Renin-angiotensin system inhibitors effect before and during hospitalization in COVID-19 outcomes: Final analysis of the international HOPE COVID-19 (Health Outcome Predictive Evaluation for COVID-19) registry

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ABSTRACT

Background The use of Renin-Angiotensin system inhibitors (RASi) in patients with coronavirus disease 2019 (COVID-19) has been questioned because both share a target receptor site.

Methods HOPE-COVID-19 (NCT04334291) is an international investigator-initiated registry. Patients are eligible when discharged after an in-hospital stay with COVID-19, dead or alive. Here, we analyze the impact of previous and continued in-hospital treatment with RASi in all-cause mortality and the development of in-stay complications.

Results We included 6503 patients, over 18 years, from Spain and Italy with data on their RASi status. Of those, 36.8% were receiving any RASi before admission. RASi patients were older, more frequently male, with more comorbidities and frailer. Their probability of death and ICU admission was higher. However, after adjustment, these differences disappeared. Regarding RASi in-hospital use, those who continued the treatment were younger, with balanced comorbidities but with less severe COVID19. Raw mortality and secondary events were less frequent in RASi. After adjustment, patients receiving RASi

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still presented significantly better outcomes, with less mortality, ICU admissions, respiratory insufficiency, need for mechanical ventilation or prone, sepsis, SIRS and renal failure ($p<0.05$ for all). However, we did not find differences regarding the hospital use of RASi and the development of heart failure.

Conclusion RASi historic use, at admission, is not related to an adjusted worse prognosis in hospitalized COVID-19 patients, although it points out a high-risk population. In this setting, the in-hospital prescription of RASi is associated with improved survival and fewer short-term complications. (Am Heart J 2021;237:104–115.)

Recently, the pandemic caused by the coronavirus disease 2019 (COVID-19) outbreak has produced a widespread important morbidity and millions of fatalities all over the world.[1,2] With a profound social and economic impact worldwide, the responsible agent was denominated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] This virusś spike protein has been reported to bind to human angiotensin-converting enzyme 2 (ACE2) with high affinity.[3] This enzyme acts as one of the main receptor-mediated mechanisms for SARS-CoV-2 cell entry, among other aminopeptidases (alanyl aminopeptidase-ANPEP, glutamyl aminopeptidase -ENPEP and dipeptidyl peptidase 4-DPP).[3]

In normal conditions, ACE2 plays a crucial regulatory role in the complex Renin-Angiotensine-Aldosterone System (RAS), which in turn, is present in the pathophysiology of several conditions, such as heart failure, hypertension, diabetes mellitus, coronary artery disease, where the use of RAS inhibitors is of paramount importance. In this group of drugs, ACE inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) are commonly prescribed in hypertension and other numerous medical conditions, frequently present in COVID19 patients.[5-9] Since ACEIs/ARBs have been associated with a theoretical increase in ACE2, some authors postulated that these drugs could raise the likelihoods of severe COVID-19.[4,6] On the contrary, more recent evidence aroused providing data on the potential benefit these drugs could pose in the COVID-19 setting.[4,6,8,10]

Nevertheless, our co-primary objectives are to analyze the adjusted impact of previous (study 1) and during admission (study 2) ACEI/ARBs treatment in all-cause mortality in a large multinational cohort of patients hospitalized because of COVID-19.

Our secondary aims are to assess the development of in-hospital complications regarding the historic (at admission) or in-hospital use of these drugs.

Methods

The present study was approved by the ethics committee of the promoting center, and was appraised and accepted as well by institutional board or local committees. Written informed consent was waived because of its anonymized observational design. All local principal researchers reviewed the draft and vouch for the accuracy and veracity of data included in the registry.

Study design and participation criteria

HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19, NCT04334291) is an international and voluntary initiative with no conflicts of interest.[11] It is designed as an ambispective cohort registry, all comers type, with no financial remuneration. Patients were eligible for recruitment when discharged after an in-hospital admission with a positive COVID-19 polymerase chain reaction (PCR) test or if their attending physicians considered them highly likely to have presented the infection. Confirmed cases were those with positive throat swab samples tested using real-time reverse transcriptase–PCR assays according to the WHO recommendations. All clinical procedures were performed by the attending physician team independently of this study following the local practice and protocols. The data were collected in electronic format in a secure online database (www.HopeProjectMD.com). The information presented here corresponds to the HOPE COVID-19 Registry final cutoff performed on May 31. A complete list of hospitals, investigators, collaborators and definitions is available in the Appendix. A more detailed glimpse of the design has been reported elsewhere.[10,11]

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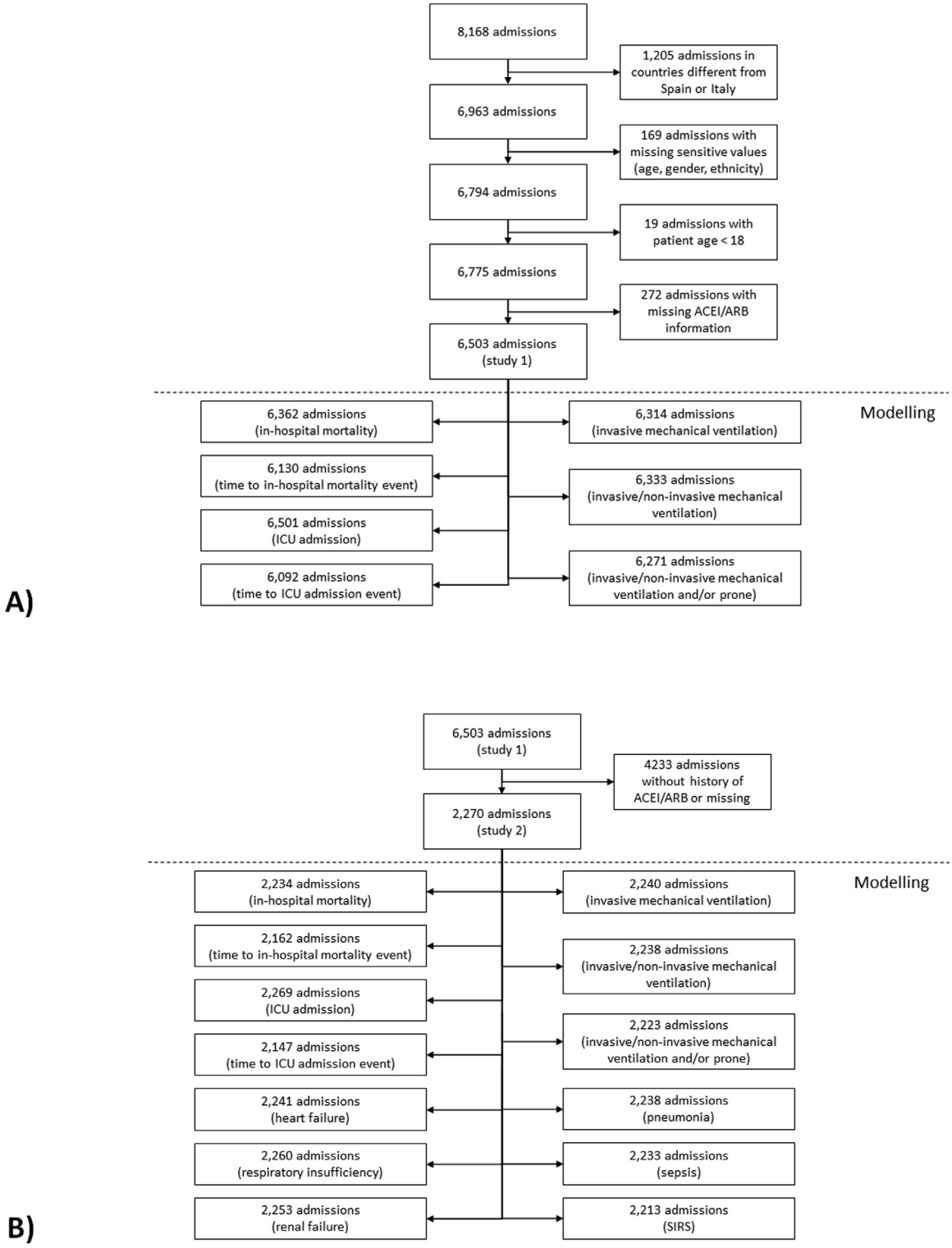
Definitions and events

In brief, we adopted a pragmatic definition for comorbidities. We accepted one disease diagnosis when the clinical records deemed the patient to present it and/or if the patient was receiving a treatment unequivocally aimed at that disease at the admission time. Further study definitions and details are available online in the study webpage and were published previously.[10,11]

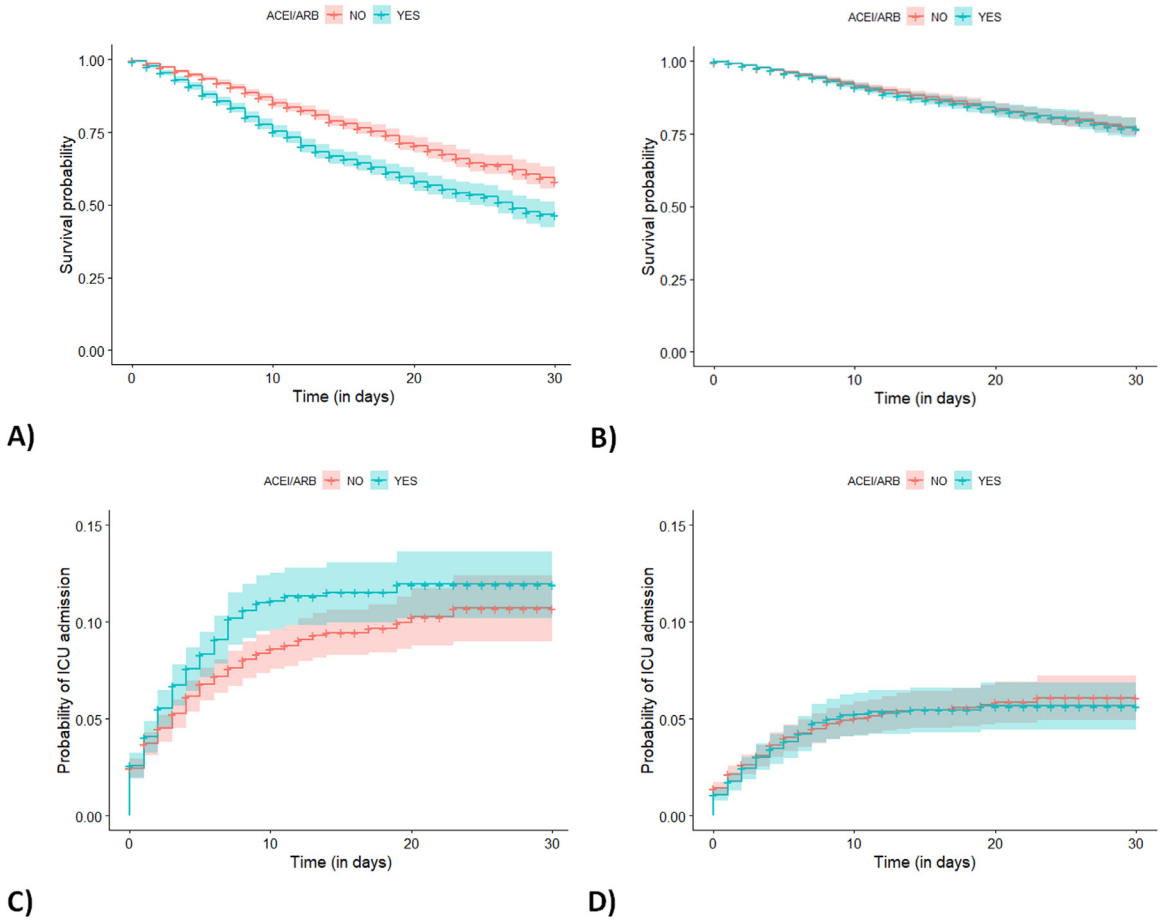
We considered all-cause mortality as the primary endpoint. Other clinically relevant events were considered as secondary end-points: intensive care unit (ICU) admission, invasive mechanical ventilation, non-invasive

Figure 1



Study flow diagram for the analysis performed in study 1 (A) and study 2 (B).

Figure 2



Study 1 data (ACEI/ARB use up to admission): **(A)** Unadjusted KM curve of survival probability stratified by history of previous ACEI/ARB use. (**B)** Adjusted KM curve of survival probability stratified by historic ACEI/ARB as estimated by Cox regression. **(C)** Unadjusted KM curve of the probability of ICU admission stratified by history of ACEI/ARB. (**D)** Adjusted KM curve of the probability of ICU admission stratified by history of ACEI/ARB as estimated by Cox regression. Data censored at day 30.

mechanical ventilation, prone, respiratory insufficiency, heart failure, renal failure, upper respiratory tract involvement, pneumonia, sepsis, systemic inflammatory response syndrome (SIRS), clinically relevant bleeding, hemoptysis and embolic events. All those events were allocated following local researchers' criteria upon HOPE COVID-19 registry definitions after a careful review of the clinical history.

Thus, we named **Study 1** the analysis between the previous history at admission of ACEI/ARBs and the adverse outcomes: in-hospital mortality, time to in-hospital death, ICU admission, time to ICU admission, invasive mechanical ventilation, invasive and/or non-invasive mechanical ventilation, and invasive/non-invasive mechanical ventilation and/or prone. **Study 2** was performed to find association between the ACEI/ARBs use during hospital stay and the adverse outcomes: in-hospital mortality, time to in-hospital death, ICU admission, time to ICU admission, invasive mechanical ventilation, invasive and/or non-invasive mechanical ventilation, invasive/non-invasive mechanical ventilation and/or prone, heart failure, respiratory insufficiency, renal failure, pneumonia, sepsis, and SIRS.

Statistical analysis

Data are presented as median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. Non-parametric Kruskal-Wallis test was used to compare continuous variables, whilst categorical variables were compared using the Chi-squared test. Multiple imputation by chained equations[12] was used to impute missing values. Multiple logistic regression analysis was performed for binary outcomes and factor associations reported as odds

Table I. Demographics, clinical characteristics, and outcomes of patients included in study 1

	No (N = 4106)	Yes (N = 2397)	*P*value
Age (in years)			<.001
Median	62.000	74.000	
Q1,Q3	49.000, 75.000	66.000, 82.000	
Age (groups)			<.001
18-49	1054 (25.7%)	95 (4.0%)	
50-64	1205 (29.3%)	452 (18.9%)	
65-74	800 (19.5%)	690 (28.8%)	
75+	1047 (25.5%)	1160 (48.4%)	
Gender (Male)	2303 (56.1%)	1483 (61.9%)	<.001
Ethnicity			<.001
Caucasian	3645 (88.8%)	2269 (94.7%)	
Latino	389 (9.5%)	101 (4.2%)	
Other	72 (1.8%)	27 (1.1%)	
Hypertension	992 (24.2%)	2296 (96.1%)	<.001
Dyslipidemia	1007 (24.7%)	1300 (54.7%)	<.001
Diabetes mellitus	552 (13.7%)	758 (32.4%)	<.001
Obesity	632 (18.8%)	604 (31.3%)	<.001
Renal insufficiency	192 (4.8%)	264 (11.4%)	<.001
Smoking (anytime)	742 (19.9%)	637 (29.8%)	<.001
Heart disease			<.001
None	3378 (83.7%)	1476 (63.0%)	
Coronary	164 (4.1%)	291 (12.4%)	
Arrhythmias	251 (6.2%)	236 (10.1%)	
Valves	65 (1.6%)	82 (3.5%)	
HF-myopathy	49 (1.2%)	89 (3.8%)	
Combined	127 (3.1%)	169 (7.2%)	
Cerebrovascular disease (any)	241 (6.0%)	298 (12.7%)	<.001
Lung disease			<.001
None	2092 (74.3%)	1107 (65.3%)	
Asthma	242 (8.6%)	124 (7.3%)	
COPD	251 (8.9%)	249 (14.7%)	
Interstitial	28 (1.0%)	17 (1.0%)	
Restrictive	21 (0.7%)	31 (1.8%)	
Other	181 (6.4%)	167 (9.9%)	
Cancer (any)	506 (12.5%)	415 (17.7%)	<.001
Immunosuppression condition (any)	279 (7.2%)	188 (8.4%)	.090
Dependency level			<.001
None	3544 (87.2%)	1929 (81.2%)	
Partially dependent	336 (8.3%)	310 (13.1%)	
Totally dependent	185 (4.6%)	136 (5.7%)	
O2 therapy (at home)	112 (2.7%)	93 (3.9%)	.010
Aspirin	402 (9.9%)	630 (26.7%)	<.001
Oral anticoagulants	316 (7.7%)	383 (16.2%)	<.001
Beta blockers	449 (11.0%)	615 (26.0%)	<.001
Inhaled beta-agonists	363 (8.9%)	303 (12.9%)	<.001
Inhaled glucocorticoids	318 (7.8%)	287 (12.1%)	<.001
D vitamin supplements	373 (9.2%)	364 (15.5%)	<.001
Tachypnea	1005 (25.5%)	735 (31.8%)	<.001
Hyposmia	266 (7.0%)	87 (3.9%)	<.001
Dysgeusia	273 (7.2%)	111 (5.0%)	.001
Sore throat	414 (10.8%)	204 (9.1%)	.034
High temperature	3281 (80.7%)	1780 (75.3%)	<.001
Persistent cough	2759 (68.2%)	1535 (65.2%)	.014
Diarrhea	766 (19.4%)	442 (19.1%)	.814
Myalgia and/or arthralgia	1320 (33.3%)	659 (28.9%)	<.001
O2 saturation less than 92%	1244 (31.3%)	1005 (43.2%)	<.001
Abnormal blood pressure	248 (6.6%)	201 (9.2%)	<.001
Elevated D-dimer	2302 (65.4%)	1540 (74.0%)	<.001
Elevated PCR	3535 (89.0%)	2155 (92.2%)	<.001
Elevated transaminases	1556 (41.2%)	872 (39.6%)	.238
Chest X-ray abnormality			.107
None	459 (12.1%)	261 (11.8%)	

(*continued on next page*)

Table I. (*continued*)

	No (N = 4106)	Yes (N = 2397)	*P*value
Bilateral	2545 (67.2%)	1542 (69.7%)	
Unilateral	781 (20.6%)	410 (18.5%)	
In-hospital mortality	634 (15.8%)	645 (27.5%)	<.001
Admitted to ICU	291 (7.1%)	219 (9.1%)	.003
Invasive mechanical ventilation	254 (6.4%)	188 (8.0%)	.013
Mechanical ventilation	654 (16.4%)	484 (20.7%)	<.001
Mechanical ventilation and/or prone position	812 (20.5%)	599 (25.8%)	<.001

Table II. Associations between the history of ACEI/ARB predictor and several adverse outcomes using the study 1 cohort

Outcome	Odds ratio (low CI-high CI)*	C-statistic-mean (Std)
In-hospital mortality	0.94 (0.78-1.14)	0.861 (0.009)
ICU admission	1.01 (0.76-1.34)	0.774 (0.016)
Invasive mechanical ventilation	0.98 (0.72-1.33)	0.808 (0.015)
Invasive/non-invasive mechanical ventilation	1.00 (0.83-1.22)	0.730 (0.006)
Mechanical ventilation and/or prone position	0.98 (0.82-1.18)	0.729 (0.010)
Outcome	Hazard ratio (low CI-high CI)*	C-statistic-mean (Std)
Time to death (in-hospital)	1.04 (0.90-1.19)	0.817 (0.011)
Time to ICU admission	0.99 (0.77-1.27)	0.788 (0.012)

Odds ratios and confidence intervals (in brackets) as estimated after performing multiple logistic regression analysis. Hazard ratios and confidence intervals (in brackets) as estimated after performing multiple Cox regression analysis, also.
Model performances were evaluated by splitting the data into 70% and 30%, for training and test, respectively. Test data subset was used to estimate the C-statistic.
*Pooled values from 5 multiple imputed datasets.

ratios (OR) with 95%CI. Time-to-event outcomes were analyzed using multivariate Cox regression and factor associations reported as hazard ratios (HR). Mortality, raw and adjusted by Cox regression, analysis was performed using Kaplan-Meier estimates and their 95% CI to compare factors. Statistical analysis was performed with R statistical programming language version 4.0. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

Finally, the HOPE registry globally collected, dead or alive, 8168 patients up to 31st May, 2020, from 50 centers in 34 cities and 9 countries (Canada, Chile, China, Colombia, Cuba, Ecuador, Germany, Italy and Spain). Due to differences in the "pandemic curve" position, the clinical protocols and to discard a "country effect" in the outcomes, we only included, in the present analysis, those patients recruited in Spain and Italy (6963 admissions).

Previous history of ACEI/ARB, at admission (study 1)

Figure 1A depicts the flow chart of the patients included in this analysis. After exclusions, we accepted 6503 patients. Of those, 36.8% were receiving ACEI/ARBs at admission. The cohort under this treatment presented a higher unadjusted probability of death during follow up (Figure 2A) and a trend to be admitted more frequently at the ICU (Figure 2C). The profile of the ACEI/ARB (+) cohort was significantly more complex, frailer, more dependent and with different clinical presentation. They were older, more frequently male and had more comorbidities (hypertension, dyslipidemia, diabetes, obesity, renal insufficiency, smokers, heart disease, cerebrovascular disease, lung disease, any cancer antecedent with many more medications at admission), Table I.

After adjustment, the association between the history of ACEI/ARB use as a predictor for adverse outcomes are reported in Table II. The supplementary tables display the complete results of multiple logistic regression analysis related to the different outcomes for study 1 (s1-s7). These multiple Cox regression analyses did not find the historic use ACEI/ARB as a predictor for adverse events, specifically regarding ICU admission, invasive mechanical ventilation, invasive and/or non-invasive mechanical ventilation, invasive/non-invasive mechanical ventilation and/or prone position, time to in-hospital death and time to ICU admission.

Figure 2B shows the differences in the curve of adjusted survival and the probability of ICU admission, Figure 2D, between the cohorts regarding the antecedent of ACEI/ARB treatment.

ACEI/ARB treatment during hospitalization or not (study 2)

During admission, we had data available for 2,270 patients (95.4%) regarding their in-hospital ACEI/ARB treatment status, Figure 1B. Table III depicts the demograph-

Table III. Demographics, clinical characteristics, and outcomes of patients included in study 2

	No (N = 1150)	Yes (N = 1120)	*P*value
Age (in years)			.002
Median	75.000	73.000	
Q1, Q3	67.000, 83.000	65.000, 81.000	
Age (groups)			.059
18-49	38 (3.3%)	54 (4.8%)	
50-64	214 (18.6%)	221 (19.7%)	
65-74	321 (27.9%)	338 (30.2%)	
75+	577 (50.2%)	507 (45.3%)	
Gender (Male)	718 (62.4%)	684 (61.1%)	.504
Ethnicity			.434
Caucasian	1083 (94.2%)	1064 (95.0%)	
Latino	55 (4.8%)	42 (3.8%)	
Other	12 (1.0%)	14 (1.2%)	
Hypertension	1102 (96.2%)	1072 (96.0%)	.817
Dyslipidemia	619 (54.2%)	604 (54.5%)	.901
Diabetes mellitus	373 (33.1%)	342 (31.3%)	.363
Obesity	297 (30.7%)	284 (32.6%)	.367
Renal insufficiency	134 (11.9%)	112 (10.4%)	.254
Smoking (anytime)	300 (28.2%)	304 (31.3%)	.128
Heart disease			.032
None	723 (64.2%)	678 (62.1%)	
Coronary	117 (10.4%)	157 (14.4%)	
Arrhythmias	129 (11.4%)	98 (9.0%)	
Valves	40 (3.5%)	35 (3.2%)	
HF-myopathy	44 (3.9%)	39 (3.6%)	
Combined	74 (6.6%)	84 (7.7%)	
Cerebrovascular disease (any)	148 (13.0%)	128 (11.8%)	.384
Lung disease			.480
None	526 (66.3%)	534 (64.9%)	
Asthma	55 (6.9%)	61 (7.4%)	
COPD	111 (14.0%)	126 (15.3%)	
Interstitial	11 (1.4%)	4 (0.5%)	
Restrictive	13 (1.6%)	16 (1.9%)	
Other	77 (9.7%)	82 (10.0%)	
Cancer (any)	220 (19.5%)	173 (15.8%)	.023
Immunosuppression condition (any)	97 (8.8%)	83 (8.0%)	.503
Dependency level			.185
None	914 (79.9%)	919 (82.8%)	
Partially dependent	163 (14.2%)	131 (11.8%)	
Totally dependent	67 (5.9%)	60 (5.4%)	
O2 therapy (at home)	43 (3.8%)	41 (3.7%)	.935
Aspirin	287 (25.3%)	309 (28.0%)	.141
Oral anticoagulants	208 (18.2%)	154 (14.0%)	.006
Beta blockers	292 (25.5%)	282 (25.7%)	.942
Inhaled beta-agonists	144 (12.6%)	138 (12.7%)	.965
Inhaled glucocorticoids	137 (12.0%)	135 (12.3%)	.817
D vitamin supplements	204 (17.9%)	141 (12.9%)	.001
Tachypnea	415 (37.0%)	290 (26.9%)	<.001
Hyposmia	35 (3.2%)	49 (4.8%)	.059
Dysgeusia	48 (4.4%)	62 (6.1%)	.074
Sore throat	68 (6.2%)	110 (10.6%)	<.001
High temperature	875 (76.8%)	823 (74.4%)	.184
Persistent cough	719 (63.3%)	733 (66.5%)	.110
Diarrhea	209 (18.6%)	214 (19.9%)	.453
Myalgia and/or arthralgia	292 (26.1%)	331 (31.1%)	.009
O2 saturation less than 92%	549 (48.6%)	400 (37.0%)	<.001
Abnormal blood pressure	125 (11.5%)	73 (7.1%)	<.001
Elevated D-dimer	780 (76.2%)	695 (71.3%)	.012
Elevated PCR	1054 (93.0%)	1005 (91.7%)	.237
Elevated transaminases	449 (41.8%)	391 (37.8%)	.059
Chest X-ray abnormality			.084
None	122 (11.2%)	129 (12.4%)	

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Table III. (*continued*)

	No (N = 1150)	Yes (N = 1120)	*P*value
Bilateral	788 (72.0%)	706 (67.7%)	
Unilateral	184 (16.8%)	208 (19.9%)	
Use of corticoids	461 (40.6%)	345 (31.7%)	<.001
Use of chloroquine or similar	973 (84.8%)	985 (88.6%)	.008
Use of antiviral drug	571 (50.2%)	635 (57.2%)	<.001
Use of interferon or similar	147 (13.1%)	121 (11.1%)	.149
Use of tocilizumab or similar	119 (10.5%)	100 (9.1%)	.253
Use of antibiotics	920 (84.4%)	829 (79.5%)	.003
Mechanical ventilation and/or prone position	341 (30.2%)	234 (21.4%)	<.001
Mechanical ventilation	268 (23.7%)	194 (17.6%)	<.001
Invasive mechanical ventilation	132 (11.6%)	49 (4.4%)	<.001
Admitted to ICU	148 (12.9%)	63 (5.6%)	<.001
In-hospital mortality	419 (37.2%)	177 (16.0%)	<.001
Heart failure during admission	129 (11.3%)	99 (9.0%)	.063
Respiratory insufficiency during admission	812 (70.8%)	587 (52.7%)	<.001
Renal failure during admission	379 (33.0%)	228 (20.6%)	<.001
Pneumonia during admission	1053 (92.7%)	988 (89.7%)	.011
Sepsis during admission	214 (18.8%)	86 (7.8%)	<.001
SIRS during admission	356 (31.5%)	223 (20.6%)	<.001

Table IV. Associations between the use of ACEI/ARB during hospital stay predictor and several adverse outcomes using the study 2 cohort

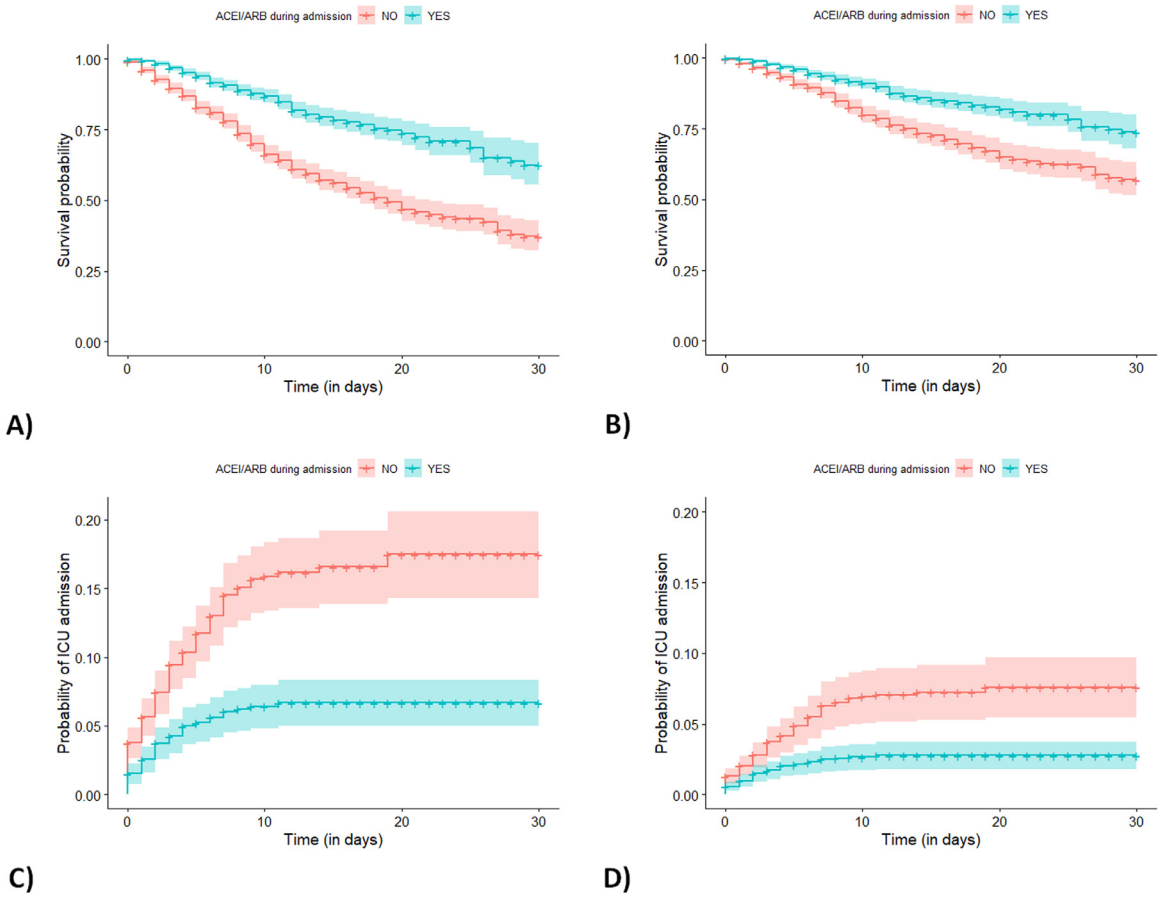
Outcome	Odd ratio (low CI-high CI)*	C-statistic-mean (Std)
In-hospital mortality	0.33 (0.25-0.42)	0.836 (0.015)
ICU admission	0.37 (0.25-0.53)	0.803 (0.024)
Invasive mechanical ventilation	0.33 (0.22-0.50)	0.854 (0.035)
Invasive/non-invasive mechanical ventilation	0.77 (0.60-0.98)	0.744 (0.032)
Mechanical ventilation and/or prone position	0.69 (0.54-0.86)	0.775 (0.021)
Heart failure during admission	0.90 (0.66-1.24)	0.756 (0.021)
Respiratory insufficiency during admission	0.53 (0.43-0.66)	0.828 (0.016)
Renal failure during admission	0.60 (0.48-0.75)	0.765 (0.027)
Pneumonia during admission	0.59 (0.38-0.90)	0.888 (0.021)
Sepsis during admission	0.42 (0.32-0.57)	0.761 (0.018)
SIRS during admission	0.68 (0.54-0.85)	0.738 (0.001)
Outcome	Hazard ratio (low CI-high CI)*	C-statistic-mean (Std)
Time to death (in-hospital)	0.47 (0.39-0.57)	0.789 (0.018)
Time to ICU admission	0.40 (0.29-0.56)	0.818 (0.024)

Odds ratios and confidence intervals (in brackets) as estimated after performing multiple logistic regression analysis. Hazard ratios and confidence intervals (in brackets) as estimated after performing multiple Cox regression analysis were concordant with the previous analysis.
Model performances were evaluated by splitting the data into 70% and 30%, for training and test, respectively. Test data subset was used to estimate the C-statistic.
* Pooled values from 5 multiple imputed datasets.

ics, clinical features, management and outcomes of the patients included in the analysis of study 2. In this case, age was slightly higher for patients not receiving ACEI/ARB without gender or ethnicity differences. Comorbidities and dependency levels were also more balanced without differences regarding cardiovascular risk factors, lung or cerebrovascular disease. However, the admission symptoms and the severity of the disease were worse in the cohort without ACEI/ARBs, Table III. This group of patients received more frequently corticoids, antibiotics and ventilation support but less chloroquine or antivirals drugs. Patients on ACEI/ARBs displayed less events during hospitalization in the univariate analysis. Supplementary Tables s8-s20 depict the results of multiple logistic regression analyses on the study 2 cohort related with the primary and the main secondary variables.

After the multivariate adjustment, we observed that the in-hospital use of ACEI/ARBs was associated with relevant clinical benefit, Table IV. Patients receiving that treatment presented better outcomes, with less mortality, ICU admissions, respiratory insufficiency, need for mechanical ventilation or prone, sepsis, SIRS and renal failure ($p<0.05$ for all). However, we did not find differences regarding the hospital use of ACEI/ARB and the development of heart failure (ORadj=0.90 CIlow:0.66, CI high:1.24, $P = .52$).

Figure 3



Study 2 analysis (ACEI/ARBs administration during the hospitalization): **(A)** Unadjusted KM curve of survival stratified by ACEI/ARB during hospital stay. **(B)** Adjusted KM curve of survival stratified by ACEI/ARB during hospital stay estimated by Cox regression. **(C)** Unadjusted KM curve of the probability of ICU admission stratified by ACEI/ARB during hospital stay. **(D)** Adjusted KM curve of the probability of ICU admission stratified by ACEI/ARB during hospital stay as estimated by Cox regression. Data censored at day 30.

Figure 3 depicts the unadjusted (A) and adjusted (B) Kaplan Meier survival curves favoring the in-hospital use of ACEI/ARBs. Same differential outcomes were observed regarding unadjusted and adjusted probability of ICU admission, Figure 3C and D, respectively.

Discussion

The main findings reported in the present study are as follows:

1) ACEI/ARBs use up to admission in patients hospitalized with COVID-19 (study 1) point out an overall worse prognosis after the non-adjusted analysis. This is probably due to their elder age with a more complex clinical profile and more comorbidities than non-users at that point. When adjusted for all these potential bias and characteristics, the historic use of ACEI/ARBs at admission displays the same outcomes in both cohorts.
2) Considering only the in-hospital use of ACEI/ARBs (study 2), the clinical profile switches. Patients on these drugs are younger with a milder COVID19 condition. Consequently, HOPE patients receiving ACEI/ARBs displayed a logical better survival and better outcomes. However, when adjusted for all relevant conditions, the in-hospital use of ACEi/ARBs was still associated with an important prognostic benefit, including survival.

Previously, in several publications, cardiovascular risk factors and heart conditions have been deemed to impact COVID-19 prognosis.[13,14] Apart from organizational issues[2] and the lockdown impact in the outcomes of several pathologies, biologically the cardiovascular system seems to be in the physiopathologic center of COVID-

19. Thus, it is of paramount importance to know the effect of a frequently prescribed group of cardiovascular drugs such ACEi/ARBs. Even more, considering the fact that the virus infects the cells, among other receptors, through a main renin-angiotensin system receptor (RAS), the angiotensin-converting enzyme 2 (ACE2),[13] which is widely expressed in many different cells of the body.

Besides the regulation of the circulatory homeostasis and systemic arterial pressure, the RAS also has a local or paracrine function, being involved in multiple biological processes (angiogenesis and thrombosis, inflammation modulation, cell proliferation, sodium and water balance, among others).

Some authors suggested the possibility of which ACE2 expression might be increased using blockers of RAS with an impact on the infectivity and prognosis of SARS-Cov2.[6,8] Without a practical basis, this hypothesis was quickly widespread in the world, causing confusion and fear in patients taking these drugs, prompting the interruption of the RAS inhibitor treatment in some patients. This encouraged the European Society of Cardiology (ESC) and The American College of Cardiology (ACC) to give a recommendation and suggested that patients, who were already on RAS blockers, should continue treatment given the low evidence of harm.[15] Later on, several studies demonstrated these statements were right and that the use of ACEi/ARBs was not associated with more SARS-CoV2 infections or, when infected, increased COVID-19 severity.[16-19] Some recent meta-analyses also disclosed the same conclusion, irrespectively of hypertension.[20,21] In fact, a randomized trial registry-based, recently published (BRACE-CORONA), supported the safety of these drugs in hospitalization because of COVID-19 in 659 participants.[22] In the same line, another open label randomized trial (REPLACE COVID) with 152 patients did not found differences in acute COVID-19 outcomes regarding the continuation or discontinuation of RAS inhibitors in hypertensive patients.[23]

Our findings, although hypothesis generating, are consistent with these previous multinational reports but add another relevant result in a larger series. In fact, concordant results have also been reported in a Chinese cohort.[24] Those patients treated with ACEI/ARBs would present better adjusted in-hospital outcomes. Thus, probably, if a COVID-19 patient has an indication for ACEi/ARBs but is not on this treatment, possibly it would be beneficial to add it.

Here, the findings could be explained by several motives:

- Sicker, intubated, hypotensive, patients discontinued their treatments. This should be a minor concern after adjustment but surely explained why the adjusted curves displayed overall less mortality or ICU admission probability.
- Discontinuation of these important therapies in a vulnerable patient population (hypertensive with heart disease or renal disease) could precipitate deterioration in cardiorenal function and increase the risk of morbi-mortality.
- A real and direct effect of the RAS in the outcome of the disease. ACE2 receptors, the virus access door to the host cells, are ubiquitous, which explicate the viral involvement in different tissues. Moreover, they are extremely abundant on the cell surface of type 2 pneumocytes, explaining the major respiratory affectation of this airborne transmitted disease. There was an initial fear that ACEI/ARBS could increase the expression of ACE2 and may facilitate the entry and diffusion of the SARS-CoV-2 virus.[22] As mentioned before, there is no clinical evidence to support that.[16-25] In fact, some researchers have demonstrated that ACE2 receptors suffer a down-regulation (i.e. the opposite of what would happen with ACE-inhibitors and ARBs) as an effect of their interaction with the virus. This phenomenon would lead to a reduced formation of angiotensin 1-7, with the consequent accumulation of angiotensin II.[25] Consequently, the excess of this hormone would favor pulmonary edema, inflammation and worsen pulmonary function among others. This deleterious effect could be prevented by RAS inhibitors.[25] Furthermore, some clinical studies published before the pandemics stated that ACEIs were superior to other antihypertensive agents in pneumonia prevention.[25] On the other hand, some experimental data on SARS-COv also showed that these drugs could be protective rather than harmful. Several Acute Respiratory Distress Syndrome (ARDS) models displayed the detrimental effects of angiotensin II as well, indicating that the pleiotropic ACE-2 activation limits pulmonary disease progression (vasodilatory, anti-inflammatory, anti-proliferative and antifibrotic effects).[18] Whether the same applies to other drugs that block the mineralocorticoid receptor and antagonize aldosterone, another mediator in the ACE-1–Ang II–AT1R pathway, is unknown.
- Additionally, the administration of recombinant soluble human ACE-2 (rh-ACE-2) in order to capture SARS-COv2 in the bloodstream has been deemed to potentially avoid its binding to its target cells, and theoretically, enhance ACE-2 activity in lung tissue, which could be beneficial for COVID-19 patients with ARDS.[25] This potential relationship remains to be assessed in the future but, in this regard, a recent association study of plasma ACE2 levels performed among 2248 patients with chronic heart failure participants in the Penn Heart Failure Study discarded that Plasma ACE2 was associated with ACEI/ARBs use.[26] Nevertheless, in this study, plasma ACE2 was slightly associated with some relevant factors for

severe COVID-19: older age, male gender, diabetes mellitus, a lower glomerular filtration rate, worse New York Heart Association class, a history of coronary artery bypass surgery, and higher pro-B-type natriuretic peptide levels.[26]

However, the specific mechanisms that regulate the metabolism of soluble or membrane-bound ACE2 remain to require further research. It is important to consider that ACE2 protein levels are not equivalent to ACE2 activity and its causal relationship with COVID-19 remains to be defined.[26]

- Some authors have also postulated a distinct inflammatory predisposition of immune cells in patients with hypertension. This correlated with COVID-19 severity.[27] In an interesting research, Trump S et al pointed out that ACEI treatment seemed to dampen COVID-19-related hyperinflammation and increase cell intrinsic antiviral responses, whereas ARB treatment could be related to enhanced epithelial-immune cell interactions. In this setting, macrophages and neutrophils of patients with hypertension, in particular under ARB treatment, exhibit higher expression of some pro-inflammatory cytokines CCL3 and CCL4 and the chemokine receptor CCR1.[27] This is of paramount importance considering the high frequency of cardiovascular comorbidities we can find in hospitalized patients with COVID-19.[28]

Limitations

The main limitation is determined by the observational design and the short term follow up of the registry. In addition, the definition of the variables, the precise management, before and during admission and the event reporting could present a certain grade of variation among centers, countries and the precise moment in their pandemic curve.[2] However, this probably would reflect the variation that medical practice has in real life and we selected only those patients admitted in Spain and Italy which provides a large multicenter cohort data with high external reproducibility in this setting. The countries assessed here, are very similar regarding the pandemic curve, in their National Health services structure, the features of their populations and their sociocultural habits. Likewise, the high mortality and events rate recorded in the HOPE registry would provide the opportunity to detect potential differences difficult to reveal with more restrictive enrollment designs or smaller samples, despite a randomized protocol.

About the treatment applied, at all times it was decided by the attending physician but we could not differentiate between ACEI/ARBs use in all cases. Thus, while these data give us an overall idea of RAS inhibitors effect in this precise cohort, they do not produce information as robust as a clinical trial would do, being unable to discard the presence of unknown bias. We await the results of the ACEI-COVID19 (NCT04353596), Controlled evaLuation of Angiotensin Receptor Blockers for COVID-19 respIraTorY Disease (CLARITY, NCT04394117), and losartan randomized trials (NCT04312009), among others, to help future clinical decision making.

Conclusions

ACEIs or ARBs use, at admission, is not related to a worse prognosis in hospitalized COVID-19 patients after an adjusted analysis, although it points out a high-risk population. In this setting, the in-hospital prescription of ACEIs or ARBs is associated with improved survival and usually fewer short-term complications.

Conflict of interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ahj.2021.04.001.

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