i>Performance status* (293 missing)</i>			

	Total	Non-users	Chronic users
	N = 1160	N = 481	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 (3.6)	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)
Ageusia (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/1.73m ²), 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 ($\mu\text{mol/L}$), 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)			

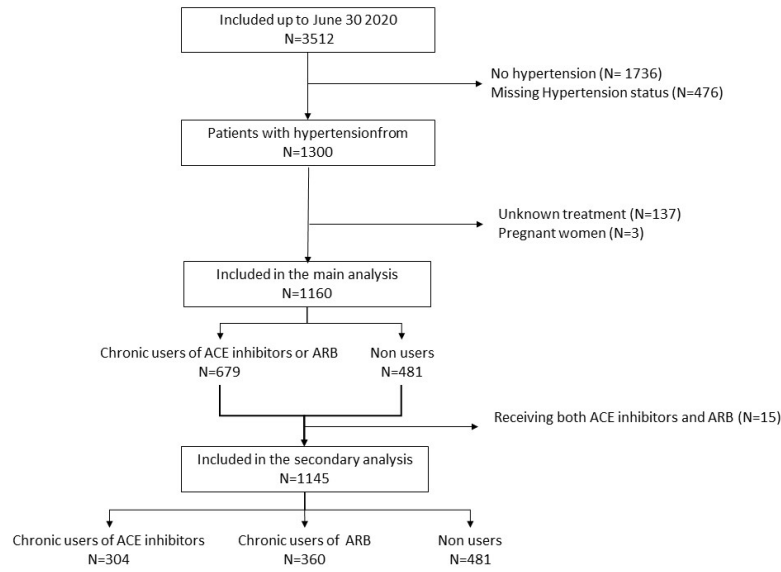
*Performance status was collected according to the Eastern Cooperative Oncology Group (ECOG)[1]. [†]According to the Chronic Kidney Disease EPIdemiology collaboration[2]. Data are expressed with N (%) unless otherwise specified. Q1: first quartile; Q3: third quartile; sd: standard deviation

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
<i>Chronic users of ACE inhibitors or ARBs versus non-users</i>		
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
<i>Chronic users of ACE inhibitors versus non-users</i>		
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
<i>Chronic users of ARBs versus non-users</i>		
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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