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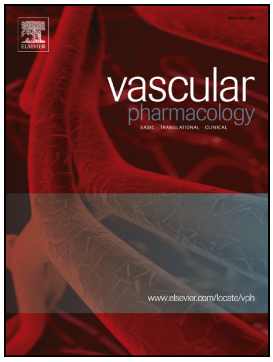

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RAAS inhibitors are not associated with mortality in COVID-19 patients: findings from an observational multicenter study in Italy and a meta-analysis of 19 studies

Short title: RAAS inhibitors and mortality in COVID-19

THE COVID-19 RISk and Treatments (CORIST) Collaboration

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ABSTRACT

Objective: The hypothesis that been set forward that use of Renin Angiotensin Aldosterone System (RAAS) inhibitors is associated with COVID-19 severity. We set-up a multicenter Italian collaboration (CORIST Project, ClinicalTrials.gov ID: NCT04318418) to retrospectively investigate the relationship between RAAS inhibitors and COVID-19 in-hospital mortality. We also carried out an updated meta-analysis on the relevant studies.

Methods: We analyzed 4,069 unselected patients with laboratory-confirmed SARS-CoV-2 infection and hospitalized in 34 clinical centers in Italy from February 19, 2020 to May 23, 2020. The primary end-point in a time-to event analysis was in-hospital death comparing patients who received angiotensin-converting–enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARB) with patients who did not. Articles for the meta-analysis were retrieved until July 13th, 2020 by searching in web-based libraries, and data were combined using the general variance-based method.

Results: Out of 4,069 COVID-19 patients, 13.5% and 13.3% received ACE-I or ARB, respectively. Use of neither ACE-I nor ARB was associated with mortality (multivariable hazard ratio (HR) adjusted also for COVID-19 treatments: 0.96, 95% confidence interval 0.77-1.20 and HR=0.89, 0.67-1.19 for ACE-I and ARB, respectively). Findings were similar restricting the analysis to hypertensive (N=2,057) patients (HR=1.00, 0.78-1.26 and HR=0.88, 0.65-1.20) or when ACE-I or ARB were considered as a single group. Results from the meta-analysis (19 studies, 29,057 COVID-19 adult patients, 9,700 with hypertension) confirmed the absence of association.

Conclusions: In this observational study and meta-analysis of the literature, ACE-I or ARB use was not associated with severity or in-hospital mortality in COVID-19 patients.

Key words: angiotensin converting enzyme inhibitors; ACE-I; angiotensin receptor blockers; ARB; sartans; COVID-19; mortality.

INTRODUCTION

Coronavirus Disease-19 (COVID-19) is caused by the beta coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Angiotensin-converting enzyme 2 (ACE2) is a functional receptor for SARS-CoV-2, which is used by the virus to enter and infect the cell, a process requiring priming of the viral S protein by the cellular serine protease TMPRSS2 [2]. ACE2 mRNA has been detected in the bronchi and lung parenchyma, as well as in the heart, the kidney and the gastrointestinal tract. This tissue distribution is consistent with the pathophysiology and clinical features of SARS infection and related disease [3]. ACE2 is a key modulator of the renin–angiotensin–aldosterone system (RAAS), which is a signaling pathway involved in the regulation of vascular and heart function [4]. The strict relationship of ACE2 with cardiovascular function supported the observation of a higher transmissibility and pathogenicity of the virus in patients with hypertension or heart failure [5]. Inhibition of RAAS by angiotensin converting-enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARB), drugs largely used in the therapy of hypertension and heart failure, may result in a compensatory increase in tissue levels of ACE2 [6]. At the beginning of the COVID-19 pandemic, this experimental observation generated the hypothesis that use of RAAS inhibitors might be detrimental in patients infected by SARS-CoV-2. The rapid diffusion of the hypothesis of detrimental effects of RAAS inhibitors in the lay press induced hypertensive patients and/or their doctors to stop or replace previously prescribed ACE-I or ARB, despite the first evidence from China was controversial [7, 8].

RAAS blockers were, however, also hypothesized to exert protective effects [4]. Indeed, recombinant ACE2 or losartan might counteract both pulmonary edema and the reduced lung function due to decreased expression of ACE2 [9, 10]. RAAS blockade was then proposed as a potential treatment for SARS-CoV-2 [4]. This hypothesis was also supported by a report showing that serum angiotensin II levels in COVID-19 patients were higher than in non-infected individuals, and were linearly associated with viral load and lung damage [11].

Against this controversial background, in March 2020, we launched a large multicenter study in Italy (ClinicalTrials.gov ID: NCT04318418) aimed at investigating the role of RAAS inhibitors in COVID-19 patients [12]. We here present the findings of this collaborative project, supported by a set of related meta-analyses. In fact, several articles on the topic have meanwhile been published, and an updated quantitative review of the entire literature may help better define the relationship between RAAS inhibitors and COVID-19.

METHODS

Setting

This national retrospective observational study was conceived, coordinated and analysed within the CORIST Collaboration Project (ClinicalTrials.gov ID: NCT04318418). The CORIST Collaboration is a set of multicenter observational studies launched in March 2020, and aimed at testing the association of inhibitors of the renin-angiotensin system, risk factors and therapies with severity and mortality of COVID-19 hospitalized patients [13]. The study was approved by the institutional Ethics Board of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed, Pozzilli, and of all recruiting centers. Data for the present analyses were provided by 34 hospitals distributed throughout Italy. Each hospital provided data from hospitalized adult (≥18 years of age) patients who all had a positive test result for the SARS-CoV-2 virus at any time during their hospitalization from February 19th to May 23rd, 2020. The follow-up continued through June 30th, 2020.

Data Sources

We developed a cohort comprising 4,312 patients with laboratory-confirmed SARS-CoV-2 infection in an in-patient setting. The SARS-CoV-2 status was defined on the basis of laboratory results (polymerase chain reaction on a nasopharyngeal swab) from each participating hospital. Clinical data were abstracted at one-time point from electronic medical records or charts, and collected using either a centrally-designed electronic worksheet or a centralized web-based database. Collected data included patients' demographics, laboratory test results, medication administration, historical and current medication lists, historical and current diagnoses, and clinical notes [13]. In addition, specific information on the most severe manifestation of COVID-19 that occurred during hospitalization was retrospectively captured. The maximum clinical severity observed was classified as: light-mild pneumonia; or severe pneumonia; or acute respiratory distress syndrome (ARDS) [14]. Specifically, we obtained the following information for each patient: hospital; date of admission and date of discharge or death; age; gender; use of ACE-I or ARB (no/yes/suspended after COVID-19 manifestations); the first recorded in-patient laboratory tests at hospital entry (creatinine, C-reactive protein (CRP)); past and current diagnoses of chronic degenerative disease or risk factors (myocardial infarction, heart failure, diabetes, hypertension, chronic pulmonary disease and cancer), and in-

hospital drug therapies for COVID-19. Chronic kidney disease was classified as: stage 1: normal or increased glomerular filtration rate (eGFR) (≥90 mL/min/1.73 m^2); stage 2: kidney damage with mild reduction in eGFR (60-89 mL/min/1.73 m^2); stage 3a: moderate reduction in eGFR (45-59 mL/min/1.73 m^2); stage 3b: moderate reduction in eGFR (30-44 mL/min/1.73 m^2); stage 4: severe reduction in eGFR (15-29 mL/min/1.73 m^2); stage 5: kidney failure (eGFR <15 mL/min/1.73 m^2 or dialysis). eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CRP levels were classified as ≤3, 3-10 and ≥10 mg/L.

Statistical analyses

The study index date was defined as the date of hospital admission. Index dates ranged from February 19th, 2020 to May 23rd, 2020. The study end point was the time from study index to death. The number of patients who either died, or had been discharged alive, or were still hospitalized as of June 30th, 2020, were recorded, and hospital length of stay was determined. Patients alive had their data censored on the date of discharge or as the date of the respective clinical data collection. Data were censored at 35 days of follow up in n=405 (10.0%) patients with a follow up greater than 35 days.

Out of the initial cohort of 4,312 patients, 243 patients were excluded from the analysis because of one or more missing data at baseline or during follow-up, including use of ACE-I (n=93) or ARB (n=79), history of hypertension (n=54), time to event (n=64), outcome (death/alive, n=8), age (n=4 with missing data and n=2 with age<18 years), or gender (n=2). At the end, the analyzed cohort consisted of N=4,069 patients. Among them, 284 (7.0%) had at least one missing value for covariates. Distribution of missing values was as follows: n=196 for C-reactive protein; n=77 for GFR; n=38 for history of ischemic disease; n=18 for history of chronic pulmonary disease; N=8 for diabetes and N=8 for cancer. We used multiple imputation techniques (SAS PROC MI, N=10 imputed datasets; and PROC MIANALYZE) to maximize data availability. As sensitivity analysis, we also conducted a case-complete analysis on 3,785 patients. For the primary analysis, we divided patients in 5 groups: a) controls, consisting of patients who used neither ACE-I nor ARB; b) patients treated with ACE-I but not ARB; c) patients treated with ARB but not ACE-I; d) patients treated with both drugs; e) patients who suspended ACE-I (ARB) and were not treated with ARB (ACE-I). Secondary analyses considered the use of ACE-I or ARB as a dichotomous exposure (no/yes). All analyses were conducted in all patients and then restricted to hypertensive patients. Cox proportional-hazards regression models were used to estimate the association between ACE-I and ARB use and in-hospital death. Since multiple imputation was applied, the final standard error was obtained using the Rubin's rule based on the robust variance

estimator in Cox regression [15]. The proportional hazards assumption was assessed using weighted Schoenfeld residuals, and no violation was identified. Multivariable Cox regression models included age, sex, diabetes, hypertension, history of ischemic heart disease, chronic pulmonary disease, chronic kidney disease, CRP, use of other anti-hypertensive drugs (different from ACE-I or ARB), use of hydroxychloroquine (classified as yes/no/missing) and use of other COVID-19 treatments (lopinavir, darunavir, tocilizumab, sarilumab, corticosteroids or remdesivir, considered as a group and classified as yes/no/missing) as fixed effects; and clustering of hospitals as random effect (frailty model). The use of a frailty model was chosen as suggested in [16]. Secondary analyses used multivariable logistic regression analyses comparing dead versus alive patients, or accounted for hospitals clustering via stratification or by robust sandwich estimator. Pre-established subgroup analyses were conducted according to the sex or age of patients, the degree of COVID-19 severity experienced during the hospital stay, history of hypertension, ischemic heart disease or diabetes or treatment with hydroxychloroquine or with other drug therapies for COVID-19. Hospitals were clustered according to their geographical distribution, as illustrated in **Table 1**. Analyses were performed with the aid of the SAS version 9.4 statistical software for Windows.

Methods used for the meta-analysis

The meta-analysis was conducted according to the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, and reported in line with the PRISMA statement.

Articles published in English were retrieved until July 12th, 2020 by searching in MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials, using the following key words “COVID-19; Coronavirus; SARS-Cov-2; RAAS inhibitors; Renin-angiotensin system Inhibitors; angiotensin converting enzyme inhibitors; ACE-I; angiotensin II receptor blockers; ARB; ARBs”. Twenty-eight publications were identified. No controlled randomized clinical trial was retrieved. To be included in this meta-analysis, each study had a) to include only COVID-19 patients; and b) to report quantitative data on the association of ACE-I or ARB use with severity of COVID-19, including mortality.

Two of us (SC and ADC) independently reviewed the studies identified, then jointly excluded the articles not adhering to one or both criteria, and agreed on a final selection of 18 studies [7, 8, 17-32]. Findings from the CORIST project presented in this manuscript were also included in the meta-analyses, for a total of 19 studies.

For each selected study, odds ratio (OR) or hazard ratio (HR) (possibly adjusted for confounders) and/or number of events (number of deaths/severe events (severe pneumonia or ARDS) and number of total

COVID-19 patients) in both the ACE-I/ARB and the corresponding control groups were extracted. Number of events were used to calculate odds ratios (OR) and 95% confidence intervals (CIs) when OR or HR were not available from the primary study. Pre-specified subgroup analyses were conducted a) in hypertensive patients or in patients irrespective of the hypertension status; b) by considering combination of ACE-I and ARB use or ACE-I or ARB alone; c) according to different outcomes used in the primary studies (total mortality, illness severity or a combination of both).

All analyses were performed using standard statistical procedures provided in RevMan5.1 (The Cochrane Collaboration, Oxford, United Kingdom). Data were combined using the general variance-based method, that requires information on the OR estimate and their 95% CI for each study. Ninety-five % CI were used to assess the variance and the relative weight of each study. Heterogeneity was assessed using the Higgin's I^2 metric. Fixed and random effects were considered, but due to the large heterogeneity observed, findings from random effects were considered as the primary analysis. The hypothesis that publication bias might have affected the validity of the estimates was visually tested by a funnel plot–based approach.

RESULTS

The CORIST project

We included in the final analyses 4,069 patients who were hospitalized with confirmed SARS-CoV-2 infection at 34 clinical centers across Italy and either died or had been discharged or were still in hospital as of June 30, 2020. General characteristics are reported in **Table 1**, separately for all (n=4,069) and hypertensive (n=2,057, 50.6%) patients. Out of all patients, 2,807 (69.0%) were treated neither with ACE-I nor with ARB, 549 (13.5%) used ACE-I, 542 (13.3%) were treated with ARB, 15 (0.4%) used both drugs and 156 (3.8%) suspended ACE-I (ARB) and were not treated for ARB (ACE-I) (**Table 1**). The prevalence of use of ACE-I or ARB was twice as common in hypertensive compared with non-hypertensive patients (**Table 1**). Another anti-hypertensive drug was used in 20.5% of all patients and in 35.8% of hypertensive patients. The large majority of patients (86.6%) received at least one treatment for COVID-19 (**Table 1**). The prevalence of either ACE-I or ARB use (considered together as a group) was strongly associated with hypertension and ischemic heart disease. After adjustment for these two conditions in multivariable logistic regression analysis stratified by hospital clustering, the use of ACE-I or ARB was slightly more prevalent in men (OR=1.21, 95%CI: 1.01 to 1.44) and in patients treated with hydroxychloroquine (OR=1.53, 95%CI: 1.25 to 1.89) or with

other COVID-19 drugs (OR=1.30, 95%CI: 1.07 to 1.59). These findings were confirmed in analyses restricted to hypertensive patients.

All patients

Out of 4,069 patients, 692 died (17.0%), 2,822 were discharged alive (69.4%) and 555 (13.6%) were still hospitalized. The median follow-up was 13 days (interquartile range: 7 to 22). Death rates (per 1,000 person-days) according to the various combinations in the use/non-use of ACE-I and ARB ranged between 10.0 and 17.7 (**Table 2**). In multivariable analysis, patients treated with ACE-I or ARB, alone or in combination, or who had suspended the use of these drugs had HR of death similar to patients not treated with any of the two drugs (**Table 2**). This null association was confirmed in secondary multivariable analyses when the use of ACE-I or ARB was considered together in a single group (HR=0.91, 95%CI: 0.76 to 1.08) or for the case-complete analyses restricted to the 3,785 patients without missing data for covariates (**Table 2**) or when the association with death was quantified by logistic regression multivariable analysis (**Table 2**). Control of hospitals clustering with different approaches (stratification or robust sandwich estimator) also yielded similar results (data not shown). **Table 3** shows that the null association of ACE-I or ARB with mortality was confirmed in all subgroups of patients.

Hypertensive patients

Incidence rates, HRs and ORs for death according to ACE-I and ARB use, in N=2,057 COVID-19 hypertensive patients (with N=471 deaths) are reported in **Table 4**. The null association with in-hospital mortality of this class of drugs was confirmed in hypertensive patients (**Table 4**). When the use of ACE-I or ARB was grouped together, the hazard for death was 0.93, 95%CI: 0.77 to 1.12.

Meta-analysis

The general characteristics of the 19 selected observational retrospective studies are shown in **Online Supplement Table 1**. A total of N=29,055 COVID-19 men and women adult patients (9,700 with hypertension) were included in the meta-analysis. Seven studies from China [7, 8, 21, 23, 27, 31, 32], one from Italy [30]

and one from the U.S. [29] only included hypertensive patients. It was not possible to separate data for patients with or without hypertension in 4 studies [17, 22, 25, 26]. The exposure to either ACE-I or ARB was analyzed separately or in combination, and was tested for association with mortality or a combined outcome of severe illness and mortality (**Online Supplement Table 1**). In all studies the control group consisted of COVID-19 patients without drug exposure.

In studies including both hypertensive and non-hypertensive patients, the use of ACE-I or ARB was not associated with COVID-19 severity (9 studies, **Figure 1A** and **Online Supplement Table 2**), as well as the use of ACE-I or ARB considered together in a single group (5 studies, **Online Supplement Table 2**).

The pooled association of 12 studies on ACE-I or ARB and mortality or severe illness in hypertensive patients is reported in **Figure 1B** and **Online Supplement Table 2**. Use of ACE-I or ARB was not associated with COVID-19 severity (pooled OR: 0.90, 95%CI: 0.80 to 1.01, low level of heterogeneity: I^2=5%, random effects, **Figure 1B**). The lack of association was confirmed excluding the CORIST study (overall HR=1.25, 95%CI:0.98 to 1.60 in **Figure 1A** and overall HR=0.86, 95%CI:0.73 to 1.02 in **Figure 1B**) and in several subgroups analyses according to type of outcome (severe COVID-19 only as the outcome; mortality only as the outcome) or exposure (ACE-I or ARB combined in a single group; ACE-I alone; or ARB alone) (**Online Supplement Table 2**). Selection bias was not revealed at visual inspection of funnel plots in all meta-analyses.

DISCUSSION

At the beginning of the COVID-19 pandemic, a diffuse suspicion emerged that the use of ACE-I and ARB drugs might be harmful in patients with COVID-19, due to their effects on the expression of ACE2, the putative SARS-CoV-2 receptor on target cells [4], causing concern among patients and physicians and leading in some cases to stop or change type of treatment with these anti-hypertensive drugs [33].

In a large cohort of 4,069 patients hospitalized for COVID-19 in 34 clinical centers all over Italy covering almost completely the period of the hospitalization for COVID-19, neither previous treatment with ACE-I or ARB nor drug suspension did modify the risk of death. Discontinuation in the use of ACE-I or ARB occurred in 156 patients, a potentially harmful circumstance that in our sample was not associated with death in comparison with no therapy, in agreement with previous findings [34]; however, this our result should be considered with caution since it was based on a low sample size.

Our cohort included 2,057 hypertensive COVID-19 patients, one of the largest collections of this kind of patients in which a null association of ACE-I or ARB with in-hospital mortality has been observed [35]. Finally, we could prove that the null association remains valid in several sensitivity and subgrouping analyses, including that by COVID-19 severity and drug treatment. Of interest, we found that use of ACE-I or ARB were associated with increased risk of death in patients not treated with hydroxychloroquine or other COVID-19 drugs. Since in our cohort the prevalence of patients untreated for COVID-19 was very low, the latter observation is highly uncertain.

Several epidemiologic studies have been conducted to test the association of RAAS inhibitors with severity of COVID-19, and fourteen articles provided data suitable for a quantitative meta-analysis that we conducted including findings of our project. All were published observational studies with some difference in patient catchment and/or data analysis. At variance with a previously published meta-analysis [36], we performed a set of meta-analyses according to type of COVID-19 patients, class and combination of RAAS inhibitors and type of outcomes and, whenever possible, we extracted and pooled odds ratio adjusted for confounders for each primary study. In addition, we also provided several sub group analyses.

Our meta-analysis does not show any evidence to support the hypothesis that ACE-I or ARB use is associated with an increased risk of severe illness or in-hospital death among patients with COVID-19, in agreement with another, more recent meta-analysis [37] and with the observation that RAAS inhibitors are not associated with the risk of COVID-19 [38].

We performed several subgroup analyses according to different drugs and/or different outcomes, and always failed to observe any association between the use of ACE-I or ARB and severity or mortality in COVID-19 patients, irrespective of their hypertensive status. As far as drug category is concerned, when ACE-Is and ARB were analyzed separately, no association with severe illness or death were consistently observed, both in all COVID-19 patients and in hypertensive COVID-19 patients.

Strengths and limitations

A major strength of the cohort CORIST study is the large, unselected patient sample from 34 hospitals, covering the entire Italian territory. Patient sampling covered all the overt epidemic period in Italy. Several statistical approaches were used to overcome possible biases due to the observational nature of the investigation.

One limitation of this study is represented by the population that pertains only to Italy thus the results might not be applicable to other populations with possibly different geographical and socio-economic conditions

and COVID-19 natural history. Furthermore, due to the retrospective nature of our study, some parameters were not available in all patients, and not all in-hospital medications might have been fully recorded.

The meta-analysis has few limitations too. All primary studies are retrospective and subgroup analyses suffer of a high degree of heterogeneity. Moreover, it was not possible to investigate subgroups according to different geographic settings, because eight out of 14 studies were performed in China.

In conclusion, in a large cohort of unselected patients with COVID-19, hospitalized in 34 different clinical centers all over Italy and in an updated meta-analysis of 19 studies, no harm of ACE-I or ARB use in COVID-19 patients has been reported. These results should be considered with caution, because all the studies analyzed were observational and retrospective, and the possibility of confounding could not be completely excluded. However, at present, this is the best available result that can help physicians in managing anti-hypertensive therapy with these drugs in COVID-19 patients.

While we could reasonably exclude a harmful effect of RAAS inhibitors on COVID-19 severity, randomized controlled clinical trials are still necessary to reach a conclusion regarding a potential benefit of these drugs in patients with COVID-19.

Perspectives

This study, as well as a meta-analysis of all the available literature indicate no either favorable nor detrimental effects of ACE-I or ARB on mortality in COVID-19 hospitalized patients. Use of this drugs should continue as per previous indications in cardiovascular disease.

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This Article is dedicated to all patients who suffered or died, often in solitude, due to COVID-19; their tragic fate gave us moral strength to initiate and complete this research.

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Prof. Iacoviello and Di Castelnuovo had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Concept and design: Di Castelnuovo, Costanzo, Iacoviello, De Caterina,

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Iacoviello, Di Castelnuovo, Costanzo

Critical revision of the manuscript for important intellectual content: Iacoviello, Di Castelnuovo, De Caterina, de Gaetano Donati, Guarnieri and all Authors

Statistical analysis: Di Castelnuovo, Costanzo, Arboretti, Stefanini

Administrative, technical, or material support: All Authors.

Supervision: Iacoviello, Di Castelnuovo, De Caterina

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FIGURE LEGEND

Figure 1: Forest plot for association of ACE-I or ARB with COVID-19 severity and/or mortality in all patients (panel A) or in patients with hypertension (panel B).

Novelty and Significance" written in a style that is understood by a general audience. This section, which should be about 100 words, comprises 3 subsections under the following headings:

What Is New?

In a large observational study in Italy, use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers was not associated with either increased or reduced mortality. This is confirmed by a meta-analysis of all published literature.

What Is Relevant?

- Use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers is not associated with either increased or reduced mortality.
- There is no heterogeneity of results in patients reported to be hypertensive as compared to non-hypertensive
- This is the largest data-set so far examining the association of angiotensin converting enzyme inhibitors or angiotensin receptor blockers with mortality in COVID-19 patiens

Summary of the conclusions of the study

We here found no association of the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers with either mortality. Use of these drugs should continue according to current indications also in COVID-19 patients.

Table 1. General characteristics of COVID-19 patients at baseline, according to hypertension status

Characteristic	All patients (N=4,069)	Hypertensive patients (N=2,057)
Age-median (IQR-yr)	67 (55-79)	74 (64-82)
Gender- no (%)		
Women	1,560 (38.3%)	803 (39.0%)
Men	2,509 (61.7%)	1,254 (61.0%)
ACE-I		
No	3,406 (83.7%)	1,442 (70.1%)
Yes	564 (13.9%)	520 (25.3%)
Suspended	99 (2.4%)	95 (4.6%)
ARB		
No	3,442 (84.6%)	1,470 (71.5%)
Yes	557 (13.7%)	521 (25.3%)
Suspended	70 (1.7%)	66 (3.2%)
ACE-I and ARB		
ACE-I no and ARB no	2,807 (69.0%)	882 (42.9%)
ACE-I yes and ARB no	549 (13.5%)	506 (24.6%)
ACE-I no and ARB yes	542 (13.3%)	507 (24.7%)
ACE-I yes and ARB yes	15 (0.4%)	14 (0.7%)
ACE-I or ARB suspended*	151 (3.7%)	148 (7.2%)
Other anti-hypertensive drug use		
No	3,235 (79.5%)	1,320 (64.2%)
Yes	834 (20.5%)	737 (35.8%)
Diabetes- no (%)^		
No	3,268 (80.5%)	1,476 (72.0%)
Yes	793 (19.5%)	575 (28.0%)
Ischemic heart disease- no (%)^		
No	3,364 (83.5%)	1,494 (73.6%)
Yes	667 (16.5%)	537 (26.4%)
Chronic pulmonary disease- no (%)^		
No	3,473 (85.7%)	1,671 (81.6%)
Yes	578 (14.3%)	376 (18.4%)
Cancer- no (%)^		
No	3,620 (89.1%)	1,782 (86.9%)
Yes	441 (10.9%)	269 (13.1%)
CKD stage¶- no (%)^		
Stage 1	1,412 (35.4%)	416 (20.6%)
Stage 2	1,493 (37.4%)	799 (39.5%)
Stage 3a or stage 3b	789 (19.8%)	571 (28.2%)
Stage 4 or stage 5	298 (7.5%)	238 (11.8%)
C-reactive protein- no (%)^		
<1 mg/L	425 (11.0%)	151 (7.6%)
1-3 mg/L	491 (12.7%)	208 (10.5%)
>3 mg/L	2,957 (76.3%)	1,622 (81.9%)
Hydroxychloroquine use^		
No	910 (22.9%)	482 (24.1%)
Yes	3,067 (77.1%)	1,520 (75.9%)
Lopinavir or Darunavir use^		
No	2,124 (54.0%)	1,093 (55.4%)
Yes	1,808 (46.0%)	879 (44.6%)
Tocilizumab or Sarilumab use^		
No	3,401 (85.9%)	1,692 (84.8%)
Yes	560 (14.1%)	304 (15.2%)
Remdesivir use^		
No	3,889 (97.2%)	1,954 (97.1%)
Yes	112 (2.8%)	58 (2.9%)
Corticosteroids use^		

No	2,376 (64.6%)	1,144 (62.1%)
Yes	1,302 (35.4%)	699 (37.9%)
Clusters of hospitals		
Northern regions (except Milan) (n)	1,088 (26.7%)	554 (26.9%)
Milan (m)	926 (22.8%)	488 (23.7%)
Center regions (except Rome) (c))	1,034 (25.4%)	539 (26.2%)
Rome (r)	498 (12.2%)	184 (9.0%)
Southern regions (s)	523 (12.9%)	292 (14.2%)

^Missing values were N=8 for diabetes, N=38 for ischemic heart disease, N=18 for chronic pulmonary disease, N=8 for cancer, N=77 for CKD stage, N=196 for C reactive protein, N=92 for hydroxychloroquine, N=9 for lopinavir or darunavir, N=108 for tocilizumab or sarilumab, N=68 for remdesivir and N=391 for corticosteroids. *ACE-I no and ARB suspended plus ACE-I suspended and ARB no plus both ACE-I and ARB suspended. ¶Stage 1: Kidney damage with normal or increased glomerular filtration rate (GFR) (>90 mL/min/1.73 m^2); Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2); Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m^2); Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m^2); Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2); Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis).

(n) includes hospitals of 5-10; (m) includes hospitals 1-4; (c) includes hospitals 11-17; (r) includes hospitals 18-20; (s) includes hospitals 21-34 (see list of clinical centers in the Online Supplemental Material).

Table 2: Incidences, hazard ratios and odds ratios for death according to ACE-I and ARB use, in all COVID-19 patients

	Death (N=692)	Patient at risk (N=4,069)	Person-days	Death Rate*	Survival analysis HR (95% CI) Univariable	Survival analysis HR (95% CI) Multivariable^	Logistic analysis OR (95% CI) Multivariable^
All patients, multiple imputation analysis (N=4,069)							
Group							
ACE-I no and ARB no	423 (15.1%)	2,807 (100%)	42,498	10.0	-1-	-1-	-1-
ACE-I yes and ARB no	116 (21.1%)	549 (100%)	8,694	13.3	1.36 (1.11 to 1.67)	0.96 (0.77 to 1.20)	0.89 (0.67 to 1.19)
ACE-I no and ARB yes	112 (20.7%)	542 (100%)	9,098	12.3	1.26 (1.02 to 1.55)	0.89 (0.71 to 1.12)	0.93 (0.69 to 1.24)
ACE-I yes and ARB yes	4 (26.7%)	15 (100%)	226	17.7	1.75 (0.66 to 4.69)	1.45 (0.54 to 3.94)	1.38 (0.32 to 6.03)
ACE-I or ARB suspended[¶]	37 (23.7%)	156 (100%)	2,929	12.6	1.32 (0.94 to 1.84)	0.76 (0.53 to 1.08)	0.85 (0.53 to 1.35)
All patients, case-complete analysis (N=3,785)							
Group							
ACE-I no and ARB no	393 (15.1%)	2,612 (100%)	39,512	10.0	-1-	-1-	-1-
ACE-I yes and ARB no	108 (21.3%)	506 (100%)	7,805	13.8	1.40 (1.13 to 1.74)	0.95 (0.75 to 1.19)	0.88 (0.66 to 1.19)
ACE-I no and ARB yes	105 (20.8%)	504 (100%)	8,294	12.7	1.29 (1.04 to 1.60)	0.91 (0.72 to 1.15)	0.93 (0.69 to 1.25)
ACE-I yes and ARB yes	4 (28.6%)	14 (100%)	201	19.9	1.96 (0.73 to 5.25)	1.54 (0.57 to 4.17)	1.44 (0.32 to 6.36)
ACE-I or ARB suspended[¶]	35 (23.5%)	149 (100%)	2,861	12.2	1.28 (0.91 to 1.82)	0.72 (0.50 to 1.04)	0.95 (0.75 to 1.21)

Abbreviations: HR, hazard ratio; 95%%CI, 95% confidence interval; OR, means odds ratio. *x1000 person-days. ^Controlling for age, sex, diabetes, hypertension, history of ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, use of other anti-hypertensive drugs, use of hydroxychloroquine (yes/no/missing) and use of other COVID-19 treatments (lopinavir, darunavir, tocilizumab, sarilumab, corticosteroids or remdesivir considered as a single group: yes/no/missing) as fixed effects, and hospitals clustering as random effect. [¶]ACE-I no and ARB suspended plus ACE-I suspended and ARB no plus both ACE-I and ARB suspended.

Table 3: Hazard ratios for mortality according to ACE-I and ARB use, in different subgroups

	Group 0	Group 1	Group 2		
	ACE-I no and ARB no (N=2,807)	ACE-I yes and ARB no (N=549)	ACE-I no and ARB yes (N=542)	Group 1 *vs* Group 0	Group 2 *vs* Group 0
Subgroups	**No. death/ patient at risk**	**No. death/ patient at risk**	**No. death/ patient at risk**	**HR (95% CI)***	**HR (95% CI)***
Women	156/1,105	39/206	39/197	0.80 (0.55 to 1.18)	1.07 (0.73 to 1.58)
Men	267/1,702	77/343	73/345	1.03 (0.78 to 1.37)	0.82 (0.61 to 1.08)
Age <75 years	139/2,006	24/286	28/307	0.78 (0.48 to 1.27)	0.66 (0.42 to 1.04)
Age ≥75 years	284/801	92/263	84/235	1.00 (0.78 to 1.29)	0.98 (0.76 to 1.28)
Highest degree of COVID-19 severity experienced at hospital^					
Mild pneumonia	55/1,523	15/312	8/268	1.06 (0.55 to 2.04)	0.64 (0.28 to 1.46)
Severe pneumonia	158/725	54/135	57/152	1.23 (0.87 to 1.75)	0.94 (0.67 to 1.32)
Acute respiratory distress syndrome	190/539	43/98	49/117	1.02 (0.71 to 1.47)	0.85 (0.59 to 1.22)
History of hypertension					
No	206/1,925	10/143	2/35	0.78 (0.40 to 1.51)	0.26 (0.06 to 1.08)
Yes	217/882	106/506	110/507	0.98 (0.77 to 1.24)	0.94 (0.74 to 1.18)
History of ischemic heart disease					
No	309/2,488	93/378	63/411	0.91 (0.68 to 1.23)	0.78 (0.58 to 1.04)
Yes	114/319	58/171	49/131	0.90 (0.64 to 1.28)	1.11 (0.76 to 1.61)
History of diabetes					
No	311/2,360	78/398	77/401	0.92 (0.70 to 1.20)	0.77 (0.59 to 1.02)
Yes	112/447	38/151	35/141	1.00 (0.67 to 1.49)	1.18 (0.78 to 1.78)
Treated with hydroxychloroquine¶					
No	135/653	36/104	34/109	1.46 (0.95 to 2.22)	1.16 (0.76 to 1.77)
Yes	256/2,091	75/437	72/417	0.78 (0.59 to 1.03)	0.90 (0.68 to 1.19)
Treated with other COVID-19 drugs‡					
No	110/797	27/151	24/104	1.05 (0.65 to 1.71)	1.62 (0.98 to 2.69)
Yes	257/1,853	78/365	73/391	0.92 (0.69 to 1.21)	0.87 (0.66 to 1.15)

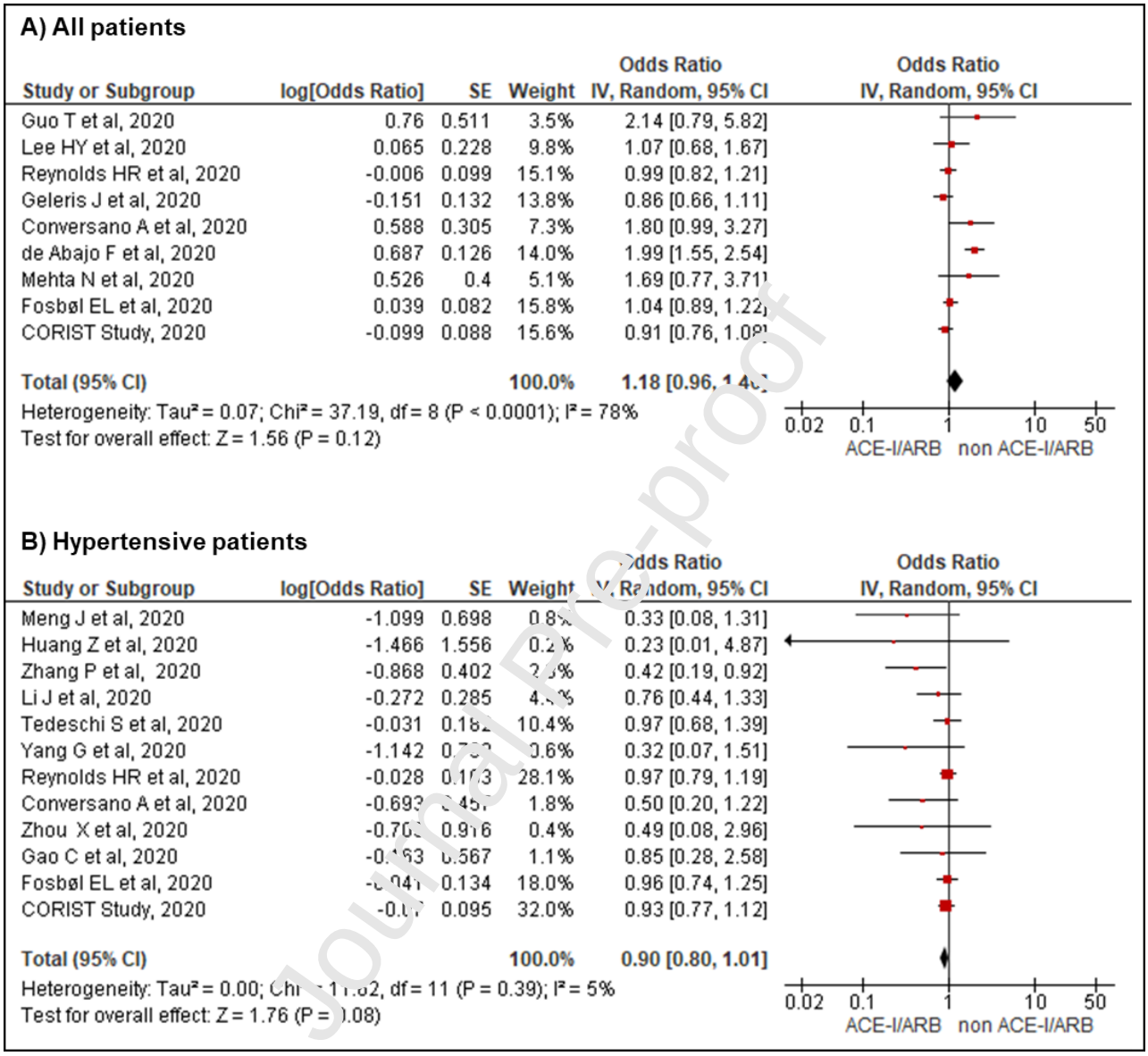
Abbreviations: HR, hazard ratios; CI, confidence intervals; *Controlling for age, sex, diabetes, history of ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, use of other anti-hypertensive drugs, use of hydroxychloroquine (yes/no/missing) and use of other COVID-19 treatments (lopinavir, darunavir, tocilizumab, sarilumab, corticosteroids or remdesivir considered as a unique group yes/no/missing) as fixed effects and hospitals clustering as random effect; multiple imputed analysis; patients with both ACE-I and ARB or patients who suspended ACE-I or ARB were excluded. ^Missing data for N=31 patients. ¶Missing data for N=87 patients. ‡Lopinavir, darunavir, tocilizumab, sarilumab, corticosteroids or remdesivir considered as a unique group, missing data for N=237 patients.

Table 4: Incidences, hazard ratios and odds ratios for death according to ACE-I and ARB use, in COVID-19 hypertensive patients

	Death (N=471)	Patient at risk (N=2,057)	Person-days	Death Rate*	Survival analysis HR (95% CI) Univariable	Survival analysis HR (95% CI) Multivariable^	Logistic analysis OR (95% CI) Multivariable^
Hypertensive patients, multiple imputation analysis (N=2,057)							
Group							
ACE-I no and ARB no	217 (14.4%)	882 (100%)	14,473	15.0	-1-	-1-	-1-
ACE-I yes and ARB no	106 (20.7%)	506 (100%)	7,946	13.3	0.88 (0.70 to 1.11)	1.00 (0.78 to 1.26)	0.88 (0.65 to 1.20)
ACE-I no and ARB yes	110 (20.9%)	507 (100%)	8,516	12.9	0.86 (0.68 to 1.08)	0.94 (0.74 to 1.18)	1.00 (0.73 to 1.35)
ACE-I yes and ARB yes	4 (26.7%)	14 (100%)	207	19.3	1.23 (0.46 to 3.32)	1.44 (0.53 to 3.91)	1.42 (0.31 to 6.47)
ACE-I or ARB suspended[¶]	34 (23.3%)	148 (100%)	2,800	12.1	0.83 (0.58 to 1.19)	0.73 (0.50 to 1.06)	0.80 (0.49 to 1.30)
Hypertensive patients, case-complete analysis (N=1,926)							
Group							
ACE-I no and ARB no	207 (14.4%)	828 (100%)	13,49[illegible]	15.3	-1-	-1-	-1-
ACE-I yes and ARB no	98 (20.7%)	469 (100%)	7,[illegible]54	13.5	1.40 (1.13 to 1.74)	0.96 (0.75 to 1.23)	0.86 (0.63 to 1.18)
ACE-I no and ARB yes	104 (20.9%)	474 (100%)	7,820	13.3	1.29 (1.04 to 1.60)	0.95 (0.75 to 1.21)	1.00 (0.73 to 1.37)
ACE-I yes and ARB yes	4 (26.7%)	13 (100%)	182	22.0	1.96 (0.73 to 5.25)	1.52 (0.56 to 4.14)	1.46 (0.31 to 6.81)
ACE-I or ARB suspended[¶]	32 (23.3%)	142 (100%)	2,749	11.6	1.28 (0.91 to 1.82)	0.68 (0.46 to 1.00)	0.73 (0.44 to 1.21)

Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; OR, odds ratio. *x1000 person-days. ^Controlling for age, sex, diabetes, history of ischemic heart disease, chronic pulmonary disease, chronic kidney disease, C-reactive protein, use of other anti-hypertensive drugs, use of hydroxychloroquine (yes/no/missing) and use of other COVID-19 treatments (lopinavir, darunavir, tocilizumab, sarilumab, corticosteroids or remdesivir considered as a single group-yes/no/missing) as fixed effects; and hospitals clustering as random effect. [¶]ACE-I no and ARB suspended plus ACE-I suspended and ARB no plus both ACE-I and ARB suspended.

Figure 1: Forest plot for association of ACE-I or ARB with COVID-19 severity and/or mortality in all patients (panel A) or in patients with hypertension (panel B).



RAAS inhibitors are not associated with mortality in COVID-19 patients: findings from an observational multicenter study in Italy and a meta-analysis of 19 studies

Short title: RAAS inhibitors and mortality in COVID-19

THE COVID-19 RISk and Treatments (CORIST) Collaboration

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CONFLICT OF INTEREST DECLARATION

Conflict of Interest Disclosures

None by any of the coauthors.

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