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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 frailier. 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...
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 virus’s 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 (alanin 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.\(^5\,\,^6\,\,^8\,\,^10\)

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 (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.\(^10\,\,^11\)

This research was supported with a non-conditioned grant (Fundación Interhospitalaria para la Investigación Cardiovascular, FIC, Madrid, Spain). This nonprofit institution had no role in the study design; collection, analysis, interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

**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).
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**

| Age (in years)          | No (N = 4106) | Yes (N = 2397) | P value |
|-------------------------|---------------|----------------|---------|
| Median                  | 62.000        | 74.000         | <.001   |
| Q1, Q3                  | 49.000, 75.000| 66.000, 82.000 | <.001   |
| Age (groups)            |               |                |         |
| 18-49                   | 1054 (25.7%)  | 95 (4.0%)      | <.001   |
| 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-myropathy            | 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%)  | 1533 (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%)  | 2153 (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)

| Outcome                                      | 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.

### 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 |
|---------------------------------------------------------------|
| **Age (in years)**                                           | **No (N = 1150)** | **Yes [N = 1120]** | **P value** |
| Median                                                      | 75.000            | 73.000             | .002        |
| Q1, Q3                                                      | 67.000, 83.000    | 65.000, 81.000     | .059        |
| **Age (groups)**                                            |                   |                    |            |
| 18-49                                                      | 38 (3.3%)         | 54 (4.8%)          | .817        |
| 50-64                                                      | 214 (18.6%)       | 221 (19.7%)        | .396        |
| 65-74                                                      | 321 (27.9%)       | 338 (30.2%)        | .367        |
| 75+                                                       | 577 (50.2%)       | 507 (45.3%)        | .367        |
| **Gender (Male)**                                          |                   |                    | .504        |
| Caucasian                                                   | 1083 (94.2%)      | 1064 (95.0%)       | .434        |
| Other                                                       | 55 (4.8%)         | 42 (3.8%)          |            |
| **Hypertension**                                           |                   |                    | .128        |
| None                                                       | 723 (64.2%)       | 678 (62.1%)        |            |
| Coronary                                                   | 117 (10.4%)       | 157 (14.4%)        |            |
| **Diabetes mellitus**                                      |                   |                    | .006        |
| None                                                       | 373 (33.1%)       | 342 (31.3%)        |            |
| **Obesity**                                                |                   |                    | .363        |
| None                                                       | 297 (30.7%)       | 284 (32.6%)        |            |
| **Renal insufficiency**                                    |                   |                    | .254        |
| None                                                       | 134 (11.9%)       | 112 (10.4%)        |            |
| **Cancer (any)**                                           |                   |                    | .128        |
| None                                                       | 300 (26.2%)       | 304 (31.3%)        |            |
| **Heart disease**                                          |                   |                    | .032        |
| None                                                       | 74 (6.6%)         | 84 (7.7%)          |            |
| **Cerebrovascular disease (any)**                          |                   |                    | .384        |
| None                                                       | 148 (13.0%)       | 128 (11.8%)        |            |
| **Lung disease**                                           |                   |                    | .480        |
| None                                                       | 526 (46.3%)       | 534 (46.9%)        |            |
| **Asthma**                                                 |                   |                    | .128        |
| None                                                       | 117 (10.4%)       | 157 (14.4%)        |            |
| **COPD**                                                   |                   |                    | .128        |
| None                                                       | 11 (1.4%)         | 4 (0.5%)           |            |
| **Interstitial**                                           |                   |                    | .006        |
| None                                                       | 13 (1.6%)         | 16 (1.9%)          |            |
| **Restrictive**                                            |                   |                    | .367        |
| None                                                       | 77 (9.7%)         | 82 (10.0%)         |            |
| **Cancer (any)**                                           |                   |                    | .023        |
| None                                                       | 220 (19.5%)       | 173 (15.8%)        |            |
| **Dependency level**                                       |                   |                    | .053        |
| None                                                       | 97 (8.8%)         | 83 (8.0%)          |            |
| Partially dependent                                        | 163 (14.2%)       | 131 (11.8%)        |            |
| Totally dependent                                          | 67 (5.9%)         | 60 (5.4%)          |            |
| **O2 therapy (at home)**                                   |                   |                    | .935        |
| None                                                       | 43 (3.8%)         | 41 (3.7%)          |            |
| Partially dependent                                        | 287 (25.3%)       | 309 (28.0%)        |            |
| Totally dependent                                          | 208 (18.2%)       | 154 (14.0%)        |            |
| **Beta blockers**                                          |                   |                    | .942        |
| None                                                       | 292 (25.5%)       | 282 (25.7%)        |            |
| Partially dependent                                        | 144 (12.6%)       | 138 (12.7%)        |            |
| Totally dependent                                          | 137 (12.0%)       | 135 (12.3%)        |            |
| **Inhaled glucocorticoids**                                |                   |                    | .817        |
| None                                                       | 204 (17.9%)       | 141 (12.9%)        |            |
| Partially dependent                                        | 415 (37.0%)       | 290 (26.9%)        |            |
| Totally dependent                                          | 35 (3.2%)         | 49 (4.8%)          |            |
| **Hyposmia**                                               |                   |                    | .059        |
| None                                                       | 48 (4.4%)         | 62 (6.1%)          |            |
| Partially dependent                                        | 68 (6.2%)         | 110 (10.6%)        |            |
| **Dysgeusia**                                              |                   |                    | .184        |
| None                                                       | 875 (76.8%)       | 823 (74.4%)        |            |
| Partially dependent                                        | 719 (63.3%)       | 733 (66.5%)        |            |
| **Diabetes insipidus**                                     |                   |                    | .453        |
| None                                                       | 209 (18.6%)       | 214 (19.9%)        |            |
| Partially dependent                                        | 292 (26.1%)       | 331 (31.1%)        |            |
| **O2 saturation less than 92%**                            |                   |                    | .009        |
| None                                                       | 549 (48.6%)       | 400 (37.0%)        |            |
| Partially dependent                                        | 125 (11.5%)       | 137 (12.3%)        |            |
| **Persisted cough**                                        |                   |                    | .012        |
| None                                                       | 780 (76.2%)       | 695 (71.3%)        |            |
| Partially dependent                                        | 1054 (93.0%)      | 1005 (91.7%)       |            |
| **Dyspnea**                                                |                   |                    | .084        |
| None                                                       | 449 (41.8%)       | 391 (37.8%)        |            |
| **Chest X-ray abnormality**                                |                   |                    | .059        |
| None                                                       | 122 (11.2%)       | 129 (12.4%)        |            |

(continued on next page)
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).

| Table III. (continued) |
|------------------------|
|                         | No (N = 1150) | Yes (N = 1120) | Pvalue |
| 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  |
| Heart failure during admission | 419 (37.2%)  | 177 (16.0%)   | <.001  |
| 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.
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. Apart from organizational issues 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 as ACEIs/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), 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-CoV-2. 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. Later on, several studies demonstrated these statements were right and that the use of ACEIs/ARBs was not associated with more SARS-CoV2 infections or, when infected, increased COVID-19 severity. Some recent meta-analyses also disclosed the same conclusion, irrespectively of hypertension. 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. 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.

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. Those patients treated with ACEIs/ARBs would present better adjusted in-hospital outcomes. Thus, probably, if a COVID-19 patient has an indication for ACEIs/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 affection 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. As mentioned before, there is no clinical evidence to support that. 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. 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. Furthermore, some clinical studies published before the pandemics stated that ACEIs were superior to other antihypertensive agents in pneumonia prevention. 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). 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. 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. 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 be 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 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 (NCT04355596), 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.

Acknowledgments

Cardiovascular Excellence SL, for their essential support in the database and HOPE webpage. All HOPE researchers.

Funding

Non-conditioned grant (Fundación Interhospitalaria para la Investigación cardiovascular, FIC, Madrid, Spain). This nonprofit institution had no role in the study design; collection, analysis, interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

Supplementary materials

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

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(5):533–4. doi:10.1016/S1473-3099(20)30120-1.
2. Nuñez-Gil IJ, Estrada V, Fernández-Pérez C, et al. The COVID-19 curve, health system overload, and mortality. Emergencias 2020;32:293–5.
3. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.
4. Aleksova A, Ferro F, Gagno G, et al. COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2)—is there any scientific evidence for controversy? J Intern Med 2020;288:410–21.
5. Lu R, Zhao X, Li J, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–74.
6. Chen L, Hao G. The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease. Cardiovasc Res 2020;116:1932–6.

7. Soro-Paavonen A, Gordin D, Forsblom C, et al. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. J Hypertens 2012;30:375–83.

8. Aghagoli G, Gallo Marin B, Soliman LB, Sellke FW. Cardiac involvement in COVID-19 patients: risk factors, predictors, and complications: a review. J Card Surg 2020 [Epub ahead of print]. doi:10.1111/jocs.14538.

9. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109:531–8.

10. Núñez-Gil JJ, Fernández-Pérez C, Estrada V, et al. HOPE COVID-19 Investigators. Mortality risk assessment in Spain and Italy, insights of the HOPE COVID-19 registry. Intern Emerg Med 2020;10:1–10 [Epub ahead of print]. doi:10.1007/s11739-020-02543-5.

11. Núñez-Gil JJ, Estrada V, Fernández-Pérez C, et al. Health outcome predictive evaluation for COVID 19 international registry (HOPE COVID-19), rationale and design. Contemp Clin Trials Commun 2020;20.

12. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res 2011;20:50–9.

13. Zheng YY, Ma YT, Zhang JY, Xie JY. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17(5):259–60. doi:10.1038/s41569-020-0360-5.

14. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID19). Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed January 5, 2021.

15. European Society of Cardiology. Position statement of the ESC council on hypertension on ACE-inhibitors and angiotensin receptor blockers. 2020. Available at: https://www.escardio.org/Councils/Council-on-Hypertension-[CHT]/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang Accessed January 5, 2021.

16. Reynolds HR, Adhikari S, Fulgarn C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of COVID-19. N Engl J Med 2020;382:2441–8.

17. Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med 2020;382:2431–40.

18. Rossi L, Malagoli A, Biagi A, et al. Renin-angiotensin system inhibitors and mortality in patients with COVID-19. Infection 2020;22:1–8.

19. Bauer AZ, Gore R, Sama SR, et al. Hypertension, medications, and risk of severe COVID-19: a Massachusetts community-based observational study. J Clin Hypertens (Greenwich) 2020. doi:10.1111/jch.14101.

20. Lee MMY, Docherty KF, Sattar N, et al. Renin-angiotensin system blockers, risk of SARS-CoV-2 infection and outcomes fromCoVID-19: systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2020;pvaa138 Online ahead of prin. doi:10.1093/ehjcvp/pvaa138.

21. Kashy N, Murphy AC, Farouque O, et al. Renin-angiotensin system inhibition and risk of infection and mortality in COVID-19: a systematic review and meta-analysis. Intern Med J 2020;50:1468–74.

22. Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. BRACE CORONA Investigators. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the BRACE CORONA trial. Am Heart J 2020;226:49–59.

23. Cohen J, Hanfl T, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet 2021. doi:10.1016/S2213-2600(20)30558-0.

24. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020;126:1671–81.

25. Rossi GP, Sanga V, Barton M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. Elife 2020;9:e57278.

26. Chirinos JA, Cohen JB, Zhao L, et al. Clinical and proteomic correlates of plasma ACE2 (angiotensin-converting enzyme 2) in human heart failure. Hypertension 2020;76:1526–36.

27. Trump S, Lukassen S, Anker MS, et al. Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19. Nat Biotechnol 2020 Online ahead of print. doi:10.1038/s41587-020-00796-1.

28. Núñez-Gil JJ, Fernández-Ortiz A, Maroud Eid C, et al. Underlying heart diseases and acute COVID-19 outcomes. Cardiol J 2020 Online ahead of print. doi:10.5603/CJ.a2020.0183.