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Original article

Chronic use of renin–angiotensin–aldosterone inhibitors in hypertensive COVID-19 patients: Results from a Spanish registry and meta-analysis

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ABSTRACT

Background: Hypertension is a prevalent condition among SARS-CoV-2 infected patients. Whether renin–angiotensin–aldosterone system (RAAS) inhibitors are beneficial or harmful is controversial.
Methods: We have performed a national retrospective, nonexperimental comparative study from two tertiary hospitals to evaluate the impact of chronic use of RAAS inhibitors in hypertensive COVID-19 patients. A meta-analysis was performed to strengthen our findings.
Results: Of 849 patients, 422 (49.7%) patients were hypertensive and 310 (73.5%) were taking RAAS inhibitors at baseline. Hypertensive patients were older, had more comorbidities, and a greater incidence of respiratory failure (−0.151 [95% CI −0.218, −0.084]). Overall mortality in hypertensive patients was 28.4%, but smaller among those with prescribed RAAS inhibitors before (−0.167 [95% CI −0.220, −0.114]) and during hospitalization (0.090 [−0.008,0.188]). Similar findings were observed after two propensity score matches that evaluated the benefit of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers among hypertensive patients. Multivariate logistic regression analysis of hypertensive patients found that age, diabetes mellitus, C-reactive protein, and renal failure were independently associated with all-cause mortality. On the contrary, ACEIs decreased the risk of death (OR 0.444 [95% CI 0.224–0.881]). Meta-analysis suggested a protective benefit of RAAS inhibitors (OR 0.6 [95% CI 0.42–0.8]) among hypertensive COVID-19.
Conclusion: Our data suggest that RAAS inhibitors may play a protective role in hypertensive COVID-19 patients. This finding was supported by a meta-analysis of the current evidence. Maintaining these medications during hospital stay may not negatively affect COVID-19 outcomes.

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Uso crónico de los inhibidores del sistema renina-angiotensina-aldosterona en pacientes con COVID-19 e hipertensión arterial: Resultados de un registro español y metaanálisis

Palabras clave:
Hipertensión arterial
COVID-19
SARS-CoV-2
Inhibidores de la enzima convertidora de angiotensina
Antagonistas de los receptores de la angiotensina II
Metaanális

R E S U M E N

Introducción: La hipertensión es una condición prevalente entre los pacientes infectados por el SARS-CoV-2. Es controvertido si los inhibidores del sistema renina-angiotensina-aldosterona (SRAA) son beneficiosos o perjudiciales.
Métodos: Hemos desarrollado un estudio comparativo nacional retrospectivo y no experimental en 2 hospitales terciarios para evaluar el impacto del uso crónico de inhibidores del SRAA en pacientes hipertensos con COVID-19. Se realizó un metaanálisis para reforzar los hallazgos.
Resultados: De 849 pacientes, 422 (49,7%) eran hipertensos y 310 (73,5%) tomaban inhibidores del SRAA al inicio del estudio. Los pacientes hipertensos eran mayores, tenían más comorbilidades y una mayor incidencia de insuficiencia respiratoria (−0,151; IC 95%: [−0,218; −0,084]). La mortalidad global en los pacientes hipertensos fue del 28,4%, pero fue menor entre los que tenían prescritos inhibidores del SRAA antes (−0,167; IC 95%: [−0,220; −0,114]) y durante la hospitalización (0,090; [−0,008; 0,188]). Se observaron hallazgos similares tras 2 emparejamientos de puntuación de propensión que evaluaron el beneficio de los inhibidores de la enzima convertidora de angiotensina y los bloqueadores de los receptores de angiotensina entre los pacientes hipertensos. El análisis de regresión logística multivariante de los pacientes hipertensos reveló que la edad, la diabetes mellitus, la proteína C reactiva y la insuficiencia renal se asociaban de forma independiente con la mortalidad por todas las causas. Por el contrario, los inhibidores de la enzima convertidora de angiotensina disminuyeron el riesgo de muerte (OR 0,444; IC 95%: 0,224-0,881). El metaanálisis indicó un beneficio protector de los inhibidores del SRAA (OR 0,6; IC 95%: 0,42-0,8) entre los hipertensos con COVID-19.
Conclusión: Nuestros datos indican que los inhibidores del SRAA pueden desempeñar un papel protector en los pacientes hipertensos con COVID-19. Este hallazgo fue apoyado por un metaanálisis de la evidencia actual. Su mantenimiento durante la estancia hospitalaria puede no afectar negativamente a los resultados de la COVID-19.

Introduction

In early December of 2019, several patients from Wuhan were found to have viral pneumonia caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nobody could imagine then that this could lead to the coronavirus disease 2019 (COVID-19) outbreak with an estimated global mortality of 2.3% after 61,299,371 infected people worldwide.[1]

The virus enters the cell by binding its trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2) and the activity of the serine protease TMPRSS2 for S protein priming.[2,3] Expression of ACE2 is upregulated in cardiovascular disease,[4] and in patients with diabetes mellitus and hypertension,[5] which may favor the entrance of the SARS-CoV-2 into the cells and increase the virulence of the virus in the lung and heart. Moreover, renin–angiotensin–aldosterone system (RAAS) blockade increases the expression and activity of cardiac ACE2.[6] On the other hand, recombinant human ACE2 has been shown to protect the ACE2-deficient mice model from lung failure in SARS induced by acid aspiration,[7] and have been seen in severe cases of COVID-19.[8]

Importantly, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) block the RAAS by means of different mechanisms, so that their effects on ACE2 expression and activity should be different as well. Therefore, some authors warn about the harmful effect of RAAS blockers and advise its discontinuation to prevent poor outcome[9] while others claim to maintain these drugs until more evidence was available.[10]

The aim of this national multicenter retrospective study was to (1) evaluate the impact of chronic RAAS inhibitors in hypertensive patients with COVID-19 and (2) estimate its average effect through a meta-analysis of the current evidence.

Methods

Study design and data collection

This is a retrospective nonexperimental comparative study from two tertiary Spanish centers (Hospital Clínico Universitario de Valladolid; Hospital Clínico Universitario de Santiago de Compostela) to evaluate the impact of chronic use of RAAS inhibitors in hypertensive COVID-19 patients. Definitive diagnosis of SARS-CoV-2 infection was confirmed through positive reverse transcriptase-polymerase chain reaction (RT-PCR). The inclusion criteria were patients > 18 years old admitted between March 1st 2020 and April 30th 2020. The exclusion criteria were pregnant women and terminally ill patients.

The study was approved by our local ethics committee and consent was waived due to the retrospective nature of the study. Following the approval, a retrospective analysis of all the COVID-19 patients was performed dividing them into two groups according to their prior history of hypertension. Hypertensive patients were further classified according to their medical therapy before hospital admission into two groups: (1) renin–angiotensin–aldosterone system (RAAS) inhibitors and (2) those without RAAS inhibitors (see supplementary material, Figure-1). A total of 422 patients were included in the final analysis. The procedural strategy was established according to the protocols of each participating institution; however, the decision to maintain or withdraw RAAS inhibitors was determined according to the criteria of the treating medical team.

Study outcomes and main definitions

The primary end-point was to evaluate all-cause mortality in hypertensive patients with and without RAAS inhibitors. Secondary

outcomes were to assess the incidence of respiratory failure and any difference between ACEIs vs. ARB inhibitors.

Fever was considered when the temperature was over > 37.5 °C. Respiratory failure was defined as paO_2 < 60 mmHg, O_2 saturation measured with pulse oximetry of <92% breathing room air, and need for invasive or non-invasive mechanical ventilation. Chronic renal failure was defined as a glomerular filtration rate <60 mL/min or need for dialysis.

Statistical analysis

Categorical variables are reported as absolute values and percentages. Continuous variables are reported as the mean ± standard deviation or median and interquartile range. The normal distribution of quantitative variables was verified with the Kolmogorov–Smirnov test. Differences and their 95% confidence interval were calculated for all comparisons and considered significantly if 0 was not within the interval.

To identify factors that were predictive of death, a logistic regression model with the maximum likelihood method was constructed by using backward stepwise selection, which included the variables that were statistically significant in the bivariate analysis or clinically relevant. No more than 1 variable per 10 outcome events was entered in the logistic model to avoid overfitting. For the final model, we calculated odds ratios (OR) adjusted for each of the variables included, along with their 95% confidence interval (CI). Goodness of fit for each model was determined with the Hosmer–Lemeshow test and area under the curve.

To evaluate the impact of ACE and ARB inhibitors to find out whether COVID-19 hypertensive patients may benefit from an increased survival, a propensity score analysis was performed. The dependent variable was either ACEIs or ARBs and the independent variables chosen were: age, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, ischemic heart disease, creatinine > 1.5 mg/dL and the hospital to match patients from the same center to inhibit potential differences in medical practices. Importantly, in the propensity analysis performed to test the benefit of ACEIs, patients taking ARBs were excluded from the matched cohort and vice versa. Pairs of patients were derived using greedy nearest neighbor method 1:1 with 1/5 of the standard deviation of the logit of the propensity score as a caliper. The MatchIt package (Ho et al., 2007) was used. All other analyses were conducted using the statistical software IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp.

In the meta-analysis, as a measure of the combined effect for the included studies, the OR was estimated, their 95 CI% and its statistical significance. The homogeneity between studies was contrasted by the QH statistic. Concerning the low sensitivity of this test, we consider $p < 0.10$ values as significant. To overcome this limitation in some way, the I2 statistic was estimated as well, which measures the proportion of the total variation of the studies explained by the heterogeneity and its 95% CI. A random-effects model was used for those cases in which the I2 statistic was greater than 50% and a model of fixed effects for the opposite cases. Publication bias was assessed by Begg's tests and inspection of the funnel plot. Sensitivity analyses were used to test the stability of results. Analysis was performed with StataCorp. 2019 (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Results

Comparison of hypertensive vs. non-hypertensive COVID-19 patients

Main baseline characteristics and outcomes are summarized in Table 1. Our study group is made up of 849 patients with a definitive diagnosis of SARS-CoV-2 infections, a total of 422 (49.7%) patients were hypertensive and 427 (50.3%) non-hypertensive. Hypertensive patients were older (−12.3 [95% CI −14.1, −10.5]), showed a greater prevalence of several comorbidities, and were more commonly under chronic treatment. Specifically, a total of 330 patients were taking RAAS inhibitors (−0.688 [95% CI −0.734, −0.641]) when admitted to the hospital and they were more commonly prescribed among hypertensive patients.

Hypertensive patients were characterized at the time of admission because of higher level of inflammatory markers and parameters of organ damage. Lymphocyte count (−80.004 [95% CI −150.005, −19.997]) was also lower among hypertensive patients. Specific COVID-19 treatment was more commonly prescribed in non-hypertensive as opposed to: corticosteroids (−0.099 [95% CI −0.186, −0.012]), statins (−0.063 [95% CI −0.100, −0.026]), ACEIs (−0.145 [95% CI −0.116, −0.104]) and ARBs (−0.183 [95% CI −0.222, −0.143]). Compared to non-hypertensive patients, the incidence of respiratory failure (−0.151 [95% CI −0.218, −0.084]) and death rate (−0.167 [95% CI −0.220, −0.114]) was greater among hypertensive COVID-19 patients.

Comparison of hypertensive COVID-19 patients with and without RAAS inhibitors

The main characteristics of hypertensive patients are summarized in Table 2. Of the hypertensive cohort ($n = 422$), 73.5% of patients had chronic treatment with RAAS inhibitors and no differences were observed in basal clinical characteristics or main comorbidities. The proportion of patients receiving RAAS inhibitors during hospitalization was greater in previous RAAS users (−0.362 [95% CI −0.462, −0.262]) with comparable rates in respect to other treatments. Interestingly, in-hospital outcomes except for higher all-cause mortality in non-RAAS users (0.099 [95% CI 0.002, 0.197] were comparable). Such difference in respect to mortality, remained significant when we evaluated those with *only* RAAS vs. non-RAAS (0.220 [95% CI 0.095, 0.346]) before admission.

Of note, the frequency of RAAS inhibitors usage during hospitalization in hypertensive COVID-19 patients with previous chronic treatment was 48.7%. During the observation period, those who kept RAAS inhibitors during hospitalization compared with their counterpart showed a smaller rate of intensive care unit admission (0.094 [95% CI 0.021, 0.168]) and need of mechanical ventilation (0.098 [95% CI 0.025, 0.171]). Furthermore, within the hypertensive patients with RAAS inhibitors during hospitalization, a lower rate of respiratory failure (0.109 [95% CI −0.004, 0.223]) and all-cause mortality (0.090 [95% CI −0.008, 0.188]) was observed. Finally, no differences were observed in respect to ACEIs vs. ARBs during hospital admission in respect to main outcomes (data not shown).

We performed a PSM to further evaluate the benefit of RAAS inhibitors, specifically whether chronic ACEIs or ARBs still show an association with lower all-cause mortality among hypertensive COVID-19 patients (see Table 3) after adjustment for potential cofounders. Compared with non-RAAS inhibitors, the incidence of all-cause mortality was lower irrespective of ACEIs (−0.136 [95% CI −0.279, −0.047]) or ARBs (−0.130 [95% CI −0.297, −0.039]) users in comparison to non-users. To further explore their potential benefit during in-hospital use, despite the small sample, we observed in the matched cohort that continuation of RAAS inhibitors were not associated with greater mortality the least

Predictors of all-cause mortality and meta-analysis

After a univariate analysis of the *hypertensive COVID-19 patients*, a logistic regression model was performed (*see* Table 4) including the following variables: age, diabetes mellitus, chronic kidney disease, ischemic heart disease, ACEIs at admission, ARBs at admis-

Table 1
Baseline characteristics and main features of hypertensive vs. non-hypertensive patients admitted due to coronavirus disease 2019.

Variable	All population *N* = 849	Hypertensive *N* = 422 (49.7)	Non-hypertensive *N* = 427 (50.3)	Difference (95% CI)
Demographics				
Female sex	421 (49.6)	421 (49.6)	211 (49.4)	0.003 (−0.064,0.071)
Age (years)	68.2 ± 14.7	74.4 ± 12.2	62.1 ± 14.5	**−12.3 (−14.1, −10.5)**
CKD	59 (7)	52 (12.4)	7 (1.6)	**−0.107 (−0.141, −0.073)**
COPD	164 (19.3)	116 (27.5)	48 (11.3)	**−0.023 (−0.063, 0.018)**
Diabetes	346 (40.9)	238 (56.4)	108 (25.5)	**−0.162 (−0.214, −0.110)**
Dyslypidaemia	347 (53.1)	236 (46.7)	111 (74.5)	**−0.309 (−0.372, −0.246)**
IHD	70 (8.3)	53 (12.6)	17 (4)	**−0.086 (−0.123, −0.050)**
Treatment prior to admission				
Antiplatelets	129 (15.2)	89 (21.2)	40 (9.4)	**−0.119 (−0.167, −0.071)**
ACEi	147 (17.3)	136 (32.2)	11 (2.6)	**−0.297 (−0.343, −0.250)**
ARB	176 (20.7)	170 (40.3)	6 (1.4)	**−0.389 (−0.437, −0.341)**
BB	157 (18.5)	124 (29.4)	33 (7.7)	**−0.216 (−0.267, −0.166)**
CCB	65 (12.6)	59 (23)	6 (2.3)	**−0.206 (−0.261, −0.151)**
Diuretics	113 (21.9)	99 (38.5)	14 (5.4)	**−0.331 (−0.397, −0.265)**
Oral anticoagulation	99 (11.7)	73 (17.4)	26 (6.1)	**−0.113 (−0.156, −0.070)**
RAAS[a]	330 (38.9)	310 (73.5)	20 (4.7)	**−0.688 (−0.734, −0.641)**
Statins	295 (35.2)	196 (46.8)	99 (23.7)	**−0.231 (−0.294, −0.168)**
Main findings at admission				
Time from onset (days)	7 [4–10]	6 [3–9]	7 [4–10]	**−0.999 (−1.999, −0.00004)**
Cough	577 (69.2)	264 (64.5)	313 (73.6)	0.091 (0.028,0.154)
Fever	590 (75.4)	286 (75.5)	304 (75.4)	−0.001 (−0.061,0.060)
Positive RT-PCR	822 (97.7)	409 (97.6)	413 (97.9)	0.003 (−0.088,0.023)
Laboratory findings at admission				
Hemoglobin (g/dL)	13.4 [12.1–14.5]	13.1 [11.7–14.4]	13.6 [12.4–14.7]	**−0.400 (−0.699, −0.199)**
C-reactive protein (mg/L)	25 [9.1–89]	36.3 [10–111.6]	20 [7.6–67.8]	**7.269 (3.300, 12.199)**
Creatinine (mg/dL)	0.9 [0.73–1.14]	1 [0.8–1.4]	0.8 [0.7–0.98]	**0.199 (0.150, 0.240)**
D-Dimer (ng/mL)	775.5 [469–1490]	927 [521–1702]	672 [427–1236]	**172 (92.99, 257.00)**
Ferritin (ng/mL)	595 [298–1164.5]	647 [320–1251]	567 [265–1100]	64.99 (−10.99, 141.00)
ALT (U/L)	36 [25–56]	36.5 [25–58]	35 [25–55]	0.999 (−1.999, 3.999)
AST (U/L)	30 [19–53]	28 [18–53]	32 [21–54]	**−3.00 (−6.001, −0.999)**
Interleukin-6 (pg/mL)	23.4 [11.1–49.8]	28 [13–55.8]	20 [9.6–41.5]	**5.399 (1.999, 9.199)**
LDH (U/L)	298 [225–405]	265 [206–331]	357 [303–460]	**18.004 (0.00002, 35.999)**
Lymphocytes (cells/mm^3)	920 [640–1300]	860 [615–1260]	965 [670–1360]	**−80.004 (−150.005, −19.997)**
Neutrophils (cells/mm^3)	4780 [3190–6850]	5320 [3635–7410]	4280 [2930–6120]	**880 (450, 1340)**
Platelets (cells/mm^3 × 10^3)	193 [151–258]	194 [147–251]	193 [158–264]	5 (−15.6)
Procalcitonin (ng/mL)	0.11[0.06–0.28]	0.13 [0.08–0.34]	0.09 [0.05–0.2]	**0.030 (0.019, 0.040)**
Specific COVID-19 treatment				
Azithromycin	756 (93.8)	375 (93.3)	381 (94.3)	−0.010 (−0.023, 0.044)
Betaferon	223 (27.6)	114 (28.4)	109 (26.9)	−0.014 (−0.076, 0.047)
Hydroxychloroquine	774 (95.7)	377 (93.8)	397 (97.5)	**0.038 (0.010, 0.066)**
Lopinavir/ritonavir	708 (87.4)	340 (84.6)	368 (90.2)	**0.056 (0.011, 0.162)**
Non-specific COVID-19 treatment				
ACEi	93 (11)	77 (18.2)	16 (3.7)	**−0.145 (−0.116, −0.104)**
ARB	89 (10.5)	83 (19.7)	6 (1.4)	**−0.183 (−0.222, −0.143)**
Anticoagulation[b]	321 (62.8)	165 (64.7)	156 (60.9)	−0.038 (−0.122,0.046)
BB	85 (16.6)	58 (22.7)	27 (10.5)	**−0.122 (−0.186, −0.058)**
CCB	79 (15.5)	67 (26.3)	12 (4.7)	**−0.216 (−0.276, −0.156)**
Corticosteroids	293 (59.8)	158 (64.8)	135 (54.9)	**−0.099 (−0.186, −0.012)**
Diuretics	165 (19.7)	123 (29.6)	42 (10)	**−0.197 (−0.249, −0.144)**
Statins	70 (8.3)	48 (11.5)	22 (5.2)	**−0.063 (−0.100, −0.026)**
Main in-hospital outcomes				
LOS (days)	9 [6–14]	9 [6–14]	9 [6–13]	0.000003 (−0.00005, 1.00005)
ICU admission	87 (10.5)	45 (11)	42 (10)	−0.010 (−0.052,0.032)
Mechanical ventilation	72 (9.7)	35 (9.7)	37 (9.6)	−0.002 (−0.044,0.041)
Respiratory failure	338 (41.6)	199 (49.1)	139 (34.1)	**−0.151 (−0.218, −0.084)**
All-cause mortality	170 (22.7)	120 (28.4)	50 (11.7)	**−0.167 (−0.220, −0.114)**

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ALT: alanine aminotransferase; ARB: angiotensin receptor blocker; AST: aspartate aminotransferase; BB: beta-blockers; CCB: calcium channel blockers; CKD: chronic kidney disease; ICU: intensive care unit; IHD: ischemic heart disease; LDH: lactate dehydrogenase; LOS: length of stay; RAAS: renin–angiotensin–aldosterone system inhibitors; RT-PCR: reverse transcription-polymerase chain reaction;

[a] Includes ACEi, ARBs and aldosterone inhibitors.

[b] Only includes complete doses.

Values are median (IQR), mean ± SD or *n* (%). Bold indicates significative differences.

sion, lymphocytes < 1000/mm^3, lactate dehydrogenase > 250 U/L, D-dimer > 500 μm/L, creatinine > 1.5 mg/dL, C-reactive protein > 10 mg/L and hospital. The final model identified that among hypertensive patients age, diabetes mellitus, C-reactive protein, and creatinine were associated with a greater risk of all-cause mortality. On the contrary, ACEIs at admission independently protected from mortality (OR 0.444 [95% CI 0.224–0.881], $p = 0.02$).

A review of the literature was conducted by two researchers (AA and PC) in PubMed and from the reference list of the retrieved studies to evaluate the impact of chronic use of RAAS inhibitors

Table 2
Baseline characteristics and main features during admission of hypertensive hospitalized patients according to chronic anti-hypertensive baseline treatment.

Variable	All population *N* = 422	Hypertensive with RAAS *N* = 310 (73.5)	Hypertensive without RAAS *N* = 112 (26.5)	Difference (95% CI)
Demographics				
Female sex	421 (49.6)	163 (52.6)	47 (42)	0.106 (−0.002,0.214)
Age (years)	74.4 ± 12.2	74 ± 11.7	75.2 ± 13.4	1.14 (−1.50,3.78)
CKD	52 (12.4)	34 (11)	18 (16.1)	0.051 (−0.021,0.122)
COPD	44 (10.8)	29 (9.6)	15 (14)	0.044 (−0.024,0.113)
Diabetes	116 (27.5)	83 (26.8)	33 (29.5)	0.027 (−0.070,0.124)
Dyslypidaemia	238 (56.4)	174 (56.1)	64 (57.1)	0.010 (−0.098,0.118)
IHD	53 (12.6)	39 (12.7)	14 (12.5)	−0.002 (−0.074,0.071)
Treatment prior to admission				
Antiplatelets	89 (21.2)	67 (21.8)	22 (19.6)	−0.022 (−0.111,0.067)
ACEi	136 (32.2)	136 (43.9)	0	**−0.439 (−0.531, −0.346)**
ARB	170 (40.3)	170 (54.8)	0	**−0.548 (0.641, −0.456)**
BB	124 (29.4)	86 (27.7)	38 (33.9)	0.062 (−0.037,0.161)
CCB	59 (23)	38 (20.7)	21 (28.8)	0.081 (−0.033,0.196)
Diuretics	99 (38.5)	78 (42.4)	21 (28.8)	**−0.136 (−0.268, −0.004)**
Oral anticoagulation	73 (17.4)	48 (15.6)	25 (22.3)	0.067 (−0.015,0.150)
Statins	196 (46.8)	147 (47.7)	49 (44.1)	−0.036 (−0.145,0.073)
Main findings at admission				
Time from onset (days)	6 [3–9]	6 [4–9]	6 [3–10]	0.0007 (−0.0001, 1.0001)
Cough	264 (64.5)	196 (65.3)	68 (62.4)	−0.029 (−0.135,0.076)
Fever	286 (75.5)	206 (74.9)	80 (76.9)	0.020 (−0.078,0.118)
Positive RT-PCR	822 (97.7)	409 (97.6)	413 (97.9)	−0.004 (−0.037,0.029)
Laboratory findings at admission				
Hemoglobin (g/dL)	13.1 [11.7–14.4]	13 [11.7–14.2]	13.4 [11.8–14.5]	−0.200 (−0.699, 0.200)
C-Reactive protein (mg/L)	36.3 [10–111.6]	32 [10–109]	42.7 [10.2–115.5]	−2.000 (−11.340, 4.299)
Creatinine (mg/dL)	1 [0.8–1.4]	1 [0.8–1.5]	1 [0.8–1.3]	0.059 (−0.029, 0.140)
D-Dimer (ng/mL)	927 [521–1702]	948 [530–1761]	683 [469–1367]	79 (−61.001, 230.004)
Ferritin (ng/mL)	647 [320–1251]	683 [334–1220]	492 [294–1257]	80 (−37.9, 207.0)
ALT (U/L)	36.5 [25–58]	37 [25–60]	35 [26–50]	1.001 (−3.005, 5.999)
AST (U/L)	28 [18–53]	30 [19–54]	25 [14–54]	**4.999 (0.999, 9.001)**
Interleukin-6 (pg/mL)	28 [13–55.8]	28 [13–59]	26 [13–50]	1.799 (−4.599, 8.698)
LDH (U/L)	265 [206–331]	312 [226–442]	297 [228–410]	8.000 (−20.995, 37.993)
Lymphocytes (cells/mm^3)	860 [615–1260]	890 [630–1250]	800 [590–1270]	30 (−70, 140)
Neutrophils (cells/mm^3)	5320 [3635–7410]	5360 [3820–7375]	4780 [3035–7160]	369.9 (−440, 1150)
Platelets (cells/mm^3 × 10^3)	194 [147–251]	202 [153–254]	178 [138–238]	**19 (2, 36)**
Procalcitonin (ng/mL)	0.13 [0.08–0.34]	0.13 [0.08–0.36]	0.11 [0.07–0.29]	0.010 (−0.010, 0.039)
Specific COVID-19 treatment				
Azithromycin	375 (93.3%)	275 (92.9%)	100 (94.3%)	0.014 (−0.046,0.070)
Betaferon	114 (28.4%)	83 (28%)	31 (29.2%)	0.011 (−0.089,0.111)
Hydroxychloroquine	377 (93.8%)	280 (94.6%)	97 (91.5%)	−0.031 (−0.089,0.023)
Lopinavir/Ritonavir	340 (84.6%)	253 (85.5%)	87 (82.1%)	−0.034 (−0.117,0.046)
Non-specific COVID-19 treatment				
RAAS[a]	165 (39.1%)	151 (48.7%)	14 (12.5%)	**−0.362 (−0.462,−0.262)**
ACEi	66 (18.2)	66 (21.3)	11 (9.8)	**−0.115 (−0.198,−0.032)**
ARB	80 (19.7)	80 (25.8)	3 (2.7)	**−0.231 (−0.315,−0.148)**
Anticoagulation[b]	165 (64.7)	122 (66.7)	43 (59.7)	−0.070 (−0.201,0.162)
BB	58 (22.7)	36 (19.7)	22 (30.6)	0.109 (−0.006,0.223)
CCB	67 (26.3)	49 (26.8)	18 (25)	−0.018 (−0.139,0.103)
Corticosteroids	158 (64.8)	111 (63.1)	47 (69.1)	0.060 (−0.074,0.195)
Diuretics	123 (29.6)	93 (30.6)	30 (27)	−0.036 (−0.135,0.064)
Statins	48 (11.5)	38 (12.4)	10 (9)	−0.034 (−0.103,0.036)
Main in-hospital outcomes				
LOS (days)	9 [6–14]	9 [6–14]	9 [6–16]	−0.0003 (−1.996,0.997)
ICU admission	45 (11)	36 (12)	9 (8.1)	−0.039 (−0.103,0.024)
Mechanical ventilation	35 (9.7)	27 (10.3)	8 (8.3)	−0.019 (−0.089,0.050)
Respiratory failure	199 (49.1)	138 (46.3)	61 (57)	0.107 (−0.004,0.218)
All-cause mortality	120 (28.4)	80 (25.8)	40 (35.7)	**0.099 (0.002,0.197)**
	All population *N* = 219	Hypertensive with only RAAS *N* = 156 (71%)	Hypertensive without RAAS *N* = 63 (29%)	Difference (95% CI), %
LOS (days)	9 [6–15]	10 [7–15]	8 [5–13]	1.0005 (−0.0002,2.9995)
ICU admission	28 (13.1)	23 (15.2)	5 (8.1)	−0.072 (−0.172,0.029)
Mechanical ventilation	20 (10.6)	15 (10.9)	5 (9.8)	−0.011 (−0.112,0.089)
Respiratory failure	100 (42.7)	68 (45)	32 (52.5)	0.074 (−0.075,0.224)
All-cause mortality	56 (25.6)	30 (19.2)	26 (41.3)	0.220 (0.095,0.346)

Table 2 (*Continued*)

	All population *N* = 310	Hypertensive with RAAS-on[c] *N* = 151 (48.7%)	Hypertensive RAAS-off[c] *N* = 159 (51.3%)	Difference (95% CI), %
LOS (days)	9 [6–14]	9 [6–14]	9 [6–15]	0.0003 (−1.0003, 1.9996)
ICU admission	36 (12)	11 (7.3)	25 (16.8)	**0.094 (0.021,0.168)**
Mechanical ventilation	27 (10.3)	7 (5.3)	20 (15.2)	**0.098 (0.025,0.171)**
Respiratory failure	100 (42.7)	59 (40.7)	79 (51.6)	0.109 (−0.004,0.223)
All-cause mortality	80 (25.8)	32 (21.2)	48 (30.2)	0.090 (−0.008,0.188)

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitors; ALT: alanine aminotransferase; ARB: angiotensin receptor blocker; AST: aspartate aminotransferase; BB: Beta-blockers; CCB: Calcium channel blockers; CKD: Chronic kidney disease; ICU: Intensive care unit; IHD: Ischemic heart disease; LDH: Lactate dehydrogenase; LOS: Length of stay; RAAS: Rening angiotensin-aldosterone system inhibitors; RT-PCR: Reverse transcription-polymerase chain reaction;

[a] Includes ACEi, ARB and aldosterone inhibitors.

[b] Only includes complete doses.

[c] Hypertensive patients with or without RAAS inhibitors during hospitalization that took them before admission.

Values are median (IQR), mean ± SD or *n* (%). Bold indicates significative differences.

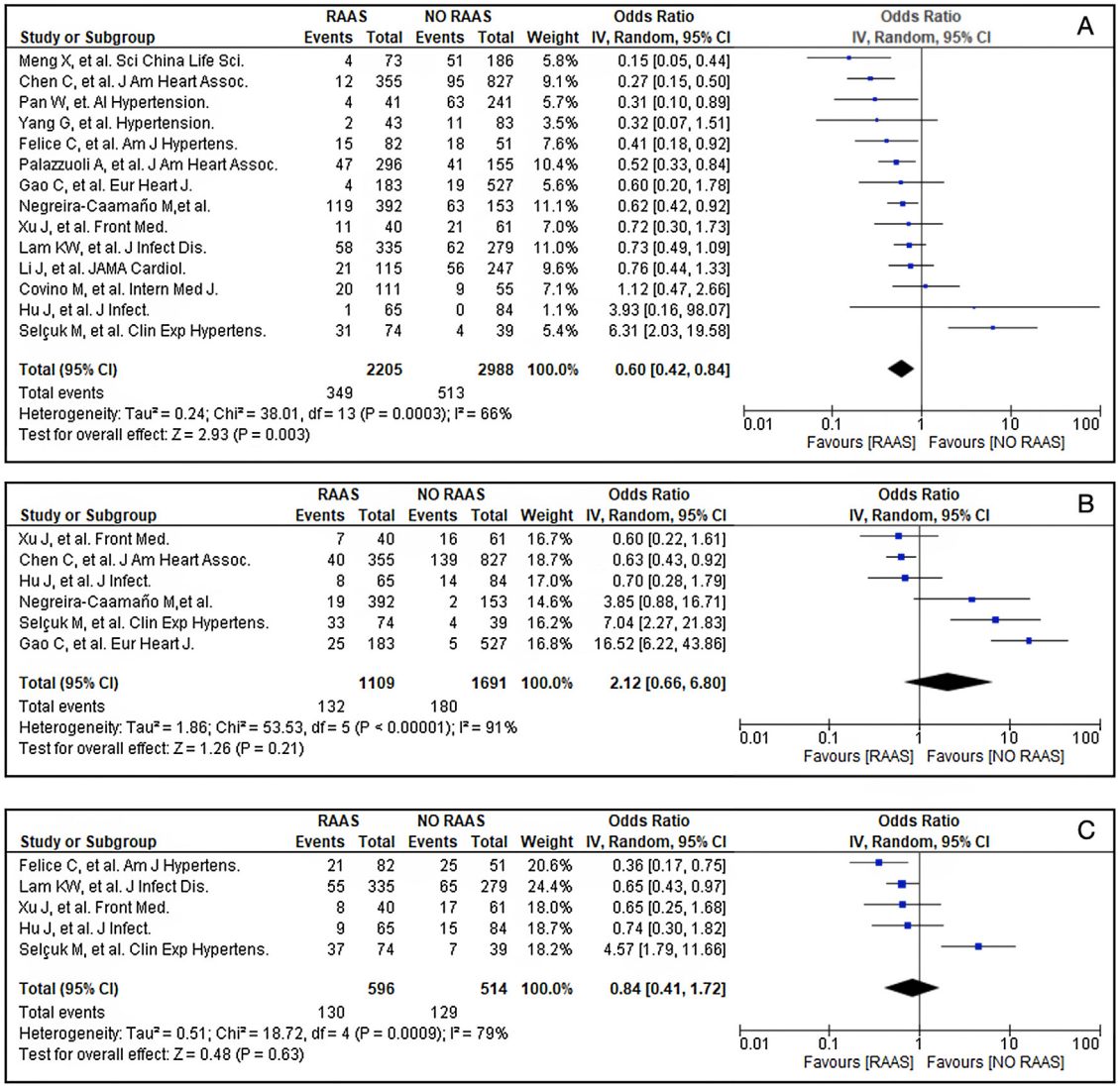

Fig. 1. Forrest plot of showing the Odds Ratio (OR) of the main outcomes: (A) All-cause mortality; (B) Mechanical ventilation; and (C) Intensive care unit admission. *Vertical line represents "no difference" point between hypertensive COVID-19 patients with chronic RAAS vs. Non-RAAS inhibitors treatment; Horizontal lines 95% confidence interval (CI). Squares represent the odds ratio for each study (the size of each square denotes the proportion of information given by each study); Diamonds represent pooled odds ratios from all studies.

among hypertensive COVID-19 admitted patients. Eligible studies were retrospective peer-reviewed published in English that evaluated the impact of RAAS inhibitors in all-cause mortality of hypertensive COVID-19 patients between January/November 2020 (see supplementary material, table* S1).[11–24] Exclusion criteria were: (1) non-peer-reviewed papers from preprint servers, (2) abstracts, and (3) samples < 100 patients. The following terms were searched: "COVID-19" or "SARS-CoV-2" and "hypertension" and "renin–angiotensin–aldosterone system" or "angiotensin receptor blocker" or "angiotensin-converting enzyme inhibitor".

Table 3
Baseline Characteristics and main features of the matched hypertensive cohort with chronic angiotensin converting enzyme inhibitors or angiotensin receptor blockers with COVID-19.

Variable	ACEi-On[b] N = 92	ACEi-Off[b] N = 92	Difference (95% CI)	ARB-On[b] N = 95	ARB-off[b] N = 95	Difference (95% CI)
Demographics						
Female sex	36 (39)	39 (42)	−0.033 (−0.184,0.119)	34 (36)	38 (40)	−0.040 (−0.181,0.097)
Age (years)	73 ± 11	74 ± 13	−1.476 (−4.5171.559)	73 ± 12	75 ± 12	−2.41 (−5.81,0.99)
CKD	4 (4.3)	8 (9)	−0.043 (−0.104,0.017)	13 (14)	14 (15)	−0.010 (−0.111,0.09)
COPD	9 (10)	12 (11)	−0.011 (−0.095,0.073)	11 (12)	10 (11)	0.010 (−0.80,0.101)
Diabetes	19 (21)	21 (23)	−0.022 (−0.119, 0.075)	29 (31)	30 (32)	−0.010 (−0.144,0.123)
Dyslypidaemia	53 (58)	50 (54)	0.033 (−0.110, 0.175)	52 (55)	54 (57)	0.280 (−0.164,0.122)
IHD	12 (13)	13 (14)	−0.011 (−0.100, 0.79)	10 (11)	10 (11)	0.000 (−0.088,0.088)
Treatment prior to admission						
BB	26 (28.3)	33 (35.9)	−0.076 (−0.200,0.048)	25 (26.3)	33 (34.7)	−0.084 (−0.216,0.048)
CCB	10 (15.6)	17 (26.6)	−0.109 (−0.264,0.046)	15 (24.2)	20 (32.3)	−0.081 (−0.235,0.084)
Diuretics	19 (29.7)	19 (29.7)	0.000 (−0.160, 0.160)	38 (61.3)	17 (27.4)	0.339 (0.142,0.480)
Oral anticoagulation	13 (14.1)	19 (20.7)	−0.065 (−0.175,0.045)	15 (16.1)	22 (23.7)	−0.076 (−0.185,0.044)
Statins	47 (51.1)	37 (40.2)	0.109 (−0.016, 0.233)	41 (43.6)	41 (43.6)	0.000 (−0.149,0.149)
Laboratory findings at admission						
C-Reactive protein (mg/L)	57.2 [13.8–127]	42.7 [8.6–119]	4.399 (−6.879,21.500)	31.8 [8.4–110]	42.1 [10.3–123.5]	3.899 (−4.409, 20.300)
Creatinine (mg/dL)	0.95 [0.80–1.20]	0.96 [0.77–1.125]	0.010 (−0.080,0.100)	0.99 [0.77–1.38]	0.98 [0.77–1.39]	−0.009 (−0.110,0.100)
D-Dimer (ng/mL)	901[485.7–1622.2]	866 [459–1367.5]	26 (−159,202)	892[455.5–1991]	882.5 [483.2–1404.2]	−25.36 (−235,177)
Ferritin (ng/mL)	845[382–1553]	492 [274.7–1260.2]	195.99 (19,416)	554.5 [258.5–1100]	492 [300.2–1270.7]	33 (−117,177)
Interleukin-6 (pg/mL)	30.8 [10.6–62.5]	25 [12.7–41.9]	1.899 (−6.500,12.003)	24.5 [11.6–47]	27 [14.3–52]	2.6 (−5.8,9.9)
LDH (U/L)	314[259.5–440]	292 [224–408]	30 (−9.9,67.0)	279 [205–420]	285 [225–377]	6.99 (−3042)
Lymphocytes (cells/mm^3)	920 [642.5–1237.5]	885[600–1300]	10 (−130,160)	1000 [640–1340]	840 [620–1270]	−60 (−21,080)
Procalcitonin (ng/mL)	0.13 [0.06–0.27]	0.11[0.07–0.31]	−0.0001 (−0.030,0.031)	0.11 [0.06–0.32]	0.11[0.07–0.40]	0.009 (−0.020, 0.039)
Specific COVID-19 treatment						
Azithromycin	83 (91.2)	85 (94.4)	−0.002 (−0.052,0.076)	88 (94.6)	85 (94.4)	0.002 (−0.059,0.097)
Betaferon	30 (33)	27 (30)	0.030 (−0.055,0.175)	25 (26.9)	25 (27.8)	−0.009 (−0.189,0.078)
Hydroxychloroquine	88 (96.7)	82 (91.1)	0.056 (−0.060,0.084)	88 (94.6)	85 (94.4)	0.002 (−0.059,0.097)
Lopinavir/Ritonavir	81 (89)	73 (81.1)	0.079 (−0.044,0.165)	80 (6)	74 (82.2)	0.038 (−0.151,0.091)
Non-specific COVID-19 treatment						
ACEi	44 (47.8)	8 (8.7)	**0.391 (0.281,0.502)**	1 (1.1)	10 (10.5)	**−0.094 (−0.029,−0.161)**
ARB	0 (0)	3 (3.3)	−0.033 (−0.070,0.004)	46 (48.4)	2 (2.1)	**0.463 (0.357,0.589)**
Anticoagulation[a]	41 (65.1)	38 (60.3)	0.048 (−0.148,0.242)	42 (68.9)	37 (60.7)	0.082 (−0.089,0.251)
BB	15 (23.8)	21 (33.3)	−0.095 (−0.221,0.030)	10 (16.4)	18 (29.5)	−0.131 (−0.263,0.038)
CCB	11 (17.5)	15 (23.8)	−0.063 (−0.213,0.086)	21 (34.4)	17 (27.9)	−0.065 (−0.246,0.085)
Corticosteroids	43 (74.1)	39 (66.1)	0.000 (−0.195,0.195)	29 (55.8)	41 (73.2)	−0.174 (−0.275,0.078)
Diuretics	21 (23.3)	21 (23.3)	0.000 (−0.113,0.113)	33 (35.5)	27 (29)	0.065 (−0.071,0.198)
Statins	13 (14.4)	8 (8.9)	0.055 (−0.041,0.152)	15 (16.1)	10 (10.8)	0.053 (−0.045,0.151)
Main in-hospital outcomes						
ICU admission	11 (12)	8 (8.4)	0.004 (−0.087,0.081)	13 (14)	8 (9)	0.050 (−0.037,0.146)
Mechanical ventilation	8 (9.6)	7 (8.8)	0.008 (−0.051,0.026)	11 (13)	7 (9)	0.040 (−0.052,0.141)
Respiratory failure	48 (52.2)	47 (52.2)	0.000	31 (33)	46 (51)	**−0.180**
All-cause mortality	20 (21.1)	33 (34.7)	(−0.170,0.170) **−0.136 (−0.279,−0.047)**	20 (22)	36 (35)	**(−0.320,−0.035) −0.130(−0.297,−0.039)**
	RAAS-on[c] N = 45	RAAS-off[c] N = 47	Difference (95% CI)	RAAS-on[c] N = 47	RAAS-off[c] N = 48	Difference (95% CI)
LOS (days)	10 [6–17]	9 [6–13]	1.00 (−1.00, 4.00)	7 [6–11]	7 [4–14.5]	−6.11 (−3.00, 2.00)
ICU admission	3 (6.8)	5 (11.1)	−0.043 (−0.164,0.079)	3 (6.4)	10 (21.7)	**−0.153 (−0.294,0.013)**
Mechanical ventilation	2 (5)	3 (8.1)	−0.031 (−0.144,0.082)	2 (5)	9 (20.5)	**−0.155 (−0.296,0.013)**
Respiratory failure	22 (53.7)	23 (48.9)	0.048 (−0.167,0.262)	9 (19.6)	22 (46.8)	**−0.272 (−0.460,0.084)**
All-cause mortality	8 (17.8)	12 (25.5)	−0.077 (−0.250,0.094)	5 (10.6)	15 (31.3)	**−0.207 (−0.369,0.044)**

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BB: beta-blockers; CCB: calcium channel blockers; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; IHD: ischemic heart disease; LDH: lactate dehydrogenase; LOS: length of stay.

[a] Only includes complete doses.

[b] Does not include patients with ARBs and vice versa.

[c] Hypertensive patients with or without RAAS inhibitors during hospitalization that took them before admission;

Values are median (IQR), mean ± SD or *n* (%). Bold indicates significant differences.

Table 4
Predictors of all-cause mortality in the study hypertensive population.

	Univariate		Multivariate	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Hospital	3.457 (2.094–5.706)	**<0.001**		
Age (years)	1.077 (1.053–1.101)	**<0.001**	1.078 (1.050–1.106)	**<0.001**
Diabetes mellitus	2.587 (1.643–4.072)	**<0.001**	2.456 (1.375–4.389)	**0.002**
Chronic kidney disease	2.700 (1.494–4.879)	**0.001**		
COPD	2.328 (1.231–4.403)	**0.009**		
Ischemic heart disease	1.627 (0.894–2.960)	0.111		
ACEi	0.654 (0.407–1.048)	0.078	0.444 (0.224–0.881)	**0.02**
ARB	0.892 (0.578–1.377)	0.607		
Lymphocyte < 1000 mm^3	1.566 (1.006–2.438)	0.047		
Lactate dehydrogenase > 500 U/L	2.023 (1.198–3.419)	**0.008**		
C-reactive protein	4.666 (2.319–9.388)	**<0.001**	3.441 (1.455–8.135)	**0.005**
D-Dimer > 500	2.167 (1.202–3.905)	**0.01**		
Creatinine > 1.5 mg/dL	5.309 (3.257–8.652)	**<0.001**	5.126 (2.796–9.357)	**<0.001**

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; COPD: Chronic obstructive pulmonary disease.
Hosmer–Lemeshow, $p = 0.530$ AUC 0.836 (0.793, 0.878).

The study quality of the selected studies was assessed by using Newcastle–Ottawa Scale (NOS; Table S1). Overall, prior use of RAAS inhibitors among admitted hypertensive COVID-19 patients was associated with lower all-cause mortality (OR 0.6 [95% CI 0.42–0.8]; $p < 0.003$) (Fig. 1A). We did not observe a protective effect of RAAS inhibitors in respect to mechanical ventilation (OR 2.12 [95% CI 0.66–6.80]; $p = 0.21$) (Fig. 1B) or intensive care unit admission (OR 0.84 [95% CI 0.41–1.72]; $p = 0.63$) (Fig. 1C).

Discussion

Ever since the beginning of the current global outbreak, the potential beneficial or harmful effects of RAAS inhibitors have been a subject of ongoing discussions. Our main findings are: (1) in hypertensive COVID-19 patients prior treatment with RAAS inhibitors were associated with a lower risk of all-cause mortality; (2) this protective benefit was also observed after PSM in both ACEIs and ARBs users; (3) a meta-analysis showed that previous RAAS inhibitors use was associated with mortality risk decrement in COVID-19 with preexisting hypertension; (4) continuation of RAAS inhibitors during hospitalization in hypertensive COVID-19 patients are not associated with adverse outcomes.

Previous studies have assessed the effect of RAAS blockade on COVID-19 hospitalized patients with overall positive results.[25] For instance, Reynolds et al.[26] obtained data from 12,594 patients' electronic health records and failed to show an association between ACEIs and ARBs with a positive test result or severe disease by performing a propensity and a Bayesian analysis. Interestingly, two retrospective studies showed a neutral effect on mortality of previous treatment with RAAS inhibitors,[27,28] these differences could be explained by the fact that they evaluate a low-risk population. On the contrary, high-risk COVID-19 patients are characterized by heart disease[29] and a great burden of several cardiovascular risk factors; In particular, hypertension is associated with disease severity and mortality.[30,SR1]

We have observed in our cohort a high prevalence of hypertensive patients (49.7%), of whom 73.5% were under chronic RAAS treatment. ACE2 favors SARS-CoV-2 entry into the cells,[SR2] RAAS inhibitors have shown in experimental models to increase ACE2 expression[6,SR3,SR4] and AG-II plasma levels were correlated with total viral load and severity of lung injury in COVID-19 patients.[SR5] An interesting clinical study performed on 1128 patients suggests that RAAS blockade is beneficial in the context of previous hypertension and COVID-19.[29] Nevertheless, the inclusion criteria were very stringent: only patients who received RAAS blockade during hospital stay were considered so that nothing is known about patients who were on those medications before admission, and only 31 patients took ACE inhibitors. More importantly, patients older than 74 years have been excluded from the study; older patients are particularly affected by COVID-19, with 35,5% older than 74 years in our series, and bear poor prognosis. Taken into account this information, we decided to explore the impact of chronic use of RAAS inhibitors in hypertensive COVID-19 separately.

Our work suggests that maintenance RAAS blockade exceeds by far the negative effects shown in experimental studies. According to our findings, hypertensive patients from our sample had higher crude mortality in comparison to non-hypertensive patients, but an adjusted regression logistic analysis and both propensity score analysis showed a positive association between previous treatment with RAAS inhibitors in hypertensive COVID-19 patients. Our results support the well-known protective effects of blocking the RAAS in hypertension, diabetes mellitus, chronic kidney disease, and ischemic heart disease that may offset any putative assistance to the SARS-CoV-2 entrance into the cells.

To further address the impact of chronic use of RAAS inhibitors in hypertensive COVID-19 patients, we performed a meta-analysis.[11–24] In this meta-analysis, previous treatment with RAAS inhibitors was associated with a lower risk of all-cause mortality among hospitalized hypertensive COVID-19 patients. Moreover, we found a neutral effect on intensive care unit admission and the need of mechanical ventilation. Several are the potential explanations, particularly if we take into account the high observed heterogenicity, but a meta-regression analysis ruled out a potential contributing role of the studied sample size. Thereby, other major explanations could be a "healthy user-sick stopper"[SR6] or delayed hospitalization among other unmeasured cofounders.

Overall, additional studies are still needed to elucidate all the potential scenarios as many studies have not been designed to detect a potential causal association or identify differences between ACEi and ARB. In this sense, some studies are testing whether losartan improves outcomes in COVID-19. Previous studies and our findings suggest that RAAS blockade is not harmful before and during the hospital stay in hypertensive patients, but the majority of ongoing trials include patients without chronic RAAS blockers intake who have respiratory failure (NCT 04312009, NCT 04340557, NCT 04335123), a completely different scenario. Based on the current evidence, losartan could be of benefit in ambulatory COVID-19 patients as it is being tested in another trial (NCT 04311177) although that is again a different subset of patients. In this regard, the investigators of the RASTAVI trial (NCT03201185), which is currently randomizing patients with severe aortic stenosis who have an indication for a percutaneous aortic prosthesis to ramipril or not, showed that randomization to ramipril had no impact on the incidence or severity of COVID-19.[SR7]

The retrospective nature of our work bears the inherent limitations of this kind of investigation and should be considered as a hypothesis generator. First, the collection of data relies on documents not always updated; data on the specific drug and dosage have been checked when possible and always with the electronic records. Second, the results may not be generalizable as we did not evaluate outpatients and the meta-analysis should be interpreted cautiously due to the high heterogenicity, likely explained by the variability of the studied samples and especially with the disease severity or other unmeasured confounding factors (such as drug doses, time of inclusion and study design). The comparison between patients who maintain and discontinue RAAS blockers during hospital stay is biased since it can be assumed that these medications are halted in those who need mechanical ventilation or are in a worse clinical condition ("indication bias"). We cannot be certain of the impact of maintaining or withdrawing RAAS inhibitors in them.

To summarize, our results suggest a positive association between ACEIs and ARBs intake and survival in COVID-19 patients with preexisting hypertension who need hospitalization. Our findings are supported by a meta-analysis. Moreover, maintaining these medications during hospital stays may be associated with better outcomes. Future studies are warranted, as only a prospective randomized study in hypertensive patients free of the infection testing RAAS blockade against placebo would give us evidence-based answers.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.medcli.2021.04.005.

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